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Connective tissue nevi: A case report of a uniquely presenting eyelid collagenoma

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ABSTRACT

Purpose: The purpose of this article is to report a unique clinical presentation of an eyelid collagenoma. Additionally, we review connective tissue nevi as a whole and describe the spectrum of collagenoma variants in relation to their specific syndromic associations.

Observations: A 71-year-old female with a past medical history of cataract extraction, and remote amblyopia requiring patching presented to ophthalmology clinic with a chief complaint of an asymptomatic orbital lesion persistent over the last two years. Physical exam revealed a 0.5 cm tan-purple erythematous left upper eyelid papule with associated mild ipsilateral ptosis. Eye exam demonstrated 20/25 vision bilaterally. The patient opted for surgical excision of the lesion. Intraoperatively the lesion was found to be adherent to the overlying skin and underlying tarsal plate. Thus, the lesion was resected *en bloc* and required orbicularis muscle repair. Postoperative follow-up exam eight days after the initial procedure demonstrated a well-apposed linear scar site with minimal ecchymosis. The patient ultimately healed without complication. Based upon clinical features including shape, color, and external vascularity the lesion was initially favored to be a benign hemangioma. However, subsequent tissue diagnosis instead revealed the lesion to be a benign collagenoma.

Conclusions and importance: While uncommon, benign connective tissue nevi including collagenomas can present as a single or rarely multiple facial lesion(s). Collagenomas can occur sporadically or as part of a genetic syndrome. Unique clinical presentations of collagenoma(s) may be a subtle indication of an underlying syndrome. Thus, the clinical features that are most important to assess on physical exam include the lesion focality (i.e., single vs. multi-focal), location of the lesion(s), and dermatologic configuration (i.e., papular or nodular vs. plaque-like vs. cerebriform etc.). Of note, while typically tan-pink in color on physical exam, collagenomas may be erythematous, as in our case, and can thus be mistaken for vascular lesions. Collagenomas are non-cystic in nature and thus from our experience do not appear to be amenable to surgical marsupialization. Lastly, if biopsy is pursued, an accurate diagnosis of collagenoma is important due to the aforementioned potential syndromic implications as well as a minimal though non-zero risk of recurrence.

1. Introduction

Collagenomas belong to a group of benign dermal hamartomas collectively termed *connective tissue nevi*. Connective tissue nevi occur as a result of fibroblast proliferation or overproduction of one or more extracellular matrix component (i.e., collagen, elastin, or proteoglycans).[1–3] Collagenomas can occur sporadically or in association with genetic syndromes including but not limited to tuberous sclerosis complex and multiple endocrine neoplasia I (MEN1) syndrome.[1] Typically, collagenomas appear as firm, flesh-colored papules, nodules, or plaques ranging in size from 0.5 to 5.0 cm in greatest dimension on the trunk and/or extremities.[1] They can present as either isolated lesions or in multiples. Presentation of collagenomas in multiples may be an indication of an underlying syndrome.[4] Presentation of multiple collagenomas tends to occur at a younger age during childhood/adolescence, while presentation of collagenoma as an isolated lesion tends to occur during adulthood.[5] While collagenomas can be treated with surgical excision and/or corticosteroids, they do not typically require treatment and can often be monitored.[6,7] Additionally, collagenomas follow a benign clinical course and have minimal risk of

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recurrence if excised.[6,8]

2. Case presentation

Our patient is a 71-year-old female with a past medical history of cataract extraction, remote amblyopia requiring patching, cerebral vasculitis, anti-cardiolipin syndrome, and low-grade non-muscle invasive papillary urothelial carcinoma. The patient presented with cosmetic complaints regarding an asymptomatic self-detected orbital lesion that had been persistent over the past two years. Physical exam revealed a 0.5 cm tan-purple erythematous left upper eyelid papule with associated vascularity and mild ipsilateral ptosis (Fig. 1A). Examination of the eyes showed 20/25 vision in both eyes and bilateral *in-situ* artificial intraocular lenses (consistent with prior cataract surgery). The patient underwent excisional biopsy of the lesion.

Initially a surgical approach commonly employed for cystic lesions was considered but ultimately not pursued. This approach involves making a superficial skin incision with subsequent marsupialization of the lesion. This technique is overall favorable as it often results in an incision smaller than the lesion itself and can be closed with superficial skin sutures. However, our patient's lesion was found to be quite adherent to the overlying skin and underlying tarsal plate, with no easily identifiable surgical planes between the lesion and surrounding tissues. Therefore, an *en bloc* excision was pursued instead. An ellipse-shaped incision was made circumferentially around the lesion using a #15 blade, which resulted in nicking of the orbicularis muscle. The posterior edge of the ellipse was dissected with Wescott scissors. The resulting defect was thus larger than the original lesion. The orbicularis muscle was repaired with buried absorbable vicryl sutures. The skin defect was then closed with non-absorbable nylon sutures to minimize scar formation. The closure allowed re-creation of the usual multi-lamellar anatomy of the eyelid. There was minimal bleeding during the procedure.

The post-surgical course was uncomplicated. At an eight-day post-operative follow-up appointment, the patient was noted to have a well-apposed linear surgical site scar with minimal associated ecchymosis. During the appointment the superficial nylon sutures were removed. Upon discharge, the patient had been instructed to apply erythromycin ophthalmic ointment (5mg/gm), once daily at the surgical site for a total of two weeks, and had overall been compliant in doing so. The patient reported no complications following this final post-operative clinic appointment.

Per the pathology report, microscopic examination of the excised lesion revealed an unencapsulated circumscribed nodule in the dermis composed of haphazardly arranged thickened, hyalinized collagen bundles (Fig. 1B and C). Collagen bundles demonstrated some clefting, and the background spindle-shaped fibroblastic cells were overall sparse and bland in appearance (Fig. 1D). Immunohistochemical stains for smooth muscle markers including smooth muscle actin and desmin were negative. Epithelial membrane antigen was also negative. An immunohistochemical stain for CD34 showed patchy positivity in the spindled cells. The overall histologic and immunophenotypic findings supported the final diagnosis of collagenoma.

3. Discussion

Collagenomas are relatively rare benign soft tissue lesions that are characterized by an abnormal increase in dermal collagen.[1,2,9] Collagenomas are grouped together with other related entities under the umbrella term *connective tissue nevi*.[1,3] The four sub-types of connective tissue nevi are delineated in Table 1.

Clinically, collagenomas typically appear as firm, slow-growing, flesh-colored papules or nodules that range in size from 0.5 to 5.0 cm in greatest dimension and tend to occur on the trunk and extremities.[1,9] Rarely, do collagenomas occur on the face, as seen in our case.[10] Papular or nodular collagenomas can either appear as a single isolated lesion or as multiple lesions. If seen in multiples, papular or nodular collagenomas can display a variety of cutaneous distributions including papulolinear, corymbose, zosteriform (i.e., dermatomal), or blaschkenoid.[1,2,6,9]

Collagenomas have several syndromic associations that are delineated in Table 2. Disease associations that present as multiple papules or nodules include familial cutaneous collagenoma and eruptive

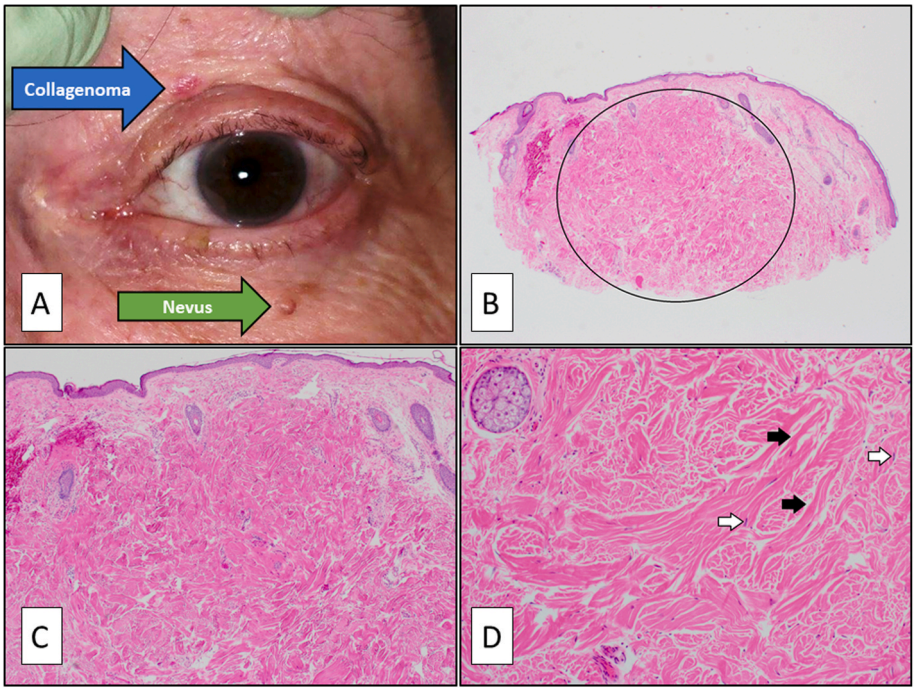

Fig. 1. A). Left eyelid collagenoma with abnormally vascular appearance (blue arrow) and incidental nevus (green arrow) **B).** Unencapsulated circumscribed nodule in the dermis (circled) (2x, H&E) **C).** Haphazard, thickened and hyalinized bundles of collagen (4x, H&E). **D).** Collagen bundle clefting (black arrows) with background spindle-shaped fibroblastic cells (white arrows) (10x, H&E).

Table 1
Connective Tissue Nevi (CTN) adapted from Arora, Harleen et al., 2017[1–3,7].

Main categories of CTN	Specific Example(s)
Collagen Type	● **Sporadic** ○ Isolated collagenoma ○ Multiple collagenomas (eruptive collagenoma) ● **Inherited*** ○ Shagreen patch ○ Plantar cerebriform collagenoma ○ Multiple collagenomas (familial cutaneous collagenoma)
Elastin Type	● **Sporadic** ○ Isolated elastoma ○ Elastosis perforans serpiginosa ● **Inherited** ○ Multiple elastomas (as part of Buschke-Ollendorff syndrome)
Proteoglycan Type	● **Sporadic** ○ Nevus mucinosis/focal cutaneous mucinosis ○ Lichen myxedematosus ● **Inherited** ○ Dermal nodules (Hunter syndrome)
Fibroblastic Type	● **Sporadic** ○ Fibroblastic connective tissue nevus ● **Inherited** ○ Unknown**

*See Table 2 for full list of syndromic associations.
**It has been suggested that fibroblastic connective tissue nevus could represent a monophasic fibrous hamartoma of infancy.[1]

Table 2
Syndromic associations of collagenomas[1–3,5,7–9,11].

Collagenoma Variant	Typical Location(s) on the Body	Syndromic Association(s)
Isolated (i.e., single, dispersed) collagenoma(s)*	● Trunk ● Extremities	● Pseudo-Hurler syndrome ● Velocardiofacial syndrome (i.e., DiGeorge syndrome) ● Down syndrome ● Ehlers Danlos (type III) syndrome
**Shagreen patch (i.e. plaque-shaped collagenoma) ** **	● Lumbosacral back ● Mid-upper back	● Tuberous sclerosis
Cerebriform collagenoma	● Soles ● Palms	● Proteus syndrome
Multiple (grouped and or/organized) collagenomas	● Trunk ● Extremities	● Familial cutaneous collagenoma (as part of Buschke-Ollendorff syndrome) ● Eruptive collagenoma, which may be associated with multiple endocrine neoplasia type I (MEN I)

* Isolated collagenomas are commonly sporadic.
** Plaque-shaped collagenomas of the scalp can also be associated with cutis verticis gyrata, a clinical finding, that in turn has independently been linked to Beare-Stevenson syndrome and Noonan's syndrome.

collagenoma.[1,2] Familial cutaneous collagenoma is a rare autosomal dominant disease that occurs due to mutation in the *LEMD3* gene and is proposed to be a variant of Buschke–Ollendorff syndrome.[1,11] It is thought to be hormonally driven, since the number of collagenomas in this disease have been observed to increase during pregnancy.[1] Eruptive collagenoma has a similar presentation on physical exam and can occur either sporadically or in association with MEN1 syndrome.[1,2,12] Papular or nodular collagenomas, occurring as either isolated or multiple lesions, have rarely been reported to occur in relation to pseudo-Hurler syndrome, velocardiofacial (i.e., DiGeorge) syndrome, Down syndrome, and Ehlers Danlos (type III) syndrome.[1,9] In one study, connective tissue nevi were observed in a few cases of confirmed Birt-Hogg-Dube syndrome; however, the sub-type(s) were not specified.[13]

Non-papular and non-nodular collagenoma variants that have key syndromic associations include Shagreen patches and cerebriform collagenomas.[1,2,9] Shagreen patches typically appear as flesh-colored "orange peel" textured plaques on the lumbosacral region and are well known for their association with tuberous sclerosis complex.[1–3,14] The cerebriform collagenoma appears as raised, undulating folds on the sole of the foot or less commonly on the palm of the hand and is associated with a very rare genetic disease known as Proteus syndrome.[1,2,9] While highly suggestive of Proteus syndrome, the finding of a plantar or palmar cerebriform collagenoma is not by itself diagnostic of Proteus syndrome.[15] Lastly, plaque-shaped collagenomas that occur on the head can result in a condition called *cutis verticis gyrata*. *Cutis verticis gyrata* is a purely clinical term used to describe a thickened, furrowed appearance of the scalp on physical exam. Though not obligatorily, *cutis verticis gyrata* can be found in association with several syndromes and anomalies including, but not limited to Beare-Stevenson syndrome and Noonan's syndrome.[1]

Of note, collagenoma is not synonymous with an entity called "storiform collagenoma" also known as sclerotic fibroma.[1,16] Instead of having the haphazard bundles of collagen seen in collagenoma, sclerotic fibromas have a more whorled, "pin-wheel" arrangement of collagen. The distinction is not entirely trivial, because unlike the previously discussed collagenomas (i.e., connective tissue nevi of the collagen type), sclerotic fibromas can present as part of Cowden's syndrome.[1,17] It also appears to be more common for sclerotic fibromas to occur on the head and neck than collagenomas.[17] A curious entity known as a giant cell collagenoma has been suggested to be a variant of a sclerotic fibroma and has also been found to arise on the face.[18] To date, Purgert et al. has reported the only known case of a sclerotic fibroma on the eyelid.[19] There is emerging evidence that sclerotic fibromas harbor recurrent genetic alterations and thus may represent true neoplasms. This is in contrast to the previously discussed collagenomas which appear to be hamartomatous in nature.[20] Finally, another entity known colloquially as "Athlete's nodule" also shows collagenous hyperplasia in the dermis. However, because these lesions form secondary to chronic friction and/or trauma, they are considered a reactive phenomenon.[1]

Overall, our patient's lesion was most consistent with a collagenoma of the hamartomatous variety (i.e., a connective tissue nevus of the collagen type). The patient did not present with any additional clinical features that would necessitate further workup of disease or syndromic associations. Thus, this particular case most likely represents an instance of isolated sporadic collagenoma. Unique features of our case include a rare presentation on the upper eyelid and an abnormally vascular clinical appearance.

CRediT authorship contribution statement

Shruti Srikumar: Writing – review & editing, Writing – original draft. **Nina Krassilnik:** Writing – review & editing, Supervision. **Milap P. Mehta:** Writing – review & editing, Writing – original draft, Conceptualization.

Consent

Verbal consent to publish this case report including clinical and histopathologic images has been obtained from the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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