CASE REPORT

Case Series of Two Patients with Primary Malignant Melanoma of the Lacrimal Sac

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ABSTRACT

Background: To demonstrate two rare case of primary malignant melanoma of lacrimal sac.
Case Illustration: Patients were both female, 38-year-old and 46-year-old, with lacrimal sac mass, bloody discharge and epiphora. The first patient was previously diagnosed with chronic dacryocystitis and treated with antibiotics and anti-inflammation for two months which resulted in worsen condition and enlarged swelling. Computed tomography scan revealed solid mass at lacrimal sac 13 x 12 x 7.4 millimeters in size with no bone destruction. Patient underwent total mass removal surgery, which revealed solid highly pigmented mass. The second patient also had enlarged mass within two months. Other complaints include obstructed left nose and epistaxis. Computed tomography scan revealed solid mass at left medial canthal region involving inferior orbit, nasolacrimal duct, left nose cavity, and maxillary sinus. Incisional biopsy revealed a malignant melanoma. Patient underwent eye exenteration, maxilectomy, and radical neck dissection.
Conclusion: Primary malignant melanoma of the lacrimal sac is a rare case and often mimics chronic dacryocystitis. It's imporant to understand this disease entity to make accurate diagnosis and management with the help of imaging modality.

Lacrimal sac melanoma is a non-epithelial primary neoplasm of lacrimal sac. Malignancy of the lacrimal sac is rare and mostly of epithelial origin. However, on rare cases lacrimal sac tumors could originate from non-epithelial cells, such as lipoma, hemangiopericitoma, neurofibroma, or melanoma.[1]

Muravleskin in Russia first diagnosed one case of lacrimal sac melanoma in 1926.[2,3] Since 1964 until 2014, approximately 25-30 reports of lacrimal sac melanoma have been published.[4] The largest cumulative series of primary neoplasms of lacrimal sac was published by Flanagan and Stokes in 1978. They reported 212 cases of lacrimal sac neoplasm, in which 128 of 212 cases (60%) were malignant. Malignant melanoma accounted for only eight cases (4%) of all malignancies.[2,3] Of 117 lacrimal sac tumors found in file by Pe'er et al over a 24-year period from 1970 until 1994, eight cases (6%) were malignant melanoma.[6] Thus, malignant melanoma of the lacrimal sac is a rare case.

The histogenesis of malignant melanoma of the lacrimal sac remains obscure.

Melanocytes are not usually found in lacrimal tissue but are seen in adjacent conjunctiva. It is presumed that melanocytes are either laid down beneath the lacrimal sac epithelium during ectodermal down growth or migrates from the embryonic conjunctival sac into the lacrimal apparatus.[1,6]

Lacrimal sac melanoma has an insidious onset. The average age of diagnosis of reported cases was at 58 years, with a range of 38 to 80 years, and the male-female ratio was 1:1.3.[6] It is usually present with signs and symptoms similar to chronic dacryocystitis.[5,6] Typically, patients have the clinical triad of epiphora, blood-stained reflux from the lacrimal punctum, and a mass in the region of the medial canthus. Because of the similarity of signs and symptoms to chronic dacryocystitis, lacrimal sac melanoma is usually late diagnosed, after excision or biopsy of the tumors. The majority of survivors have had an early diagnosis, which appears to be the most important prognostic factor.[5] Therefore, it is important to make diagnosis as early as possible.

Current management of lacrimal sac melanoma consists of surgical excision, chemo-therapy, radiation therapy, and immunotherapy in various combinations.[6] In general, melanomas in mucosal tissues are far more aggressive and lethal than other cutaneous lesions.[7]

This paper describes two rare cases of malignant melanoma of the lacrimal sac, including the diagnosis and management of each cases. The aim of this report is to demonstrate clinical presentations of lacrimal sac melanoma and its management considerations to prevent misdiagnosis.

CASE ILLUSTRATION

The First Case

A 37-year-old female came to Plastic and Reconstructive Division of Cipto Mangun-kusumo Hospital with chief complaint of swelling and redness on her right eyelid since eight months before admission. The swelling had slowly enlarged within the past eight months. There was history of clear discharge with no blurred vision. She had no history of any trauma, no swelling in other regions or any other systemic abnormalities. No other family members had reported history of ocular malignancies or any othe tumors.

Upon the ophthalmological examination, there was a firm palpable mass on the medial canthus region of her right eye with the size of 1 x 0.5 x 0.2 cm. Eye movement was good to all directions. Anel test revealed negative result with purulent regurgitation. No abnormality was found in the left eye.

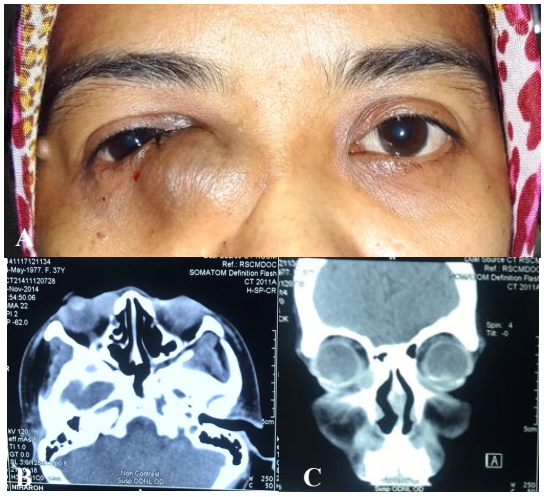

Fig 1. Mass at medial canthal region showed in clinical appearance (A) and from computed tomography scan (B & C).

Computed tomography scan showed an extraconal isohypodens lesion, suspicious of mass at the right medial canthal region, involving the right lacrimal sac and cutis subcutis. The mass was 1.3 x 1.2 x 0.74 cm in dimension. There was haziness at the right lacrimal duct suspicious of dacriocystitis. No sign of bone destruction and there were no abnormal findings on the left eye.

Patient was diagnosed with naso-lacrimal duct obstruction with differential diagnosis of lacrimal sac mass and treated with oral antibiotics and anti-inflammation for about two months without any improvement. She was planned to undergo dacryocysto-rhinostomy or mass removal of the right eye in general anesthesia but unfortunately she was lost to follow up for about a year.

One year later, patient came with complaint of worsen swelling on the right eye and bloody discharge. There were no complaints of pain or blurred vision. Ophthalmological examination revealed a palpable non-tender mass in the medial canthus region of the right eye, with the size of 3 x 3.5 x 2 centimeters. The mass was hyperemic, immobile, and smooth surface.

Computed tomography scan revealed a hypodensity lesion at medial canthal region, 3 x 3.2 x 2 centimeters in dimension. There were no bone destruction and no abnormality found on the left eye.

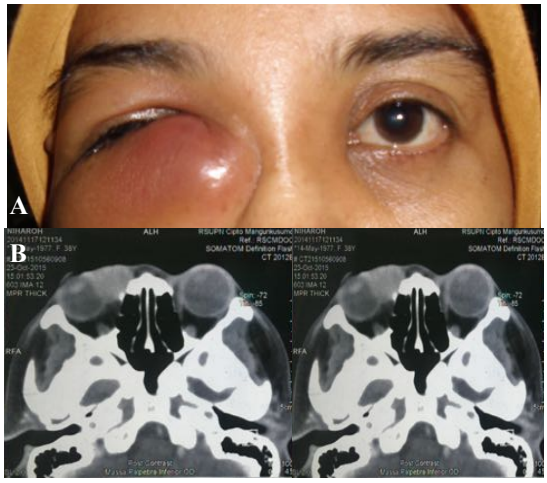

Fig 2. Worsen hyperemic swelling of the right medial canthal region (A) confirmed with CT scan (B).

Patient was diagnosed with lacrimal sac abscess and preseptal cellulitis of the right eye with lacrimal sac mass as differential diagnosis. She was consulted to Infection and Immunology Division and treated with oral antibiotics, anti-inflammation, and eye ointment. Two weeks after treatment, the swelling reduced and patient was then consulted to Oncology Division of Cipto Mangunkusumo Hospital and planned to undergo join surgery of dacryocystorhinostomy or mass removal, depending on intraoperative findings.

One year after admission, patient finally underwent total mass removal under general anesthesia. There was a solid, blackish appearance, pigmented mass with 1.5 x 0.8 x 0.8 centimeters in size found intraoperative. After the surgery, patient received antibiotic eye ointment, oral analgetic and antibiotic.

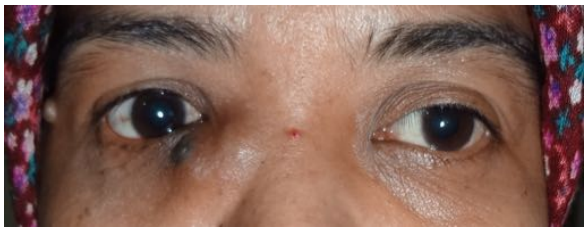

Fig 3. Pre-operative picture

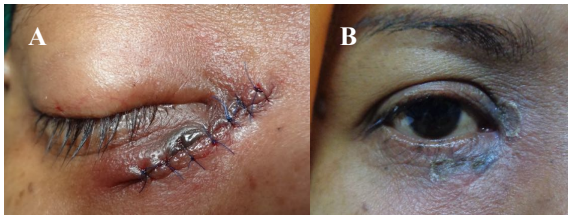

Fig 4. Eyelid condition one day post-surgery (A) and three months post-surgery showed scar tissue at medial canthal region (B).

Histological result revealed malignant melanoma of the lacrimal sac. It was an unexpected result since melanocyte is an unusual founding on the lacrimal sac. Although the mass was totally removed during surgery, frozen section was not planned beforehand. Therefore, patient was consulted to radiotherapy for local control of the tumor. Bone survey and abdominal ultrasonography revealed no abnormality.

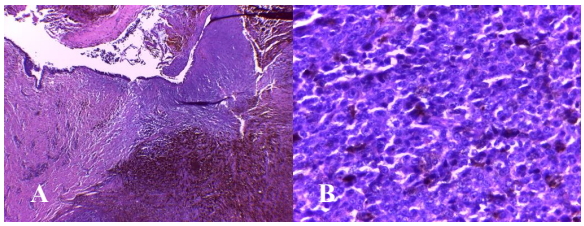

Fig 5. Tumor cells with enlarged nucleoli and pigmented cytoplasm with hematoxylin-eosin staining, magnified 4x (A) and 40x (B)

Three months after the surgery, patient came to Oncology Division with no complaints of the eye. There were no pain, watery eye, discharge, nor swelling on her right eye. There were minimal scar tissues at medial canthal region. Patient already underwent 20 times of radiation with hair loss as her only complaint. Six months after the surgery, patient had no complaints involving the eye. Ophthalmological examination showed scar tissue at the medial canthal region and no other abnormality.

The Second Case

A 46-year-old female came to Oncology Division of Cipto Mangunkusumo Hospital with chief complaint of swelling and redness on her left eye. Swelling started one year prior and had worsen since one month. She also had complaints of watery eye and bloody discharge. She had no complaints of epitaxis but felt obstructed sensation on her left nose. There was history of tumor resection surgery 7 months prior at the previous hospital, but the swelling reoccured. No information was found about the tumor resection pathological findings.

Ophthalmological findings showed an immobile palpable mass at the medial canthal region, 2.5 x 2.5 cm in dimension with smooth surface and distinct edge. Eye movement was good to all directions. Best-corrected visual acuity was 6/6 for both eyes. She had no other swelling or lumps in other parts of her body.

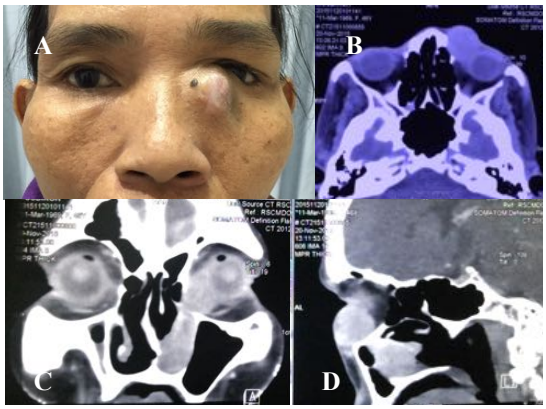

Fig 6. Mass on the left medial canthal region; clinical appearance (A) and CT scan results (B, C, D)

Computed tomography scan showed solid mass on the medial canthal region and inferomedial part of the orbita, involving inferior palpebral, nasolacrimal duct, and left nose cavity. Patient was assessed with lacrimal sac tumor of the left eye and planned for incisional biopsy under local anesthesia.

One month after admission, patient underwent incisional biopsy of the lacrimal sac mass. Intraoperative, the mass was heavily pigmented and suspected as malignant melanoma.

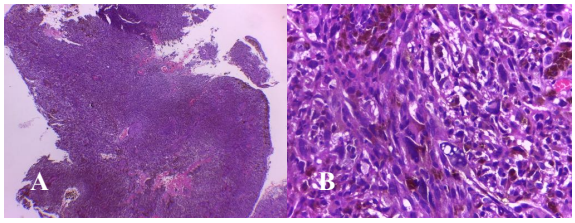

Fig 7. Tumor cells with enlarged nucleoli and pigmented cytoplasm with hematoxylin-eosin staining, magnified 4x (A) and 40x (B).

Pathological findings revealed malignant melanoma of the lacrimal sac, involving periorbital tissues. There were no infiltration to intraocular nor optical nerve. Bone survey, chest x-ray, and abdominal ultrasonography showed no distant metastatic lesion.

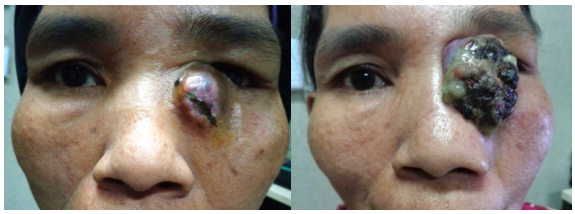

Fig 8. Mass at medial canthal region, two months (A) and three months after initial assessment, with enlarged mass and hyperpigmentation

Three months after initial assessment, patient came to the clinic with enlarged swelling. There were enlarged palpable mass with pus and hyperpigmentation on its surface. There were restricted movements of the left eye to the temporal side. Patient was consulted to ENT Department with lacrimal sac melanoma involving the nasal cavity and a meeting was held. The conclusion of the meeting was to plan for left eye exenteration, wide mass excision, maxilectomy, and supraomohyoid neck dissection join surgery with ENT Department.

Six months after her initial assessment, patient underwent left eye exenteration, wide excision, maxilectomy, and supraomohyoid neck dissection under general anesthesia. After the surgery, she received analgetic and antibiotic.

One month after the surgery, patient came to the clinic with no complaints. There were minimal discharges on the left orbita with no active bleeding. Patient was educated on how to change her bandages daily and

planned for bone survey, chest x-ray and abdominal ultrasonography 6 months after surgery. Two months follow up post-surgery showed stable condition.

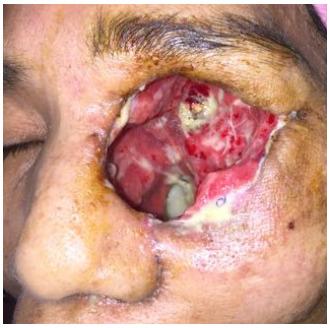

Fig 9. Exenterated left eye, two weeks post-surgery

DISCUSSION

The lacrimal system is a rare site for primary malignant melanoma. This disease entity is often misdiagnosed or late diagnosed due to its similarity in signs and symptoms to chronic dacryocystitis and its rarity, which leads to low suspiciousness of practitioners.[7] It is potentially life threatening because one of the prognostic factors is timing of diagnosis. Therefore, it is important to make the right diagnosis as early as possible.

In the largest cumulative series published by Flanagan and Stokes in 1978, only 4% of 212 lacrimal sac tumors were malignant melanoma. None of them was metastatic and a metastatic tumor to the lacrimal sac is also rare. It has insidious onset and, in contrast with cutaneous melanoma, are more common in darker-skinned individuals.[8,9] Multiple risk factors include family history of melanoma, presence of dysplastic moles or nevi, other sites with cutaneous melanoma, and an older age. Previous reports show age range at diagnosis is 38 to 80 years old, average at 58 years old and slight female predominance.[2,4,10] Both of our patients are female at the age of 37 and 48 years old when they first came for treatment. They both had no family history of melanoma.

From previous studies, 65% patients with lacrimal sac melanoma came with complaints of epiphora and 35% of blood-stained reflux from the lacrimal punctum. Along with swelling of the lacrimal sac area, these three signs became the triad for lacrimal sac melanoma. Bloody tears are caused by the tendency of lesion to erode the epithelium lining and filling the lumen of the lacrimal sac, rather than being confined to the sac wall. Pain is relatively uncommon, but has also been reported in some patients, which is the result of swelling within the lacrimal compartment that causes pressure on the fascial envelope.[3,11,12] These findings were present in our patients, who had complaints of swelling of medial canthal region. Both of them also had complaints of bloody discharge and epiphora.

Although similar, there are differences between swelling in dacryocystitis and lacrimal sac tumors. Swelling in dacrocystitis is usually limited to the inferior area to the medial canthal tendon, whereas a lacrimal sac tumor often involves the area both below and above the tendon.[7] The mass usually expanded below the palpebral ligament and appeared between 6 to 13 months after initial symptoms. In our first patient, it took eight months for the patient to realize the swelling had not subsided and for her to seek medication, while our second patient came after one year of initial complaints.

Radiological examinations are needed to evaluate the extension of lacrimal sac melanoma. Dacryocystography could only reveal filling defect or obstruction, so it's essential to perform other ancillary examination. Computed tomography (CT) scan of the orbita and paranasal sinus is imperative where tumor is suspected and will provide evidence of expansion or erosion of the lacrimal sac fossa, or invasion into neighboring structures.[9,14] It is the best examination to confirm the widening of lacrimal sac occupied by a solid lesion. In every patient suspected with lacrimal sac tumor, CT scan is mandatory to evaluate the invasiveness of the mass, thus providing information for therapy considerations.

Recently, magnetic resonance imaging (MRI) has been used to identify characteristic

of lacrimal sac melanoma. Unlike most other neoplasms, MRI results in lacrimal sac melanoma may display high-signal intensity due to the paramagnetic properties of well-melanized melanin granules.[8,10] Malignant melanoma appears hyperintense on T1 weighted imaging and hypointense on T2 weighted imaging. However, high signal intensity on T1 is not specific for malignant melanoma. Subacute haemorrhage and other tumors with tendency to bleed could have the same MRI result.[13]

CT scan in our first patient revealed solid mass at the lacrimal sac, with no bone erosion and no extension to other structures. Our second patient showed much larger solid mass occupying the lacrimal sac with extension to the nasal cavity, hence the difference of treatments for both patients. Imaging is useful to show local extent of disease, but it is not to be used as a way to confirm the diagnosis of melanoma. The definitive diagnosis for lacrimal sac melanoma is made with histopathological examination.[13-15]

Histopathologic examination of lacrimal sac melanoma uses special training, which are Fontana-Mason and Whartin-Starry. In general, the staining patterns of lacrimal sac melanoma are similar to those found in cutaneous melanoma. Because of the unusual location in the lacrimal sac, the melanoma can be histologically mistaken for a poorly differentiated carcinoma.[11,17] Therefore, additional pathological evaluation is needed to make a diagnosis of malignant melanoma such as electron microscopy or immuno-histochemistry. Melanomas show an intense positive immunoreactivity with S-100 protein and and HMB-45, appearing as intracyto-plasmic brown granularity with both anti-bodies. On electron microscopy, melanosomes or premelanosomes appear as membrane-limited vesicles.[11,12,16]

Melanocytes, a mature melanin-forming cells, are derived from the neural crest and will insinuate themselves into various surface epithelium or nonepithelial connective tissue sites, such as dermis of the skin, substansia propria of the conjunctiva and the uvea. Facial morphogenesis is responsible for melanocytes populations in the lacrinal drainage system.[8,18] Development of lacrimal sac and canaliculi started in a 7-week-old embryo as an embryonic cleft forms between the lateral nasal and maxillary processes. An ectoderm fold evaginates as a solid cord of cells into the underlying mesenchyme. This chord of cells extends towards the pre-sumptive eyelid to produce the canaliculi and down to the lower nasal space as the nasolacrimal duct.[7,8] Central canalization occurs and forms the lacrimal sac. Most of the lacrimal sacs are lined by a ciliated pseudostratified columnar epithelium.[8,14,19]

Therefore, the lacrimal sac has the same embryological origin as the conjunctiva, so it is suspected that the melanocytes found on lacrimal sac are migrated from the neural crest during embryological downgrowth.

There are three know pathways that contribute to melanocytes acquisition within the lacrimal sac epithelium. The first mechanism, neural crest-derived melanocytes migrated directly to the lacrimal sac epithelium and remained there. This is the most attractive and only mechanism as long as the drainage anlagen remain isolated due to imperforate foramina. Second, melanocytes from intraepithelial conjunctiva migrated through the punctum and canaliculi to reach the lacrimal sac. Third, intranasal epithelial melanocytes migrated up the nasolacrimal duct to reach the lacrimal sac after the valve of Hassner became patent.[8,14,20]

The ability of normal or non-atypical melanocytes to reach higher epithelial levels than in the conjunctiva is caused by the distinctive microanatomic differences between the intercellular spaces of a multi-laminar squamous epithelium in conjunctiva and the pseudostratified, single layer lacrimal sac epithelium. Lacrimal sac epithelium allows easier movement of melanocytes from a basal location to higher levels. As the lacrimal sac is a chronically inflamed specimens, it is suggestive that inflammation could cause hyperplasia of melanocytes.[8,14] An early detection of atypical melanocytes within the lacrimal sac epithelium through microscopic

evaluation of any excised portion of the sac wall during dacryocystorhinostomy should lead to the urgent treatment of suspicious lesions. This approach could improve survival in more cases if it leads to early detection of lacrimal sac melanoma.

Theoretically, either intraepithelial or subepithelial melanocytes could be the sources of lacrimal sac tumors. In darkly complexioned individuals, the subepithelial melanocytes, which look spindled but in three dimensions are actually multiplar, do not transfer melanin to other cells, which are called continent melanocytes.[8,9] They are located in the dense connective tissues deep in lamina propria. These deep melanocytes are generally considered to be postmitotic and inert, hardly ever transforming into a melanoma. On the other hand, stromal melanocytes, which are fusiform or multi-polar, are located in the deeper layer of connective tissue.[8]

Due to its rarity and follow-up studies, there isn't any clear consensus regarding treatment of lacrimal sac melanoma. Therapy often requires multidisciplinary approach due to its aggressiveness. Current treatment usually consist of surgery and radiotherapy.[7,11] The goal of surgery is complete resection with clear margins. Some authors suggest resection should include wide-field en-bloc excision. In a localized tumor, a complete excision including its surrounding tissues must be performed. Local radiation therapy and immunotherapy could be added if the tumor is not completely resected.[9,11,15] If local recurrence occurs, surgery should be repeated and supplemented with radiation.[21,22]

With technological advancement in head and neck high-technique radiotherapy, optically guided intensity modulated radio-therapy or carbon ion radiotherapy has been used to treat lacrimal sac melanoma, although wide excision is still the standard treat-ment.[10,19] Carbon-ion radiotherapy has the advantages of favorable dose localization and is considered more effective against locally advanced or pathologically radiotherapy resistant tumors at an acceptable level of morbidity compared with other external beams, megavoltage photons or electrons.[10] Recent studies show that the majority of melanomas are as radiosensitive as many other solid tumors. Post-operative radio-therapy has been shown to improve local tumor control while chemotherapy and immunotherapy are useful only for palliation.[23,24]

Of all the reported cases since 1926, tumor resection surgery is the most common primary treatment. Three patients underwent dacryocystectomy as a sole treatment and in all three of them, recurrence were reported. Two authors had combined dacryocystectomy with radiation and chemotherapy, and also found recurrence in both patients.[11,15,24] Therefore, between dacryocystectomy and tumor resection surgery, most author prefer the latter. Radiation is also preferred as an adjuvant after surgery if complete resection could not be ensured.

Our first patient received mass excision and post-operative radiation. The first patient was given post-operative radiotherapy for local control. After six months of observation, there were no recurrence and no distant metastatic lesion. Our second patient received eye exenteratuon and radical neck dissection. After two months of observation, the condition also remained stable and patient continued to be observed.

Based on a review of patients with head and neck mucosal melanoma, metastatic work-up should include chest radiograph, ultrasound and thorough examination of chest, abdomen, and pelvis. Its location provides multiple possibilities for haemato-genic and lymphatic spread of the tumor, which is another factor of low cure rate. Reported cases showed 35% (6/22 patients) developed metastasis more than six months after treatment.[10-12] It is mandatory to perform metastatic work-up as early as possible in patients with lacrimal sac melanoma, due to its tendency to spread.

In general, melanomas in mucosal tissues are far more aggressive and lethal than cutaneous lesions. Lacrimal sac melanoma has poor prognosis even with aggressive treatment.[11] In common with other head and neck mucosal melanomas, by the time a

lacrimal sac melanoma has developed, the prognosis is only 20-30% of 5-year survival rate. The average survival for other mucosal melanoma receiving local excision is about 18 months, with major factor regarding treatment failure is local recurrence of mucosal melanoma.[7] This poor prognosis have various factors.

The majority of lacrimal sac melanomas are fatal because they are concealed by their deep location and their similarity as an inflammation thus discovered late in their course, which leads to poorer prognosis in comparison with externally visible cutaneous melanomas. Other prognostic factors include the impossibility of achieving safe surgical margins at excision because of its close proximity to important structures. Other study suggests another factor, which is reduced host reaction, as seen by the lack of peripheral lymphoid reaction around the tumor during histological examination. Tumor cells were also possible of disseminating during operation. Lacrimal sac also has a complicated vascularization and lymphatic drainage that provides multiple possibilities for hematogenic and lymphatic spread of the tumor.[12,21,25] These are the probable reasons of poor prognosis in lacrimal sac melanoma. Due to these reason, it is important to make early diagnosis, give aggressive treatment and perform thorough metastatic work-up in patients with lacrimal sac melanoma.

CONCLUSION

This paper shows two case series of 37-year-old and 69-year-old female with malignant melanoma of the lacrimal sac. The first patient was first diagnosed with chronic dacryocistitis and was treated for infection. She later underwent total mass removal and post-operative radiotherapy, while the second patient underwent incisional biopsy continued with eye exenteration and radical neck dissection. The definite diagnosis in both patients were made based on histopathological findings.

One of the major factors regarding prognosis of this disease entity is the timing of diagnosis. Early diagnosis is often difficult to make because of the similarity of signs and symptoms to chronic dacryocystitis. It is important to be suspicious of lacrimal sac melanoma in patients with clinical triad of epiphora, bloody-discharge, and swelling of the medial canthal region. There is currently no clear consensus regarding treatment for lacrimal sac melanoma, although most authors suggested tumor resection combined with radiotherapy and tight follow-up due to its poor prognosis and possibility of re-currence.

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