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Multiple endocrine neoplasia type 2B

A 27-year-old male presents with multiple eyelid lesions

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Chief complaint

Multiple eyelid lesions

History of Present Illness

A 27-year-old male with a history of multiple endocrine neoplasia type 2B (MEN2B) was referred to the University of Iowa oculoplastic surgery clinic by his oncologist for a large lesion on the outer corner of his right eye. He reported that the lesion had been present for 6 months and stable in size for the 2 months prior to presentation. The patient's eyes were comfortable and he denied any tenderness, swelling, discharge, itchiness, dryness, or watering. He was seen by an outside ophthalmologist who was unable to provide a diagnosis, but offered to "cut it off".

Past Ocular History

None

Medical History

- Multiple endocrine neoplasia type 2B (diagnosed at age 12) with the following features:

- Metastatic medullary thyroid carcinoma status-post (s/p) thyroidectomy and parathyroidectomy at age 12
- Pheochromocytoma of right adrenal gland s/p right adrenalectomy at age 22
- History of tethered spinal cord s/p repair as a teenager
- Neurogenic bladder

Medications

- Levothyroxine
- Oxybutynin

Allergies

- No medication allergies

Family history

- No known history of MEN2B
- Unspecified cancer in maternal grandmother

Social history

- Non-contributory

Review of Systems

- Negative except for what is detailed in the history of present illness

OCULAR EXAM

Visual Acuity without correction

- Right eye (OD): 20/20-1
- Left eye (OS): 20/20-1

Ocular Motility

- Full both eyes (OU)

Intraocular Pressure (IOP)

- OD: 17 mmHg
- OS: 18 mmHg

Pupils

- OD: 4 mm in dark, 3 mm light, no relative afferent pupillary defect (RAPD)
- OS: 4 mm in dark, 3 mm light, no RAPD

Confrontation visual fields

- Full OU

External

- Full appearing lips with thickened mucosa [Figure 1]



(../cases-i/case230/fig1-LRG.png)

Figure 1 – Full appearing lips with thickened mucosa



(../cases-i/case230/fig2A-LRG.png)



(../cases-i/case230/fig2B-LRG.png)

Figure 2 – A) Large, erythematous upper eyelid lesion on the lateral canthus of the right eye with a smaller upper eyelid margin lesion medial to the larger lesion. Fullness of both upper eyelids with a yellow lower eyelid lesion near the puncta with scalloping of the medial lower eyelid on the left. B) Magnified view of right upper eyelid lesion

Slit lamp exam

- Lids/lashes
 - OD: Large, erythematous upper eyelid lesion on the lateral canthus with a smaller upper eyelid margin lesion medial to the larger lesion. Meibomian gland dysfunction (MGD) and fullness to upper lid margin. [Figure 2]
 - OS: Yellow lower eyelid lesion near the puncta with scalloping of the medial lower eyelid margin. MGD and fullness to upper lid margin.
- Conjunctiva/sclera: Clear and quiet OU
- Cornea: Clear, prominent corneal nerves OU
- Anterior chamber: Deep and quiet OU
- Iris
 - OD: Normal architecture with nevus
 - OS: Normal architecture
- Lens: Clear

Dilated fundus examination (DFE)

- Vitreous: Clear OU
- Disc: Normal OU
- Cup-to-disc ratio: 0.1 OU
- Macula: Normal OU
- Vessels: Normal OU
- Periphery: Normal OU

Differential Diagnosis

- Palisaded encapsulated neuroma of the skin (PEN)
- Neuroma secondary to MEN2B
- Chalazion ([193-chalazion.htm](#))
- Sebaceous cell carcinoma ([62-Sebaceous-Cell-Carcinoma-Eyelid-Masquerade-Syndrome.htm](#))
- Epidermal cyst
- Traumatic neuroma

CLINICAL COURSE

The patient underwent incisional biopsies of the right upper and left lower eyelid lesions. ([excisional biopsy video \(../video/plastics/3/8-lid-margin-biopsy.htm\)](#)) The conjunctiva demonstrated papillary hyperplasia with a dense infiltrate of neutrophils on the surface and scattered neutrophils throughout the conjunctival epithelium. The underlying stroma demonstrated a circumscribed area consisting of bundles of spindle cells with fibrillary extracellular matrix and wavy slender nuclei. Cells stained positive on immunohistochemistry for S100. The diagnosis was neuroma with acute inflammation of the surrounding tissue. After a 6-month follow-up and no recurrence, he was discharged from the oculoplastics clinic. He continues close, regular follow-up with both his endocrinologist and hematologist/oncologist.

DIAGNOSIS

Conjunctival neuromas in the context of known MEN2B.

DISCUSSION

Etiology/epidemiology

Multiple endocrine neoplasia (MEN) is an autosomal dominant syndrome that results in the predisposition to tumor formation in two or more endocrine glands. MEN is further classified into MEN1 (OMIM 131100), MEN2A (171400), or MEN2B (162300) based on the mutation and the type of endocrine gland tumors that the patient develops [1].

Table 1: Characteristics and mutations of MEN variations [1]

	Tumors	Mutation
MEN1	Parathyroid glands, endocrine pancreas and duodenum, anterior pituitary, adrenal, thyroid; carcinoid tumors; lipomas and facial angiofibromas	<i>MEN1</i> gene on 11q13
MEN2A	Medullary thyroid cancers, pheochromocytomas, Hirschsprung disease	<i>RET</i> gene on 10q11
MEN2B	Medullary thyroid cancers, pheochromocytomas, Marfan-like habitus, mucosal neuromas, intestinal ganglioneuroma, delayed puberty	<i>RET</i> gene on 10q11

MEN2B remains a relatively rare condition with a prevalence of $\sim 0.2 \times 10^{-5}$ and an estimated annual incidence of 4 per 100 million per year [2].

Pathophysiology

MEN2B is secondary to a germline mutation in the *RET* proto-oncogene on chromosome 10q11. The most common mutation (95%) is M918T in exon 16 and second most common mutation (2-3%) is A883F in exon 15 [3]. The *RET* gene codes for the protein RET, which is a tyrosine kinase receptor that is important for activating signaling pathways. A gain of function mutation in the RET protein leads to constitutive action of the receptor and subsequent unregulated growth resulting in the predisposition to tumor formation [4].

Mutations in the *RET* gene are also associated with MEN2A, Hirschsprung disease (HSCR; 142623), and medullary thyroid carcinoma (MTC; 155240) [4].

Signs/symptoms

Typically, the first clinical signs of MEN2B are gastrointestinal symptoms (most commonly constipation), mucosal neuromas, and marfanoid habitus [5]. It is important to identify these patients as early as possible because they have a high likelihood (80-100%) of the development of early, aggressive medullary thyroid carcinoma (MTC). Additional signs of MEN2B include pheochromocytomas, often bilateral, and thickened corneal nerves. Characteristic physical features include full lips (**see figure 1**), thickened eyelids, and high-arched palate[3]. The thickening of the lips and eyelids are secondary to the mucosal neuromas.

Ocular findings

Ocular findings include thickened corneal nerves, small plexiform and nodular subconjunctival tumors (neuromas), keratitis sicca, and thickened upper and lower lids (also related to neuromas) [6-10]. As noted above, early diagnosis is critical for these patients. Thickened corneal nerves are seen in a number of conditions

including keratoconus, Noonan syndrome, multiple myeloma, leprosy, and lipoid proteinosis [11-15]. (see related atlas entry (<http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Enlarged-corneal-nerves/index.htm>))

Testing/lab work up

Any patient with clinical signs and symptoms of MEN2B should undergo molecular genetic testing of the *RET* gene. Additionally, any individual diagnosed with MTC should be offered testing. Genetic testing should first screen exons 16 and 15 for M918T and A883F mutations. If negative, the point mutation V804M in exon 14 should be screened followed by sequencing of the entire *RET* gene [4].

Before prophylactic thyroidectomy is performed, baseline calcitonin (CT) and carcinoembryonic antigen (CEA) should be measured. These are biochemical markers of MTC and are useful for follow-up after surgery [5].

If signs of pheochromocytoma are present, urinary catecholamines and catecholamine metabolites (epinephrine, norepinephrine, metanephrine, and vanillylmandelic acid) should be measured in addition to an abdominal MRI or CT [4].

Management

From an ophthalmic perspective, if there is any doubt about the clinical diagnosis of a neuroma, excisional biopsy should be performed. Although bilaterally is more likely indicative of a systemic disease, other etiologies such as basal cell carcinoma should be ruled out. Additionally, excision may be indicated if the patient is experiencing symptomatic irritation from a lesion.

In the case that a neuroma is diagnosed on biopsy and the patient does not have a known MEN2B diagnosis, they will need a referral for systemic work-up. Ultimately the patient will need prophylactic thyroidectomy [3] as medullary thyroid carcinoma is the major cause of mortality [4]. Patients should then have annual CT scans and carcinoembryonic antigen (CEA) levels to screen for MTC relapse [5]. They need regular follow-up with a primary care provider, endocrinologist, and hematologist/oncologist. Prognosis for the patient is good with early diagnosis and surgical intervention [4].

<p>Epidemiology</p> <ul style="list-style-type: none"> • Prevalence $\sim 0.2 \times 10^{-5}$ • Annual incidence of 4 per 100 million per year 	<p>Signs</p> <ul style="list-style-type: none"> • Mucosal neuromas – including eyelid • Marfanoid habitus • Medullary thyroid carcinoma (MTC) • Pheochromocytomas • Thickened corneal nerves
<p>Genetics</p> <ul style="list-style-type: none"> • <i>RET</i> proto-oncogene on chromosome 10q11 <ul style="list-style-type: none"> ◦ First screen exons 16 and 15 for M918T and A883F mutations ◦ If negative screen for the point mutation V804M in exon 14 	<p>Management</p> <ul style="list-style-type: none"> • Excisional biopsy for diagnosis of neuroma • Prophylactic thyroidectomy • CT scan and carcinoembryonic antigen (CEA) measured yearly • Urinary metanephrines measured if signs of pheochromocytoma present

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- Excisional biopsy video ([../video/plastics/3/8-lid-margin-biopsy.htm](http://www.eyeforall.com/video/plastics/3/8-lid-margin-biopsy.htm))

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