

## Grand Rounds

# A 10-year-old girl with multiple eyelid neuroproliferative tumors

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## History

A 10-year-old girl with a known diagnosis of MEN2B and a history of medullary thyroid cancer (MTC) presented at Children's National Hospital ophthalmology clinic with recurrent eyelid lesions. She had a history of hypothyroidism, mild hypocalcemia, and café-au-lait spots—all consistent with her MEN2B diagnosis. She was already followed closely by her pediatrician as well as an endocrinologist. There was no prior family history of MEN2B. The patient had undergone repeat shave biopsies of the eyelid lesions at an outside facility on two separate occasions and was experiencing regrowth after just one year. She noted that the lesions had continued to increase in size and was bothered by their appearance as well as by associated ocular surface irritation.

## Examination

On ophthalmologic examination, uncorrected visual acuity was 20/20 in each eye. Close inspection of her eyelids and adnexa revealed a 4.1 mm gelatinous, flesh-colored, ovoid nodule on her right lower lid margin adjacent to the punctum (Figure 1A). A similar lesion, 4.4 mm in its greatest diameter was on her left lower lid margin (Figure 1B). Neither demonstrated high-risk features, such as overlying scab, scale, color change, or sentinel vessels. She also had thickening of the right upper eyelid, from a normal thickness of 1–2 mm to 5 mm (Figure 1C). Slit-lamp examination showed bilateral prominent corneal nerves in an otherwise clear cornea. The conjunctiva was white and quiet. The remainder of her anterior and posterior segment examination was normal in both eyes. Additional clinical features of MEN2B, such as marfanoid habitus, sublingual neuroomas, or low muscle mass, were not present.

## Ancillary Testing

Histopathologic results of the shave biopsies performed at the outside facility 1 year prior were reexamined by our pathologist and revealed multiple plexiform schwannomas, a benign tumor with no potential for malignant transformation (Figure 2A). The plexiform appearance was noted with the finding of disorganized aggregates of nerve twig proliferations (Figure 2B). A pan-cytokeratin immunohistochemical stain highlighted the surrounding epithelial surface, and S100 immunohistochemical staining confirmed the neural origins of the lesions (Figure 2C–D).

## Treatment

Our patient remains in remission from MTC, is medically stable, and continues to be followed by endocrinology. From an ophthalmologic standpoint, she is being carefully observed and treated conservatively with artificial tears for surface irritation. If needed in the future, repeat excision of the eyelid schwannomas with a wedge resection may be performed to help prevent regrowth, with an understanding that similar lesions may recur elsewhere on the eyelids.

## Differential Diagnosis

This patient's past medical history of MEN2B, thickened eyelids, prominent corneal nerves and reoccurring eyelid lesions prompted a most likely diagnosis of multiple eyelid schwannomas. However, it was important to consider other possible eyelid lesions, including both benign and malignant tumors. Chalazia are the most common benign eyelid tumors resulting from blockage of a meibomian gland and present as dome-shaped, ele-

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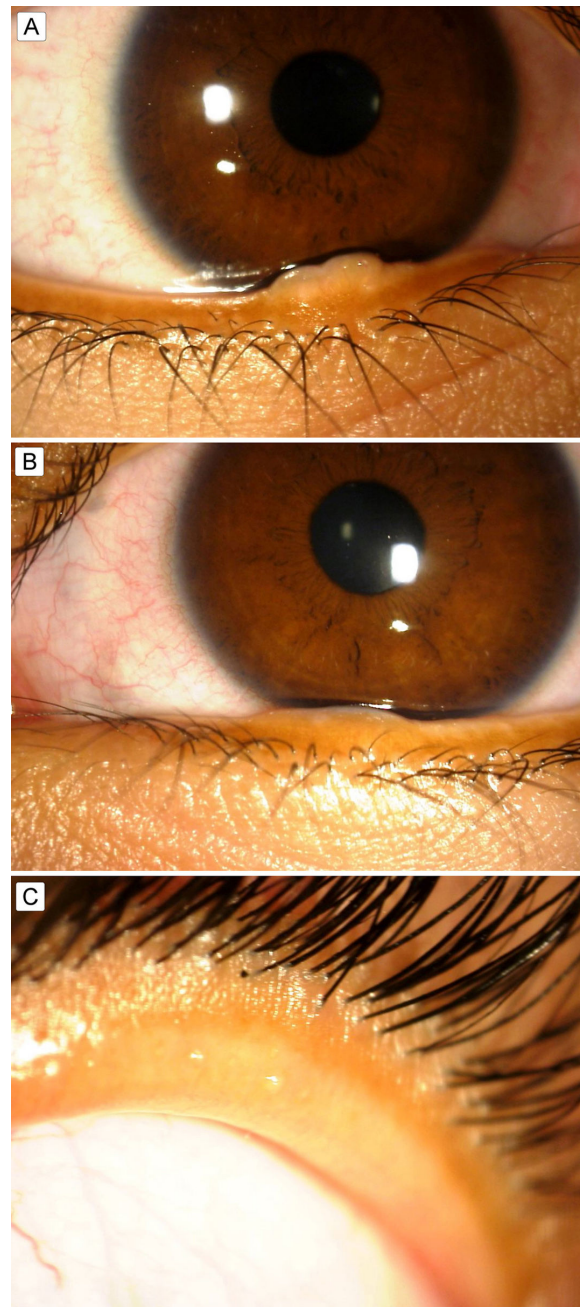
vated, smooth lesions, much like our patient's.<sup>1,2</sup> However, histopathology of a chalazion would show signs of chronic inflammation, not present in our patient.<sup>3</sup> Neurofibroma was also considered, given the known association with MEN2B, although it is more commonly found in neurofibromatosis type 1.<sup>4</sup> Plexiform neurofibromas are benign nerve sheath tumors that may cause proptosis, ptosis, and cosmetic disfigurement.<sup>4</sup> On histopathology, they present as a combination of Schwann cells, axons, perineural cells, and fibroblasts, whereas schwannomas are composed predominantly of Schwann cells.<sup>5</sup> Plexiform neurofibromas have malignant potential, unlike our patient's plexiform schwannomas, which have no malignant potential.<sup>4</sup> Additional benign lesions, such as epidermal inclusion cyst, sebaceous cyst, and papilloma were less likely, based on appearance.

Malignant eyelid lesions are generally rare in the pediatric population. Examples include basal cell carcinoma, squamous cell or sebaceous cell carcinoma, and keratoacanthoma, which is categorized as a premalignant lesion. Malignant features such as sentinel vessels, bleeding or ulceration, distortion of the lid margin, or madarosis were all absent in this case.

## Diagnosis and Discussion

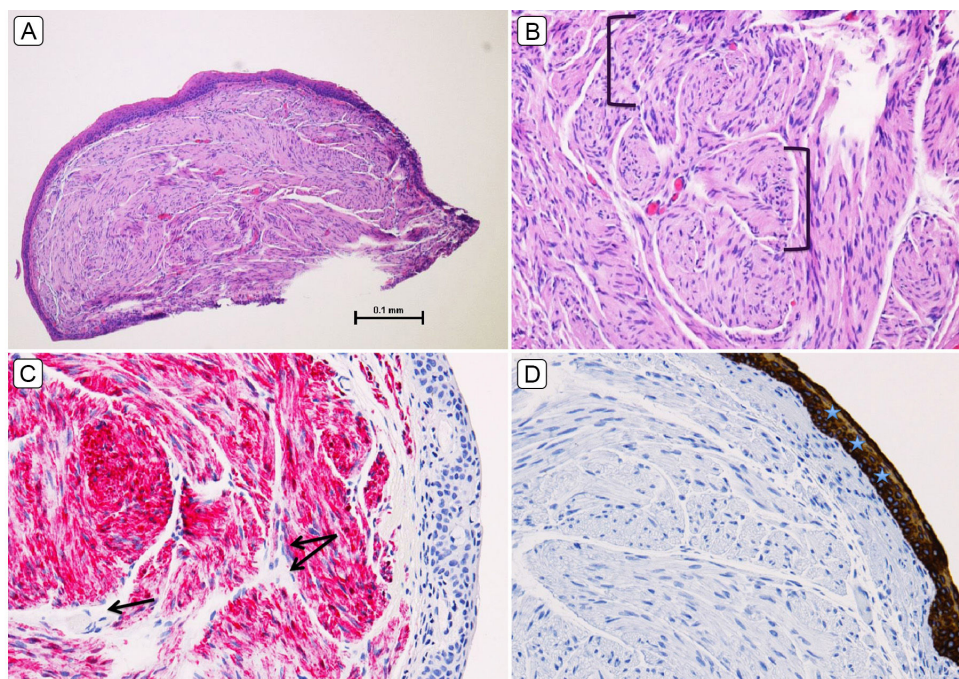
Multiple endocrine neoplasia type 2B (MEN2B) describes a spectrum of disorders that presents with tumors in two or more endocrine glands, most commonly MTC, pheochromocytoma, and mucosal neuroproliferative tumors.<sup>6–10</sup> This condition can also present with nonendocrine features, such as marfanoid body habitus, gastrointestinal ganglioneuromas, thickened lips, tongue nodules, café-au-lait spots, and ocular abnormalities.<sup>6,7,9,11</sup> MEN2B is caused by a *RET* proto-oncogene mutation, which is heritable in approximately half of cases, located on chromosome 10, and confers 100% penetrance but variable expressivity.<sup>9–11</sup> MTC occurs in nearly 100% of patients with MEN2B. Late diagnosis can be fatal, with a 5-year survival rate of 35% for patients with MTC in MEN2B.<sup>9,11</sup> Diagnosing patients before the development of MTC can be lifesaving.

With genetic testing becoming more available, it is now common to screen newborns with a family history of MEN2B, allowing for earlier molecular diagnosis and thus improved outcomes.<sup>10</sup> However, 50% of MEN2B cases stem from de novo mutations, resulting in delayed diagnosis and poorer prognosis.<sup>10</sup> In nonfamilial MEN2B, patients are most often diagnosed at an advanced stage, triggered by systemic symptoms related



**Figure 1.** A, Right lower lid margin showing a 4.1 mm gelatinous, flesh-colored, ovoid nodule. B, Left lower lid margin showing a 4.4 mm gelatinous, flesh-colored nodule. C, Thickened right upper eyelid to 5 mm.

to elevated catecholamines due to pheochromocytoma or elevated calcitonin due to MTC.<sup>6</sup> By this point in time, MTC has often progressed to an advanced stage, marked by metastatic cancer most commonly seen in the liver and lungs.<sup>8</sup>



**Figure 2.** A, Plexiform schwannoma (hematoxylin-eosin [H&E], original magnification  $\times 4$ ). B, Eye lesion highlighting disorganized nerve pattern (H&E, original magnification  $\times 10$ ). C, Positive S100 immunohistochemical stain highlighting the neural origin of the lesion (original magnification  $\times 20$ ). D, Pan-cytokeratin stain highlighting epithelial tissue (original magnification  $\times 20$ ).

Early MEN2B diagnosis allows for prompt MTC surveillance, surgical resection of the tumor or even prophylactic thyroidectomy if needed, which can be life-saving.<sup>11</sup> Early diagnosis of asymptomatic patients with de novo mutations is challenging and relies on clinical findings, including ocular abnormalities.<sup>12</sup> Ocular changes may be the first manifestations of MEN2B, presenting before systemic signs and symptoms of pheochromocytoma and/or MTC.<sup>6,11</sup> In addition, ocular findings can be detected with a noninvasive examination, whereas identifying other systemic findings in MEN2B may require imaging, lab work, and even diagnostic biopsies. Although the ophthalmic signs are not visually significant, they can play a critical role in early detection.<sup>11</sup> The exact incidence of ocular findings is unknown since MEN2B itself is rare.<sup>11</sup> However, of 33 reported ocular cases, 100% of patients were found to have prominent corneal nerves. Additional findings included eyelid neural tumors or thickening (88%), subconjunctival neuromas (79%), decreased tear production (48%), rostral displacement of the cilia (12%), and poor pupillary dilation (12%).<sup>11</sup>

Our patient was found to have prominent corneal nerves, thickened eyelids, and multiple eyelid conjunctival plexiform schwannomas. Histologic studies have demonstrated that the appearance of prominent corneal

nerves is due to nonmyelinated axons associated with Schwann cells.<sup>13</sup> Although prominent corneal nerves have been reported in 100% of MEN2B cases, they can also be seen in a number of other diseases such as MEN2A, Refsum disease, pheochromocytoma, primary amyloidosis, ectodermal dysplasia, leprosy and herpes zoster keratopathy.<sup>(6,9)</sup> Therefore, it is important to be aware of additional distinctive ocular features of MEN2B, such as eyelid thickening, ptosis, impaired pupillary dilation, and eyelid, conjunctival, and subconjunctival neuroproliferative tumors.<sup>11</sup>

Plexiform schwannomas—also referred to as neurilemmas, neurolemomas, or neuromas—are benign tumor proliferations of nerve tissue. In MEN2B, they are seen as multiple unencapsulated lesions in the palpebral conjunctiva or subconjunctiva.<sup>14</sup> A diagnostic biopsy can help confirm the suspected diagnosis of MEN2B associated neural lesion, which reacts positively with the immunohistochemical S100 and demonstrates a disorganized conglomeration of nerve twigs.<sup>10,11</sup> The formation of nodules is attributed to prominent nerves forming plexiform bundles aligned parallel to the epidermis.<sup>6,7,14</sup> These lesions often increase in size over time, which in many patients, as in ours, prompt further ophthalmologic evaluation.<sup>10</sup>

Such tumors can be surgically removed under local anesthesia with a shave biopsy or full-thickness wedge resection under monitored sedation.<sup>15</sup> However, with the former, there is a risk of residual tumor being left behind, possibly leading to recurrence.<sup>14,15</sup> In order to prevent eyelid notching during direct closure of the lid defect following wedge resection, the tarsus and eyelid margin are meticulously reapproximated.<sup>15</sup> If the lesion is large (greater than 30% of the eyelid width), a more complex eyelid reconstruction is necessary, requiring tarsoconjunctival and skin grafts from adjacent tissues to reconstruct the anterior and posterior lamellae of the eyelid.

This pediatric case of MEN2B highlights important ocular findings in MEN2B, some of which can be detected by the naked eye, with no need for a slit-lamp examination or invasive testing. Ophthalmologists aware of its ocular manifestations can play a vital role in detecting MEN2B at an early precancerous stage, establishing care with other subspecialists as needed (ie, endocrinology), and helping to screen immediate family members who may also be affected.

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