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# EDITORIAL BROAD

**Vol. 15 Issue 2** **July-December 2020**

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## Data and knowledge to empower healthcare in South East Asia and beyond

To our readers,

I would like to welcome all readers to this new issue of EyeSEA journal. This issue contains current research of original studies, case reports and educational articles from over South East Asia.

The world has started changing rapidly after the COVID-19 outbreak. We continue our focus on publishing data that represents the South East Asian population in all domains of Ophthalmology ranging from common eye diseases to rare case reports. We believe that anyone who interest in Ophthalmology will browse through our journal and discover benefits from this issue. We hope that our journal can also fulfill the need for a valuable work of reference of lasting usefulness to practicing ophthalmologists.

Our editorial team is committed to constant improvement of publication standards. Thanks to our authors and reviewers who dedicated their valuable time and efforts to the creation of this edition. We will continue its way to attain the highest level of international recognition and readership.

Warmest regards,

Associate Professor Sakchai Vongkittirux, MD
Head of Thammasat Eye Center,
Faculty of Medicine Thammasat University
and Former President of The Royal College of Ophthalmologists Thailand

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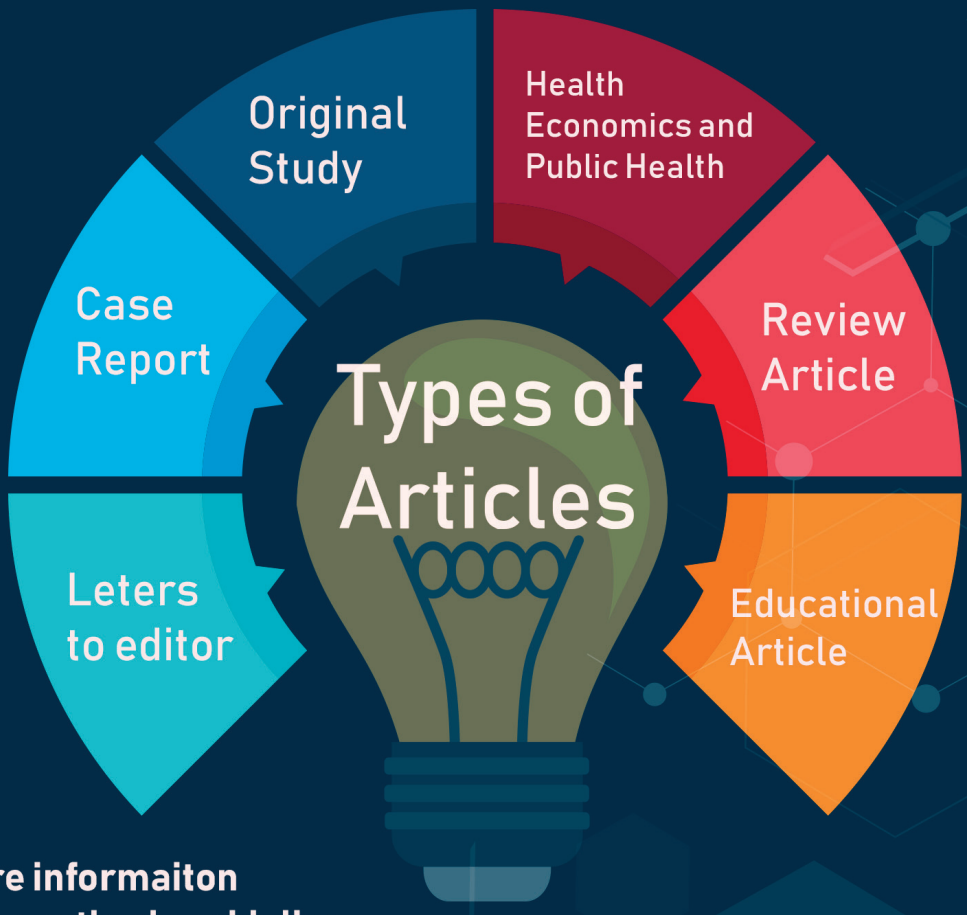


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# *Aims and Scope and Publication Policy*

## *Aims and Scope*

Eye South East Asia (EyeSEA) strives to promote the dissemination of regionally relevant academic publications and discourse in the field of Ophthalmology. The South East Asian population has a unique spectrum of eye diseases due to pathophysiologic, geographic, socioeconomic and cultural contexts – although often underrepresented in literature. EyeSEA supports the growing number of ophthalmic healthcare professionals in the region seeking to produce and disseminate academic publications, developing robust clinical methodology and quality of original publications in Ophthalmology from South East Asia to the world.

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Dates and Distribution

Publication frequency is twice per year (once every 6 months)

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### *Abstract*

Word count: Minimum 150 words -Maximum 250 words including subheadings
Key Words: minimum 2, maximum 5
Your abstract must contain content for the following headings:

1.Title
2.Purpose ("Background" for case report)
3.Methods (Leave this section blank for case report)
4.Results ("Case report", summarise the case for case report, "Case series" summarise all cases for case series)
5.Conclusion
6.Conflicts of Interest
7.Keywords

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-This section should be the shortest part of the abstract and should very briefly outline the following information:
-What is already known about the subject, related to the paper in question
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-What was the research design? e.g. Diagnostic Study, Etiognostic Study, Prognostic Study, Therapeutic / Efficacy Study -in addition to the study method: Case report, Case Control, Cohort, Randomised Controlled Trial.
-What type of patients are recruited?
-What was the clinical setting of the study? (if relevant)
-How were the patients sampled
-What was the sample size of the patients? (whole/and or in different groups)
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-What was the primary outcome measure and how was it defined?

***Results***

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-The results of the analysis of the primary objectives, mentioning statistical method, expressed in words and numbers along with P values in parenthesis
-The results of the analysis of the more important secondary objectives
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***Conclusion***

-The primary take-home message
-The additional findings of importance
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Our guidelines are based on the following reference:
Andrade C. How to write a good abstract for a scientific paper or conference presentation. Indian Journal of Psychiatry. 2011;53 (2):172.

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- Results
- Discussion
- Conclusion
- Acknowledgements and conflict of interest

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Supplementary materials should be collected in an Appendix and placed before the Reference section.

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# Persistent painless eyelid hematoma as an atypical ocular manifestation in Hemoglobin E (HbE) trait hemoglobinopathy: A Case Report

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*[2]Department of Ophthalmology and Visual Sciences, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

**Background:** Hemoglobinopathies encompass all genetic diseases of haemoglobin and fall into two main groups which are thalassemia syndromes and structural hemoglobin variants or abnormal hemoglobins. These diseases can affect any organ in the body. Ocular manifestations in thalassemia cases reported include decreased visual acuity, colour vision anomalies, cataract, visual field defects and optic neuropathy.
**Objective:** To report an atypical ocular manifestation of Hemoglobin E (HbE) trait haemoglobinopathy who presented with persistent painless lower lid bruising.
**Method:** Case report
**Results:** A seven-year-old boy with no known medical illness presented with painless right eye lower lid bruising for the past one year. The patient denied any history of trauma. There were no other ocular or systemic symptoms and the child was otherwise well. Visual acuity was 6/6 in both eyes. There was black discolouration of the right eye lower lid which extended to the temporal upper lid. No swelling or proptosis was noted. The bruising did not increase with Valsalva maneuver. Further examination of the right eye was normal. Examination of the left eye was unremarkable. Systemic examination revealed a round black discolouration of the skin measuring 1.5cm in diameter over the left mid-thoracic region. Retrospective history from the patient's mother noted the trunk discolouration appeared shortly after the right eyelid bruising which persisted until now. The patient was diagnosed as HbE trait hemoglobinopathy carrier via peripheral blood film and hemoglobin electrophoresis testing. In conclusion, persistent painless eyelid discolouration should raise suspicion of bleeding disorders.
**Keywords:** Hemoglobinopathy, HbE trait, Ocular manifestation
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## Introduction

Hemoglobin is a protein heterotetramer composed of two chains of α-globin and two chains of β-globin along with four molecules of heme and iron. HbA (α2β2) is the major

component of hemoglobin in normal adults and in children over 7 months old, usually comprising about 97% of the total hemoglobin. The remainder is Hb A2 ($\alpha 2\delta 2$), which usually constitutes about 2−3% in normal individuals.[1]

The hemoglobinopathies encompass all genetic diseases of hemoglobin. They fall into two main groups which are thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobins).[2] Both groups of hemoglobinopathies are caused by mutations and/or deletions in the α- or β-globin genes. When gene defects cause hemoglobin synthesis disorders, this gives rise to thalassemia whereby hemoglobin structure in these cases is normal. When they cause changes in hemoglobin structure, this gives rise to abnormal haemoglobin such as HbS, HbE and HbC.[2-5] There are also many mixed forms that combine features of both groups, such as β0/β+-thalassemias, HbSC disease and HbE α-thalassemias.

Alpha and beta thalassemia are the main types of thalassemia. The highly variable clinical manifestations of the hemoglobinopathies range from mild hypochromic anemia to moderate hematological disease to severe, lifelong, transfusion-dependent anemia with multiorgan involvement. With approximately 7% of the worldwide population being carriers, hemoglobinopathies are the most common monogenic diseases and one of the world's major health problems.[2] They were originally found mainly in the Mediterranean area and large parts of Asia and Africa.[1, 2] International migration has spread them from those areas all over the world.

Ocular findings in beta-thalassemia may correlate to the disease itself, iron overload or the chelating agents used.[6, 7] Various studies have documented ocular manifestations of beta-thalassemia such as ocular surface disease, decreased visual acuity, colour vision anomalies, night blindness due to cataract, visual field defects and optic neuropathy.[2, 6, 7] To the best of our knowledge, no studies have reported about the ocular manifestation in cases of abnormal haemoglobin or haemoglobin variant. We discuss a case of atypical presentation of haemoglobin E trait patient who presented with persistent painless eyelid hematoma.

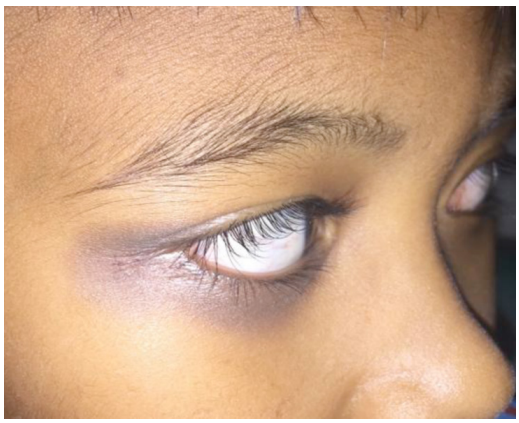
**Case Report**

A seven-year-old boy with no known medical illness presented with painless right eye lower lid bruising for the past one year. The patient denied any history of trauma preceded the symptom. The bruise was not increasing in size and not causing any proptosis. He had no bleeding tendencies and there was no known family history of malignancy or bleeding disorder. Retrospective history from the patient's mother revealed that a small coin-shaped discolouration at patient's trunk appeared shortly after the right eyelid bruising and has persisted until now. There were no other ocular or systemic symptoms and the child was otherwise well. None of his family members had similar symptoms like him.

At presentation, his visual acuity was 6/6 in both eyes and his intraocular pressure was normal. There was no relative afferent pupillary defect (RAPD). On examination, there was black discolouration of the right eye lower lid which extended to the temporal upper lid (Figure 1 and 2). No swelling or proptosis was noted. The

bruising did not increase with the Valsalva maneuver. Further examination of the right eye was normal. Examination of the left eye was unremarkable. Systemic examination revealed a round black discolouration of the skin measuring 1.5cm in diameter over the left mid-thoracic region (Figure 3). There was no similar skin discolouration at other parts of his head and body. As the lower lid bruising did not cause any proptosis, not increasing in size and has persisted for about one year, there was no radio imaging such as CT scan or MRI done for him.

Subsequently the patient was referred to the paediatric team for further assessment and to rule out any bleeding disorder. His full blood count and coagulation profile result were within normal range.



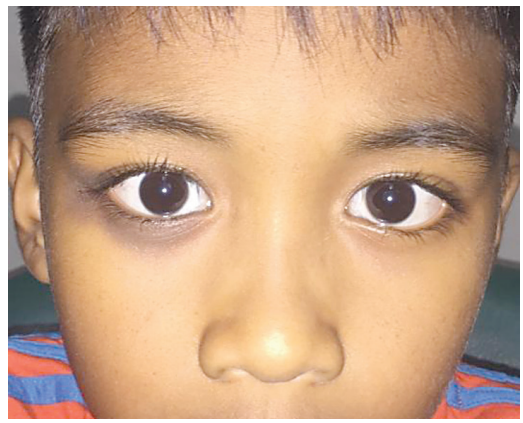


**Figure 1 and 2:** Right lower lid bruising which extended to the temporal upper eyelid

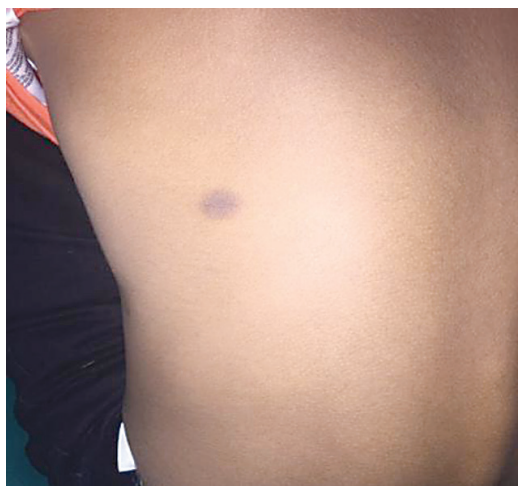


**Figure 3:** A coin-size bruise noted over the patient's trunk

His peripheral blood film result showed hypochromic microcytic features and his haemoglobin electrophoresis test revealed Hemoglobin E trait (Heterozygous HbE). The patient was eventually diagnosed as having Hemoglobin E trait and family members were screened for haemoglobinopathy.

**Discussion**

Hemoglobin E (HbE) is an abnormal hemoglobin with a single point mutation in the β chain. At position 26 there is a change in the amino acid, from glutamic acid to lysine.8,9 HbE is the second commonest abnormal hemoglobin after sickle cell hemoglobin (HbS). It is common in South East Asia, where its prevalence can reach 30-40% in some parts of Thailand, Cambodia and in Laos.[8] Hb E is also found in Sri Lanka, North Eastern India, Bangladesh, Pakistan, Nepal, Vietnam, Malaysia.

The βE mutation affects β-gene expression creating an alternate splicing site in the mRNA at codons[25-27] of the β-globin gene. Through this mechanism, there is a mild deficiency in normal β mRNA and production of small amounts of anomalous β mRNA. The reduced synthesis of the β chain may cause β-thalassemia. Also, this hemoglobin variant has a weak union between α- and β-globin, causing instability when there is a high amount of oxidant.

Hemoglobin E disease results when the offspring inherits the gene for HbE from both parents. At birth, babies homozygous for the hemoglobin E allele do not present symptoms because they still have HbF (fetal hemoglobin).[8, 9] In the first months of life, fetal hemoglobin disappears and the amount of hemoglobin E increases, so the subjects start to have a mild β-thalassemia. Subjects homozygous for the hemoglobin E allele (two abnormal alleles) have a mild hemolytic anemia and mild enlargement of the spleen.

Heterozygous AE occurs when the gene for hemoglobin E is inherited from one parent and the gene for hemoglobin A from the other. This is called hemoglobin E trait, and it is not a disease. People who have hemoglobin E trait (heterozygous) are asymptomatic and their state does not usually result in health problems. They may have a low mean corpuscular volume (MCV) and very abnormal red blood cells (target cells), but clinical relevance is mainly due to the potential for transmitting E or β-thalassemia.[8]

In our case report, the patient was initially presented with persistent painless lower lid bruising for the past one year with no history of trauma preceded the symptoms or no other bleeding tendencies. His full blood count and coagulation profile result were within normal range, while his peripheral blood film result showed hypochromic microcytic features. The haemoglobin electrophoresis test revealed Hemoglobin E trait (Heterozygous HbE).

The presence of painless hematoma is a coincidence finding in this case and the pathophysiology of hematoma is unknown. The hematoma was soft on palpation, non tender and no indurated or hard mass palpable beneath it. The patient has no other remarkable ocular findings such as conjunctival chemosis, corkscrew vessels, limitation in extraocular movement and optic nerve compression. However radio imaging was not performed in this case to see the extension of hematoma. Patient was given six monthly appointments to monitor the progression of his signs and symptoms and during his subsequent appointment, the lower lid bruising and coin-shaped discolouration at his trunk were static and similar in size.

**Conclusion**

There is no study reported about eyelid involvement in the ocular manifestation of haemoglobin E trait, specifically eyelid bruising. Persistent painless eyelid discolouration should raise suspicion of bleeding disorders. Screening also should be done among other family members for early detection and prompt intervention.

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# Corneal bee sting with retained stinger – is surgical removal always indicated?

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**Background:** Corneal bee sting is an environmental eye injury which can be blinding, while its management remains controversial. We share two similar cases which were managed differently by non-surgical and surgical methods.

**Objective:** To report cases of corneal injury by bee sting, presenting features, management, and clinical outcomes.

**Method:** Case series with literature review

**Results:** A 45 year old gentleman presented early with a history of bee sting to his right eye. His vision was counting fingers. He had two retained stingers at the deep corneal stroma layer. Treatment was initiated with intensive topical steroid, antibiotic and cycloplegia. Symptoms and vision improved with final best corrected vision acuity (BCVA) of 6/6 at 1 month. Second case was a 56 years old gentleman, presented late after a similar injury with vision of 6/60 and a paracentral corneal ulcer with retained stinger in mid stroma layer. Similar topical treatment was initiated using broad spectrum antibiotic and antifungal eye drop. The stinger was eventually surgically removed. At one year the ulcer healed with scarring and achieved BCVA of 6/12, pinhole 6/9.

**Conclusion:** Corneal bee sting injury management depends on severity of the corneal reaction, the distance and depth of the stinger from the visual axis, and its external accessibility.

**Conflicts of Interest** :The authors reports no conflicts of interest.

**Keywords :** Cornea bee sting, trauma, surgical stinger removal.

***EyeSEA 2019;15(2):6-11***

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## Introduction

Bees play a vital role in the preservation of ecological balance and biodiversity in nature. However bee sting on the ocular surface is uncommon and could potentially result in devastating ocular complications. Ocular morbidity depends on the etiology of the stinger, penetration into the ocular structures, the immunologic and toxic effects of the stinger which contains infected venom and also the presence of secondary infection.[1] We report two cases which were managed

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differently. Analysis of the final outcome revealed important observation.

**Result**

Case 1:

A 45 year old gentleman presented with severe right eye pain, epiphora and decreased vision two hours after a bee sting to the eye. His vision was counting fingers. A retained stinger was lodged at 10 o'clock position, 4 mm from the limbus, extending into the posterior stroma with an overlying central epithelial defect measuring 5.2 mm vertically (V) and 6.0 mm horizontally (H). There is generalised corneal oedema with endothelial striation involving the visual axis (Figure 1 and 2). The anterior chamber (AC) was deep with moderate inflammation with no hypopyon The Intraocular pressure (IOP) was normal and there was no relative afferent pupillary defect (RAPD). B-scan ultrasound was normal.

Intensive topical steroid (Prednisolone Forte 1%) hourly and antibiotics (Levofloxacin 0.5%) QID were initiated with cycloplegics. Preservative free artificial tears were commenced every hour to provide comfort due to the presence of epithelial defect. Symptoms improved rapidly over the next few days with resolution of the epithelial defect with no signs of secondary infection. His vision recovered to 6/6 hence the stinger was not removed (Figure 3). At one month follow up, his best corrected visual acuity (BCVA) remained at 6/6.

Case 2:

A 56 year old gentleman was referred for right eye bee sting induced corneal ulcer. He presented with eye pain, redness, and decreased vision for 4 days. His BCVA was 6/60 OD. There was a paracentral corneal ulcer at 9 o'clock measuring 1.2mm (H) x 1.2mm (V) (Figure 4). A retained stinger at mid stromal level with moderate inflammation in the anterior chamber was

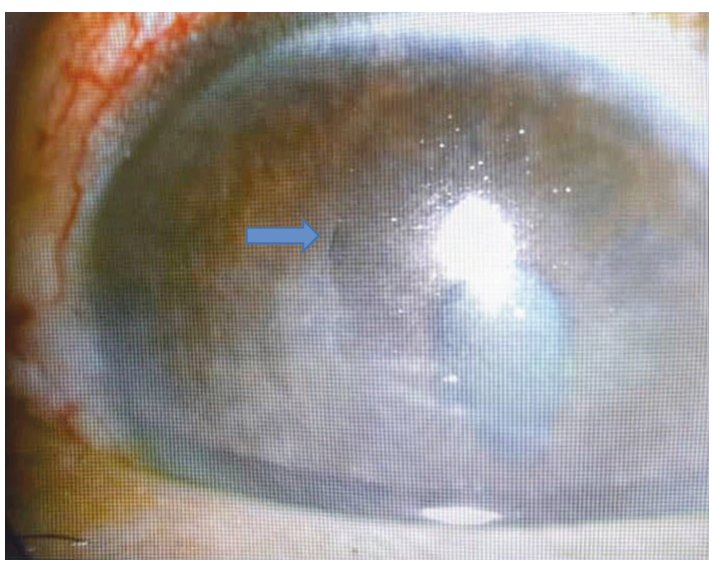

**Figure 1:** Bee stinger embedded in the cornea (arrow) with generalized corneal edema and descemet striae of the right eye

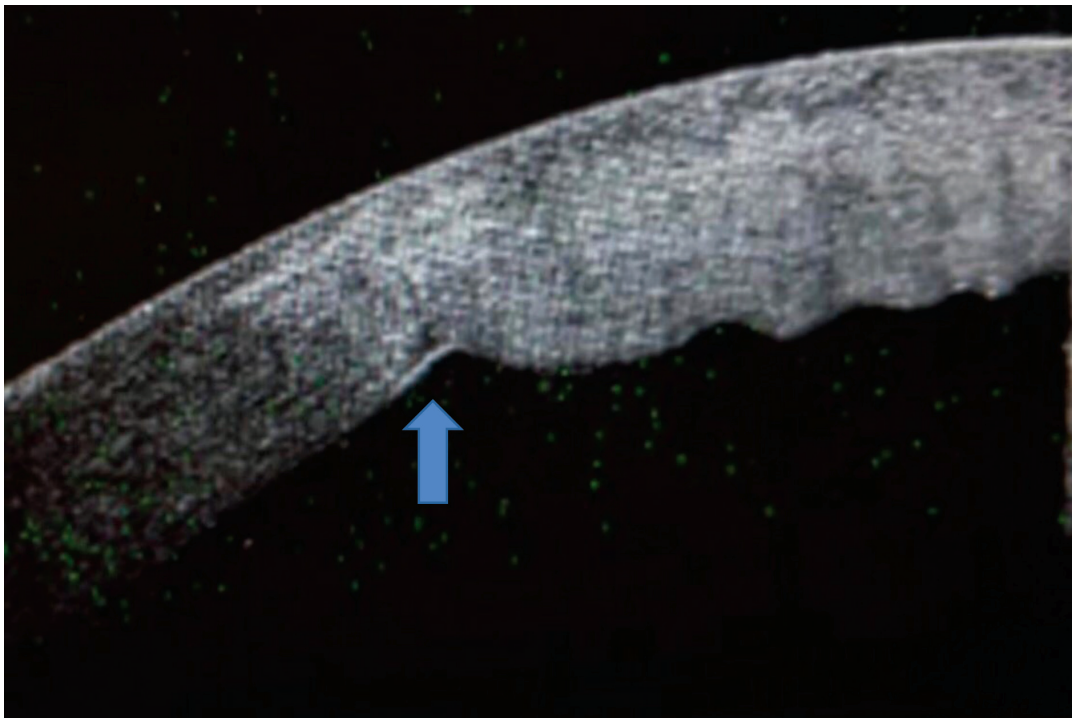

**Figure 2 :** Anterior segment optical coherence tomography (AS-OCT) showing embedded intrastromal bee stinger with surrounding corneal edema and inflammatory cells in the anterior chamber.

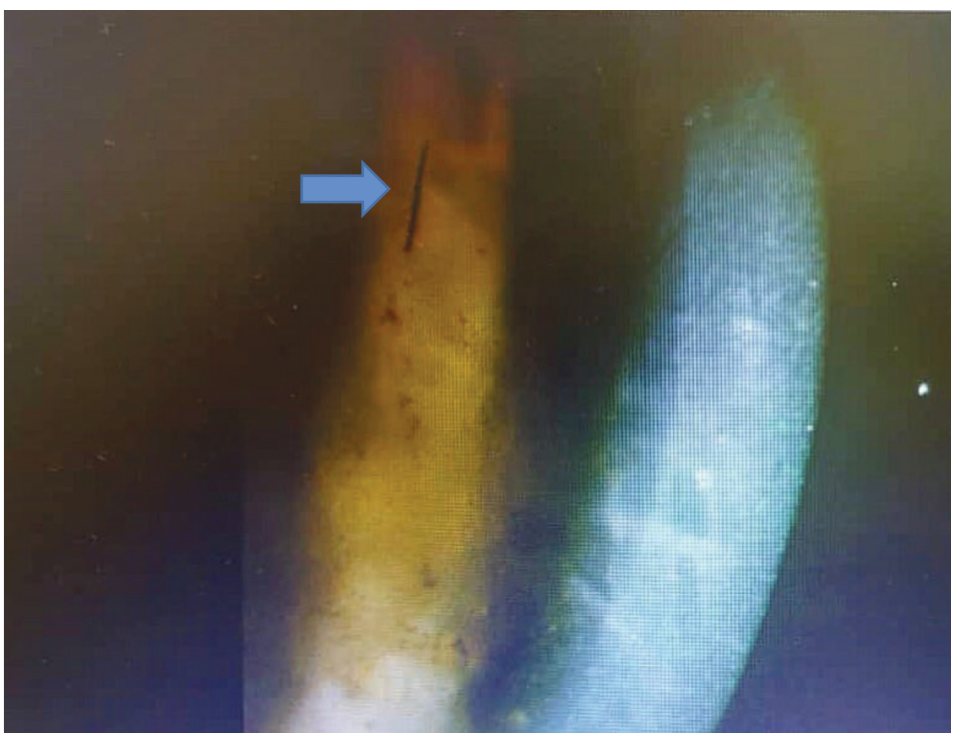

**Figure 3 :** Retained stinger (arrow) in the deep corneal stroma layer with improvement of the corneal edema after treatment initiation.

observed (Figure 5). He was treated with broad spectrum topical antibiotics. While waiting for the corneal scraping report, antifungal was also initiated due to the fuzzy ulcer margins with a suspicion of superimposed fungal infection. The corneal ulcer did not improve significantly and thus the retained stinger was surgically removed and the cornea was repaired with nylon 10/0. The corneal scraping culture and sensitivity revealed Acinetobacter baumannii sensitive to Ciprofloxacin, hence antifungal were stopped, and topical Dexamethasone 0.1% and Ciprofloxacin 0.3% were initiated. Postoperatively, his vision improved to 6/24. The corneal ulcer continued to improve and eventually healed with corneal scarring resulting in BCVA of 6/12.

**Discussion**

The sting of Hymenoptera flying insects (honeybees, bumble bees, and wasps) involving the ocular structures are rare but tend to occur at the eyelid and cornea. Bee stingers contain venom and toxin

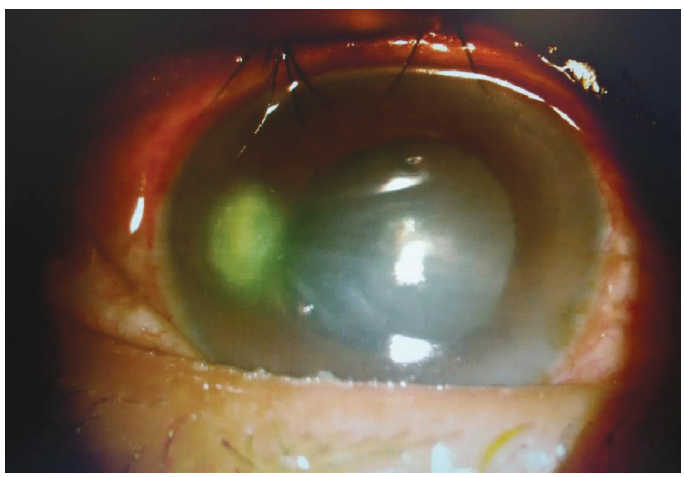

**Figure 4:** Paracentral corneal ulcer at 9 o'clock measuring 1.2mm x 1.2mm in the right eye.

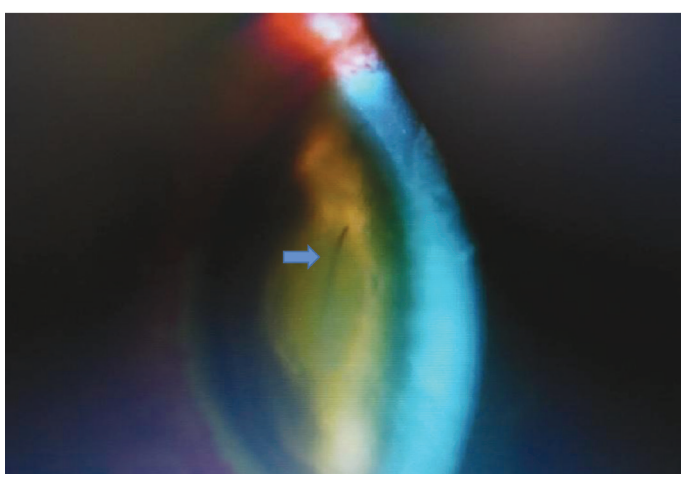

**Figure 5:** The retained stinger (arrow) in the mid corneal stroma layer

which cause various sight threatening complications affecting both the anterior and posterior segment.[2] This involves toxic injuries to the cornea, secondary infections with bacterial or fungal ulceration, anterior uveitis, cataract or even posterior segment involvement such as optic neuropathy or retinitis.[3 4] The act of stinging introduces two bodily components comprising of the stinger and its specific venom into the eye.[5] Venom contains biological amines (histamine), polypeptide toxins (melittin) and enzymes (hyaluronidase) which induce ocular inflammation by increasing capillary protein permeability which leads to greater leakage of protein and accumulation of inflammatory cells and ultimately cell death. This manifest clinically as corneal edema with sterile infiltrate around the stinger followed by decrease of endothelial cell density at a later stage.[6]

Management strategies of corneal bee sting injury are controversial depending on the time of presentation following the injury, severity of ocular complications and the status of the stinger within the eye. In the first case, we observed a more severe ocular inflammation with poorer presenting vision, however the patient presented early to our center. Prompt initiation of steroid and antimicrobial treatment led to a good response and recovery. The primary aim of corneal bee sting treatments is to control the inflammatory response. Most ophthalmologists prescribe early intensive topical corticosteroids and topical broad-spectrum antibiotics to prophylactically prevent secondary infection.[7 8] Topical cycloplegics are added to reduce ciliary spasm and stabilize the blood-aqueous barrier. The patient should be monitored closely for any ocular complications

Gilboa postulated that once the venom from the bee stinger is neutralized, the stinger itself becomes completely inert and can remain within the cornea without causing further adverse reactions[2]. The stinger can be barbed (honeybee) with a saw-like architecture therefore an attempt to grasp and pull the embedded stinger out in the reverse direction usually results in its retention requiring operative intervention.[9] Although the straight stinger (wasp, bumblebee) is easier to remove, external pressure may crush it into two separate lancets.[10] If the venom gland is still adherent to the stinger, manipulation can cause attached muscle fibers to contract resulting in additional venom discharge and continued toxicity. On the other hand, Al Towerki reported that immediate removal of the stinger mitigated the need of any additional therapy with good outcome.[11] Our second patient presented late with corneal ulceration which did not improve with medical therapy alone, hence removal of the stinger was crucial to reduce the source of inflammation and infection. Lin et al. reinforced that early stinger removal along with topical antibiotics and steroids ensured a good visual outcome.

The decision to leave the stinger in place depends on the severity of the corneal reaction in the first few hours, the distance of the stinger from the visual axis and the depth of the protrusion and its external accessibility. Both surgical and non-surgical approaches were used in the cases described above. A good control of inflammation and prevention of secondary infections prevented any visual impairments at the end of treatment.

**Conclusion**

Cornea bee sting injuries are rare. The retain insect part is usually very thin with surrounding inflammatory reaction and necrosis hence they can be easily missed and may mimic microbial keratitis even under slit lamp biomicroscopy. Corneal bee sting injury management depends on severity of corneal reaction, the distance and depth of the stinger from the visual axis, and its external accessibility. To prevent permanent corneal damage, early and prompt action is important while considering surgical removal where it is necessary. AC-OCT has been a complimentary tool in demonstrating the depth of stinger in the cornea.

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# Malignant Lymphoma of The Lacrimal Canaliculi: A Rare Case Report

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**Background:** Malignant lymphoma in the lacrimal system is a rare case of ocular malignancy. It is often caused by immunosuppressive conditions or associated with older age. We aim to conduct a careful examination of canaliculi mass especially a suspect for malignant to be completed with histopathology and discuss the diagnosis and management of malignant lymphoma in the lacrimal canaliculus.

**Results:** A woman, 60 years old, presented with a swollen left upper eyelid, red eye, and eye discharge. She had been assessed as blepharoconjunctivitis and received adequate antibiotics for the last four months. However, her complaints persisted. She had ocular pain, itchiness, yellowish thick eye discharge. History of previous tumor was denied. Physical examination revealed a swollen lacrimal punctum on the left upper eyelid, depicted a 'fish mouth appearance' with volume 3.0 x 3.0 x 3.0 mm. Irrigation test showed a negative result with a positive regurgitation discharge. Punctum incision and curettage were performed using local anesthesia. The curettage procedure revealed a dacryolith on the upper side and a purplish-red mass on the lower side. Culture test showed a positive result for *Staphylococcus aureus* infection. The mass was sent to pathology which suggested a lymphoproliferative lesion, suggestive of a malignant lymphoma. The patient was referred to the Hematology-Oncology division to determine the stage and further treatment.

**Conclusion:** The diagnostic tests needed for malignant lymphoma cases include biopsy, immunohistochemistry, laboratory, and computed tomography scan. Biopsy must be done assuming that the mass is malignant, until proven otherwise. Management of malignant lymphoma itself is based on the type and severity degree of the lymphoma.

**Keywords:** canalicular lymphoma, lacrimal system, ocular malignancy, TNM staging, ocular adnexal lymphoma

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## Introduction

Malignant lymphoma in the lacrimal system is one of the rare cases of ocular malignancy.The majority of these lymohomas are classified into Non-Hodgkin Lymphoma (NHL).[1-2] NHL is a type of malignancy that can originate from 3 types of lymphocyte cells, namely B cells, T cells, and natural killer (NK) cells.[3] The incidence of lymphoma in the lacrimal system is estimated at 0.2 per 100,000 individuals.[2]

Malignant lymphomas are often caused by some conditions such as immunosuppression conditions, HIV-AIDS, the use of immunosuppression drugs, or associated with older age.[4] However, current literature also showed that malignant lymphomas may be associated with bacteria or viruses infection, such as *Chlamydia psitacii, Helicobacter pylori,* Hepatitis-C virus, human herpes virus, human T-cell lymphotrophic virus type-1 (HTLV-1) and Epstein-Barr virus (EBV).[4]

In this case report, we will discuss the examination, diagnosis, and management of a patient with malignant lymphoma in the lacrimal canaliculus.

## Case Report

A 60-year-old woman came with a swollen left upper eyelid, red eye, and eye discharge. This patient had been assessed with blepharoconjunctivitis for the last four months. She had received antibiotics yet her complaints were still existed. She also complained about having ocular pain, itchiness, and yellowish thick eye discharge. She had a history of hypertension and diabetes mellitus.

No history of bleeding and decreased visual acuity were found. History of previous tumor or lump in the eye or any part of the body was denied. She had never experienced trauma, previous eye surgery or systemic infection. No history of similar complaints on her family.

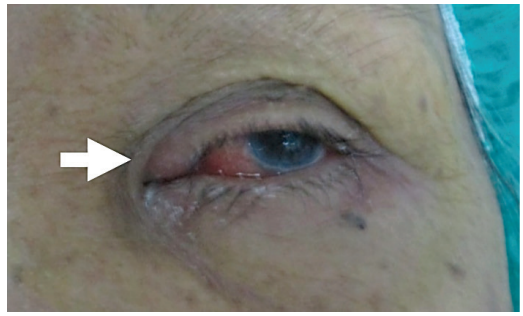

**Figure 1.** Visible superior canaliculus lumps on the left eyelid was pointed with white arrow.

General physical examination was normal. Visual acuities were 6/6 for both eyes. There was a swollen lacrimal punctum on the left upper eyelid which depicted a 'fish mouth appearance' with 3.0 x 3.0 x 3.0 mm in volume (see Figure 1). There was reddish discharge from the punctum of lacrimal and tenderness on the left eyelid. Right eyelid was normal as well as the other ophthalmologic examinations.

Irrigation test (Anel test) showed a negative result with a positive regurgitation discharge. Blood test of the patient also showed a normal range (haemoglobin 13.8 g/dL, red blood cell 4.8x1012 cells/L, hematocrit 42.2%, leukocyte 5000/L, platelet 241,000/mm3, random blood glucose 191 mg/dL, HbA1c 6.2%). The patient was assessed with chronic canaliculitis of the left eye. As seen in Figure 2, punctum incision and curettage were performed using local anesthesia. In this patient, curettage revealed a purplish-red mass and the tissue biopsy was sent to

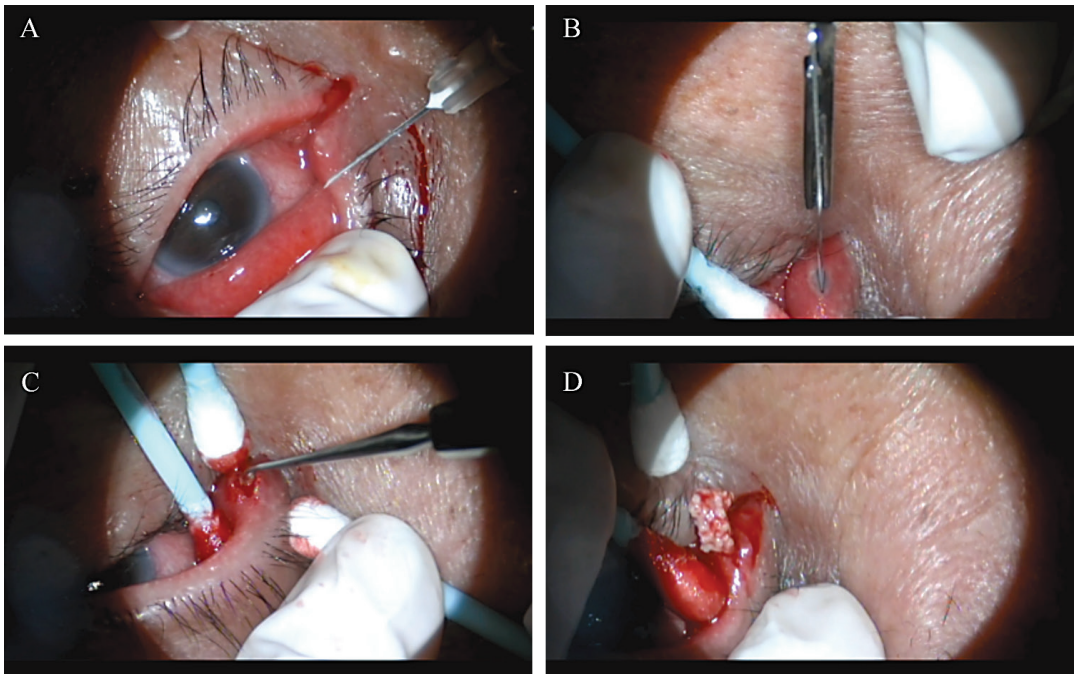


**Figure 2.** Incision and curettage followed by biopsy. (A) Local anesthesia; (B) Superior lacrimal canalicular incision; (C) Curettage; (D) Mass extraction

pathology anatomy for further examination.

Culture test showed a positive result for *Staphylococcus aureus* infection. Furthermore, the sensitivity test revealed that this patient was sensitive with several antibiotics. On the other hand, the negative sensitivity test showed resistant to piperacillin, benzylpenicillin, and amoxicillin.

Pathology anatomy result showed that the tumor was a lymphoproliferative lesion, raising a suspect of a malignant lymphoma. Furthermore, it is crucial to classify the staging of malignant lymphoma by immune-histochemical and genetic testing. The examinations would lead to proof the type of lymphoma before further treatment. However, the immune-histochemical and genetic testing had not been performed since the patient was reluctant due to financial matter. The patient was consulted to the Hematology-Oncology division Internal Medicine for determining the definitive therapy, although the patient was lost to follow up at our hospital.

**Discussion**

Malignant lymphoma cases in the lacrimal system are one of the rare conditions in the ocular malignancy. Based on reports in the United Kingdom, a third of lacrimal system lymphoma cases are MALT lymphoma type and a third of them are DLBCL type. Other data from Japan states that DLBCL has an incidence rate of 46.2%, while MALT lymphoma has an incidence rate of 15.4%.1 Several other studies have also shown that MALT lymphoma and DLBCL are the two types of lymphoma that most commonly occur in the lacrimal system.[2]

Early development of malignant lymphoma in the lacrimal system begins with a sudden growth of the mass, which

is followed by a slow progression.[3] In this patient, swollen eyelids appeared for the previous 4 months. There were no other non-specific symptoms of malignant lymphoma found in this patient, namely, enlargement of lymph nodes, malaise, weight loss, fever, and night sweats.

Both irrigation and curettage procedures were planned based on the 'fish mouth appearance' that was found in the physical examination. Despite the negative irrigation test, canaliculectomy was still managed to be performed. If there is no improvement in the patient's symptoms despite the adequate medication, incision and curettage followed by a mass biopsy should better be performed. After an adequate duration of treatment with antibiotics for four months, the culture test was also done to have a further look at the possible etiology. In this case, if we referred to the outcome of the culture-sensitivity test, there was a secondary infection from *Staphylococcus aureus*. These gram-positive bacteria are found in the respiratory system which is very close to the lacrimal system.

Figure 3. TNM Lymphoma Ocular Adnexa Staging

Blockage in the lacrimal system due to malignant lymphoma can trigger an infection around the lacrimal system. At the end of the procedure, a mass was found in situ but it was not a dacryolith. Therefore, we sent the mass to the pathology anatomy.

Age ranges from 50 to 70 years old is considered as carrying the highest risk of malignant lymphoma, hence, our sixty-year-old patient is classified

**TNM Clinical Staging for Ocular Adnexal Lymphomas (OALs)[a]**

| | |
|---|---|
| **Primary tumor (T)** | |
| TX | Lymphoma extent not specified |
| T0 | No evidence of lymphoma |
| T1 | Lymphoma involving the conjunctiva alone without orbital involvement |
| T1a | Bulbar conjunctiva only |
| T1b | Palpebral conjunctiva ± fornix ± caruncle |
| T1c | Bulbar and nonbulbar conjunctival involvement |
| T2 | Lymphoma with orbital involvement ± any conjunctival involvement |
| T2a | Anterior orbital involvement,[b] but no lacrimal gland involvement (± conjunctival disease) |
| T2b | Anterior orbital involvement with lacrimal gland involvement (± conjunctival disease) |
| T2c | Posterior orbital involvement (± conjunctival involvement ± any extraocular muscle involvement) |
| T2d | Nasolacrimal drainage system involvement (± conjunctival involvement but not including nasopharynx) |
| T3 | Lymphoma with preseptal eyelid involvement[23,c] ± orbital involvement ± any conjunctival involvement |
| T4 | Orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain |
| T4a | Involvement of nasopharynx |
| T4b | Osseous involvement (including periosteum) |
| T4c | Involvement of maxillofacial, ethmoidal ± frontal sinuses |
| T4d | Intracranial spread |
| **Lymph node involvement (N)[d]** | |
| NX | Involvement of lymph nodes not assessed |
| N0 | No evidence of lymph node involvement |
| N1 | Involvement of ipsilateral regional lymph nodes[d] |
| N2 | Involvement of contralateral or bilateral regional lymph nodes |
| N3 | Involvement of peripheral lymph nodes not draining ocular adnexal region |
| N4 | Involvement of central lymph nodes |
| **Distant metastasis (M)** | |
| MX | Dissemination of lymphoma not assessed |
| M0 | No evidence of involvement of other extranodal sites |
| M1 | Lymphomatous involvement in other organs recorded either at first diagnosis or subsequently |
| M1a | Noncontiguous involvement of tissues or organs external to the ocular adnexa (eg, parotid glands, submandibular gland, lung, liver, spleen, kidney, breast) |
| M1b | Lymphomatous involvement of the bone marrow |
| M1c | Both M1a and M1b involvement |

as having the peak age.[4] The diagnosis process of malignant lymphoma begins with the staging process of the disease. Several references can be used for staging lymphoma, including REAL, Ann Arbor, and TNM.[5] For lymphoma cases in the orbital/ocular adnexa, the staging system using TNM provides a more specific result (see Figure 3).

Based on the staging system, staging T explains the expansion of the primary lymphoma tumor. In the case of adnexal ocular lymphoma, lymphoma expansion ranges from the conjunctiva to the entire structure in the periorbital structure. Staging N explains the involvement of lymph nodes. Lymph nodes involvement ranges from ipsilateral regional lymph nodes to central lymph nodes. Staging M explains the metastasis away from the lymphoma. The degree of metastasis is ranged from external organs from ocular adnexa to bone marrow involvement. In this case, the only staging that can be done is T2d-NX-MX which involved the nasolacrimal system with or without conjunctival involvement and no involvement of nasopharynx with no examination of lymph node (N) and distant metastasis (M) involvement.

The diagnostic tests needed for malignant lymphoma cases include biopsy, immunohistochemistry, laboratory, and computed tomography or positron emission tomography (PET) scan. Biopsy examination is done by taking a tissue sample and a biopsy of the nearest lymph node (sentinel lymph node biopsy). In the case of the lacrimal system lymphoma, the favorable closest lymph node taken is from pre-auricular, cervical, and supraclavicular lymphoma. The biopsy process is followed by routine histopathological examination to determine the cell type and continued with an immunohistochemical examination.[5,6]

The biopsy result of this case showed a

| Neoplasm | sIg; cIg | CD5 | CD10 | CD23 | CD43 | CD103 | BCL6 | IRF4/ MUM1 | Cyclin D1 | ANXA1 |
|---|---|---|---|---|---|---|---|---|---|---|
| CLL/SLL | +;-/+ | + | - | + | + | - | - | (+PC) | - | - |
| LPL | +/-;+ | - | - | - | -/+ | - | - | +* | - | - |
| Splenic MZL | +;-/+ | - | - | - | - | - | - | - | - | - |
| HCL | +;- | - | - | - | - | + | - | - | +/- | + |
| Plasma cell myeloma | -;+ | - | -/+ | - | -/+ | - | - | + | -/+ | - |
| MALT lymphoma | +;+/- | - | - | -/+ | -/+ | - | - | +* | - | - |
| Follicular lymphoma | +;- | - | +/- | -/+ | - | - | + | -/+# | - | - |
| MCL | +;- | + | - | - | + | - | - | - | + | - |
| Diffuse large B-cell lymphoma | +/-;-/+ | -*** | -/+## | NA | -/+ | NA | +/-## | +/-** | - | - |
| Burkitt lymphoma | +;- | - | + | - | +/- | NA | + | -/+ | - | - |

+, >90% of cases +; +/-, >50% of cases +; -/+, <50% of cases +; -, <10% of cases +. IRF4/MUM1, interferon regulating factor 4; ANXA1, Annexin A1; PC, proliferation centres; *, plasma cell component positive; #, some grades 3a and 3b; ##, DLBCL of germinal centre B-cell type (GCB) express CD10 and BCL6; **, DLBCL of activated B-cell type (ABC) are typically positive for IRF4/MUM1; ***, some DLBCL are CD5+; NA, not applicable; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma.

**Figure 4.** Immunohistochemical characteristics of malignant lymphomas originating from B-cells

lympho-proliferative lesion with a possibility of malignant lymphoma. Ideally, to find out more about the type of lymphoma, an additional examination is needed, such as immunohistochemical examination and genetic testing.

Immunohistochemical examination in malignant lymphoma cases is used to differentiate the histopathological character of the lymphoma cells. This examination aims not only to diagnose the lymphoma cell, but also to determine the management for patient. Figure 4 shows various characteristics of the types of lymphomas that are associated with differences in immunohistochemical examination.

There are various regimens available for immunohistochemical examination of malignant lymphoma cases, including CD10, CD20, CD3, CD5, CD19, CD45, bcl-2, bcl-6, Ki-67, MUM1.[5,8] Laboratory tests that can support the diagnosis of malignant lymphoma are routine haematological examinations (haemoglobin, haematocrit, leukocytes, platelets, type counts), peripheral blood morphology, SGOT, SGPT, bilirubin, LDH, albumin, ureum-creatinine, and electrolytes. Other examinations that can help are detection of Hepatitis C, tuberculosis, and HIV.[5,9] In this case, a relatively normal laboratory result was obtained from this patient.

**Table 1.** Low-Grade and High-Grade Malignant Lymphoma[12]

| Low Grade | High Grade |
|---|---|
| · MALT Lymphoma | · Mantle Cell Lymphoma |
| · SLL (Small Lymphocytic Lymphoma) | · DLBCL (Diffuse Large B-Cell Lymphoma) |
| · MZL (Marginal Zone Lymphoma) | · Burkitt Lymphoma |
| · Lymphoplasmacytic Lymphoma | · T-Cell Lymphoma |
| · Follicular Lymphoma | |

Management of malignant lymphoma is based on the severity of the lymphoma. There are 2 groups of severity, low grade (Ki-67 <30%) and high grade (Ki-67>30%) lymphoma.[5, 9, 10] The table below shows the types of lymphomas based on the degree of severity.

The first-line therapies of low-grade lymphoma and small size lymphoma (<7.5 cm) are chemotherapy with R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) for 3 cycles, followed by radiotherapy. For high-grade lymphoma, the first-line therapies are chemotherapy with the R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) for six cycles and continued with radiotherapy. In patients with cardiac disorders, the chemotherapy regimen can be replaced with alternative regimens such as RCEPP (Rituximab, Cyclophosphamide, Etoposide, Procarbazine, Prednisone), RCDOP (Rituximab, Cyclophosphamide, Liposomal, Doxorubicin, Vincristine, Prednisone, Procarbazine), DA-EPOositu (DA-EPO), RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone), and RGCVP (Rituximab,

Gemcitabine, Cyclophosphamide, Vincristine, Prednisone).[5,9]

Radiotherapy in lymphoma cases show good efficacy. Radiotherapy has a local tumor control level of 86-100% and a local recurrence rate ranged from 0% to 15%. Radiotherapy or External Beam Radiation Therapy (EBRT) is given externally. The targets of this radiotherapy include the localized area of the lymphoma tumor and nearby lymph nodes involved. CT Simulator is used to plan the radiotherapy. PET Scan can help determine the target volume of radiotherapy. The dose given is approximately 30 – 36 Gy for cases that respond to chemotherapy, or 40 – 50 Gy in cases that do not respond to chemotherapy. The dose is given in 15 – 20 divided doses.[5,9,12]

In general, malignant lymphoma in the lacrimal system has a good prognosis for low-grade type. The five year survival rate for this condition varies from 50-94%.[5] Excision therapy or surgery alone is not enough to prevent tumor recurrence. For small-sized tumors, therapy with multiple modalities is recommended such as chemotherapy followed by radiotherapy. This therapy is useful to prevent recurrence and the development or metastasis of the lymphoma to other organs.

**Conclusion**

Malignant lymphoma in the canalicular system is a rare case in ocular malignancy. This condition may be related to immunosuppressive condition, such as HIV-AIDS and the use of immunosuppressive drugs, or associated with older age. The most common type of malignant lymphoma is Non-Hodgkin Lymphoma. It is imperative that biopsy must be done assuming that the mass is malignant, until proven otherwise.

**Acknowledgement**

None.

**Conflict of interest**

None.

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# Phacoemulsification Tunnel Keratitis: A report of 2 cases with different outcomes

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**Background:** Phacoemulsification tunnel wound keratitis can occur, with various aetiologies. This condition is difficult to treat and often leads to poor visual outcome.

**Method:** Case report

**Results:** A 66 year-old diabetic male (Patient 1) and a 68 year-old non-diabetic female (Patient 2) were treated for presumed fungal keratitis at their phacoemulsification tunnel wound sites. They had previously undergone uneventful phacoemulsification through temporal corneal incisions around 4-5 months prior to presentation. Both had prolonged post-operative inflammation which did not respond to topical steroids. Topical and oral antifungals were started after the appearance of suspicious fungal infection stigmata including fern-like infiltrates with fluffy edges and satellite lesions. Patient 1 needed a penetrating keratoplasty, and intracameral voriconazole was given when his condition did not resolve. His best-corrected visual acuity at last review was light perception, as compared to 6/60 at first presentation. Patient 2 was given intrastromal amphotericin B. Her condition improved with best corrected visual acuity being 6/60, compared to 1/60 on presentation.

**Conclusion:** We should have a high index of suspicion of fungal infections in patients with prolonged inflammation post-phacoemulsification which do not respond to steroids. Early diagnosis and treatment is important because complications of fungal keratitis often result in poor visual prognosis.

**Conflicts of interest:** The authors declare no conflicts of interest.

**Keywords:** fungal, phacoemulsification tunnel, keratitis

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## Introduction

During phacoemulsification, a 3-step self-sealing main incision wound is often made either through the sclera, limbus or cornea.[1] Infection involving this phacoemulsification tunnel wound can occur, often presenting as scleritis or keratitis, and can result in poor visual outcome.[2] This is due to the space created when the wound is not well-constructed, leading to poor wound apposition.[3] Other than keratitis,

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endophthalmitis has also been reported with clear corneal incisions having a greater risk of developing post-operative endophthalmitis when compared to scleral incisions.[4] We report 2 cases of phacoemulsification tunnel keratitis, with different outcomes for each one.

**Case 1**

A 66 year-old poorly controlled diabetic male was referred from a secondary centre for persistent right eye anterior chamber inflammation for 5 months, which did not respond to topical steroids. He had earlier undergone uneventful phacoemulsification via a temporal corneal wound, but developed redness and pain 6 weeks post-operatively while using topical steroids. His visual acuity was 6/60 unaided, 6/18 pinhole when he presented to our centre. On examination, fern-like infiltrates were seen at the inner part of the temporal phacoemulsification main tunnel, which also had fluffy edges and irregular margins (Figure 1). Granulomatous keratic precipitates and anterior chamber cells were also present. Intraocular pressure was 24mmHg in that eye. Fundus examination showed moderate non-proliferative diabetic retinopathy. B-scan ultrasonography showed no evidence of loculations which suggest vitreous inflammation.

He was diagnosed as having fungal keratitis, based on the clinical findings. Topical natamycin 5% hourly, topical voriconazole 1% hourly, oral fluconazole 200mg daily, and topical moxifloxacin 2-hourly were given, as well as anti-glaucoma drops which included topical brimonidine 0.1% tds, topical timolol 0.5% bd, topical dorzolamide 2% tds, and topical latanoprost 0.005% once per night. His topical steroids were discontinued. However, his condition did not improve. Right eye penetrating keratoplasty was performed after 3 weeks of antifungal therapy. Post-penetrating keratoplasty, he again developed persistent inflammation and high intraocular pressure. Intracameral voriconazole 1% (with cefuroxime) was given twice (1 week apart) and intracameral amphotericin B (with moxifloxacin) was given once (1 week after the 2nd voriconazole) after the penetrating keratoplasty, which helped to resolve the infection. However, his final visual outcome remained poor, with only perception to light vision. Corneal scraping for Gram stain, potassium hydroxide preparation and culture media was negative for bacterial or fungal infection. Polymerase chain reaction (PCR) for aqueous humor was also negative for fungal aetiology.

**Case 2**

A 68-year old non-diabetic female underwent phacoemulsification via a temporal corneal incision in her right eye. She initially had a suture abscess, which was removed 6 weeks post-operatively, but then was referred to our centre for persistent anterior chamber inflammation 4 months later which did not respond to topical steroids. Her best corrected visual acuity then was 1/60. On examination, there were anterior stromal infiltrates at the phacoemulsification tunnel site with poorly defined margins, fluffy edges, satellite lesions, and anterior chamber inflammation (Figure 2). There were no keratic precipitates. Intraocular pressure and fundus examination were otherwise normal.

She was diagnosed with right eye fungal keratitis, with the diagnosis being made clinically. Corneal scraping was negative for fungal infection. Topical amphotericin B 0.15% hourly, topical fluconazole 0.2% hourly, topical moxifloxacin 2-hourly and oral fluconazole 200mg daily were given. Intrastromal amphotericin B was also given. Her condition improved with best-corrected visual acuity becoming 6/60.

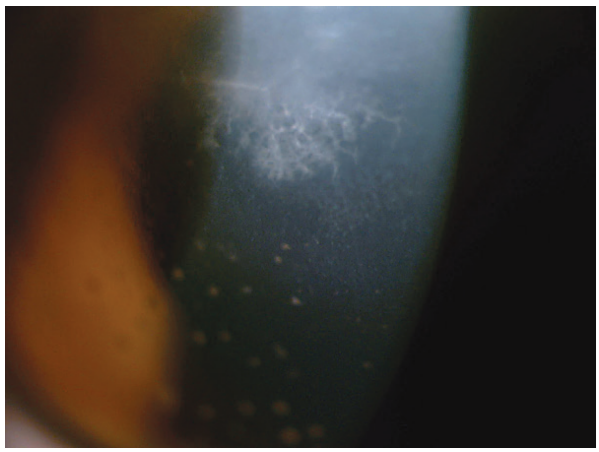

**Figure 1a:** Anterior segment photograph of right eye (Patient 1) showing stromal infiltrate at the inner part of temporal main wound tunnel, with irregular margins, fluffy edges and fern-like pattern, 5 months after uneventful phacoemulsification.

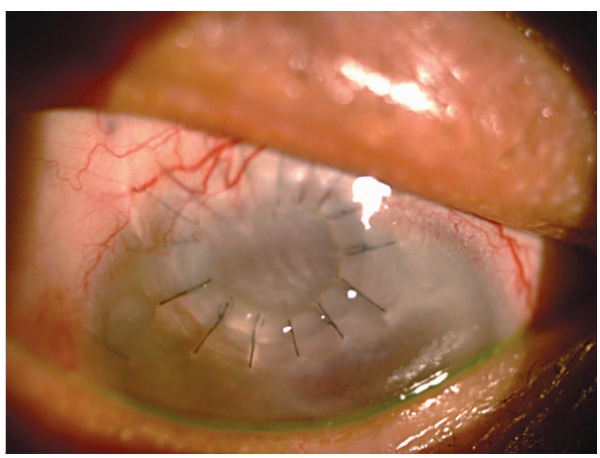

**Figure 1b:** Anterior segment photograph of right eye (Patient 1) post-penetrating keratoplasty and intracameral voriconazole.

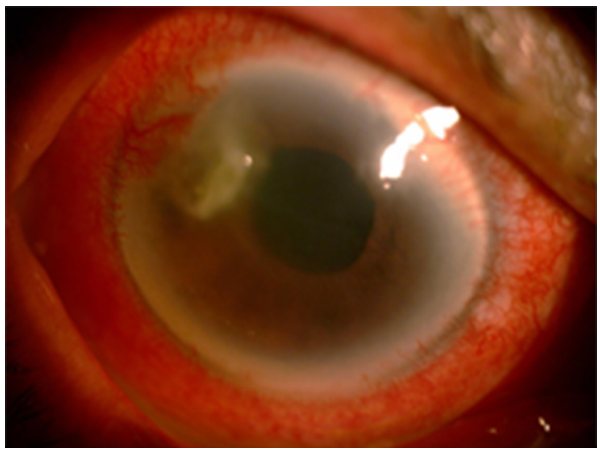

**Figure 2a:** Anterior segment photograph of right eye (Patient 2) showing stromal infiltrate at the phacoemulsification tunnel main wound temporally with clinical suspicion of fungal aetiology, 4 months after uneventful phacoemulsification.

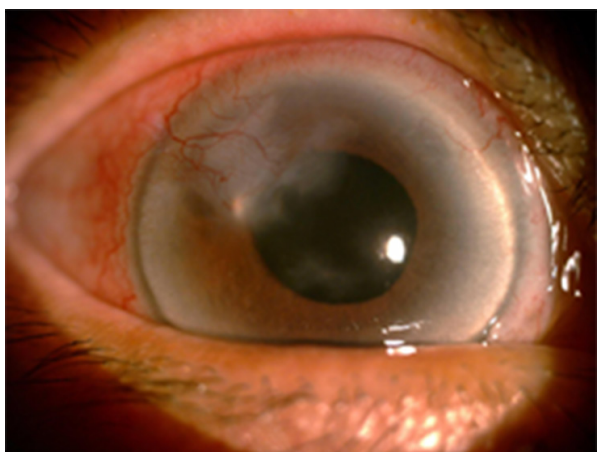

**Figure 2b:** Anterior segment photograph of right eye (Patient 2) following resolution of infection.

**Discussion**

Phacoemulsification tunnel fungal keratitis remains a diagnostic and therapeutic challenge. Both our patients had histories of uneventful phacoemulsification through corneal wounds, but then presented with keratitis later. Both were initially treated with prolonged topical steroids. The diagnoses of fungal keratitis were made clinically in both cases. In both cases, there was no history of trauma, contact lens use, foreign body or chemical injury prior which could be potential risk factors for infection post-operatively.

There are various aetiologies of fungal keratitis post-phacoemulsification surgery. These include common organisms such as *Aspergillus sp., Candida sp.* and *Fusarium sp.,* which can be refractory.[2] Other less common fungi include

Alternaria,[5] Scedosporium apiospermum,[6] Beauveria alba,[7] and Cladopialophora carrionii,[8] which had been reported following uneventful phacoemulsification surgery as well.

We were unable to isolate fungal organisms from microbiological investigations in both cases. Polymerase chain reaction (PCR) has been reported to provide high sensitivity and specificity in detecting most fungi.[9] Our negative PCR results suggested one of two possibilities, either a fungal species was difficult to detect, or this was a rare incidence of failure to detect fungi by PCR. We were unable to perform antifungal susceptibility testing due to the negative results.

Our decision to start antifungal treatment was based upon clinical diagnoses of presumed fungal keratitis. The exact source of infection was unknown in both cases, whether from the eyelid and conjunctiva, contaminated surgical instruments, or breach in aseptic technique. The selection of antifungals was challenging in both cases, due to the unknown aetiology. There has been reported improvement in fungal tunnel infection with the use of topical and oral voriconazole.[10] Some other studies have also suggested the benefit of intrastromal voriconazole in the treatment of recalcitrant fungal keratitis.[11] Both patients had intrastromal injections of amphotericin B. Patient 1 also had intracameral injection of voriconazole in view of the deep-seated infection.

Diabetes mellitus is a significant risk factor for fungal keratitis at the phacoemulsification tunnel.[12] Other predisposing factors include underlying immunosuppression, prolonged use of topical steroids, and loose sutures.[13] Despite being on voriconazole, Patient 1's condition worsened, which suggested other potential factors, such as poorly controlled diabetes, or a more virulent type of fungal species. For medical management, both our patients required a combination of topical, systemic and intraocular antifungals. Medical management alone was sufficient to prevent the spread of infection in Patient 2. In both cases, we managed to prevent complications such as endophthalmitis, however the outcome was different in each patient.

**Conclusion**

We should have a high index of suspicion of fungal infections in patients with prolonged inflammation post-phacoemulsification which do not respond to steroids. Early diagnosis and treatment is important because complications of fungal keratitis often result in poor visual prognosis.

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# Case series of retinal capillary hemangioma in patients with and without von hippel lindau disease

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**Background:** To report six cases of retinal capillary hemangioma (RCH) in patients with and without Von Hippel Lindau (VHL) disease to observe the presenting age, clinical features, treatment modalities and visual outcome of each patient.
**Methods:** Case series
**Results:** All patients showed unilateral involvement. The presenting symptoms for both groups were mainly chronic generalised painless blurring of vision and central scotoma. Among three of VHL patients, fundus examinations revealed one patient had solitary retinal angioma with exudates and the other two had multiple retinal angioma with various sizes and locations. Two of the patients had focal laser done to each eye and one patient had both focal laser and intravitreal ranibizumab injection. In three other patients without VHL (sporadic), fundus examinations revealed multiple peripheral retinal angioma with pre-retinal haemorrhage in one patient and juxtapapillary RCH in two patients. The first patient developed vitreous haemorrhage and underwent vitrectomy twice and endolaser therapy. The other two patients with juxtapapillary RCH received intravitreal ranibizumab in each eye and one of them had Verteporfin photodynamic therapy.
**Conclusion:** Age at presentation of sporadic tumors can be as early as in teenagehood. From the case series, juxtapapillary RCH occurs more in sporadic cases with higher risk to develop vision threatening complication. Current treatment is able to achieve vision stability but not a complete regression of the retinal lesion hence the eyes are always at risk.
**Conflict of Interest:** The authors declare no conflict of interest
**Keywords:** von hippel lindau, retinal capillary hemangioma, juxtapapillary
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## Introduction

The Von Hippel Lindau (VHL) is a rare disease first reported in the twentieth century. It is an autosomal dominant disorder that implies a genetic alteration resulting in the loss of the tumor suppressor function of the VHL gene[1] located in chromosome 3 (3p25.3).

In 1904, Eugene von Hippel, a German ophthalmologist, described some cases of retinal angiomatosis. After some 20 years, Lindau, a Swedish pathologist,

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established the relationship between the cerebellar and retinal lesions in 1926. In 1964, Melmon and Rosen reported cases of von Hippel disease and Lindau disease with overlapping ophthalmic, central nervous system, and visceral manifestations, establishing the clinical spectrum and diagnostic criteria of "von Hippel-Lindau" disease (VHL)[2]. The incidence of the disease is approximately 1/36,000 in the general population, but with a high penetrance in the affected families, reaching 90% at 65 years of age[3,4], which justifies the high risk of developing its related diseases in the individuals that carry the mutation.

The main manifestations of VHL are hemangioblastomas of the central nervous system and retina, renal carcinomas and cysts, bilateral pheochromocytomas, cystic and solid tumors of the pancreas, cystadenomas of the epididymis, and endolymphatic sac tumors

Retinal capillary hemangioma (RCH) is a benign vascular tumor of the retina that can occur sporadically or in association with von Hippel-Lindau (VHL) disease[5]. When it is related to VHL disease, RCH is the common feature of VHL disease and are often the first manifestation of the disease (up to 43% of gene carriers)[6].

The purpose of this report is to present six cases of RCH in patients with and without VHL to observe the presenting age, clinical characteristics (including tumor growth type and location), treatment modalities and visual outcome in each of the treatment given to patients.

**Case Presentation**

Six patients with retinal capillary hemangioma with VHL and without VHL disease were seen at Ophthalmology Clinic, Hospital Selayang. Background ocular history, associated symptoms and thorough eye examinations including fundus photo, OCT and FFA were taken and performed in each individual patient.

**Case 1**

A 24-year-old gentleman with a family history of VHL presented with progressive worsening blurring of vision of the left eye for 2 months. The LE BCVA was 6/9. His right eye was normal. Dilated fundus examination showed a solitary retinal angioma with surrounding exudates at the peripheral superotemporal region (Figure 1). LE focal laser to the feeder artery was given and the lesion seemed stable as the retinal angioma contracted with surrounding fibrosis during the last clinic visit after a year of treatment (Figure 2). Final LE BCVA for the patient was 6/9. The patient was further subjected to whole body MRI screening for concurrent existing of other hemangioma or visceral lesions. His MRI was revealed to be normal.

**Case 2**

A 38-year-old gentleman with a family history of VHL with RCH initially presented in 2018 for right eye blurring of vision for 2 months. His left eye was blind since childhood. The RE BCVA was 3/60 ph 6/60. Right eye fundus examination showed presence of multiple retinal angioma, the largest being at the temporal quadrant and few at the superior and inferior retina. RE FFA showed leakage near the lesions (Figure 3) and OCT showed presence of subretinal fluid on macula. Hence the eye was treated with two sessions of intravitreal Ranibizumab and focal laser. During subsequent follow up, the lesion at the

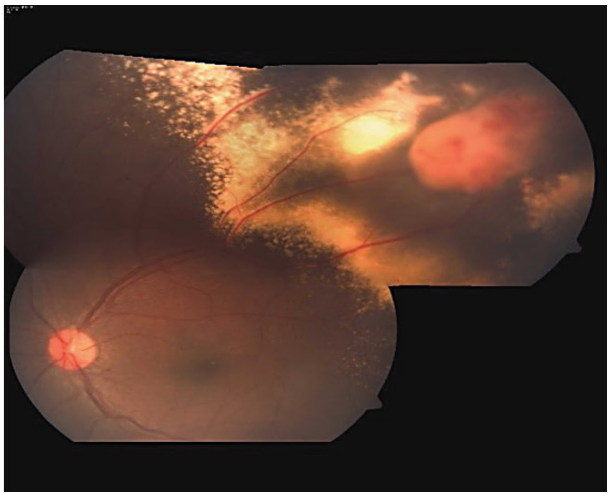

**Figure 1** Montage fundus photography showing left solitary RCH over superotemporal retina with surrounding exudates

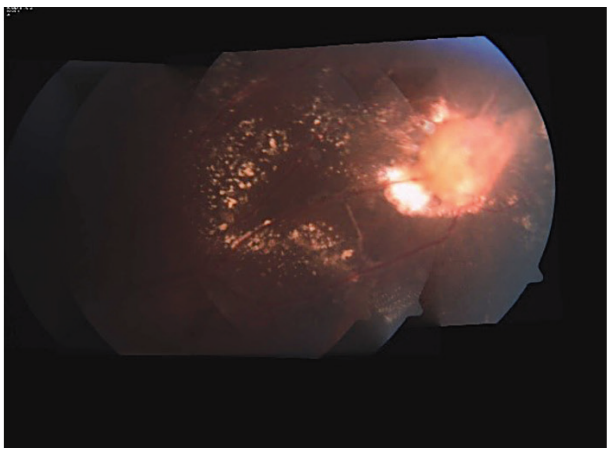

**Figure 2** Fundus photography showing contracting tumor post focal laser

temporal quadrant had focal detachment with persistent small angioma at inferior quadrant. Barricade laser was done at the detachment area and another focal laser given to the area of the smaller tumor. A month later revealed a dilated, tortuous feeding vessel located temporally to the angioma. Laser ablation was given to the vessel and post laser treatment resulted in a sclerosed feeder vessel but not completely obliterated nevertheless the lesion seemed stable. The final BCVA of the RE was 6/36 ph 6/18.

**Case 3**

A 38-year-old man with VHL disease, pheochromocytoma and post nephrectomy complained of right eye central scotoma for 2 weeks. The visual acuity in the right eye was 6/36. The left eye was normal. Funduscopic examination of the right eye revealed 2 retinal angiomas superotemporally with surrounding oedema and exudates. RE focal laser was performed on the lesions. Subsequent follow up showed contraction of the smaller angioma but the bigger angioma did not

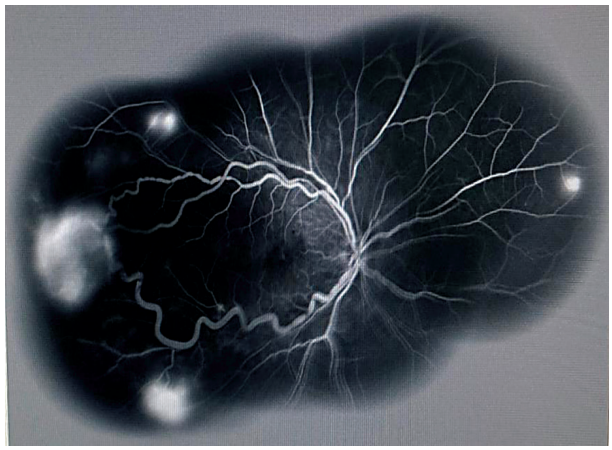

**Figure 3** Right eye montage FFA showing multiple lesions with leakage near the lesions: largest at temporal and 1 smaller lesion each at superior, nasal and inferior retina

show any improvement and was seen projecting into the vitreous. The lesion was observed in view of high risk of bleeding. Over the next 2 years, the lesion remains stable and contracted (Figure 4&5). Repeated FFA showed no leakage from the angioma and was treated conservatively. The visual acuity of 6/36 remained stable in the right eye till the date of writing the case.

**Case 4**

A 13-year-old boy complained of left eye squint with reduced vision for 2 months. The visual acuity in the left eye was 6/60. The right eye was normal. Funduscopic examination revealed an abnormal peripapillary vascularisation with fibrosis nasally (Figure 6). He was treated with LE intravitreal Ranibizumab.

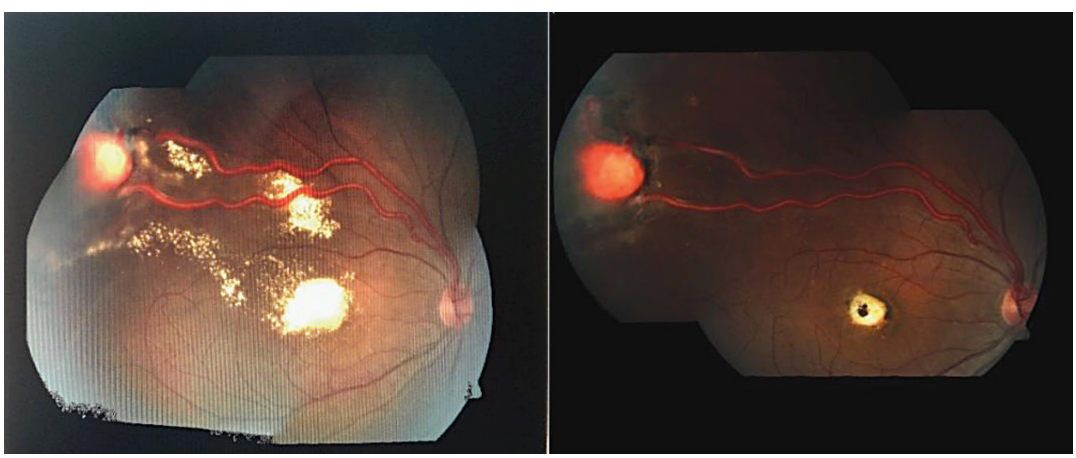

**Figure 4 &5** Right eye serial fundus photography showing contraction of retinal hemangioma and resolution of macula exudates

Post injection, the patient developed a localised TRD at angioma. LE vitrectomy and endolaser was done. A year later, the contracting angioma at the disc caused retinal traction at the surrounding area including the macula (Figure 7). No active intervention was done. His final visual acuity was 6/60.

**Case 5**

A 37-year-old man presented with the complaint of progressive left eye blurring of vision for 1 month. The visual acuity of the LE was 6/18. Dilated fundus examination showed a reddish subretinal lesion at the juxtapapillary region with surrounding exudates and SRF

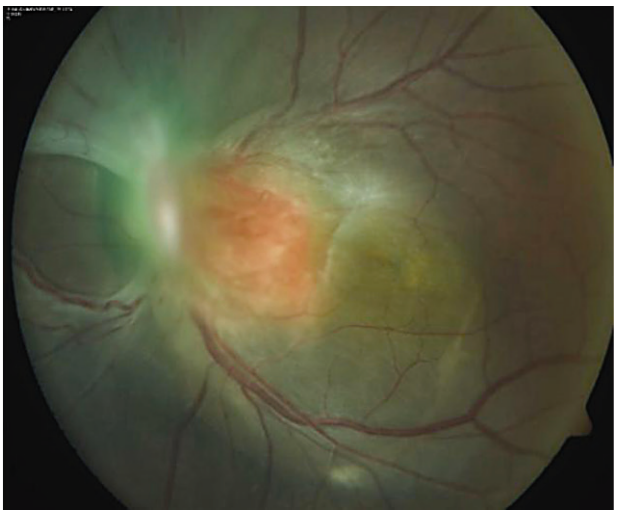

**Figure 6** Left eye fundus photography showing peripapillary abnormal vascularization with nasal fibrosis

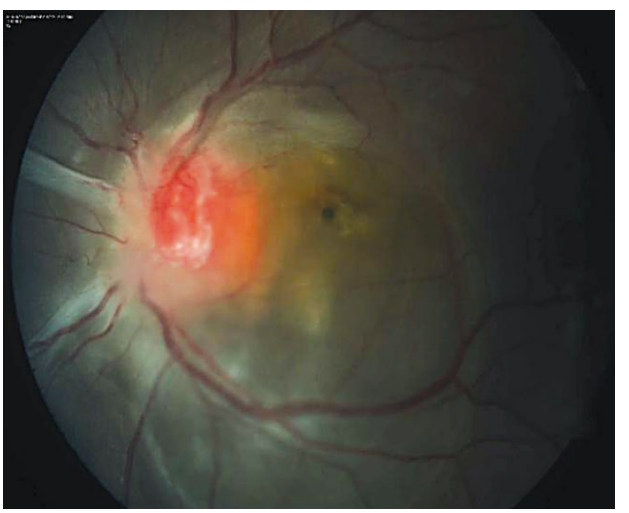

**Figure 7** Left eye fundus photography 1 year post treatment

(Figure 8). OCT showed subretinal and intraretinal fluid near the OD and FFA resulted in increased hyperfluorescence juxtapapillary (Figure 9). Patient was treated with intravitreal Ranibizumab. Subsequent follow up at 3 months post intravitreal Ranibizumab, his visual acuity dropped to CF 3 ft and more subretinal exudates were seen. Repeated FFA showed a hyperfluorescent lesion with increasing size and intensity, well defined margin with no feeder vessel. Patient was then treated with LE full fluence PDT. Post PDT, patient had persistent macular oedema. His best last recorded final VA was 6/60. He then migrated to another country and had his eye follow up over there.

**Case 6**

A 62-year-old man with chronic myeloid leukaemia and LE pseudophakia presented with generalised LE blurring

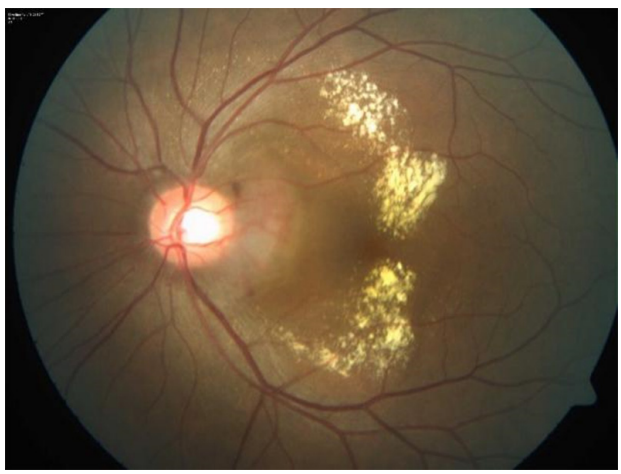

**Figure 8** Left eye fundus photography showing subretinal reddish lesion at juxtapapillary with surrounding exudates and SRF

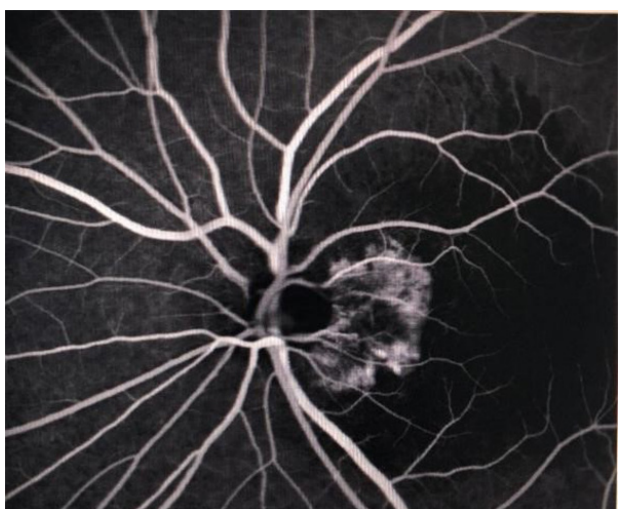

**Figure 9** Left eye FFA showing peripapillary hyperfluorescent lesion

of vision for 3 months. The visual acuity of the LE was HM. The RE was normal. Fundus examination revealed LE pre-retinal haemorrhage at the superior quadrant and 3 vascularized lesions, 1DD each at peripheral temporal quadrant. Subsequently, the patient developed vitreous hemorrhage and underwent LE PPV/ endolaser. FFA postoperatively noted LE chronic macula edema and capillary fall out area seen at nasally and inferiorly with no feeder vessels seen. LE PRP laser was performed to the nonperfused retina. Patient had LE recurrent VH 1 year later and underwent another LE PPV with endolaser treatment. Post operatively, the LE retinal lesion reduced in size with surrounding fibrosis and a final VA of 6/18.

**Results**

A total of six cases of RCH (three patients with VHL and three without VHL disease) were collected to observe the presenting age, clinical features and treatment prescribed. All the patients were male and had unilateral involvement. Presenting symptoms for both groups were mainly chronic generalised painless blurring of vision with central scotoma.

For VHL patients, the age ranged from 24 to 38 years old. The presenting best-corrected visual acuity (BCVA) ranged from 6/9 to 3/60. Fundus examinations revealed 1 patient had solitary retinal angioma with exudates and the other 2 had multiple retinal angioma with various sizes and locations. Two of them had focal laser done to each eye and the third patient was given focal laser and intravitreal ranibizumab.

Meanwhile, for cases without VHL, the age ranged from 13 to 62 years old. The presenting BCVA ranged from 6/18 to HM. Dilated funduscopic examinations revealed multiple peripheral retinal angioma with pre-retinal haemorrhage in one patient and juxtapapillary RCH in the other two patients. The first patient developed vitreous haemorrhage and underwent vitrectomy twice and endolaser therapy. The remaining two patients with juxtapapillary RCH, the first one was treated with intravitreal Ranibizumab and Verteporfin photodynamic therapy whilst the other was treated with intravitreal Ranibizumab only. The latter developed localised TRD at angioma and underwent vitrectomy and endolaser.

**Discussion**

Retinal capillary hemangioma (RCH) are benign vascular tumors that can appear sporadically or are associated with VHL disease. Although RCH usually manifests as a solitary unilateral tumor, when associated with VHL disease, up to half the cases may have multifocal or bilateral involvement[7]. In the current case series, all the patients including in association with VHL show unilateral involvement and 2 out of 3 patients with VHL have multifocal lesions (case 2 and 3).

In bilateral cases, they generally exhibit symptoms and produce severe visual impairment in 5–8% of patients. The growth of RCH is usually slow and endophytic, with peripheral retinal location although they could also be juxtapapillary.

Arun D Singh et al in 2002 found that approximately half of the patients with solitary RCH are expected

to have underlying VHL disease and detailed clinical evaluation in patients with solitary RCH is recommended using standard screening protocols[7]. In this current study, one of the RCH patients with VHL presented with a solitary lesion underwent screening protocols as well (case 1). Juxtapapillary RCH tends to occur more commonly in sporadic cases, as in this series, 2 out of 3 patients without VHL presented with has juxtapapillary RCH (case 4 and 5).

Epidemiologically, in one of the case series, McCabe CM et al in 2000 found that the age at diagnosis of hemangioma was younger for patients with VHL disease, who were first seen at a mean age of 20 years, compared with those without VHL, who were first seen at a mean age of 44 years[6]. In contrast to previous study, the youngest age at presentation was found in sporadic cases in this case series, as early as at the age of 13 years old (case 4).

The diagnosis of VHL is based on the assessment of three criteria: retinal or CNS hemangioma, visceral lesions, and family history. If the patient has a family history of VHL disease, only one hemangioma or visceral lesion confirms the disease. In cases with no family history of VHL disease, the presence of two or more hemangiomas, or a hemangioma and a visceral lesion are needed for the diagnosis[1]. Even though the clinical diagnosis can be based solely on the presence of typical lesions, genetic testing to establish and/or confirm the definite diagnosis is indicated for all patients with suspected VHL disease[8]. In the current study, two of the diagnosed VHL patients have positive family history (case 1 and case 2) whereby another one patient with VHL was diagnosed due to presence of RCH and pheochromocytoma (case 3).

Juxtapapillary retinal capillary hemangioma (JRCH) are vascular hamartomas that occur on the optic nerve head or within the juxtapapillary region. It is usually misdiagnosed with papillitis, papilledema, choroidal neovascularization or choroiditis[9]. JRCH is almost always related to progressive loss of vision secondary to macular exudates or serous retinal detachment . It occurs most commonly on the temporal side of the disc, and therefore adjacent serous retinal detachment tends to affect the macular region, resulting in loss of vision. Both complications could be seen from this case series as one of the patients with JRCH had extensive macular exudates (case 5) and complicated with serous retinal detachment resulting in poor visual outcome.

The treatment of RCH depends on location, size and clinical expressions. RCH is most frequently managed by observation, laser photocoagulation, and cryotherapy. Careful observation in a reliable patient is recommended if the RCH is very small (up to 500 micrometer), not associated with exudation or subretinal fluid, and is not visually threatening because of a nasal location. All of our patients had some form of intervention, none were purely observed. Photocoagulation is currently used to treat smaller RCH located in the posterior retina in eyes with clear media. Laser photocoagulation, applied over many sessions, is most effective in tumors that are 1.5 mm or smaller but can be considered for RCH that are up to 4.5 mm. The technique of photocoagulation includes

placement of photocoagulation marks, delimiting the lesion, on the surface of the lesion, and on the feeding artery[7]. In a study by Blodi CF et al in 1990 who compared different techniques of direct and feeder vessel photocoagulation, both were found to be safe and effective, but the feeder vessel technique required a greater number of treatment sessions[10]. The resolution of subretinal fluid, tumor shrinkage with narrowing of vessels, or change of color of RCH from red to pale pink is indicative of an adequate response to treatment, and complete obliteration of the RCH is not necessary to achieve clinical resolution. In our case series, focal laser photocoagulation was performed in all 3 of the RCH with VHL patients (case 1, 2 and 3). It is due to their peripheral location, small to medium sized RCH and in a clear media.

Cryotherapy is preferable to photocoagulation when the RCH is located anteriorly with a significant amount of subretinal fluid and the RCH is more than 3.0 mm in diameter[7]. However, none of our patients are suitable for the cryotherapy treatment.

Vitreoretinal surgical intervention is usually required for larger RCHs complicated by rhegmatogenous or tractional retinal detachment[11]. During vitrectomy, direct diathermy and endolaser can also be performed. From our case series, 1 of the patient in RCH group without VHL required vitrectomy and endolaser as he developed complication of vitreous haemorrhage.(case 6)

Rarely, enucleation is performed for management of a blind painful eye because of end-stage complications[7].

Intravitreal injection of anti-VEGF has been proposed but in isolation as it does not appear to be efficient even though it could diminish the progression of small lesions and retinal edema[12, 13]. One of the patients with RCH and VHL was supplemented with intravitreal Ranibizumab twice as he had multiple retinal angioma with subretinal fluid that threatened the macula (case 2).

In general, juxtapapillary RCHs (JRCHs) are treated if they are progressive or if they affect visual acuity (VA)[7]. There is no single effective treatment in treating JRCH to date. If the JRCH is not associated with SRF, exudation, and vision-threatening, careful observation is recommended. Laser photocoagulation is effectively used to treat small RCH (up to 1.5 mm) in the posterior retina but carries additional risk for JRCH due to the proximity to the optic nerve[14]. The treatment of JRCH usually requires multiple and intense burns and damages the nerve fiber layer, causing a permanent scotoma and irreversible decline of the VA. However, repeated applications of low to moderate-intensity photocoagulation to the angioma can result in stabilization or improvement in visual acuity[6].

Radiotherapy, cryotherapy, and transpupillary thermotherapy are commonly used to treat large JRCHs, located in the peripheral retina and away from the optic nerve. Vitreoretinal surgery can also serve as an alternative when glial proliferation leads to epiretinal membrane development or tractional retinal detachment. As can be seen in case 4, the patient had LE intravitreal Ranibizumab complicated with localised TRD at angioma post injection and underwent LE vitrectomy and endolaser.

Anti-VEGF therapy has been reported to reduce vascular permeability by altering the

balance of vasoactive cytokines like nitric oxide and endothelin-1 or by directly altering endothelial tight junction proteins[15]. It is postulated that excessive accumulation of hypoxia-induced factor in the neoplastic stromal cells of RCH leads to the production of other angiogenic factors that are able to maintain and promote the growth of primary hemangiomas[11].

E Chelala et al in 2013 reported a case of a JRCH patient with von Hippel–Lindau with well-preserved visual acuity (VA) and visual field (VF) received a single injection of intravitreal ranibizumab (IVR). Six months after IVR injection, the JRCH showed reduced vascularisation, fibrosis, and mild shrinkage, and VA and VF remained unchanged. Ranibizumab likely inhibited VEGF in and around the tumor and also suppressed permeability via the blockage of VEGF. Also, IVR seems to have the advantage of a decreased potential for retinal damage compared with other treatments for JRCH[13].

PDT is an alternative method to treat JRCH as it enables a selective vascular occlusion and appears to be less damaging to adjacent neural structures[16]. PDT might cause fibrosis and involution of the small JRCHs. In the case of large tumors, verteporfin may only be activated on the surface of the tumor, and the reactive oxygen species may not allow closure of the deeper tumor vessels[17]. Although PDT has been reported to be effective in treating macular edema and SRF in JRCH[18], it has some complications, such as retinal vessel occlusion, optic neuropathy, tractional retinal detachment, epiretinal membrane, and massive subretinal hemorrhage[19].

According to Schmidt-Erfurth et al, 2002, they conducted a study on 5 patients with papillary RCH treated with PDT and found out that tumor regression with resolution of macular exudate and serous retinal detachment was obtained in all eyes but PDT did not helps in improvement of vision and yet worsening of vision in 3 patients. A decline in VA of 1, 3, and 10 lines, respectively, were documented in three patients[17].

Tong et al 2018 conducted study in JRCH patients treated with two sessions of full-fluence PDT at an interval of 3 months. After 2 years of follow-up, they found that the VA improved, the hemangioma significantly reduced in size, the SRF reabsorbed, and exudation and macular edema regressed[20].

Recent reports of combined therapy with anti-VEGF and PDT have shown promising results in these lesions. A few study conducted including Ziemssen et al in 2007 reported a case of JRCH successfully treated with a single combination of intravitreal bevacizumab and PDT. The patient had marked regression of the hemangioma, an increase in VA, regression of the scotoma on VF testing, and macular drying that persisted after 1 year[21].

A study by Mennel et al in 2010 found that the combination of intravitreal anti VEGF and PDT proved to be an effective strategy for the treatment of retinal juxtapapillary capillary haemangioma without side-effects. A patient was given two sessions of PDT (sparing the part of the haemangioma located within the optic disc) and five injections of bevacizumab were applied in a period of 5 months. One year after the last injection, there was an improvement in visual acuity, resolution

of all lipid exudates at the posterior pole and restoration of normal central macular architecture. Visual field testing and angiography did not show any treatment-related vaso-occlusive side-effects[22].

By combining anti-VEGF with reduced fluence PDT, the outline of the primary angioma can be better delineated and may thus reduce the energy and the treatment area, thereby minimizing the damage to the neurological tissues.

In contrast with the current study, both patients (case 4 and 5) with JRCH were given intravitreal ranibizumab but the outcome differed. In case 4, the patient developed tractional retinal detachment shortly after the injection requiring vitrectomy and endolaser. As in case 5, due to poor vision post injection caused by more subretinal exudates, the patient was treated with full fluence PDT. Unfortunately, post PDT, the patient still had persistent macular oedema but was able to gain better final visual acuity which was 6/60. None of the complications related to PDT was observed in this patient and none of our patients received combination treatment at first sitting.

**Conclusion**

Retinal capillary hemangioma (RCH) with or without VHL are all unilateral involvement but age at presentation of sporadic tumors can be as early as in teenage. From the case series, juxtapapillary RCH occurs more in sporadic cases with higher risk to develop vision threatening complication. Current treatment is able to achieve vision stability but not a complete regression of the retinal lesion hence the patient's vision is always at risk.

**Disclosures**

**Human subject:** consent was obtained by all participants in this study.

**Conflicts of interest:** all of authors have declared that no financial support was received from any organization for the submitted work, no financial relationship at present with any organization that might have an interest in the submitted work and there are no other relationship or activities that could appear to have influenced the submitted work.

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# Acute Ocular Manifestations and Long-term Ocular Complications of Stevens Johnson Syndrome Pattern in Thammasat University Hospital

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**Objectives :** The objectives of this study are to identify the acute and chronic ocular manifestations and severity of acute ocular involvement of Stevens-Johnson syndrome (SJS) and Toxic epithelial necrolysis (TEN) in Thammasat university hospital.

**Methods:** We did a retrospective study by chart review of patients with confirmed dermatological diagnosis of Stevens-Johnson syndrome and Toxic epithelial necrolysis with ocular involvement. The data were recruited from a database of Thammasat University Hospital. Thirty consecutive patients diagnosed between June 2013 and May 2018 were recruited. We reviewed age, sex, causes of the disease process, acute ocular complications, acute symptoms, visual acuity, and late ocular complication. We used Darren G Gregory's new grading system to identify the severity of acute manifestation of SJS and TEN.

**Results:** There were 30 consecutive patients. All were drug-induced. Antibiotics were the most commonly implicated group of drugs in this series (36.6%), followed by antiepileptic drugs (23.3%). The severity of acute ocular involvement was mild in 30%, moderate in 36.6%, severe in 13.3% and extremely severe in 20% of patients. Dry eye was the most common late complication (66.7%) followed by punctate epithelial erosion (58.3%) and trichiasis (41.7%). Two patients had visual loss (16.6%).

**Conclusions :** Ocular manifestations occurred in a high proportion of patients with SJS/TEN during both acute and late phases. The most common causes were antibiotic and antiepileptic drugs. A careful medication history should be obtained from these patients. Ophthalmic evaluation, and management are mandatory.

**Keywords :** Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; acute ocular manifestation; late ocular manifestation; severity

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## Introduction

In 1922, Stevens and Johnson described two boys with Stevens-Johnson syndrome (SJS), a severe mucocutaneous

disease with ophthalmologic manifestations[1]. Later Lyell described a condition characterized by extensive epidermal ''scalding,'' naming it ''toxic epidermal necrolysis'' (TEN)[2]. The incidence of SJS and TEN are 9.2 and 1.9 per million person-years, respectively[2].

SJS and TEN are variants belonging in the same class and are defined based upon the amount of epidermal detachment; SJS, 10% or less of total body surface area involvement, TEN, 30% or greater involvement and SJS/TEN overlap, involvement between 10-30%.[3,4]

The pathogenesis of SJS/TEN is controversial. The genetic risk factors are drug-specific and vary among populations and/or ethnic groups. For the molecular pathogenesis of SJS/TEN, a cytotoxic T lymphocyte (CTL) immune-mediated reaction is known as the major immunologic component of SJS/TEN[5,6].

Clinical findings include a prodromal symptom of fever and malaise, followed by the development of a generalized, tender cutaneous eruption consisting of a variety of morphologic macules, papules, atypical target lesions and vesicles or bullae. Ocular manifestations in both SJS/TEN patients are common. More than 50-88% suffer from acute ocular manifestations, and 35−90% develop long-term sequelae[7].

Ocular involvement in the acute phase of SJS/TEN occurs due to rapid-onset keratinocyte apoptosis and secondary effects of inflammation and loss of ocular surface epithelium. Early involvement is highly variable and can range from self-limited conjunctival hyperemia to near total sloughing of the entire ocular surface epithelium, including the tarsal conjunctiva and eyelid margin. Ocular surface inflammation can be intense, with pseudomembrane or frank membrane formation, early symblepharon formation, fornix foreshortening, and corneal ulceration and perforation[8].

Chronic ocular complications of SJS/TEN are multifactorial in origin and occurred in up to 35% of SJS/TEN patients[9]. There are three categories of chronic ocular complications classified by Sotozono and colleagues[10]. The corneal complications included superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization. The conjunctival complications included hyperemia and symblepharon formation. The eyelid complications included trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal occlusion.

Fusion between the bulbar and forniceal surfaces due to conjunctival ulcerations or conjunctival membrane formation acutely, or persistent inflammation later, causes permanent symblepharon and ankyloblepharon, disrupting an already compromised tear film meniscus and inhibiting proper eyelid closure and blink, and at times restricting ocular motility. Tarsal conjunctival scarring can be associated with eyelid malpositions and other disorders, including ectropion, entropion, trichiasis, distichiasis, meibomian gland atrophy and inspissation, punctal occlusion, and keratinization of the eyelid margin, tarsal and bulbar conjunctival surfaces. These changes not only cause debilitating pain in affected patients, but also threaten vision and is related with the development of late corneal blindness[11], at least in part due to the chronic limbal stem cell dysfunction (LSCD). If not removed, misdirected and/or districhiatic lashes, the

latter from metaplastic meibomian glands, can mechanically abrade the corneal epithelium, leading to corneal epithelial defects, infection, and stromal scar. Repeated friction from a keratinized inner eyelid surface can lead directly to chronic corneal inflammation, neovascularization, scarring, and LSCD[12].

The aim of this study is to identify the acute and chronic ocular manifestations of Stevens-Johnson syndrome and TEN in Thammasat university hospital.

**Method**

This retrospective study was approved for ethical research in humans with the human research ethics committee of Thammasat university. (Certificate number 064/2562 )

A chart review of patients with confirmed dermatological diagnosis of SJS and TEN with ocular involvement was performed, where patients were recruited from a database of Thammasat University Hospital. A total of 30 consecutive patients diagnosed between June 2013 and May 2018 were recruited for the study.

Patients with clinical evidence of acute ocular complications were reviewed by an ophthalmologist to determine the type, extent and severity of ocular involvement. Patients with a minimum follow-up period of 6 months were reviewed for late complications.

Records were reviewed for age, sex, causes of the disease process, acute ocular complications, acute symptoms, visual acuity, and late ocular complications.

To identify the severity of SJS and TEN in the acute phase, we used the new grading system for the acute ocular manifestations of Stevens-Johnson syndrome, written by Darren G, Gregory[13].

SPSS version 23.0 has been used for statistical analysis in this study. The data was shown by using mean, standard deviation and percentage. Independent t-test and chi-square test were used for comparing the data between two groups. *P-value* less than 0.05 was statistically significant.

**Result**

There were 30 consecutive patients with SJS/TEN with ocular involvement during the study period. The mean age was 47.3 ± 20.6 years (range 10−89).

**Table 1**

| Implicated group of drug | | No. (%) |
|---|---|---|
| Antibiotics | Co-trimoxazole | 3 (10%) |
| | Penicillin | 3 (10%) |
| | Cephalosporin | 1 (3%) |
| | Other | 4 (13.3%) |
| Phenytoin | | 5 (16.6%) |
| Allopurinol | | 4 (13.3%) |
| NSAIDs | | 5 (16.6%) |
| Danazol | | 2 (6.6%) |
| Other | | 3 (10%) |

There were 13 male patients (43.3%) and 17 female patients (56.7%). There were 1 (3.33 %) deaths during the acute phase of disease. Twenty-five (83.3%) had a diagnosis of SJS and five (16.7%) had a diagnosis of TEN. All cases of SJS/TEN were drug-induced. Antibiotics were the most commonly implicated group of drugs in this series (36.6%), followed by antiepileptic drugs (23.3%). Co-trimoxazole (10%) and Penicillin (10%) were the most common antibiotic implicated. The most commonly implicated non-antibiotic drugs were phenytoin (16.6%) , NSAIDs (16.6%) and allopurinol (13.3%). The details of the implicated drugs in this study were shown in Table 1.

**Table 2** The severities of acute ocular involvement

| Disease | Acute Ocular Involvement No. (%) | | | |
|---|---|---|---|---|
| | Mild | Moderate | Severe | Extremely Severe |
| SJS | 9(36%) | 7 (28%) | 4 (16%) | 5 (20%) |
| TEN | 0 (0%) | 4 (80%) | 0 (0%) | 1 (20%) |
| Total | 9 (30%) | 11 (36.6%) | 4 (13.3%) | 6 (20%) |

The severities of acute ocular involvement were shown in Table 2. The acute ocular involvement was mild in 30%, moderate in 36.6%, severe in 13.3% and extremely severe in 20% of patients.

The treatment during the acute presentation of ocular involvement included topical corticosteroid eye drops, non-preservative lubricant eye drops, and topical antibiotic eye drops. These three types of eye drops were given to thirty (100%) patients who were diagnosed SJS/TEN with ocular involvement as a basic treatment in acute phase. Nineteen (63.3%) patients who developed conjunctival membrane underwent membrane peeling everyday until the membrane disappeared. Two (6.7%) patients who developed persistent epithelial defect underwent amniotic membrane patching.

Sixteen (53.3%) patients had a follow-up period of more than 6 months and twelve (75%) patients (75%) developed late complications. The demographic data, disease groups, severity of the acute

**Table3** shows late ocular complications of SJS/TEN

| Late ocular complications | No. (%) |
|---|---|
| Dry eye | 8 (66.7%) |
| Punctate epithelial erosion | 7 (58.3%) |
| Trichiasis | 5 (41.7%) |
| Symblepharon | 3 (25%) |
| Corneal ulcer | 4 (33.3%) |
| Limbal stem cell deficiency | 3 (25%) |
| Corneal perforation | 2 (16.6%) |
| Conjunctival scar | 4 (33.3%) |
| Visual loss | 2 (16.6%) |

**Table 4** shows the demographic data, disease groups, severity of the acute ocular manifestation in 16 patients with at least 6 months of follow-up period.

| Characteristic | Late ocular complications | | Total | *P-value* |
|---|---|---|---|---|
| | Yes (N=12) | No (N=4) | | |
| Age Mean (SD) | 48.5 (18.2) | 35.25 (25.84) | 45.19 | 0.273+ |
| Median (range) | 48 (20-83) | 30.5 (10-70) | 43.50 | |
| Sex | | | | |
| Female | 6 | 3 | 9 | 0.383++ |
| Male | 6 | 1 | 7 | |
| Disease | | | | |
| SJS | 10 | 3 | 13 | 0.712++ |
| TEN | 2 | 1 | 3 | |
| Severity | | | | |
| Mild | 1 | 0 | 1 | 0.242++ |
| Moderate | 4 | 3 | 7 | |
| Severe | | | 2 | |
| Extremely severe | 1 | 1 | 6 | |
| | 6 | 0 | | |

+ One-way anova
++ Chi-square test

ocular manifestation of sixteen patients was shown in Table 4. There was no significant difference between two groups ( twelve patients who developed late ocular complications and four patients who did not develop late ocular complications) in terms of age (*P-value* 0.273), sex (*P-value* 0.383), disease group (*P-value* 0.712), and severity of acute ocular manifestation (*P-value* 0.242). Dry eye was the most common late complication (66.7%) followed by punctate epithelial erosion (58.3%) and trichiasis (41.7%). Two patients had visual loss (16.6%). The first patient developed corneal ulcer of the right eye and finally developed corneal perforation. She underwent penetrating keratoplasty after that. The other developed total corneal conjunctivalization which caused visual loss. The details of late ocular complications are shown in Table 3.

**Discussion**

In our study, the most common causative drug in SJS/TEN was antibiotics (36.3%) followed by Phenytoin (16.6%), NSAIDs (16.6%), and Allopurinol (13.3%). Co-trimoxazole was the most common drug implicated (10%). This findings were similar to L.W.Yip et al[10].We found that the most common severity of acute ocular involvement in SJS/TEN was moderate severity (36.6%) whereas Darren G. Gregory reported that

the most common severity in his study was severe severity (35.4%)[13]. In Darren G. Gregory's grading system, he suggested that mild and moderate severity should be treated by medical treatment while severe and severely severe degree should be treated by amniotic membrane transplantation. In our study, every patient was initially treated by medically, but when the epithelial defect tended to persist, the amniotic membrane patching was used for treatment.

For the late complication of SJS/TEN, we found that severe dry eyes, which presented in 66.6% of our cases, was the most common late complication of those with long-term follow-up. This finding was consistent with the report by L.W.Yip et al. that the most common late complication was dry eye syndrome[14]. Other late complications such as punctate epithelial erosion, trichiasis, symblepharon, corneal ulcer, limbal stem cell deficiency, corneal perforation, conjunctival scar, and visual loss were also reported[15]. We also found that the severity of acute ocular manifestation did not predict late ocular complications. This finding was consistent with the report of L.W.Yip et al.

There are weaknesses in this study. Firstly, because of the retrospective method, there was the limitation of the quality of data that was collected. Secondly, almost half of the follow up period of patients were shorter than 6 months, so there were just 16 patients who were included for analysis of late complications.

**Conclusions**

Ocular manifestations occurred in a high proportion of patients with SJS/TEN during both acute and late phases. The most common causes were antibiotic and antiepileptic drugs. A careful medication history should be obtained from these patients. Good ophthalmic evaluation and management in the acute stages are mandatory for preventing or decreasing long-term ocular complications.

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# Outcomes of pterygium surgery by first-year ophthalmology residents

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**Purpose:** To evaluate outcomes of pterygium surgery by first-year ophthalmology residents at Thammasat hospital

**Design:** Retrospective study

**Methods:** Eighty-seven patients who underwent the pterygium excision by seven first-year ophthalmology residents at Thammasat hospital from July 2017 to June 2018 were enrolled. Characteristics of patients and pterygium, method of surgery, recurrence rate and complications were analyzed.

**Main outcome measures:** The primary outcome measure was recurrence of pterygium.

**Results:** The mean age of the patients was 58.5±11.7 years. Most of the participants were female (n=55; 63.2%). All cases have primary pterygium were single-headed (n=76; 87.4%), the rest were double-headed (n=11; 12.6%). Mean size of pterygium on the corneal surface was 6.2 $mm^2$ (0.8-17.5 $mm^2$ in range). Pterygium was excised by and grafted using amniotic membrane graft transplantation technique in 77 patients (88.5%) and conjunctival autograft transplantation technique in 10 patients (11.5%). The mean of follow-up duration was 8.2±3.1 months. There was recurrence of pterygium in 13 cases (14.9%), most of which (n=12; 92.3%) recurred within 6 months after surgery.

**Conclusions:** The outcomes of pterygium surgery operated by first-year ophthalmology residents at Thammasat hospital was satisfactory. The recurrent rate was not high and there were no serious complications.

**Keywords:** Pterygium surgery, Ophthalmology residents, Amniotic membrane transplantation, Conjunctival autograft transplantation, Recurrence

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## Introduction

Pterygium, a wing-shaped centripetal growth of fibrovascular tissue on the superficial cornea, is a common disease in Thailand. Ultraviolet light is a major risk factor, so the prevalence of the disease is high among people in the peri-equatorial latitudes, mountainous and highly reflective environments.[1] The problems caused by pterygium include changes in corneal topography and refraction, reduction in

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visual field and visual acuity, chronic inflammation, dry eye, diplopia and cosmetic concerns. To treat the pterygium, patient' symptoms can be relieved by medications such as artificial tears, corticosteroid eye drops, although surgery still remains the definite treatment. One of the most important goals of pterygium excision is prevention of recurrence, which can be achieved by a well-performed surgical procedure, with good subsequent pre and postoperative care.

Generally speaking, in ophthalmology training courses, first-year ophthalmology residents are expected to be capable of independently performing pterygium surgery. Moreover, previousstudies showed that patient's age, gender, size and corneal involvement of pterygium, method of surgery and surgical experience are influential factors for pterygium recurrence.[2-4] To improve the training processes and surgical outcomes, we are interested in the results of pterygium surgery operated by first-year ophthalmology residents at Thammasat hospital.

**Methods**

Our study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Thammasat University, Thailand. We performed a retrospective study by collecting data from medical records of patients who were undergone pterygium excision by first-year ophthalmology residents at Thammasat hospital over a period of one academic year, from July 2017 to June 2018. The subjects whose follow-up period less than 3 months were excluded.

Age and gender of patients, laterality and location, type of pterygium, number of pterygium heads, size of pterygium in square millimeters (calculated by 1/2 X horizontal length X vertical length), best corrected visual acuity (BCVA), keratometry, intraocular pressure, method of surgery, and intraoperative and postoperative complications were documented. Quantitative data were calculated as mean and standard deviation. Qualitative data were calculated into percentage. Paired t-test was used to compare pre and postoperative corneal astigmatism. Pearson Chi-Square was used to assess recurrent rate of pterygium and influencing factors including age, gender, number of pterygium heads, size of pterygium and surgical techniques. A p-value of less than 0.05 was considered to be statistically significant.

**Results**

Ninety-four participants were enrolled in our study but 7 of them were excluded for having a follow-up period of less than 3 months. (There were no complications or recurrence of pterygium in the excluded participants). 87 patients with a mean age of 58.5±11.7 years participated in this study, of those patients, 55 were females (63.2%), and 32 males (36.8%).

Each participant underwent pterygium excision in one eye. All cases of pterygium were diagnosed as primary in this study. Pterygium were single-head in 76 eyes (87.4%) and double-head in 11 eyes (12.6%), most of them (82.7%) were on the nasal side. Mean size of pterygium on the corneal surface was 6.2±4.4 square millimeters (0.8-17.5 in range).

There were 7 first-year ophthalmology residents operating in this study. Mean number of patients operated by each

surgeon were 12.4 with a range of 10-14 patients.

Seventy-seven patients (88.5%) had pterygium excision with amniotic membrane graft transplantation technique and 10 patients (11.5%) had surgery with conjunctival autograft transplantation technique.

Preoperative BCVA was equal or better than 20/40 in 48 participants (55.2%) and 3-month postoperative BCVA was equal or better than 20/40 in 68 participants (78.2%).

Corneal astigmatism was significantly decreased after pterygium excision ($p$=0.001, paired t test). The preoperative and 3-month postoperative corneal astigmatism mean was 2.1±1.6 and 1.5±1.1 diopter, respectively.

With regards to steroid responders, 16 participants (18.4%) had an increase of over 5 mmHg in intraocular pressure, nevertheless, the intraocular pressure was decreased after cessation of topical corticosteroids.

The follow-up time mean was 8.2±3.1 months, ranging from 3 to 12 months. Recurrent pterygium was defined as the encroachment of fibrovascular tissue across the limbus. During follow-up period, we found recurrence of pterygium in 13 cases (14.9%). Most of the recurrent cases (12/13; 92.3%) recurred within 6 months postoperative, which the mean of recurrence time was 4.2±1.9 months, ranging from 1 to 7 months. The number of operating eyes and recurrence eyes by each surgeon were shown in table 1.

Influencing factors that might affect recurrence of pterygium after excision were analyzed including age, gender, size of pterygium, number of pterygium heads and surgical technique. The result showed no statistical significance (*p-value* >0.05) were identified (as shown in table 2)

**Discussion**

There were some previous studies regarding recurrence rate of pterygium surgery performed by trainee ophthalmologists. Kositphipat et al.[5] and Akrapipatkul K.[6] from Thailand reported a recurrence rate of 9.7% and 11.94% respectively, in addition to Farrah et al.[7] from Australia reported 19.4%. Our study found a 14.9 percent recurrence rate.

In this study, most of the recurrent cases (92.3%) recurred within 6 months postoperatively, corresponding with

**Table 1** Number of eyes operated eyes by each surgeon and recurrence rate per individual surgeon

| Surgeon | Number of eyes operated (%) | Number of eyes with recurrence (%) |
|---|---|---|
| **A** | 12 (13.8) | 2 (16.7) |
| **B** | 13 (14.9) | 3 (23.1) |
| **C** | 14 (16.1) | 3 (21.4) |
| **D** | 12 (13.8) | 1 (8.3) |
| **E** | 10 (11.5) | 2 (20.0) |
| **F** | 13 (14.9) | 1 (7.7) |
| **G** | 13 (14.9) | 1 (7.7) |
| **Total** | 87 (100) | 13 (14.9) |

**Table 2** Number of recurrences according to influencing factors

| variable | Number of recurrence N (%), n = 13 | *p-value* (Chi-squared) |
|---|---|---|
| Age (years) | | |
| < 40 years (n = 6) | 1 (16.7) | 0.902 |
| ≥40 years (n = 81) | 12 (14.8) | |
| Gender | | |
| Male (n = 32) | 4 (12.5) | 0.626 |
| Female (n = 55) | 9 (16.4) | |
| Number of pterygium heads | | |
| Single-head (n = 76) | 11 (14.5) | 0.784 |
| Double-head (n = 11) | 2 (18.2) | |
| Size of pterygium (horizontal) | | |
| < 4 mm (n = 57) | 7 (12.3) | 0.337 |
| ≥4 mm (n = 30) | 6 (20.0) | |
| Surgical technique | | |
| Amniotic membrane graft (n = 77) | 12 (15.6) | 0.641 |
| Conjunctival autograft (n = 10) | 1 (10) | |

previous literature. Kositphipat et al.[5] found that all recurrences (100%) occurred within 6-month postoperatively. Kampitak and Bhornmata8 reported most eyes (73.8%) recurred within 20 weeks.

Individual surgeon recurrence rate in this study was variable, ranging from 7.7 to 23.1%. Kositphipat et al.[5] found a high variation in the recurrence rate (0-25%). Ti et al.[4] also showed an even wider range of recurrence rate from 5 to 82%.

Previous studies showed that young age[3, 9-11], male gender[9, 12], bigger size and large area of corneal involvement of pterygium[13] and surgical technique[14-16] are influencing factors for pterygium recurrence. Nevertheless, our study did not demonstrate statistical significance in any of those previously mentioned significant risk factors for the recurrence of pterygium. This may be due to the small sample size in our study.

The practice of pterygium excision at Thammasat hospital favors amniotic membrane transplantation method over conjunctival autografting due to the fact that this procedure is less time consuming, has favorable early recovery outcomes, and saves the conjunctiva for future surgery if required. Moreover, Akrapipatkul from Thailand reported that pterygium excision with sutured amniotic membrane transplantation is considered an appropriate training procedure for ophthalmology residency training due to the duration needed to reach the learning curve.[6]

Outcomes of pterygium surgery in our study were favorable as demonstrated by improvements in visual acuity and significant decreases of corneal astigmatism. The number of patients who had BCVA

equal or better than 20/40 increased from 55.2% preoperative to 78.2% 3-month postoperatively. Kositphipat et al. showed 19.4% of patients had vision gained equal or more than one line postoperatively.[5]

For the present study, the corneal astigmatism was significantly decreased after pterygium excision and it could be one factor for improvement of visual acuity.

After pterygium surgery, steroids are used to reduce inflammation, although ocular hypertension is a common side effect. Kampitak and Bhornmata[8] suggested 10.2% of eyes prescribed ocular steroids had an increase of intraocular pressure of over 5 mmHg. In our study, 18.4% of eyes had increased intraocular pressure of more than 5 mmHg after steroid use. Therefore, patients receiving steroids should undergo close monitoring.

Surgical training in ophthalmology residents at Thammasat hospital allows residents to practice surgical techniques by wet-laboratory and workshop training prior to performing ocular surgery on patients. This method could be one factor of improving the surgical performance in ophthalmology residents, shortening the learning curve and decreasing the surgical morbidity and the risk of iatrogenic trauma.

**Conclusions**

The outcome of pterygium surgery operated by first-year ophthalmology residents at Thammasat hospital was satisfied. Corneal astigmatism was significantly decreased after pterygium excision. The recurrent rate was not high and there were no serious complications.

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**Conflicts of interest**

The authors have no conflict of interest.

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# Medication Adherence of Patients with Uveitis in Thailand

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**Objective:** To evaluate the medication adherence of patients with uveitis and their related factors associated with medication non-adherence.

**Methods:** A cross-sectional study conducted in uveitis clinic, Thammasat university hospital, Thailand, during June 2018 to January 2019. The questionnaires were collected from the patients.

**Results:** One hundred and fifty-one patients were enrolled. Forty-five patients (29.8%) demonstrated medication non-adherence. Factors significantly associated with medication non-adherence included lack of knowledge regarding proper medication use ($P<0.001$), forgetfulness ($P<0.001$), experiencing side effects from medications ($P=0.025$), difficulties in travelling to the doctor's office ($P=0.001$) and difficulties in using eye drops ($P=0.025$). However, it was not significantly associated with age ($P=0.377$), gender ($P=0.861$), education level ($P=0.069$), occupation ($P=0.191$), healthcare coverage ($P=0.189$), underlying diseases ($P=0.727$), regular medications ($P=0.930$), patient's knowledge of own diagnosis ($P=0.283$), duration of the disease ($P=0.089$), number of eye drops (bottles/day, $P=0.061$), number of oral medications ($P=0.328$), administration of medications by self/caregiver ($P=0.726$) and duration between medical visits ($P=0.870$).

**Conclusion:** This study showed that 29.8% of patients did not adhere to their uveitis medications. Factors associated with medication non-adherence included lack of knowledge regarding proper medication use, forgetfulness, experiencing side effects from medications, difficulties in travelling to the doctor's office and difficulties in using eye drops. The most significant factor was forgetfulness.

**Keywords:** Adherence; Compliance; Medication; Questionnaire; Uveitis

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## Introduction

Uveitis is a form of intraocular inflammation which can be a sight threatening condition. Medical therapy is generally a mainstay of treatment in many cases therefore medication adherence is an essential key of treatment success. In the past, physicians usually focused on medication compliance which was a doctor-centered term, referring to the degree to which patients properly followed the instructions or recommendations provided by their health care providers[1]. Currently, physicians value medication adherence which is a patient-centered term, describing the extent to which a patient continues the agreed-upon mode of treatment

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under limited conditions when faced with conflicting demands, for example, the patients can choose their own treatment[2, 3]. The outcome of this mode will give the better result of treatment.

Many studies reported problems associated with medication non-adherence in patients with glaucoma including forgetfulness, young age, the large numbers of eye drops, education, life entourage, monthly income and duration between medical visits [4, 5].

To date, there were no reports about medication adherence in patients with uveitis. The objective of this study was to evaluate the medication adherence in this particular group and their related factors associating with medication non-adherence.

## Materials and Methods

### Patients

This was a cross-sectional study conducted in an outpatient department, uveitis clinic, Thammasat university hospital, Thailand during June 2018 to January 2019. The subjects were diagnosed with uveitis, aged 13 years or older, and received medications for at least 2 weeks. We excluded patients who supervised the medications by caregivers but caregivers did not come to the hospital. Patients who did not speak Thai were also excluded. This research was approved by the human research ethics committee of Thammasat university.

During the patients' regular visit, the investigator selected and enrolled the subjects from those who met all the selection criteria and expressed interest in participating in the research. The patients signed an informed consent. All questionnaires were collected from the patients via an interviewer using 10 minutes in a private and quiet room in a uveitis clinic.

### Data collection

The questionnaire comprised of four parts:

The first part included questions evaluating the adherence to ocular medication. We used the 8-item Morisky Medication Adherence Scale (MMAS-8). This instrument was popularly applied in chronic diseases such as hypertension[6]. It was also used in ocular disease especially in glaucoma[4]. We translated the original English version into the Thai language. This questionnaire was composed of eight questions which were answered as yes or no. Questions 1, 2, 3, 4, 6, 7 were worth 1 point if answer was no. Question 5 was worth 1 point if the answer was yes and the answer for question 8 was divided into 5 scales started with score 1 to zero, divided into increments of 0.25. Finally, a sum of all scores were made, scores of 6 to 8 qualified as medication adherence.

The second part included questions of demographic characteristics such as age, gender, education level, occupation, healthcare coverage, underlying diseases and regular medications.

The third part included questions related to diseases and treatment such as patient's knowledge of own diagnosis, duration of the disease (defined as the time from the first diagnosis to data collection), number of eye drops (bottles/day), number of oral medications, whether the medication was administered by self/caregiver, and knowledge regarding proper use of medications (defined as knowing the drug administration correctly), and lastly,

duration between medical visits.

The fourth part consisted of questions regarding the problems affecting the patients' adherence, such as forgetfulness, experiencing side effects from medications, discouragement or stress, believing in uselessness of medications, difficulties in travelling to the doctor's office, difficulties in using eye drops (being unable to instill eye drops as prescribed, or imprecise instillation of eye drops), whether they feel overwhelmed by the amount of medications to take and financial issues. The patients can answer more than 1 choice in this part.

After completing the questionnaire, the researcher classifies participants into 2 groups by using the score in the first part. If the MMAS-8 score was ≥6, this group was classified as medication adherence. If the MMAS-8 score was < 6, it was classified as medication non-adherence. Afterwards, all items in part 2, 3 and 4 were interpreted and assessed for statistical associations.

**Calculation of sample size**

In order to estimate the sample size, we used two independent proportions (two-tailed test) based on data from a previous study[4]. The participants were divided into 2 groups: medication adherence (N = 105) and medication non-adherence (N=45, ratio 0.43) with a statistical power of 80%.

**Statistical analysis**

The data was collected in a standardized form, and stored in an electronic datasheet (Microsoft Excel). We used mean and standard deviation for continuous variables. Mann-Whitney U test was chosen for comparison. We used frequency and percentage for categorical variables and chi-square was chosen for comparison. The significant level was set at $P < 0.05$. Statistical analysis was conducted using SPSS software version 22.

**Results**

Of a total of 151 cases, 79 patients (52.3%) were male and 72 patients (47.7%) were female. One hundred and six patients (70.2%) were adherent to uveitis medications, and 45 patients (29.8%) were medication non-adherent (table 1). The average age of the medication adherent group (51.6 ±16.4) was older than the medication non-adherent group (48.9±15.1). However, it was not statistically significant ($P$=0.29).

Patients' demographic characteristics were summarized in table 2. Patients' adherence to medication were not significantly associated with age ($P$=0.377), gender ($P$=0.861), educational level ($P$=0.069), occupation ($P$=0.191), healthcare coverage ($P$=0.189), underlying diseases ($P$=0.727) and regular medications ($P$=0.930).

Questions related to ocular diseases and treatment were concluded in table 3. Patients' adherence to medication was significantly associated with the patients' knowledge regarding proper use of medications ($P$<0.001). However, medication adherence was not significantly associated with patient's knowledge of own diagnosis ($P$=0.283), duration of the disease ($P$=0.089), number of eye drops ($P$=0.061), number of oral medications ($P$=0.328), administration of medications by self/ caregiver ($P$=0.726) and duration between medical visits ($P$=0.870).

Table 4 summarized questions about problems affecting the patients' adherence. There were four statistically significant factors associated with patients' adherence

to medications including forgetfulness ($P$<0.001), experiencing side effects from medications ($P$=0.025), difficulties in travelling to the doctor's office ($P$=0.001) and difficulties in using eye drops ($P$=0.025). The most significant reason was forgetfulness answered by 60 patients (39.7%). The side effects of medications that patients suffered were burning sensation, itching and irritation of the eye. Two patients

**Table 1.** Table shows questions evaluating the adherence to the ocular medications (8-item Morisky Medication Adherence Scale).

| Questions | Yes | No | | | |
|---|---|---|---|---|---|
| 1. Do you sometimes forget to take your medications over the past two weeks? | | | | | |
| 2. Do you sometimes miss taking your medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicines? | | | | | |
| 3. Have you ever cut back or stopped taking your medicines over the past two weeks because you felt worse when you took it? | | | | | |
| 4. When you travel or leave home over the past two weeks, do you sometimes forget to bring along your medicines? | | | | | |
| 5. Did you take all your medicines yesterday? | | | | | |
| 6. When you feel like your symptoms are under control, do you sometimes stop taking your medicines over the past two weeks? | | | | | |
| 7. Taking medicines every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan over the past two weeks? | | | | | |
| 8. How often do you have difficulty remembering to take all your medicines over the past two weeks? | Never (0%) | Once in a while (1-19%) | Sometimes (20-49%) | Usually (50-99%) | All the time (100%) |

experienced difficulties in using eye drops (1.3%) because they could not follow the frequency of the eye drops as prescribed by ophthalmologist.

**Discussion**

Medication non-adherence was one of the main problems aggravating uveitis disease which led to poor prognosis. This study showed 29.8% (45/151) of patients who did not adhere to their own medications. There were no significant differences with age and gender, consistent with a study on patients with glaucoma[7]. Young age may be the factor involving medication adherence. However, the patients aged less than 13 were excluded in this study.

This study showed that education levels were not significantly associated with

**Table 2.** Table shows demographic characteristics of participants.

| Demographic characteristics | | Medication adherence (%) | Medication non-adherence (%) | *p-value* |
|---|---|---|---|---|
| Age(years) | <50 | 50(66.7) | 25(33.3) | 0.377 |
| | ≥ 50 | 56(73.7) | 20(26.3) | |
| Gender | Male | 56(70.9) | 23(29.1) | 0.861 |
| | Female | 50(69.4) | 22(30.6) | |
| Education level | ≤ High school | 69(65.7) | 36(34.3) | 0.069 |
| | Bachelor degree | 37(80.4) | 9(19.6) | |
| Occupation | Self-employed | 52(68.4) | 24(31.6) | 0.191 |
| | Government officer | 21(60.0) | 14(40.0) | |
| | Student | 5(83.3) | 1(16.7) | |
| | No work | 28(82.4) | 6(17.6) | |
| Healthcare coverage | Universal coverage scheme | 33(84.6) | 6(15.4) | 0.189 |
| | Social security scheme | 19(63.3) | 11(36.7) | |
| | Government officer | 31(63.3) | 18(36.7) | |
| | Life insurance | 1(100.0) | 0(0.0) | |
| | Spend money | 22(68.8) | 10(31.2) | |
| Underlying diseases | no | 54(67.5) | 26(32.5) | 0.727 |
| | 1 disease | 22(78.6) | 6(21.4) | |
| | 2 diseases | 17(68.0) | 8(32.0) | |
| | ≥3 diseases | 13(72.2) | 5(27.8) | |
| Regular medications | no | 55(67.9) | 26(32.1) | 0.930 |
| | 1 drug | 11(73.3) | 4(26.7) | |
| | 2 drugs | 11(73.3) | 4(26.7) | |
| | ≥3 drugs | 29(72.5) | 11(27.5) | |

Table 3. Table summarizes the questions about problems affecting the patients' adherence.

| Demographic characteristics | | Medication adherence (%) | Medication non-adherence (%) | *p-value* |
|---|---|---|---|---|
| Patient's knowledge of own diagnosis | Correct | 97(68.8) | 44(31.2) | 0.283 |
| | Incorrect | 9(90.0) | 1(10.0) | |
| Duration of the disease | < 1 year | 33(66.0) | 17(34.0) | 0.089 |
| | 1-5 years | 48(80.0) | 12(20.0) | |
| | >5 years | 25(61.0) | 16(39.0) | |
| Number of eye drops | ≤ 1 eye drop | 76(75.2) | 25(24.8) | 0.061 |
| | > 1 eye drop | 30(60.0) | 20(40.0) | |
| Number of oral medications | ≤ 1 oral medicine | 78(72.9) | 29(27.1) | 0.328 |
| | > 1 oral medicine | 28(63.6) | 16(36.4) | |
| Administered medications by | self | 99(69.7) | 43(30.3) | 0.726 |
| | caregiver | 7(77.8) | 2(22.2) | |

| Demographic characteristics | | Medication adherence (%) | Medication non-adherence (%) | *p-value* |
|---|---|---|---|---|
| Knowledge regarding proper use of medications | Yes | 106(73.6) | 38(26.4) | <0.001 |
| | No | 0(0.0) | 7(100.0) | |
| Duration between medical visits | < 1 month | 22(66.7) | 11(33.3) | 0.870 |
| | 1 − 3 months | 63(71.6) | 25(28.4) | |
| | >3 months | 21(70.0) | 9(30.0) | |

**Table 4.** Table shows the questions about problems affecting the patients' adherence.

| Problems affecting the patients' adherence | | Medication adherence (%) | Medication non-adherence (%) | *p-value* |
|---|---|---|---|---|
| Forgetfulness | Yes | 19(30.2) | 44(69.8) | <0.001 |
| | No | 87(98.9) | 1(1.1) | |
| Experiencing side effects from medications | Yes | 0(0.0) | 3(100.0) | 0.025 |
| | No | 106(71.6) | 42(28.4) | |
| Discouragement or stress | Yes | 0(0.0) | 2(100.0) | 0.087 |
| | No | 106(71.1) | 43(28.9) | |
| Believing in uselessness of medications | Yes | 0(0.0) | 2(100.0) | 0.087 |
| | No | 106(71.1) | 43(28.9) | |
| Difficulties in travelling to the doctor's office | Yes | 2(20.0) | 8(80.0) | 0.001 |
| | No | 104(73.8) | 37(26.2) | |
| Difficulties in using eye drops | Yes | 0(0.0) | 3(100.0) | 0.025 |
| | No | 106(71.6) | 42(28.4) | |
| Feel overwhelmed by the amount of medications to take | Yes | 0(0.0) | 2(100.0) | 0.087 |
| | No | 106(71.1) | 43(28.9) | |
| Financial issues | Yes | 0(0.0) | 0(0.0) | - |
| | No | 106(70.2) | 45(29.8) | |

patients' adherence to medication. This was different from a previous study[8] showing that the higher education levels were associated with a higher understanding of the necessity for medication adherence. This study demonstrated that the patients' knowledge regarding proper use of medications was significantly associated with patients' adherence to medication. Improving patients' understanding regarding medication administration was the important key to enhancement of medication adherence. This study emphasizes the need for ophthalmologists and pharmacists to explain frequency and adverse effects of medications to patients.

Regarding the number of eye drops and oral medicine in the adherent group, most patients used 0-1 eye drops, accounting for 71.7% of patients and used 0-1 oral medications accounting for 73.6% of patients. In the non-adherent group, 40% of cases used at least 2 eye drops compared to 24.8% of cases used less than 2 drops. These findings could explain the smaller number of

medications resulted in better convenience for the patients. Nevertheless, these findings showed no significant relationship which was not in line with the previous study[9].

This study showed that forgetfulness, experiencing side effects from medications, difficulties in travelling to the doctor's office and difficulties in using eye drops were the reasons significantly affecting the patients' adherence. This was consistent with other studies[4, 10]. The most important reason was forgetfulness. There were some techniques helping the patient remember how to take the drugs correctly such as an alarm device, automated text note[11, 12] or application to remind on medical time. Strategies developed to promote medication adherence included providing clear instructions to the patients, modifying patient misunderstanding, enhancing patient communication, simplifying the treatment regimen and evaluating adherence[3]. Nowadays, there are many technological tools to increased efficiency of the patients' adherence such as online appointment and patient-doctor video conference.

Nonetheless, there were several limitations in this study. The participant could not represent all patients who came to the uveitis clinic, for instance, younger patients (< 13 years old) and patients who could not take the drugs without caregivers. We used MMAS-8 to assess the patients over two weeks. Therefore, it could not represent the patients' whole life. Lastly, our study did not examine the frequency of instillation which may impact the patients' adherence.

**Conclusion**

This study showed that 29.8% of patients did not adhere to their uveitis medications. Factors associated with medication non-adherence included lack of knowledge regarding proper medication use, forgetfulness, side effects of medications, difficulties in travelling to the doctor's office and difficulties in using eye drops. The most common reason was forgetfulness.

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# Color vision defect in patients with tuberculosis receiving Ethambutol treatment

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**Purpose:** To evaluate the incidence of color vision defect in patients with tuberculosis receiving ethambutol (EMB) treatment and to evaluate the sensitivity of the two methods of color vision tests in detecting the color vision defect.

**Materials and methods:** The authors prospectively evaluated patients newly diagnosed with tuberculosis from the infectious diseases clinic at Thammasat Hospital, Pathum Thani, Thailand. The patients were enrolled from October 2018 to December 2019. The patients underwent complete eye examinations including optical coherence tomography (OCT) optic nerve analysis and visual field at their first visit. Color vision measured using the Ishihara Pseudo-isochromatic 17-plates and Farnsworth-Munsell D-15 test at initial visit and monthly were recorded. The patients were followed-up for at least 6 months or until they stopped EMB treatment.

**Results:** Twenty-seven patients (54 eyes) were included in the study. Thirteen were female and fourteen were male. They had a mean age of 49.8 ±17.6 years (range 22 to 77 years). The mean daily dose of ethambutol is 17.38 ±2.39 mg/ kg (range 13.6-21.8 mg/kg). Baseline color vision and monthly color vision was remained normal in all patients. After following up the patients for about 6 months after anti-tuberculous drugs were stopped, color vision remained normal in all patients using both color vision tests.

**Conclusion:** Although the present study did not find the incidence of color vision defects in our patients as predicted, the authors still emphasize the importance of color vision test screening in patients receiving EMB treatment because color vision defect may indicate early toxic optic neuropathy.

**Keywords:** Color vision, Tuberculosis, Ethambutol, Toxic optic neuropathy

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## Introduction

Ethambutol (EMB) induced toxic optic neuropathy is one of the drug toxicities in patients receiving anti-tuberculous drugs that result in visual loss. EMB activates intracellular metal-containing enzymes such as zinc or copper-containing cytochrome oxidase which result in cell membrane damage.[1] The daily dose and the duration of drug administration affects drug accumulation and toxic optic neuropathy. No safe dose has been reported with EMB-induced toxic optic neuropathy was

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observed with doses as low as 12.3 mg/kg.[2] The mean duration of ocular toxic effects has been reported to be 3 to 5 months.[3] No study has reported with the onset of ocular toxicity after withdrawal of the drug. In a recent systematic review, Ezer N, et al. reported the cumulative incidence of any visual impairment in patients with active tuberculosis receiving EMB was 22.5 per 1000 cases. Here, 4.3 per 1,000 cases have been reported to have permanent vision loss. However, after analyzing only those who received an average dose of 27.5 mg/kg/day (MKD) or less and the duration treatment was about 2-9 months, the incidence of any visual impairment has been reduced to approximately 19.2 per 1,000 cases.[4]

EMB-induced toxic optic neuropathy has been classified with regards to its clinical manifestation into 2 types; axial and periaxial toxic effects. Patients with axial toxic effect usually present with decreased visual acuity, color vision defect or central scotoma field defect. Patients with periaxial toxic effect usually present with slightly decreased visual acuity, color vision defect or peripheral field defect.[5] Previous studies reported that changes in color vision can occur before visual acuity is decreased.[6,7] Therefore, color vision defect may be the earliest sign of ocular toxicity.

Wong JKW, et al. reported the Farnsworth-Munsell D-15 test appears to be more sensitive than the Ishihara Pseudo-isochromatic plates in detecting color vision defects as subjective screening tool for suspected EMB-induced toxic optic neuropathy.[8] In the present study, the primary outcome is to evaluate the relative incidence of color vision defect without having blurring vision by monthly follow-up during the course of anti-tuberculous drugs treatment. The secondary outcome is to evaluate the sensitivity of the two methods of color vision tests in detecting the color vision defect.

**Material and methods**

The study was approved by the Medical Ethics Committee of Thammasat University (MTU-EC-OP-2-183/61), Pathum Thani, Thailand, and was conducted in accordance with the tenets of the Declaration of Helsinki. The authors prospectively evaluated patients newly diagnosed with tuberculosis from the infectious diseases clinic at Thammasat Hospital. The patients were enrolled from October 2018 to December 2019. The inclusion criteria included subjects of either gender between the age of 20 to 70 years old, subjects who recently diagnosed pulmonary tuberculosis or extrapulmonary tuberculosis that have been started EMB within the first month of treatment and subjects can test both Ishihara color test and Farnsworth panel D-15 test. Subjects with congenital color vision defect, previous retina or optic nerve damage, best corrected visual acuity (BCVA) worse than 20/200, a history of drug use that may affect color vision such as Hydroxychloroquine and Amiodarone were excluded.

Demographic data (age, gender), details of anti-tuberculous drug treatment such as daily dosage, duration of treatment, and visual symptoms were collected. Baseline visual function included best corrected visual acuity (BCVA) on the Snellen chart, pupillary function, average retinal nerve fiber layer (RNFL) thickness, visual field, duration of follow-up, and results of color vision tests by

Ishihara Pseudo-isochromatic plates and Farnsworth-Munsell D-15 test. were collected. RNFL measurements were derived from a 200 × 200 cube optic disc scan using a Cirrus® HD OCT 4000 (Carl Zeiss, Meditec, Dublin, CA, USA). An abnormally thickened RNFL was reported when the thickness is greater than 99% of age-matched normal database. While thin RNFL was defined as thickness belonging to less than 1% of the age-matched normal database. Visual field measurements were derived from the 30-2 Swedish Interactive Thresholding Algorithm (SITA) full-threshold Humphrey visual field (HVF) (Carl Zeiss Meditec Inc., Dublin, CA). Pattern deviation represents focal depressed areas in the points tested when accounting for overall depression as estimated by the mean deviation plot. An abnormal visual field was reported when the localized defect that represented nerve fiber layer defect is detectable.

**Study protocol**

The patients underwent complete eye examinations included optical coherence tomography (OCT) optic nerve analysis and visual field at their first visit. Color vision measured using the Ishihara Pseudo-isochromatic 17-plates and Farnsworth-Munsell D-15 test at initial visit and monthly were recorded. The patients were followed-up for at least 6 months or until they stopped EMB treatment.

Ishihara Pseudo-isochromatic 17-plates test instruction; patients must identify the correct number, or correctly trace the wiggy lines in plates 1-17. Patients with color vision defect should be able to distinguish these. The correct answers of eight or more than is normal (score= 0). The correct answer of seven or less out of seven is abnormal (score = 1). Farnsworth-Munsell D-15 test instruction; patients must select the color cap which most closely matches the reference cap and placed in the bottom of the box and slide next to the reference cap. Patients then continue to select the next closest color disc and places each in sequence in the bottom of the box. The patient's selection of the caps is mapped on a color diagram template, evaluation determines color vision defects in deutan, protan or tritan axis discrimination. If the patient's selection order was reference cap,1, 2,3,4,5,6,7,8,9,10,11,12,13,14,15, the interpretation is normal (score = 0). For example, if the patient's selection order was reference cap, 1,15,2,3,14,13,12,11,10 ,9,8,7,6,5,4 the interpretation is abnormal (deutan pattern) (score =1). Patients with color vision defects were re-evaluated as described above. Internist will be notified when the authors suspect EMB-induced toxic optic neuropathy.

**Statistical analysis**

We analyzed the data with excel tables (Microsoft windows XP professional version 2002 service pack3) and the statistical analysis was performed with SPSS software version 14.0 (IBM Inc, Chicago, IL). Demographic data and other characteristics are described in terms of mean and range. Primary outcome was described in percentage. Secondary outcome was analyzed statistically by using chi-square-test and the *p-value* was obtained. A *p-value* of less than 0.05 indicated statistical significance.

**Results**

A total of 55 patients were enrolled in the study. Twenty-eight patients did not return to follow up after the first visit and were excluded from the final study. Thus, 27 patients (54 eyes) completed the number of follow ups and were included in the final study. Thirteen were female and fourteen were male. They had a mean age of 49.8 ±17.6 years

**Table 1** summarizes the demographic data and the clinical profiles of the patients. Figure 1 shows the daily dosage of EMB in each patient based on body weight.

| | Total (N=27) | |
|---|---|---|
| | **Numbers** | **Percentage** |
| Gender | | |
| Female | 13 | 48.2 |
| Male | 14 | 51.8 |
| Etiologies of tuberculosis | | |
| Pulmonary tuberculosis | 24 | 88.9 |
| Extrapulmonary tuberculosis | 3 | 11.1 |
| Ishihara Pseudo-isochromatic 17-plates | | |
| Score = 0 | 24 | 100 |
| Score = 1 | 0 | 0 |
| Farnsworth-Munsell D-15 test | | |
| Score = 0 | 24 | 100 |
| Score = 1 | 0 | 0 |

**Table 1.** The numbers and percentage of patients' demographic data, etiologies, and color vision score tests

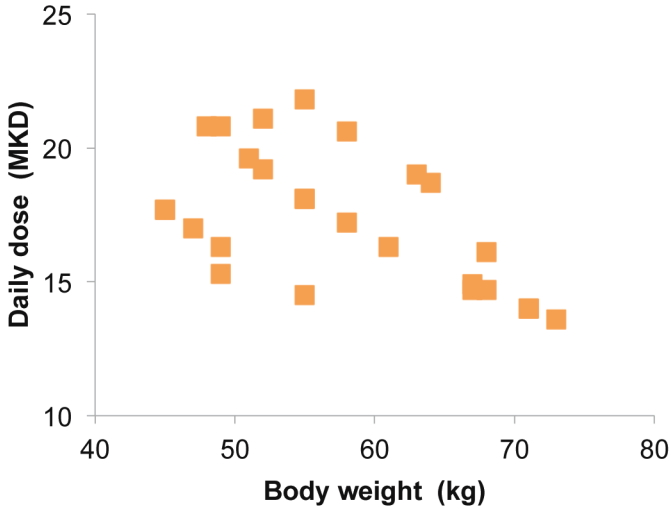


Figure 1 Graph plotting shows the daily dosage of EMB in each patient based on body weight.

(range 22 to 77 years). Twenty-four patients (88.9%) have pulmonary tuberculosis (TB), two patients (7.4%) have tuberculous lymphadenitis, and one patient (3.7%) has shoulder joint tuberculosis. The mean daily dose of EMB is 17.38 ±2.39 MKD (range 13.6-21.8 MKD). At the first visit, the visual acuity ranged from 20/20 (log minimum angle of resolution; log MAR 0.0) to 20/200 (log MAR 1), with a mean acuity of 0.15 ±0.19 log MAR. Slit-lamp examination, fundus examination, OCT optic nerve analysis, and visual field were all normal at their first visit.

Baseline color vision and monthly color vision remained normal in all patients. After following up the patients for at least 6 months or until they stopped EMB treatment, color vision remained normal in all patients using both color vision tests. No patient had any color abnormalities in the color vision test in one method without any abnormalities in the other method.

**Discussion**

Tan et al. reported the incidence of EMB-induced toxic optic neuropathy varies between 15% in patients receiving EMB 50 MKD, 5% with 25 MKD, and less than 1% with 15 MKD.[9] Trusiewicz et al. stated that red-green color defects were the most common and early defect in asymptomatic patients.[10] In Thailand, the recommended daily dose of EMB from the national tuberculosis program guideline is 15-20 MKD. Melamud et al. reported onset of EMB-induced toxic optic neuropathy varies between 3 to 5 months and does not develop until at least 1.5 months after EMB treatment.[3] In previous studies; Kaimbo KW, et al. reported the incidence of color vision defect without decreased visual acuity in 42 patients with tuberculosis receiving EMB was 36%.[12] Cruz EM, et al. reported the incidence of color vision defect without decreased visual acuity in 64 patients with tuberculosis receiving EMB was 47.88%.[13]

In the present study, the patients received an average daily dose of 17.38 ±2.39 MKD (range 13.6-21.8 MKD) and the duration lasting from 6-9 months, which is a safety dose for our patients. Because the patient has a baseline complete eye examination since the beginning of receiving EMB. Moreover, baseline OCT optic nerve analysis and visual field are objective tests confirming that they had normal optic nerve function. If during the study, patients develop color vision defect, it will help to confirm that color vision defect may be the result of ocular toxicity. Majority of our patients with pulmonary tuberculosis are currently treated with a sixmonth combination of drugs that include isoniazid, rifampicin, ethambutol, and pyrazinamide for two months, followed by isoniazid and rifampicin without ethambutol for four months. Visual loss rarely occurs before the patient has been receiving the drug for at least 2 months. No study has reported onset after withdrawal of drug, the authors then monitor the patients until the treatment is complete. If there is no color vision defect, the authors do not continue to monitor. Therefore, majority of our patients received EMB for about 2 months, but the patients were followed up until at least 6 months or until they stopped EMB treatment. Therefore, although the patients in the study had not been monitored for at least 9 months as in the previous study, they were thought to have obtained relevant data

to the results. Comorbidity such as diabetes, hypertension, renal disease, tobacco/alcohol-induced toxic optic neuropathy is associated with an increased risk of pre-existing optic nerve damage. Although the authors did not exclude patients with comorbidity of EMB-induced toxic optic neuropathy such as diabetes, hypertension, and renal disease in the exclusion criteria, none of the patients had underlying disease. This may be another reason why the authors did not find the incidence at all.

Previous studies reported the Farnsworth-Munsell D-15 test appears to be more sensitive than the Ishihara Pseudo-isochromatic plates in detecting color vision defects in EMB-induced toxic optic neuropathy.[5] Since no patient included in the present study developed color vision defects, the authors cannot compare the sensitivity of the two methods of color vision tests in detecting the color vision defect. The limitation of the study is the small sample size. Although this is a prospective study, many patients were lost to follow up o and some patients died due to other reasons during the follow-up period. This study requires further evaluation with larger sample sizes before its results can be recommended for the multidisciplinary care for patients.

In conclusion, although the present study did not find the incidence of color vision defect in patients with tuberculosis receiving EMB treatment like other studies have predicted, the authors still emphasize the importance of color vision test screening in patients receiving EMB treatment because color vision defect may indicate early toxic optic neuropathy.

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All authors report no conflicts of interest relevant to this article.

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# Comparison of the Efficacy of Topical 0.2% Loteprednol Etabonate and Topical 0.1% Dexamethasone in Impending Recurrent Pterygium.

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**Background:** Recurrence is a common complication of pterygium excision. The objective of this study was to evaluate the efficacy of topical 0.2% loteprednol etabonate, a 'soft steroid', compared to topical 0.1% dexamethasone widely used in postoperative pterygium excision to prevent the recurrence of pterygium.

**Methods:** A Randomized control trial study, patients undergoing pterygium excision with amniotic membrane transplantation who developed impending recurrent pterygium stage 3 were randomized into 2 groups. Group 1 received 0.2% loteprednol etabonate and group 2 received 0.1% dexamethasone. The rate of true recurrence of pterygium, impending recurrent pterygium scores, and intraocular pressure were compared between the groups.

**Results:** Fifty-four eyes of 54 patients in each group were included. The true recurrence of pterygium in between groups was not significantly different (15 patients [27.8%] in group 1 vs. 17 patients [31.5%] in group 2, $p = 0.67$). However, the time to recurrence ± SD was longer in group 2 than in group 1 (3.35 ± 1.7 vs. 1.47 ± 0.8 months, respectively, $p = 0.0002$). No ocular hypertension was found in group 1, but found 6 patients (11.1%) in group 2.

**Conclusions:** This study found the efficacy of 0.2% loteprednol etabonate was non-inferior to 0.1% dexamethasone in preventing the recurrence of pterygium and controlling inflammation after pterygium excision with better safety in avoiding steroid-induced ocular hypertension.

**Conflicts of Interest:** No conflicts of interest in this study.

**Keywords:** Loteprednol etabonate, dexamethasone, impending recurrent pterygium
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## Introduction

Pterygium is a triangular fibrovascular tissue expanding from conjunctiva into limbus and cornea, commonly found at the nasal side. It can cause irritation, itching, dryness, red eye, and blurred vision from corneal astigmatism or obscuring central

vision. The major cause of pterygium is prolonged exposure to solar ultraviolet radiation.[1-2] The mainstay of treatment is pterygium excision.

A common complication of pterygium excision is the recurrence of pterygium. The results after pterygium excision are classified into 4 stages: stage 1 is the normal appearance of the conjunctiva after pterygium excision, stage 2 is the appearance of small conjunctival vessels in the area of excision reaching the limbus without fibrovascular occurrence, stage 3 is fibrovascular growth into the area of excision without invasion into the cornea, and stage 4 is fibrovascular growth into the cornea, which is defined as the true recurrence of pterygium (Table 1).[3] The recurrence rate after pterygium excision with bare sclera is as high as 80%.[4] Pterygium excision with conjunctival autograft or with amniotic membrane transplantation (AMT) can reduce the rate of recurrence to 2-35%.[5] The use of other adjunctive treatments such as beta radiation, mitomycin C (MMC) or 5-fluorouracil (5-FU) intraoperatively or postoperatively can also further reduce the recurrence rate.[6] In highly inflamed eyes or impending recurrent pterygium, the use of 5-FU, MMC, or dexamethasone subconjunctival injection can be added to reduce the recurrence rate. 5-FU is commonly used because it has low complication rates and does not effect intraocular pressure (IOP) to the extent as that of dexamethasone.

An important aspect of care in pterygium excision is controlling the conjunctival inflammation in both the preoperative and postoperative period.[7] Currently, there is no standard guideline for reducing inflammation postoperatively by topical steroids. Therefore, it depends on the individual ophthalmologist's judgement for the selection of type, concentration, and frequency of steroid used. Frequently, topical steroid is prescribed every 2-4 hours in the early postoperative period and then gradually reduced depending on the severity of the conjunctival inflammation for 1-3 months. Complications of topical steroid include ocular hypertension or secondary glaucoma, cataract, infectious keratitis, ptosis, scleral thinning and macular edema.[8] Certain types of 'soft steroids' have lower rates of steroid-induced ocular hypertension although with a lower efficacy in reducing inflammation compared with other steroids. One of these is loteprednol etabonate 0.5% and 0.2%. The 0.2% loteprednol etabonate is a new and very low potency soft steroid that was selected for comparison with 0.1% dexamethasone in this study.

The objective of this study was to evaluate the efficacy of topical 0.2% loteprednol etabonate, a 'soft steroid', compared with topical 0.1% dexamethasone, which is widely used in postoperative pterygium excision to prevent the recurrence of pterygium. If 0.2% loteprednol etabonate is non-inferior in efficacy compared with 0.1% dexamethasone, it may be used postoperatively in pterygium excision patients with the benefit of a low incidence of ocular hypertension or secondary glaucoma.

**Materials and Methods**

A prospective randomized control trial was performed from October 2015 to April 2019 at the Department of Ophthalmology, Thammasat Hospital, Thailand and Panyananthaphikkhu Chonprathan Medical Center, Thailand.

**Subjects**

Patients who had pterygium excision with AMT and impending recurrent pterygium stage 3 defined as fibrovascular tissue not invading the cornea (Table 1 and Figure 1) were included.

Patients were excluded if they had 1) recurrent pterygium, 2) received adjunctive treatment with beta radiation, MMC or 5-FU, 3) glaucoma or IOP > 21 mmHg, or 4) history of 5-FU or chloramphenicol allergy.

The included patients were randomized into 2 groups. Group 1 were treated with subconjunctival 5-FU injection and topical 0.2% loteprednol etabonate while group 2 were treated with subconjunctival 5-FU injection and topical 0.1% dexamethasone (CD-oph: dexamethasone sodium phosphate 1 mg/mL, chloramphenicol 5 mg/mL, tetrahydrozaline hydrochloride 0.25 mg/mL).

**Methods**

Patient data were collected before treatment including age, sex, effected eye, IOP, and severity score of impending recurrent pterygium (Table 2 and Figure 1).

The patients who developed impeding recurrent pterygium stage 3 included in this study were randomized into 2 groups. Both groups received subconjunctival 5-FU injection 5mg/0.1 mL with 27-gauge needle in the area of fibrovascular tissue, and then the eyes were irrigated with 30 mL of normal saline. 0.2% loteprednol etabonate was prescribed in group 1, and 0.1% dexamethasone (CD-oph) was prescribed in group 2 every 4-6 hours for 4 weeks. After that, the regimen was gradually decreased until cessation at 3 months. 5-FU was repeatedly injected monthly in the presence of marked inflammation and not more than 3 times to prevent complications.

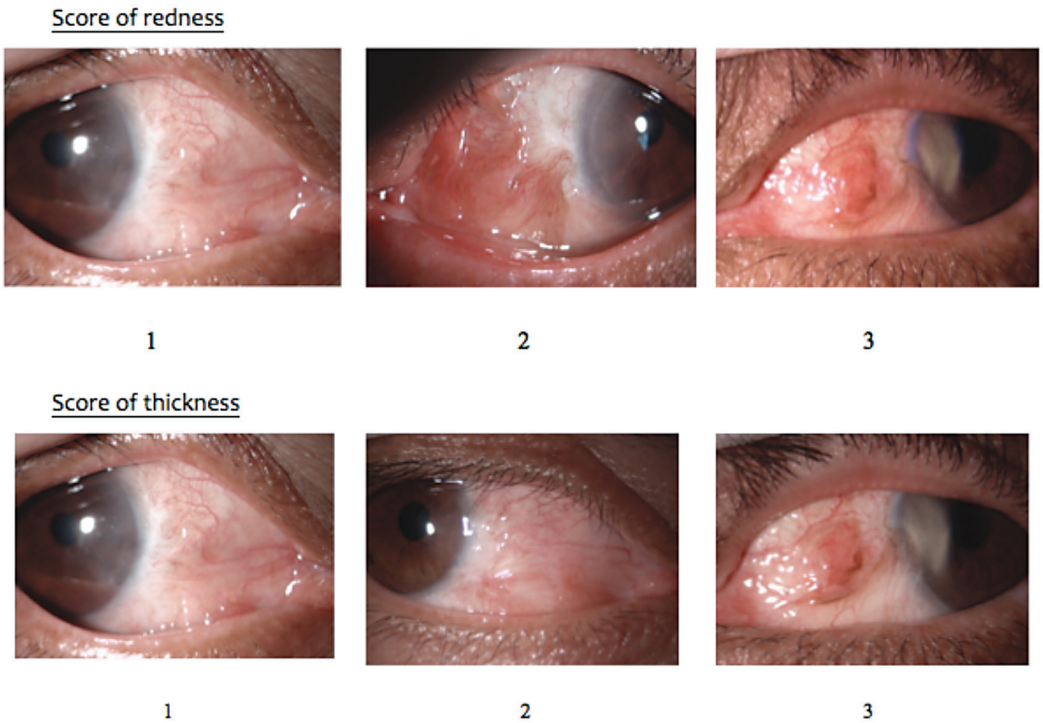


**Figure 1.** Severity score of impending recurrent pterygium (redness and thickness)

**Table 1. 4** stages of postoperative pterygium excision.

| 4 stages of postoperative pterygium excision | |
|---|---|
| Stage 1 | Normal appearance of conjunctiva after pterygium excision |
| Stage 2 | Appearance of small conjunctival vessels in the area of excision reaching limbus without fibrovascular occurrence |
| Stage 3[a] | Fibrovascular growth into the area of excision without invasion into the cornea |
| Stage 4 | Fibrovascular growth into the cornea (true recurrence of pterygium) |

[a]Defined as impending recurrent pterygium in the present study

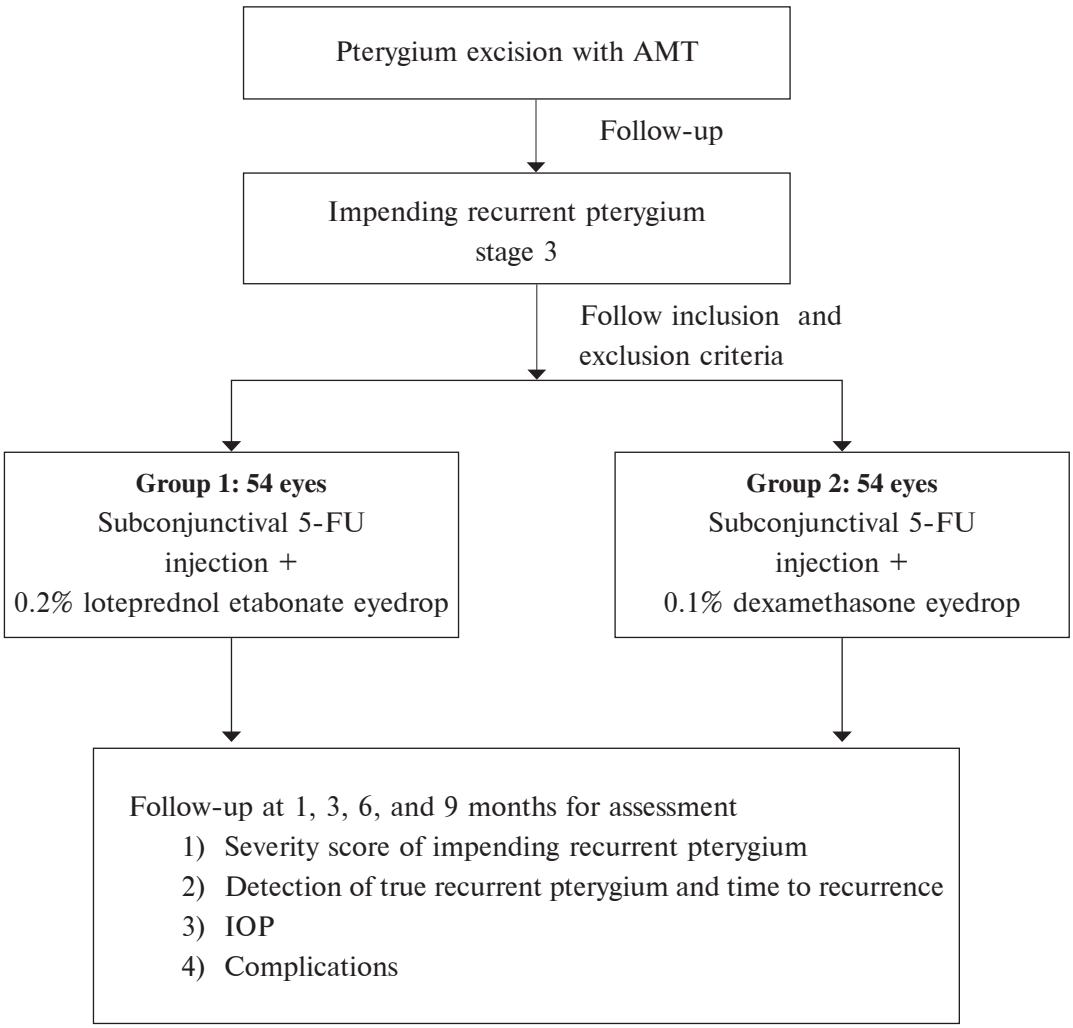


**Figure 2.** Flow chart of the progress through the randomized control trial. Abbreviations: AMT, amniotic membrane transplantation; 5-FU, 5-fluorouracil; IOP, intraocular pressure.

**Table 2.** Severity score of impending recurrent pterygium

| Factors | Severity score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Redness | Mild injection | Moderate injection | Marked injection |
| Thickness | Thin fibrovascular tissue that dose not obscure underlying vessels | Thick fibrovascular tissue that obscures underlying vessels | Marked elevated fibrovascular tissue |
| Size (vertical plane at 3 mm from limbus) | <3 mm | 3-6 mm | >6 mm |
| Score 2-4 = mild, Score 5-6 = moderate, Score 7-9 = severe | | | |

All patients were followed-up at 1, 3, 6, and 9 months to assess the impending recurrent pterygium severity score, IOP, complications, detection of true recurrent pterygium, and time to recurrence.

**Statistical Analysis**

Baseline characteristics of patients were analyzed as mean ± SD for continuous data such as age, preoperative IOP, and score of impending recurrent pterygium. Sex and affected eye were analyzed using frequencies and percentages.

The chi-squared test was used to determine a significant difference of recurrent rate between groups. The significant difference of score of impending recurrent pterygium were analyzed using Mann-Whitney U test for ordinal data while continuous data, such as size of impending recurrent pterygium, IOP, and time to recurrence were analyzed by the independent t-test.

Correlation between the true recurrence of pterygium and factors such as age, sex, and pretreatment score of impending recurrent pterygium were analyzed by point biserial correlation coefficient and chi-square test.

**Ethics**

Informed written consent was obtained from all participants before inclusion in this study at department of ophthalmology. The present study was approved by the institutional review board and human research ethics committee of Faculty of Medicine, Thammasat University, and Panyananthaphikkhu Chonprathan Medical Center, Thailand. The study was performed in accordance with the Declaration of Helsinki. And this study has no conflict of interest.

**Results**

Fifty-four eyes of 54 patients in each group were included in the study. In the 0.2% loteprednol etabonate group (group 1), the mean of age ± SD was 61.39 ± 10.3 years with 16 (29.5%) males and 38 (70.4%) females. In the 0.1% dexamethasone group (group 2), the mean of age ± SD was 57.2 ± 10.9 years with 15 (27.8%) males and 39 (72.2%) females. All baseline characteristics including age, sex, affected eye, preoperative IOP, and score of impending recurrent pterygium did not show significant differences between both groups (Table 3).

The true recurrence of pterygium

in group 1 and 2 were seen in 15 patients (27.8%) and 17 patients (31.5%) respectively, and there was no significant difference ($p$ = 0.67). The mean time to recurrence ± SD was 1.47 ± 0.8 months in group 1 and 3.35 ± 1.7 months in group 2, and there was a significantly longer time to recurrence in group 2 compared with group 1 ($p$ = 0.0002). The mean score of impending recurrent pterygium at 1 month and 6 months after treatment were not significantly different between both groups ($p$ =0.26 at 1 month and $p$ = 0.1 at 6 months). However, the score was significantly higher in group 2 compared with group 1 at 3 months ($p$ = 0.015). The mean number of 5-FU injection ± SD was not significantly different between the groups (1.5 ± 0.6 in group 1 vs. 1.37 ± 0.6 in group 2, $p$ = 0.13) (Table 4).

Regarding complications, the study found ocular hypertension, defined as IOP > 21 mmHg, in 6 patients (11.1%), all of which were in the 0.1 % dexamethasone group. The mean rise in IOP ± SD, defined as the maximum IOP minus the baseline preoperative IOP, was 1.43 ± 1.3 mmHg and 2.94 ± 2.8 mmHg in group 1 and group 2, respectively.

**Table 3.** Baseline characteristics

| Characteristics | **Group 1** 0.2% Loteprednol etabonate (n = 54) | **Group 2** 0.1% Dexamethasone (n = 54) | *P-value* |
|---|---|---|---|
| Age, mean ± SD, yr. | 61.39 ± 10.3 | 57.2 ± 10.9 | 0.23 |
| Sex, n (%) | | | |
| Male | 16 (29.5) | 15 (27.8) | 0.83 |
| Female | 38 (70.4) | 39 (72.2) | |
| Affected eye, n (%) | | | |
| Right eye | 24 (44.4) | 17 (31.5) | 0.17 |
| Left eye | 30 (55.6) | 37 (68.5) | |
| Preoperative IOP, mean ± SD, mmHg | 14.0 ± 3.6 | 14.4 ± 3.1 | 0.28 |
| Score of impending recurrent pterygium, mean ± SD | 5.63 ± 1.4 | 5.98 ± 1.5 | 0.1 |
| Injection | 1.65 ± 0.7 | 1.87 ± 0.7 | 0.06 |
| Thickness | 2.06 ± 0.5 | 2.06 ± 0.7 | 0.48 |
| Size | 4.30 ± 1.5 | 4.34 ± 1.4 | 0.44 |

Abbreviations: IOP, intraocular pressure

**Table 4.** Comparison of recurrence rate, score of impending recurrent pterygium, and complications between the 0.2% loteprednol etabonate and 0.1% dexamethasone groups

| Characteristics | **Group 1** 0.2% Loteprednol etabonate (n = 54) | **Group 2** 0.1% Dexamethasone (n = 54) | *P-value* |
|---|---|---|---|
| True recurrent pterygium, n (%) | 15 (27.8) | 17 (31.5) | 0.67 |
| Time to recurrence, mean ± SD, mo. | 1.47 ± 0.8 | 3.35 ± 1.7 | <0.001 |
| Score of impending recurrent pterygium, mean ± SD | 4.81 ± 0.9 | 5.12 ± 1.3 | 0.26 |
| Score at 1 month | 1.23 ± 0.6 | 1.31 ± 0.5 | 0.32 |
| Injection | 1.65 ± 0.6 | 1.78 ± 0.8 | 0.29 |
| Thickness | 4.40 ± 1.3 | 4.56 ± 1.1 | 0.27 |
| Size | 3.69 ± 0.9 | 4.44 ± 1.4 | 0.015 |
| Score at 3 months | 0.74 ± 0.5 | 0.85 ± 0.6 | 0.25 |
| Injection | 1.28 ± 0.5 | 1.58 ± 0.7 | 0.06 |
| Thickness | 3.69 ± 1.4 | 4.42 ± 1.2 | 0.06 |
| Size | 3.31 ± 0.9 | 3.62 ± 1.0 | 0.10 |
| Score at 6 months | 0.36 ± 0.5 | 0.43 ± 0.5 | 0.29 |
| Injection | 1.26 ± 0.4 | 1.32 ± 0.6 | 0.42 |
| Thickness | 3.90 ± 1.4 | 4.07 ± 0.9 | 0.27 |
| Size | | | |
| 5-FU injection, mean ± SD, n | 1.5 ± 0.6 | 1.37 ± 0.6 | 0.13 |
| 1 injection, n (%) | 29 (53.7) | 36 (66.7) | |
| 2 injections, n (%) | 23 (42.6) | 16 (29.6) | |
| 3 injections, n (%) | 2 (3.7) | 2 (3.7) | |
| IOP rising, mean ± SD, mmHg (maximum IOP− pre-op IOP) | 1.43 ± 1.3 | 2.94 ± 2.8 | <0.001 |
| Complications, n (%) Ocular hypertension | 0 | 6 (11.1) | |

Abbreviations: 5-FU, 5-fluorouracil; IOP, intraocular pressure

There was a significantly higher IOP elevation in the 0.1% dexamethasone group ($p$= 0.0002) (Table 4).

Correlations between true recurrence of pterygium and pretreatment factors were analyzed. The age of patients had a significantly negative correlation with the recurrence of pterygium (r = -0.28, $p$ =0.002). Male sex had a significant association with recurrence rate ($p$ = 0.02). However, initial score of impending recurrent pterygium, including score of injection, thickness, and size, were not significantly correlated with the recurrence of pterygium.

**Discussion**

Previous studies have found many factors associated with higher recurrence rate of pterygium, including some patient characteristics, such as younger age, area or size of pterygium, current active growth, family history, and concurrent ocular surface inflammation.[9-16] The present study also found association between younger age and male sex with higher recurrence rate.

Controlling ocular surface inflammation is the key to reducing recurrence of pterygium, and topical steroids of various types and regimen are the most common form of medication to control this inflammation.[17] Yaisawang found a high recurrence rate of pterygium in patients who received inadequate post-operative topical steroid.[3] Prabhasawat, et al. reported subconjunctival injection of triamcinolone or 5-FU added to topical steroid was more effective in halting the progression of impending recurrent pterygium.[18]

Unfortunately, topical steroids can cause many ocular side effects. An important one is steroid-induced ocular hypertension, which may progress to secondary glaucoma. Amaly found one-third of the normal population and 90% of primary open angle glaucoma developed ocular hypertension after 4 weeks of using topical 0.1% dexamethasone.[19] Makornwattana reported the incidence of steroid responders to be 9.68% in postoperative pterygium excision when 0.1% dexamethasone eye drops were used.[20] To avoid this unwanted side effect, 'soft steroids', including loteprednol etabonate 0.5% and 0.2% were developed by retrometabolic engineering that replaces the C-20 ketone with a C-20 ester, producing a compound designed to induce rapid metabolism to inactive metabolites.[21-22] Preclinical and clinical studies have confirmed the safety and efficacy of loteprednol etabonate for the treatment of many ocular inflammatory conditions, including giant papillary conjunctivitis, seasonal allergic conjunctivitis, anterior uveitis, blepharokeratoconjunctivitis, keratoconjunctivitis sicca along with the control of postoperative inflammation following PRK, LASIK, and cataract surgery.[22] John, et al. suggested loteprednol etabonate QID drops or BID ointment were sufficient for controlling inflammation in postoperative pterygium excision patients in a retrospective case series.[22] However, there are currently no prospective studies to evaluate the efficacy of loteprednol etabonate in postoperative pterygium excision.

This study demonstrated the non-inferior in efficacy of 0.2% loteprednol etabonate to 0.1% dexamethasone Although recurrence rates of pterygium were not significantly different between the 2 treatment groups, longer time to recurrence in the 0.1% dexamethasone

group was demonstrated. Moreover, no ocular hypertension (IOP > 21 mmHg) was found in the loteprednol etabonate group, compared to 6 patients (11.1%) in the 0.1% dexamethasone group. Rise in mean IOP ± SD was also significantly lower in 0.2% loteprednol etabonate group compare with the 0.1% dexamethasone group (1.43 ± 1.3 vs. 2.94 ± 2.8 mmHg, respectively, p = 0.0002). Our results concord with previous studies that demonstrated a low propensity for loteprednol etabonate to cause significant elevation of IOP ≥ 10 mmHg in both short-term (< 28 days, 0.8%) and long-term use (≥ 28 days, 1.5%) when compared to prednisolone acetate and dexamethasone.[23]

Experience of the surgeon is one factor that affects the recurrence rate of pterygium, the limitation of this study is the lack of control of this confounding factor. I recommend further studies of the use of several topical steroids, especially soft steroid, to compare pterygium recurrence rate after surgery and if other interfering factors such as surgeon can controlled, the results may be more reliable.

**Conclusion**

The efficacy of 0.2% loteprednol etabonate was non-inferior to 0.1% dexamethasone in preventing the recurrence of pterygium and controlling inflammation after pterygium excision. 0.2% loteprednol etabonate was also safer with regards to avoiding steroid-induced ocular hypertension.

**Acknowledgement**

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**Pontential Conflicts of Interest**

Researchers have no financial interest in any products or instruments mentioned in this study.

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# Trends in education and career choices after ophthalmology residency training in academic year 2017

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**Objective:** To investigate the trend toward subspecialty training among ophthalmology residents as well as factors influencing the residents' decision to train that can be used as guidelines for further education.

**Method:** Cross-sectional study

**Results:** A total of 64 residents responded to the research questionnaire. It was found that the most preferred subspecialty was retina (28.12%). The second most preferred was glaucoma (20.31%) followed by cornea and refractive surgery (17.18%) respectively. Factors and the respondents' choice of subspecialties showed that gender, age, hometown, and funding were not associated with the respondents' decision concerning subspecialty training in the future (*P-value*>0.05). Marital status was a factor associated with the residents' consideration of subspecialty training (*P-value*= 0.001). The factor that influenced most respondents in making the choice of subspecialty training was good prior knowledge in that particular subspecialty as documented (25%). The second most influential factor was the application of both medical and surgical treatment in subspecialty practice (23.72%). Most residents in this study expressed the desire to have subspecialty training after residency training.

**Conclusions:** The influential factors for subspecialty training was good prior knowledge in that subspecialty, which was also the main reason among the respondents preferring retina which was the most popular subspecialty in this study.

**Keywords :** Trend in ophthalmologist residency training,subspecialty training,motivation and factor of rescident

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## Introduction

Subspecialist preferences have received more attention than in the past. One of these reasons may be due to the public, having people can greater access to informationaccess information about diseases which they are concernend and find out which specialist doctor is best suited for them. Almost general ophthalmologists realize this, for effective treatment, training in subspecialties may be the solution for them. According to

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Kanchanaranya N et al[1] (2015), they found that ophthalmology training has been increasingly in demand and it has become one of the most popular medical specialties among general practitioners. There are 65 ophthalmologists completing residency training in Thailand each year, and this number shows increasing trends in the future so this study establishes future trends.

According to the Royal College of Ophthalmologists of Thailand, the subspecialties available for fellowship are: retina, pediatric and strabismus, oculoplastic, neuro-ophthalmology, glaucoma, low vision, ocular pathology, uveitis and ocular inflammation, and research. This study was conducted to investigate the trend toward sub-specialization and subspecialty preferences among ophthalmology residents currently in training. The obtained information could be used in making decisions about subspecialty training. Moreover, the comparison of trends toward sub-specializations could provide useful information, not only to residents, but also to training institutions as they could better prepare for the residents' choice of subspecialties. This study analyzed information concerning socio-demographic including age, gender, hometown, original affiliation, and marital status as well as subspecialty preference.

**Material and Methods**

This is a cross-sectional descriptive study approved by the Ethics committee at Thammasat University, Thailand. Data was collected through a research questionnaire which modified from Kanchanaranya N[1] study. Paired t-test and Chi-square test were used to analyze data by Statistical Package for the Social Science (SPSS) software. The questionnaires were contributed at the symposium organized by the Royal College of Ophthalmologists in 27-29 November 2017. The researchers of this study gave out the questionnaires themselves so that they could answer to the respondents if there was any query. The questionnaire obtained information concerning age, gender, hometown, year of residency training, the most preferred subspecialty, the reason for the choice. Only the questionnaires with complete answers for all questions were used for data analysis. The questionnaires without complete answers were excluded from this study.

This study was given out to ophthalmology residents especially focused on third-year residents as they had been in training for several years and were about to complete training. Therefore, these senior residents were more likely to have certain plans for further study, unlike residents in the first and second year of training who might not be aware of their preference yet.

**Results**

From the questionnaire given to first, second, and third year ophthalmology residents who attended the symposium organized by the Royal College of Ophthalmologists of Thailand in 2017, the total number of respondents was 64. Twenty-seven respondents were male (42.18%) and thirty-seven were female (57.82%). Two respondents were in the first year of training (3.12%), three were in second year (4.68%) and fifty-nine were in third year (92.18%). Fifty-seven respondents were single (89.17%) and seven were married (10.83%). The majority were in the age group 25-30 years (64.06%), followed by 30-35 years (29.69 %) and 35-40 years (6.25%). Residency training of most

respondents (59.37 %) was funded by their affiliated hospital and their hometown was mostly Bangkok (46.87%). The numbers of respondents from other regions were similar (Table 1).

The analysis of associations between various factors and the respondents' choice of subspecialties showed that gender, age, hometown, and funding were not associated with the respondents' decision concerning subspecialty training in the future (*P-value*>0.05). In addition, these factors did not have an effect on the residents' decision to continue their study in Thailand or abroad. However, single status was a factor associated with residents' consideration of subspecialty training (*P-value* 0.001) (Table 1). Residents who have scholarships tend to study in subspecialist (54.69%) more than those without (37.5%) but did not reach statistical significance (*P-value* 0.97) (Table 1).

**Table 1:** Demographic Characteristics and future decision

| | | Subspecialty | General Ophthalmologist | P-value | Total | Study in Thai | Study abroad | P-value |
|---|---|---|---|---|---|---|---|---|
| Sex | Male | 25 (39.06%) | 2 (3.12%) | 0.86 | 27 (42.18%) | 27 | 0 | 0.715 |
| | Female | 34 (53.14%) | 3 (4.68%) | | 37 (57.82%) | 35 | 2 | |
| | Total | 59 (92.18%) | 5 (7.82%) | | 64 (100%) | 62 | 2 | |
| Age | 25-30 | 37 (57.81%) | 4 (6.25%) | 0.55 | 41 (64.06%) | 39 | 2 | 0.561 |
| | 30-35 | 18 (28.13%) | 1 (1.56%) | | 19 (29.69%) | 19 | 0 | |
| | 35-40 | 4 (6.25%) | 0 | | 4 (6.25%) | 4 | 0 | |
| Status | Single | 54 (84.38%) | 3 (4.69) | 0.03 | 57 (89.17%) | 56 | 1 | 0.001 |
| | Married | 5 (7.71%) | 2 (3.12) | | 7 (10.83%) | 6 | 1 | |
| Hometown | Bangkok | 5 (7.81%) | 0 | 0.53 | 5 (7.81%) | 5 | 0 | 0.491 |
| | Northern | 6 (9.38%) | 1 (1.56%) | | 7 (10.93%) | 7 | 0 | |
| | Central | 5 (7.81%) | 0 | | 5 (7.81%) | 5 | 0 | |
| | Southern | 8 (12.5%) | 1 (1.56%) | | 9 (14.06%) | 8 | 1 | |
| | Eastern | 1 (1.56%) | 0 | | 1 (1.56%) | 1 | 0 | |
| | Western | 28 (43.75%) | 2 (3.12%) | | 30 (46.87%) | 29 | 1 | |
| | North-eastern | 6 (9.38%) | 1 (1.56%) | | 7 (10.93%) | 7 | 0 | |
| Scholarship | Yes | 35 (54.69%) | 3 (4.68%) | 0.97 | 38 (59.37%) | 37 | 1 | 0.355 |
| | No | 24 (37.5%) | 2 (3.13%) | | 26 (40.63%) | 25 | 1 | |

For subspecialty preferences in 2017 (Table 2), the five most preferred subspecialties were the following: retina was the top preference as a choice from 18 respondents (28.12%), followed by glaucoma from 13 respondents (20.31%), cornea and refractive surgery from 11 respondents (17.18%), the fourth in order of preference was oculoplastic chosen by 9 respondents (14.06%), the fifth was uveitis and ocular inflammation from 3 respondents (4.68%). The sixth preferred subspecialty was pediatric ophthalmology and strabismus (3.12%). Three respondents

**Table 2:** Number of responder considering in each subspecialties program

| Subspecialties | Responder | |
|---|---|---|
| | Number | Percent |
| Retina | 18 | 28.12 |
| Glaucoma | 13 | 20.31 |
| Cornea and refractive surgery | 11 | 17.18 |
| Oculoplastic | 9 | 14.06 |
| Uveitis and ocular inflammation | 3 | 4.68 |
| Neuro-ophthalmology | 2 | 3.12 |
| Pediatric and strabismus | 2 | 3.12 |
| Ocular pathology | 1 | 1.56 |
| Low vision | 1 | 1.56 |
| Research | 1 | 1.56 |

expressed the desire to study abroad but did not specify their preferred subspecialty.

The analysis of preferences in subspecialty training (Table 3) showed that there was one respondent (6.25%) who expressed no desire for further training in each of the following subspecialties: retina, oculoplastic, cornea and refractive surgery, and glaucoma. As for other subspecialties, the respondents expressed their intention to continue their training in the subspecialty of their choice.

Factors influencing the respondents' choice of subspecialty was analyzed from the three most preferred subspecialties. For retina subspecialty, 8.19% of the total respondents made this choice because the practice involves both medical and surgical treatment, 6.55% made the choice because of their good knowledge in the subject and the practice. For glaucoma, which was the second most preferred subspecialty, 9.83% of the respondents gave the same reason as those who chose retina - the practice involves both medical and surgical treatment. The following reason for choosing this subspecialty was because the practice involves medical treatment (3.27%). For cornea and refractive surgery, 8.19% of the respondents reported having good knowledge in the preferred subspecialty and 3.27% reported that the preference was due to the application of both medical and surgical treatment (Table 4).

**Discussion**

The demand for sub-specialization among ophthalmology residents in Thailand has continuously increased as shown in their responses to the questionnaire distributed in a symposium organized by the Royal College of Ophthalmologists of Thailand. This study collected a large amount of information about the trends toward sub-specialization among ophthalmology residents. It was found that the present cohort of residents expressed a high level of interest in sub-specialization (95.32% of total respondents). This study should provide us with information to forecast and make better plans concerning sub-specialization in the future.

The three most preferred subspecialties were retina (28.12%), glaucoma (20.31%),

**Table 3:** Number of respondents make decision between subspecialties that consider and general ophthalmologist

| Subspecialty preference | Pursuit of preferred subspecialty | Intention to remain as general ophthalmologist | Total | *P-value* |
|---|---|---|---|---|
| Retina | 17(94.4%) | 1(5.6%) | 18(100%) | 0.161 |
| Pediatric and strabismus | 2(100%) | 0 | 2(100%) | 0.769 |
| Research | 1(100%) | 0 | 1(100%) | 0.676 |
| Oculoplastic | 8(88.8%) | 1(11.11%) | 9(100%) | 0.379 |
| Neuro-ophthalmology | 2(100%) | 0 | 2(100%) | 0.054 |
| Cornea and refractive surgery | 10(90.90%) | 1(9.1%) | 11(100%) | 0.57 |
| Ocular pathology | 1(100%) | 0 | 1(100%) | 0.769 |
| Uveitis and ocular inflammation | 3(100%) | 0 | 3(100%) | 0.092 |
| Low vision | 1(100%) | 0 | 1(100%) | 0.769 |
| Glaucoma | 12(92.03%) | 1(7.97%) | 13(100%) | 0.263 |

and cornea and refractive surgery (17.81%) respectively. The results of this study were compared to the study by Kanchanaranya N et al[1] in 2015 to examine the trend toward sub-specialization, the respondents, the age group of residents entering fellowship, and the ratio between free-training follows and those with an affiliation hospital. The study in 2015 found that 47.2% of respondents expressing interest in sub-specialization were third-year residents whereas the corresponding number increased to 92.18% in 2017. This could indicate the higher level of awareness and interest in sub-specialty training (Table 5). The average age of doctors commencing residency training was 30 years in 2015, compared to the age group 25-30 years in 2017 at 75.5% and 64.06% respectively. It is possible that general practitioners are ready to have specialty training at this age (Table 6).

The hometown of most respondents was Bangkok in both 2015 and 2017 study as documented in 48.4% and 46.8% of the total respondent, respectively. The majority of residents received training funds from affiliated hospitals, 65.8 % in 2015 and 59.37 in 2017 respectively(Table 7). This reflects the importance of educational funds as it is a factor in considering a candidate for ophthalmology training.

Retina was the most preferred subspecialty in this study as reported by 28.12% of total respondents. This subspecialty emphasizes the study of structure, function, mechanism and all diseases concerning retina. There are various types of treatment including laser therapy, eye drop, and surgery depending on the symptoms and diagnosis. The main reason for making this choice of subspecialty was the application of medical and surgical treatment in clinical practice. This finding is consistent with the study by Kanchanaranya N et al in 2015 (Table 8) which found similar reasons for making this choice as well as similar proportion of respondents (28.10%). In a study by Sivachandran N et al[2] which investigated the preference for subspecialty training in Canada from 1990 to 2014 among 528 ophthalmologists, it was found that the three most preferred subspecialties were 1. Retina,

**Table 4:** Relation between subspecialty preference and main motive for choice of preference

| Subspecialties /Reason | Retina | Pediatric and strabismus | Research | Oculoplastic | Neuro-ophthal-mology | Cornea and refractive surgery | Ocular pathology | Uveitis and ocular inflammation | Low vision | Glaucoma | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Good prior knowledge | 4 (6.55%) | 0 (0%) | 0 (0%) | 3 (4.91%) | 0 (0%) | 5 (8.19%) | 0 (0%) | 2 (3.27%) | 1 (6.66%) | 1 (6.66%) | 16 |
| 2. Medical treatment | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (6.66%) | 0 (0%) | 2 (3.27%) | 3 |
| 3. Surgical treatment | 3 (4.91%) | 0 (0%) | 0 (0%) | 5 (8.19%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3.27%) | 10 |
| 4. Both medical and surgical | 5 (8.19%) | 1 (1.63%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (3.27%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (9.83%) | 15 |
| 5. Job description | 4 (6.55%) | 1 (1.63%) | 1 (1.63%) | 1 (1.63%) | 2 (3.27%) | 2 (3.27%) | 1 (1.63%) | 0 (0%) | 0 (0%) | 1 (1.63%) | 13 |
| 6. Income | 1 (1.63%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 |
| 7. Time length of study | 1 (1.63%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.63%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.63%) | 3 |
| Total | 18 | 2 | 1 | 9 | 2 | 11 | 1 | 3 | 1 | 13 | 61 |

*numbers without brackets represent the number of correspondents who selected the motive

**numbers in brackets are percentages of all correspondents (n=61)

**Table 5:** Compare participant between year 2015 and 2017

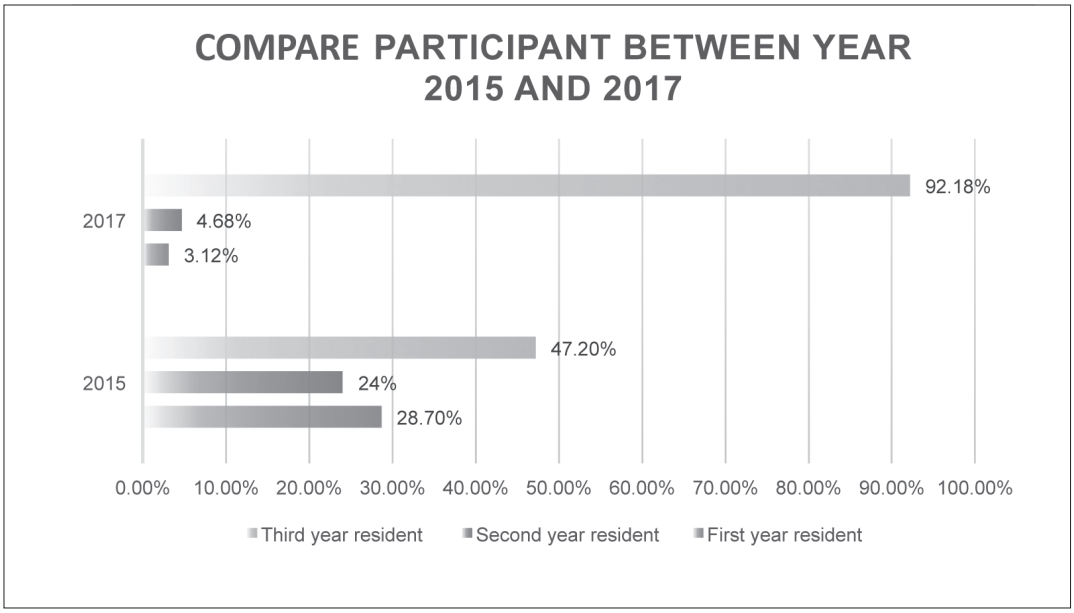
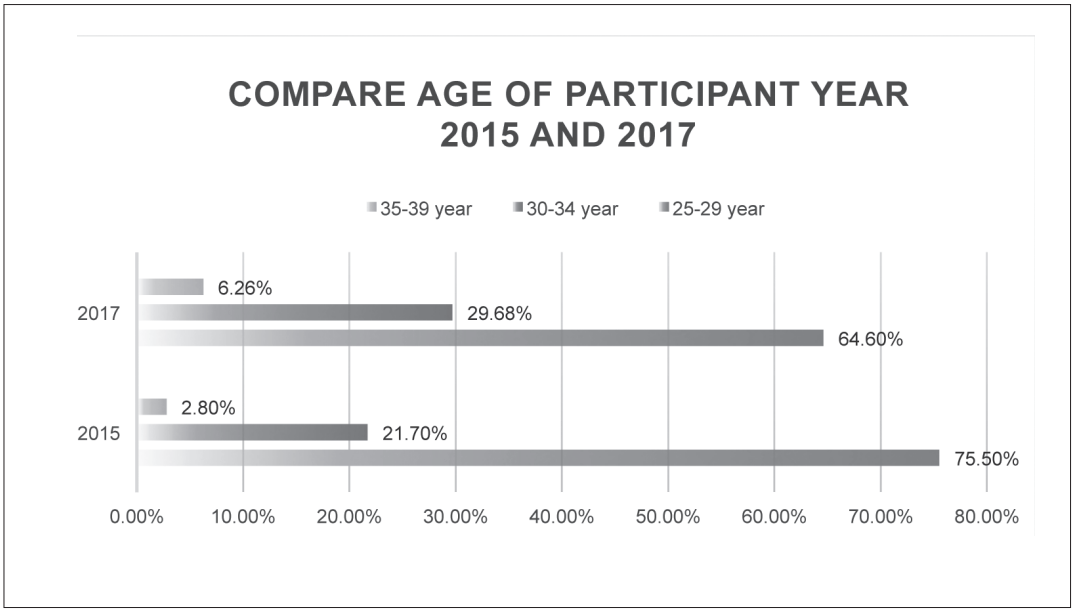
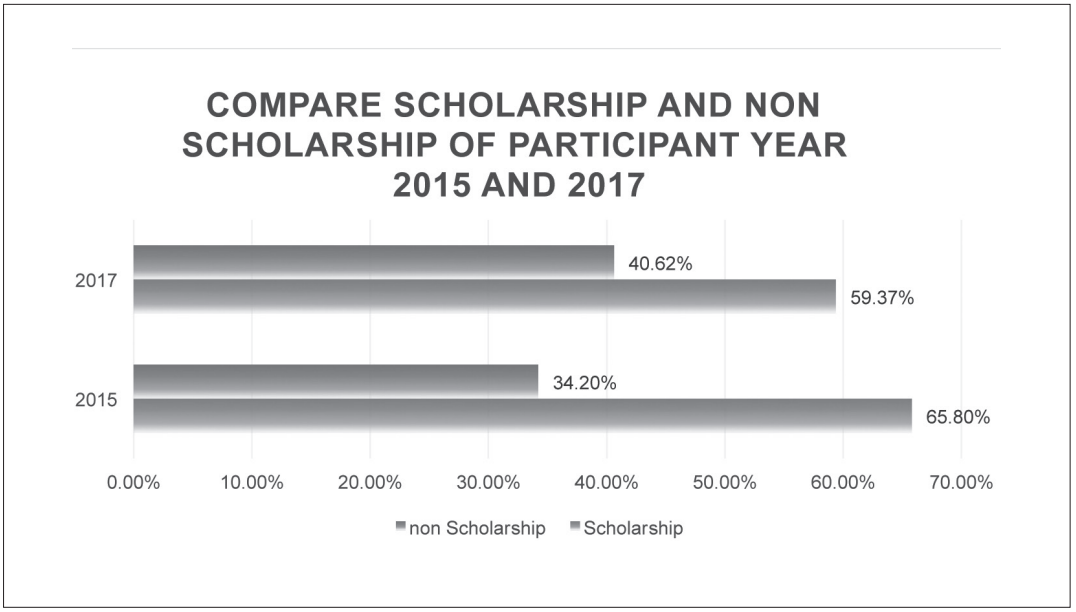



**Table 6:** Compare age of participant between year 2015 and 2017




2. Glaucoma, 3. cornea and refractive surgery. These findings corresponded with the result of this study. However, in a study of specialty preferences among 299 ophthalmology residents in Nigeria conducted by Kareem O Musa et al[7], it was found that the most preferred subspecialty was cornea and refractive surgery, followed by retina and pediatric ophthalmology and strabismus. This indicates different demand

Table 7: Compare scholarship and non-scholarship of participant between year 2015 and 2017



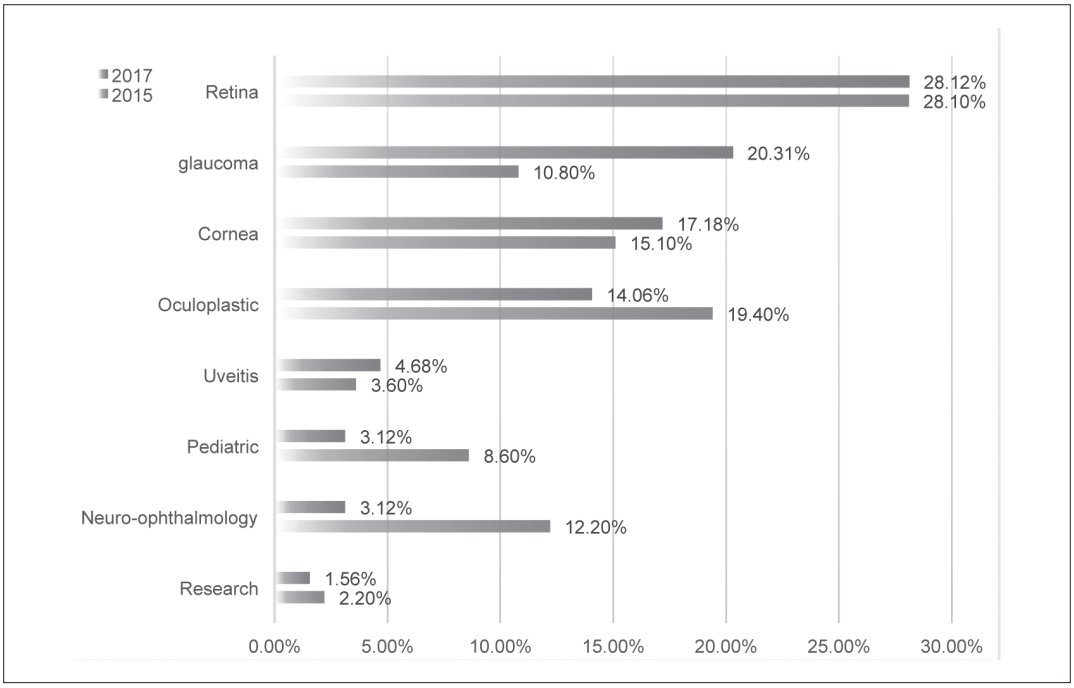

and preferences for sub-specialization, depending on the characteristics of the population.

Even through retina is the most attended but the number who prefer retinal specialist and number who interests but still want just only general ophthalmologist not significant in statistic according to table 3 (*P-value* = 0.161) and it's also the same in other subspecialty. This may be from the number of participant wasn't much enough between two group if the higher participant, the statistic significant will show.

The second most preferred subspecialty was glaucoma, which involves various types of treatment. The reason for making this choice was the application of both medical and surgical treatment, which is the same reason as those who preferred retina. This indicates that most residents preferred the subspecialties that use both medical and surgical approach, it means the most of residents still attend the subspecialty which can use the both of treatment. In this study 20.31% of respondents expressed preference for this subspecialty. This finding is similar to that of the study conducted by Sivachandran N et al[2]. However, it is different from the findings of Kareem O Musa et al[7] and Kanchanaranya N et al1. According to Kanchanaranya N et al[1], in the year of their study the residents preferred oculoplastic. However, the preference for each subspecialty varied, depending on the subspecialty popularity at that time.

Cornea and refractive surgery was the third subspecialty in the order of preference. In this study 17.18% of respondents expressed preference for this subspecialty. The finding is consistent with the result of Kanchanaranya N et al's study[1] which also found cornea and refractive surgery the third most preferred subspecialty with 15.10% of total respondents. However, the main reason for making this choice in 2015 study was the use of medical

**Table 8:** Preferred specialties compared between year 2015 and 2017




and surgical treatment whereas the main reason in 2017 study was good knowledge in that subspecialty. It's indicated that even through the rank of sub specialists not change but the reason for the chosen can change with time. This result demonstrates different reasons for making choices among residents at different periods of time even though the subspecialty was in the same order of preference. The popularity of other subspecialties was at lower levels (Table 8) and it could be different each year.

This study has some limitations. For instance, the information was collected at a symposium organized by the Royal College of Ophthalmologists of Thailand on 27-29 November 2017. At this time most third-year residents made decisions about their career plan, either going back to work as a specialist or training to be subspecialists. However, first-year and second-year residents who also attended the conference did not make certain plans about the fellowship and were likely to change their plan in the future. In addition, the study was conducted in limited time as the symposium scheduled many interesting lectures and presentations thus the respondents might complete the questionnaire in a hurry so that they can attend the lectures on time. It is possible that the interpretation of results may not reflect actual subspecialty preference. The distribution of questionnaires may not cover all subjects. Moreover, the number of respondents in this study may not sufficiently represent the preference of all residents because some questionnaires were not completely responded to, some answers were difficult to interpret, and some couldn't be used in the analysis of results.

Nevertheless, the analysis of results has shown the trend toward sub-specialization among residents. The most popular subspecialty was

retina and the main reason for this choice remained the same as previous study: the application of both medical and surgical treatment. The order of preferences for other subspecialties varied in each year due to aforementioned reasons. Moreover, the training of most residents was funded by their affiliation hospital, as they were found in a larger proportion than free-training residents. Therefore, they had to study the trend toward sub-specialization in order to plan and prepare for their fellowship training in the future.

**Conclusion**

Subspecialty preferences among ophthalmology residents are changeable each year due to various reasons. Nevertheless, the main reason influencing subspecialty choices was the application of both medical and surgical treatment in that subspecialty practice. The following influential factor was good knowledge in that subspecialty, which was also the main reason among the respondents preferring retina which was the most popular subspecialty in this study. Other subspecialties in lower order of preference were chosen on the basis of personal reasons.

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# Smart Mobile Application Based Portfolio; Is It Convenient For Assessment?

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**Background:** Portfolios are an important widely used tool for evaluating medical students' progression in clinical competence and professionalism. Smart Mobile application-based portfolio was developed because technology is now playing a crucial part in today's learning style and aids both students and instructors in the process of learning, revision, assessment and reflection. The beta-test application is available on both IOS and android phones for use by medical students rotating through ophthalmology departments.

**Methods:** Five attending ophthalmologists and 110 medical students rotating in the ophthalmology department from Thammasat University, Chulalongkorn University and Chumphon hospital were enrolled in this study. All participants used the application from the first to the final day of their ophthalmology clinical rotation. On the final day of their rotation, an evaluation form was completed by all participants regarding their feedback about the application.

**Results:** A majority of the students and attending ophthalmologists completely agree that the essential skills the students need to learn are listed in the application (54%), the medical skills listed were actually trained (59%), the attending doctor's advice is helpful for personal development (62%), the application is easy to use (60%), attending doctors and students can record what they have learned (47%), and the application touchscreen is easy to use (58%). Most of the students and attending ophthalmologists somewhat agree that the application is flexible for the students (40%), the students and attending doctors will use the application regularly (43%), and the medical skills guide and recommendation are useful in practice (42%).

**Conclusion:** A smart mobile application-based portfolio is feasible and convenient for assessment. However, the application still needs further development to meet the users' expectations.

**Keywords:** Smart Mobile, application, portfolio, Ophthalmology
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## Introduction

Portfolios are used for all levels of medical education and evaluation.[1] Portfolios are also used in other situations. A Portfolio is a collection of evidence that learning has taken

place.[2] A Portfolio is a purposeful collection of a student's or other's efforts or achievements in one or more areas.[3] Portfolios include all kinds of evidence which give the possibility to draw valid conclusions about competence.[4] The practice of a portfolio is suitable for assessing professional competence through several areas of competences and for achieving the highest level of the Miller pyramid as an assessment tool.[5]

Electronic web portfolios have also been developed and replace old fashion paper portfolios. There are many advantages over paper based. One of the most powerful is to offer feedback which is mainly focused on the assessment of generic skills and provides quantification of progress.[6] However, in the disruptive world, there may be new tools that are faster to use and more convenient than electronic web portfolios. We hypothesize that application-based portfolios are this tool.

Smart Mobile application based portfolio was developed based on the fact that technology is now playing a crucial part in today's learning style and aids both students and instructors in the process of learning, revision, assessment and reflection.

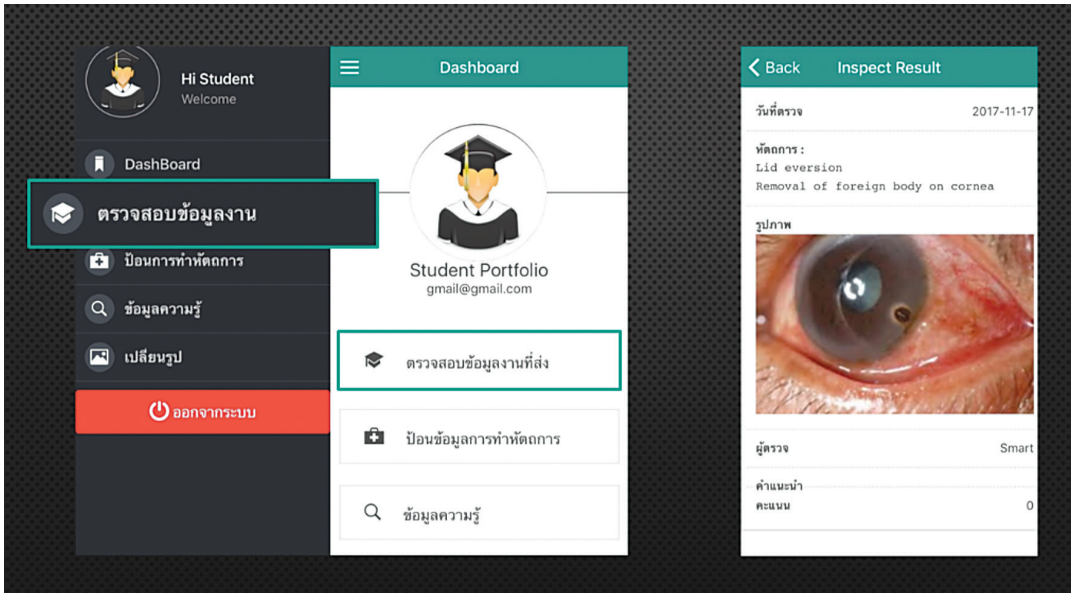
**Material and methods**

The Smart Mobile Application was designed in accordance with a competent management pattern. The skills that medical students are required to attain are collected and then demonstrate what they have learned from the following sources (A) Official program of medical student (B) Medical Competency Assessment Criteria for National License (C) the logbook of Thammasat eye center for medical students.

The participants in this study are 5 attending ophthalmologists; 3 at Thammasat University, 1 ophthalmologist at Chulalongkorn University and 1 ophthalmologist at Chumphon hospital. There are 110 medical students in these hospitals that attended in ophthalmology clinics. On the first day both ophthalmologists and students received handouts about how to download,register and use the application (picture 1-3). The application is available on both IOS and android phones. After they register and log into the application, students can view the menu that is divided into 3 categories: general ophthalmology knowledge for medical students, surgical skills that should be performed and status checked. In general knowledge, there is an Ophthalmology E-book for medical students. In surgical skills, medical students need to fill in the form and take a photo of what kind of surgery they have done and submit them to the attending ophthalmologists. After they submit the documents there will be an email alert to those attending ophthalmologists. In Status checked, a student can compare what they have learned with their colleagues. At the end of the rotation, students are required to fill in an evaluation-form (table1) and send it back to the department of ophthalmology of each institute.

**Results**

All of the students completed their questionnaires and sent them back to the department of ophthalmology of each institute. The majority of the students and attending ophthalmologists strongly agreed that the essential skills the students need to learn are listed in the mobile application (54%), the medical skills listed are actually




**Picture 1:** Features inside smart mobile application portfolios

**Picture 2 and 3:** Students at Thammasat university hospital learn to use the application on the first day of their rotations.

**Table 1:** Application Evaluation Questionnaire

**แบบประเมินการใช้ Application : Smart Mobile Application Based Portfolio**

**คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์**

ชื่อ-นามสกุล_____วันที่_____

| | ไม่เห็นด้วย>>เห็นด้วยอย่างยิ่งมาก | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1.ทักษะที่ได้รับการฝึกฝนมีความสอดคล้องตรงตามหลักสูตรการเรียนการสอน | | | | |
| 2.ทักษะต่างๆได้รับการฝึกฝนในสถานการณ์จริง | | | | |
| 3.ข้อเสนอแนะที่ได้รับจากอาจารย์ช่วยให้นักศึกษาแพทย์สามารถพัฒนาตนเองได้ | | | | |
| 4.แอพพลิเคชั่นมีความยืดหยุ่นและสามารถปรับตามความต้องการของนักศึกษาได้ | | | | |
| 5.แอพพลิเคชั่นใช้งานได้ง่าย ไม่ซับซ้อน | | | | |
| 6.นักศึกษามีแรงจูงใจในการใช้แอพพลิเคชั่น และเลือกใช้งานแอพพลิเคชั่นเป็นประจำ | | | | |
| 7. แอพพลิเคชั่นสามารถประเมินและสรุปผลการเรียนรู้ให้แก่นักศึกษาและอาจารย์ได้ | | | | |
| 8.คำแนะนำและขั้นตอนในการทำหัตถการที่จัดเตรียมให้นักศึกษาในแอพพลิเคชั่น ช่วยนักศึกษาในการเรียนรู้ได้ดี เข้าใจง่าย | | | | |
| 9.การกดใช้งานหน้าจอของแอพพลิเคชั่น touchscreen ใช้ได้ดี ไม่ติดขัด | | | | |

**ข้อเสนอแนะ**

.....

.....

.....

**Application-user evaluation form of ' Smart Mobile Application Based Portfolio '**

Name-Surname .....
Date of assessment .....

| | Disagree >> Agree | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1. The medical skills that is required are listed and were actually trained | | | | |
| 2. The medical skills that you trained is also in the clinical practice | | | | |
| 3. An attending-ophthalmologist advice is helpful for clinical skills development | | | | |
| 4. The application is flexible for user-assessment and evaluation | | | | |
| 5. The application is not too complicated to assess | | | | |
| 6. You thick that ' Smart Mobile Application based portfolio ' is feasible and convenient for assessment | | | | |
| 7. The application will report exactly result of the medical skills that were trained | | | | |
| 8. The medical skills that performed in the application is helpful for clinical-performance learning | | | | |
| 9. The touch-screen application is user-friendly | | | | |

**Recommendation**.....

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trained (59%), the attending doctor's advice is helpful for personal development (62%), the application is easy to use (60%), attending doctors and students can record what they have learned (47%), the application touchscreen is easy to use (58%). Most of the students and attending ophthalmologists somewhat agree that the application is flexible for the students (40%), the students and attending doctors will use the application regularly (43%), the medical skills guide and recommendation are useful in practice (42%).

**Discussion**

Qualitative methodology from data analysis was considered an appropriate tool for evaluation and convenient for assessment.[7] A limitation of this study was its relatively small sample size. The portfolio itself also had the limitation that it focused mainly on reflective competence and did not include general clinical knowledge competency.[8] However, using this smart mobile portfolio application, students can integrate specific knowledge, skills, and progress to meet curriculum objectives.

Disadvantages of electronic portfolios include the need for internet access and IT literacy among medical staff and students.[9] Although everyone involved in this study met those requirements, some students may not, in which case they would be unable to use the electronic portfolio. Nevertheless, this pilot study was successful; participants were generally enthusiastic about the new learning and assessment method.

**Conclusion**

Smart Mobile application based portfolios seem to be feasible and convenient for assessment. However, the application still needs further development to meet the users' expectations.

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