Epibulbar complex cartilaginous choristoma: A distinctive clinicopathological case series and literature review

Zongduan Zhang, MD¹,²,∗, Zhengwei Yang, MD², Qintuo Pan, MD², Xiaoyi Qin, MD², Yuxuan Deng, MD², Yuehong Cao, MD²

Abstract
To newly describe the clinical and histopathological characteristics of epibulbar complex cartilaginous choristoma incidentally observed in a series of pterygium excision patients. During a 4-year period, we identified 8 cases of conventional unilateral nasal subpterygial cartilaginous choristoma in 1799 pterygium patients and analyzed their clinicopathological features. The incidence rate of this entity is 0.44% in pterygium patients. All of the cartilaginous choristomas were buried deep in the caruncle, covered by the pterygium, and embedded in tenon fascia tissue. Its clinicopathological characteristics include hyaline cartilaginous tissue that is surrounded by fibrous connective tissue and smooth muscle bundles. S-100 protein-staining specifically revealed chondrocytes embedded within chondroid matrix.

Epibulbar complex cartilaginous choristoma covered by pterygia and predominantly observed in the older population is rare. The lesions were buried deep in the caruncle, covered by the pterygium and embedded in tenon fascia tissue. These findings are inconsistent with those in previous reports.

Abbreviation: ECCC = epibulbar complex cartilaginous choristoma.

Keywords: cartilaginous choristoma, clinicopathological features, epibulbar, pterygium

1. Introduction
Epibulbar choristomas are a group of congenital lesions, a mass of histologically normal tissue in an abnormal location. They are classified as limbal dermoids, dermolipomas, osseous choristomas, and complex choristomas.¹² Complex choristomas contain cells from 2 or more different tissue types, such as bone, cartilage, nerve, muscle, sebaceous secretions, dermal appendage, or lacrimal tissues.¹⁻³ Choristomas are all very slow-growing and benign.¹⁻⁴ Excision is generally done either for cosmetic purposes or to rule out any possibility of malignancy.¹⁻⁵ Cartilaginous choristoma tissues are found in different locations, including mouth, lip, tongue, gingiva, tonsillar region or pharynx, nasopharynx, neck, and other reported locations. There are very few reported cases of cartilaginous choristoma in the eye.

Only 1 literature about cartilaginous choristoma associated with recurrent pterygium is documented. We present 8 cases of unilateral cartilaginous choristoma buried deep in the caruncle, covered by the pterygium, and embedded in tenon fascia tissue. They were observed as an incidental finding during pterygium excision. This is the first report with 8 cases describing the clinical manifestations and histopathology of cartilaginous choristoma located in an unusual place. It is also the largest review of epibulbar complex cartilaginous choristoma (ECCC) cases.

2. Methods
Records of 1799 primary pterygia cases who presented to the Eye Hospital of Wenzhou Medical University from January, 2012 to May, 2016 were reviewed. All of the pterygia patients did not have any other palpable masses overlying the ocular surface.

Among these patients, 8 cases were found to have an epibulbar tumor during the pterygium excision. Pertinent clinical findings, histopathology, and treatment outcomes were documented. Each patient was evaluated for age at the time of mass detection, race, sex, and mass features. Each eye was evaluated for signs and which eye was involved. Each mass was evaluated for location, color, largest base dimension in millimeters, wide base dimension in millimeters, thickness in millimeters, and mass attachment to episclera or within sclera. This study was approved by the Institutional Review Committee at the Wenzhou Medical University. The research adhered to the tenets of the Declaration of Helsinki.

3. Results
A solid mass was incidentally palpable and found beneath the tenon fascia tissue in 11 patients after the pterygia was completely
removed in 1,799 patients. Of these 11 cases, 8 cases met the inclusion criteria and were enrolled in our study, whereas the other 3 cases were complex choristomas without cartilaginous tissue. The incidence was around 0.44% (8/1,799) among pterygium patients. The mean (median) patient age of the 8 cases at presentation was 59 (60) years. There were 3 male and 5 female patients, all involving the left eye. There was no evidence of previous ocular trauma, infection, tumor, or systemic calcium metabolic disorder. The patients had signs of the pterygia ranging from 5 to 10 years.

All 8 cases suffered from primary pterygium, and their clinical manifestations were the same as the common pterygia. A solitary and nodular mass buried deep in the caruncle were incidental findings and covered by the tenon fascia tissue after the pterygium was removed. The mass was not attached to the sclera or medial rectus muscle (Fig. 1A). All lesions were small, white, and painless nodules with sharply demarcated margins. They differed in surface covering, shapes, and sizes. The clinical characteristics of the 8 patients are summarized in Table 1. The mean largest basal dimension was 3.6 mm (median 3.5 mm; range 2–5 mm), and mean wide basal dimension was 1.88 mm (median 2 mm; range 1–2 mm) (Fig. 1B). Some nodules were covered by tenon fascia tissue when excised (Fig. 1C). The pterygium excision with conjunctival autograft transplantation surgery was operated after the lesions were completely separated and removed from the nasal sclera (Fig. 1D).

The histopathologic findings are summarized in Table 2. It revealed complex choristomas composed of hyaline cartilaginous tissue, fibrous connective tissue, and smooth muscle bundles (Fig. 2A). The cartilaginous tissues were fully differentiated, with chondrocytes distributed within cartilage matrix. The cartilaginous tissues were surrounded by sequential fibrous tissue named
perichondrium. In the central cartilage, hematoxylin-stained chondrocytes were completely mature, and at the periphery, eosin-stained chondrocytes were relatively immature (Fig. 2B). Clustered smooth muscle bundles were also seen in some fibrous connective tissues (Fig. 2B). Isogenous groups were formed by single, nearly circular, and mature chondrocytes in the perichondrium. Circular nuclei and lipid droplets can be seen in the cytoplasm of chondrocytes (Fig. 2C). S-100 staining was positive in the chondrocytes and negative in the cartilage matrix (Fig. 2D), similar to normal cartilage, leading to the diagnosis of an ECCC.

Follow-ups ranged from 12 to 18 months after the first operation. Both the patients and the surgeon reported improvement and cosmetic satisfaction. No recurrence was noted during the follow-up period.

4. Discussion
Choristomas are the most common type of epibulbar and orbital tumor in the pediatric age group, and are most often located in the epibulbar region, ocular adnexa, or choroid. They originate from ectopic multipotent cells, which can differentiate into either a complex growth consisting of several elements (lacrimal and other glands, adipose tissue, cartilage, bone, teeth, smooth muscle, nerve bundles, and brain) or lesions containing predominantly a single tissue. Epibulbar choristomas contain

| Case | Mature bone | Cartilage type (compact or spongy) | Cartilage matrix (woven or lamellar) | Haversian canals | Cartilage | Surrounded by perichondrium | Fibrous connective tissue | Inflammation | Hemorrhage | Other tissue elements |
|------|-------------|-----------------------------------|-------------------------------------|-----------------|-----------|---------------------------|--------------------------|--------------|------------|---------------------|
| 1    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |
| 2    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | Yes                  |
| 3    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |
| 4    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |
| 5    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | Yes                  |
| 6    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |
| 7    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |
| 8    | MIC,IMIP    | Compact                            | Lamellar                            | No              | Yes       | Yes                       | Yes                      | No           | No         | No                  |

IMAP = immature at the periphery, MIC = mature in the center.
Smooth muscle.

Figure 2. Histopathological studies of cartilaginous choristoma cases. (A) The excised lesion composed of hematoxylin-eosin-stained cartilaginous tissue (C), surrounded by fibrous connective tissue and smooth muscle (×40 original magnification). (B) Cartilaginous component of the mass showing chondrocytes distributed within the cartilage lacunae and surrounded by perichondrium (P). At the periphery of the cartilage, eosin-stained, small, oblate, and immature chondrocytes (IC) can be seen. In the middle region of the cartilage, hematoxylin-stained, nearly circular and mature chondrocytes (MC) can be seen. Smooth muscle (SM) is arrayed among the fibrous connective tissues (F) (×100 original magnification). (C) Isogenous groups (IGs) can be seen, which are formed by division of chondrocytes within the cartilage capsule (×400 original magnification). (D) S-100 staining of cartilaginous choristoma cases. S-100 protein appearing as brown particles, which are mainly accumulated in the cartilage lacuna or cartilage capsule of the chondrocytes, and are absent in the cartilage matrix (×100 original magnification).
There is a clinical distinction from dermoids, and have histologic evidence originating from the palpebral lobe. In our cases, the ECCCs are asymptomatic lesions buried deep in the lacrimal caruncle and covered by pterygia. They do not come to clinical attention until after pterygium excision.

Epibulbar choristomas are relatively rare, with reported prevalence rates of 1/10,000 to 1/30,000, and represent 36% of epibulbar lesions found in the first decade of life.[3,25] The PubMed database was searched to identify all the previously reported cases of ECCCs (using key words cartilaginous choristomas, and eye). Review of the literature identified 20 patients with cartilaginous choristomas (Table 3). All the reports in the literature are sporadic cases, but we report 8 cases that are from primary pterygium.

One of the reported patients demonstrated histopathologic findings similar to the 8 cases reported here. Bialasiewicz et al[10] reported a 24-year-old patient who had a pterygium recur 6 times over 15 years, and epibulbar cartilage was found in an unusual location during the excision of the pterygium. In both Bialasiewicz et al’s study and our report, the choristoma is found under the pterygium. The biopsy of the resected tumor revealed cartilage histologically after the sixth excision of the recurrent pterygium reported by Bialasiewicz et al, whereas our patients found cartilage choristoma during the primary pterygium excision. There is still insufficient evidence that indicates whether the pterygium is a risk factor in the formation of the cartilage choristoma.

Most of the literature reports young patients (less than 10 years old) with cartilaginous choristoma, and most of the choristomas occur as isolated congenital lesions. The reported adults with cartilaginous choristoma did not specify whether they were congenital or acquired. The presence of cartilaginous choristomas has also been associated with several types of syndromes, including Goldenhar syndrome, nevus sebaceous of Jadassohn, organoid nevus syndrome, and linear nevus sebaceous syndrome. Cartilaginous choristomas are also related to chalazion and dermoids. The 8 cases reported here are cartilaginous choristomas found under the lacrimal caruncle, covered by the pterygium and completely embedded in the connective tissue.

According to the review of the literature, cartilaginous choristomas have been detected in many areas of the eye, typically in the cornea, limbus, subconjunctival space, subpter应聘al space, and even in the fundus. They vary in appearance, ranging from small, flat lesions to large masses that fill most of the epibulbar region. There is no reported case detailing fast growth in cartilaginous choristomas regardless of the site. According to the published literature, they appear to be either extremely slow-growing or not growing at all. The cases we are reporting also do not show history of appreciable growth over time.

These solid tumors can have a smooth or rough surface, ranging from creamy yellow to pink in color, and vary in size from a flat lesion measuring a few millimeters to large mass filling most of the epibulbar region. There may be isolated or multiple lesions, and most are located inferotemporally.[24–28] The histopathology of the mass typically demonstrated a well-circumscribed lesion composed of complete hyaline cartilaginous tissue distributed within a chondroid matrix. The soft tissue was composed of fibrous connective tissue, smooth muscle bundles, and adipose tissue. These unilateral eye lesions are complex choristomas and can range in size.

The cartilaginous choristomas differ from hamartoma, which is an excessive proliferation of normal tissue at the normal site.

### Table 3

| Author                      | Year reported | Age (y, mos, d)/sex | Eye Quadrant | Management | Complex cartilaginous choristoma | Underlying attachment | Diagnosis                                   |
|-----------------------------|---------------|---------------------|--------------|------------|---------------------------------|----------------------|--------------------------------------------|
| Grob et al[1]               | 2015          | 2 y, F              | Right Temporal | Excision   | Yes                             | Cornea               | Lacrimal gland choristoma                 |
| Pittka et al[3]             | 1983          | Young, F            | Right Nasal   | Excision   | No                              | Sclera               | Cartilage choristoma                      |
| Bialasiewicz et al[10]      | 1998          | 24 y, M             | Left Nasal    | Excision   | No                              | Conjunctiva          | Pterygium                                 |
| Heming et al[11]            | 2011          | 22 wks, M           | Left Temporal | Excision   | Yes                             | Choroid               | Goldenhar syndrome                       |
| Pinna et al[12]             | 2015          | 3 wks, M            | Right Temporal hemicornea | Excision   | Yes                             | Episcleral tissue and the cornea | Limbal choristomas                        |
| Alyaheya et al[13]          | 2011          | 15 y, M             | Left Medial epibulbar part | Excision   | No                              | Subconjunctival      | Cartilaginous choristoma                  |
| Ojha et al[14]              | 2017          | 34 y, M             | Left Palpebral conjunctiva | Excision   | No                              | Conjunctiva          | Chalazion                                 |
| Diaz-Perez and Barajas-Sambo[15] | 2012         | 34 y, M             | Left Caruncle  | Excision   | Yes                             | Collagenized connective tissue | Lacrimal caruncle complex choristoma     |
| Kraus et al[24]             | 2010          | 10 D, M             | Ocular Lateral canthus and | Excision   | Yes                             | Anterior sclera and limbus | Nevus sebaceous syndrome                 |
| Pokorny et al[7]            | 1987          | Infant              | Right Superotemporal | Excision   | Yes                             | Anterior sclera and cornea | Complex choristoma                      |
| Ojha et al[14]              | 2013          | 34 y, M             | Left Temporal | Excision   | Yes                             | Conjunctiva          | Cartilaginous choristoma                  |
| Wilkes et al[20]            | 1981          | 13 y, M             | Left Intrascleral | Excision   | Yes                             | Sclera               | Ipsilateral facial nevus of Jadassohn     |
| Gogi et al[21]              | 1978          | 5 y, F              | Left Upper fornix | Excision   | No                              | Conjunctiva          | Cartilaginous choristoma                  |
| Sangwan et al[22]           | 2003          | 3 mos, F            | Left Temporal | Excision   | Yes                             | Conjunctiva          | Dermoids                                  |
| Greiner et al[23]           | 2002          | 54 y, F             | Left Anterior lens capsule | Excision   | No                              | Cornea and fornix    | Dermoids                                  |
| Kraus et al[24]             | 2010          | 10 D, M             | Ocular Lateral canthus and fundus | Excision   | No                              | Anterior Capsule     | Cartilage                                 |
They also differ from teratoma, which is a neoplasm comprising of tissues from all three germ layers.\textsuperscript{[13]} Choristomas are commonly seen in the head and neck region.\textsuperscript{[3,29]} They usually consist of smooth muscle fibers interspersed with adipose and connective tissue, which sometimes includes some specialized components. The other differential diagnoses include epibulbar dermoid, limbal dermoid, epithelial inclusion cyst, prolapsed orbital fat, papilloma, osseous choristoma, and dermolipoma. In older patients, the differential diagnoses should also include age-related calcifications involving the insertion of the lateral recti muscles or the presence of an intraorbital foreign body.\textsuperscript{[30,31]}

Our report shows different features compared to those in the general literature. All patients were older, with a mean age of 59 years, and all lesions were found under the lacrimal caruncle, covered by the pterygium, and completely embedded in the connective tissue. Most masses have been reported without growth of size among young patients. We believe that the small cartilaginous nodule most commonly formed at a young age, but due to its asymptomatic and stationary nature, is often undetected until pterygium surgery in elderly patients. Therefore, we speculate that cartilaginous choristoma is unassociated with the pterygium.

Subpterygial cartilaginous choristoma is predominantly seen in the older population, and is a rare, sporadic condition that can originate from beneath the tenon tissue in the affected eye. These findings are inconsistent with previous reports regarding the age of onset, site, and size of lesion. The signs and symptoms of cartilaginous choristomas in the pterygium patients are often masked by the overlying pterygium. This study augments our understanding of the ECCC and contributes to the clinical and pathological data regarding this entity.

References

[1] Hadjadj E, Conrath J, Denis D. Bilateral osseous choristoma. J Pediatr Ophthalmol Strabismus 1999;36:347–8.
[2] Cunha RP, Cunha MC, Shields JA. Epibulbar tumors in children: a survey of 282 biopsies. J Pediatr Ophthalmol Strabismus 1987;24:249–54.
[3] Mansour AM, Barber JC, Reinecke RD, et al. Ocular choristomas. Surv Ophthalmol 1989;33:339–58.
[4] Kim BJ, Kazim M. Bilateral symmetrical epibulbar osseous choristoma. Ophthalmology 2006;113:456–8.
[5] Moon JH, Yoon DY, Cho S, et al. Bilateral ocular osseous choristomas. Pediatr Radiol 2005;35:1147–6.
[6] Stefanos K, Wollmann RL, Moore BW, et al. S-100 protein in human chondrocytes. Nature 1982;295:63–4.
[7] Pokorny KS, Hyman BM, Jakobiec FA, et al. Epibulbar choristomas containing lacrimal tissue: clinical distinction from dermoids and histologic evidence of an origin from the palpebral lobe. Ophthalmology 1987;94:1249–57.
[8] Grond SR, Jakobiec FA, Stagner AM, et al. Diffuse epibulbar complex lacrimal-cartilaginous choristoma: diagnostic clues and management. Cornea 2015;34:1321–3.
[9] Pintke EC, Marquardt R, Mohr W. Cartilage choristoma of the eye. Arch Ophthalmol 1983;101:1569–71.
[10] Balasiewicz AA, Wiezorek R, Richard G. Recurrent pterygium over 15 years: epibulbar cartilage in unusual location. Klin Monbl Augenheilkd 1998;213:112–6.
[11] Herwig MC, Gerbruch U, Born M, et al. Preterm diagnosis of choristoma and choroidal coloboma in Goldenhar’s syndrome. Pediatr Dev Pathol 2011;14:322–6.
[12] Pinna A, Oggiorno R, Marras V, et al. Isolated complex limbal choristoma in a newborn baby. Int Ophthalmol 2015;35:703–4.
[13] Alyahya A, Alkhudhi H, Alshuwaibi AH. Simple epibulbar cartilaginous choristoma. J AAPOS 2011;15:109–10.
[14] Ohja PR, Deshpande AH, Garagde CB, et al. Epipalpebral conjunctival chondroid choristoma: interesting developmental anomaly presenting in an adult. Indian J Ophthalmol 2017;65:613–4.
[15] Diaz-Perez JA, Barajas-Gamboa JS. Complex choristoma of the lacrimal caruncle: a case report of an unusual congenital tumor with clinical and histopathological classification. Int Ophthalmol 2012;32:37–9.
[16] Kruse FE, Rohrschneider K, Burk RO, et al. Nevus sebaceus of Jadassohn associated with macro optic discs and conjunctival choristoma. Arch Ophthalmol 1998;116:1379–81.
[17] Duncan JL, Golabi M, Fredrick DR, et al. Complex limbal choristomas in linear nevus sebaceous syndrome. Ophthalmology 1998;105:1459–65.
[18] Hayasaka S, Sekimoto M, Setogawa T. Epibulbar complex choristoma involving the bulbar conjunctiva and cornea. J Pediatr Ophthalmol Strabismus 1989;26:231–3.
[19] Pe’er J, Ilar M. Epibulbar complex choristoma associated with nevus sebaceous. Arch Ophthalmol 1995;113:1301–4.
[20] Wilkes SR, Campbell RJ, Waller RR. Ocular malformation in association with ipsilateral facial nevus of Jadassohn. Am J Ophthalmol 1981;92:344–52.
[21] Gogi R, Nath K, Shukla M. Cartilagenous choristoma of lacrimal gland. Indian J Ophthalmol 1978;26:22–3.
[22] Sangwan VS, Sridhar MS, Vemuganti GK. Treatment of complex choristoma by excision and amniotic membrane transplantation. Arch Ophthalmol 2003;121:278–80.
[23] Greiner K, Mackenzie JM, Ross N, et al. Cartilage in the anterior lens capsule of a diabetic patient. Arch Ophthalmol 2002;120:1394–6.
[24] Kraus NJ, Ramasubramanian A, Shields CL, et al. Ocular features of the organoid nevus syndrome. Retin Cases Brief Rep 2010;4:385–6.
[25] Simons BD, Flynn HW Jr, Kaiser PK, et al. Bilateral choristomas in the ocular adnexa, lids, and posterior segment. Retina 1998;18:380–2.
[26] Gayre GS, Proia AD, Dutton JJ. Epibulbar osseous choristoma: case report and review of the literature. Ophthalmic Surg Lasers 2002;33:410–5.
[27] Vachette M, Moulin A, Zografos L, et al. Epibulbar osseous choristoma: a clinicopathological case series and review of the literature. Klin Monbl Augenheilkd 2012;229:420–3.
[28] Shields CI, Qureshi A, Eagle RCJr, et al. Epibulbar osseous choristoma in 8 patients. Cornea 2012;31:756–60.
[29] Bansal R, Trivedi P, Patel S. Cartilaginous choristoma of the tongue: report of two cases and review of literature. Oral Oncol Extra 2005;41:25–9.
[30] Verty DH, Rose GE, Uddin JM, et al. Epibulbar osseous choristoma: benign pathology simulating an intraorbital foreign body. Orbit 2007;26:29–32.
[31] Gommering RS, Fuerster FH, Lemke BN, et al. Epibulbar osseous choristomas with scleral involvement. Ophthalm Plast Reconstr Surg 1988;4:63–6.