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A microanatomic abnormality of the lacrimal gland associated with Goldenhar syndrome

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ABSTRACT

A 12-month-old male infant, noted from birth to have a diffuse right temporal epibulbar thickening that encroached on the limbus inferotemporally, was found to manifest stigmata of Goldenhar syndrome, including a limbal dermoid with vellus hairs, esotropia, astigmatism, fullness and ectropion of the lower eyelid, preauricular skin tag, agenesis of the right kidney, and a supernumerary rib. In the excised epibulbar specimen, in addition to a solid dermoid, lobules of lacrimal gland tissue were interpreted as a portion of the palpebral or orbital lobes. This tissue displayed a unique histopathologic finding. Within some of the lobules were cuffs of eosinophilic squamous (epidermoid) cells that surrounded the intralobular ductules and made variable incursions into, with replacement of, the acinar units. Immunohistochemistry disclosed that the normal acinar and lumen-forming ductular cells were intermediate weight cytokeratin7-positive. The acinar cells were additionally gross cystic disease fluid protein-15 positive. The cells of the squamous cuffs were heavy weight cytokeratin 5/6-positive. The outermost basal cells of the cuffs were cytokeratin 14-positive, in common with the myoepithelial cells of the acini. The intraacinar squamous cells were negative for smooth muscle actin and gross cystic disease fluid protein-15. These findings suggest, but do not prove, that the source of the periductular and acinar squamous metaplasia was the germinal transitional cells where the acinar myoepithelium interfaces and imperceptibly converts into ductular basal cells. The foregoing findings are evaluated in the context of the panoply of ocular, facial, and visceral anomalies manifested in Goldenhar spectrum.

1. Introduction

Histopathologically documented instances of structural abnormalities of the lacrimal gland from maldevelopment are virtually unknown, except for rare instances of alacrima (negligible tear production or total absence of the gland) and faulty innervation in familial dysautonomia that is responsible for tear insufficiency.[6] We describe a peculiar, and

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presumably congenital, microanatomic alteration of the lacrimal gland intralobular ductules that occurred in association with Goldenhar syndrome (GS), a condition now officially designated in the online catalog of human genes and genetic disorders as the hemifacial microsomia syndrome (online Mendelian inheritance in man or OMIM #164210).

The previously unreported abnormality consisted of a multilaminar squamous (epidermoid) cellular sleeve that surrounded the intralobular ductules and also involved the acini. The lacrimal tissue was not a part of the solid dermoid but represented a portion of the palpebral and orbital lobes of the gland included in the excision. Squamous metaplasia of lacrimal gland units has never been observed in the hundreds of lacrimal gland biopsies, lacrimal gland tumors with adherent normal tissue, and exenteration specimens containing lacrimal gland evaluated microscopically by 2 of the authors (Frederick A. Jakobiec and Ralph C. Eagle). Immunohistochemistry aided in determining which normal glandular cell type was likely responsible for the squamous metaplasia.

2. Clinical history

A 12-month-old male infant had a right temporal limbal and extensive lateral epibulbar solid dermoid with projecting vellus hairs and lower eyelid fullness noted at birth. On examination, it was found to extend into the deep lateral and inferolateral fornices. His medical history was remarkable for preauricular skin tags, agenesis of the right kidney, and a supernumerary rib on the right side (14 on the right and 13 on the left). A diagnosis of GS was made. Because his right epibulbar dermoid was causing a mass effect on the right eye with an induced esotropia, astigmatism, and entropion of the lower eyelid; a decision was made to remove the epibulbar lesion and its anterior orbital and lower eyelid extensions via a right anterior lamellar keratectomy with the excision of the limbal dermoid. The lesion extended laterally to a point 3 mm posterior to the insertion of the lateral rectus below the lacrimal gland and was debulked without injuring the lateral rectus muscle. Immediately after surgery, examination revealed persistence of only a small right esotropia. Within 2 weeks, the area of excision had healed with mild residual epibulbar hyperemia.

3. Histopathologic and immunohistochemical findings

Received in 10% buffered, formalin fixative was a pink-white, multilobular, rubbery membranous, and fibrofatty fragment of tissue measuring grossly 2.6 × 1.4 × 1.2 cm which was sectioned into 3 pieces. One fragment histopathologically contained a segment within the mucous membrane that displayed a keratinizing epidermis-like covering (Fig. 1B) surmounting thickly textured collagen-resembling dermis in place of the more delicate and loose collagen of the normal substantia propria. Hair follicles and vestigial sebaceous glands, but no sweat glands, were embedded in the dense connective tissue (Fig. 1C). Deep to this layer was a thin pad of fibroadipose tissue consistent with orbital fat.

Histopathologically, there were lobules of normal unencapsulated lacrimal gland tissue (Fig. 1C) in fibroadipose tissue (Fig. 1D). Beneath a nonkeratinizing conjunctival-type squamous epithelium (Fig. 2D) was lacrimal tissue with a large excretory duct that had a spiraling lumen (Fig. 1E) lined by cuboidal cells with a subjacent smaller population of basal germinal cells (Fig. 1F). Fibroadipose tissue separated lobules of lacrimal gland tissue which were composed of cuboidal to pyramidal acinar cells with an intensely eosinophilic, granular cytoplasm forming indistinct-to-small lumens (Fig. 2A). The cytoplasmic granules were periodic acid Schiff reaction-positive (Fig. 2B) and diastase resistant.

Immunohistochemical staining for cytokeratin (CK)7 was positive in the adluminal cells of the acini and intralobular ductules (Fig. 2C). Antibodies against CK5/6 immunoreacted strongly with the abluminal myoepithelial cells and outer basal cells of the intralobular ductules (Fig. 2D); CK14 displayed a similar pattern (Fig. 2E). Gross cystic fluid disease protein-15 was discovered in the cytoplasm of the acinar cells but not in the ductules (Fig. 2F). The most striking observation was the focal presence of brightly eosinophilic intralobular, periductular polygonal squamous (epidermoid) cells that surrounded the luminal cuboidal cells (Fig. 3A). These cells possessed small, oval-to-round regular nuclei bereft of nucleoli and mitotic figures. They also encroached on the acini (Fig. 3B), eventually leading to their partial-to-total replacement in some lobules and the lining cells of ectatic ductules (Fig. 3C).

The squamous cells immunostained for the presence of CK5/6. These cells formed demilunes as they progressively replaced increasingly larger portions of many of the acini (Fig. 3D, E and F). The squamous cells became the predominant lining cells of the ductules which lost their CK7 positivity (Fig. 4A). Ectasia of squamified ducts (Fig. 4B) was occasionally seen, but their lumens did not contain any obstructed secretory material. CK14 was discovered in the outermost basal cells of the squamous cuffs (Fig. 4C). GCFDP-15 (Fig. 4D) and smooth muscle actin (Fig. 4E, left panel) were both negative in these cells. P63 stained the nuclei of the squamous cells and the acinar myoepithelial cells but not the adluminal ductular or acinar cells (Fig. 4E, right panel). Epithelial membrane antigen stained the apical or lateral cell membranes of the acinar cells (Fig. 4E, right panel). The diffuse disappearance of this pattern indicated ductulization of the acini (Fig. 4F).

4. Discussion

4.1. *Background and spectrum of findings in GS*

GS was first described by von Arlt in the 19th century. It was eponymously named after the Belgian ophthalmologist Maurice Goldenhar (1924–2001) subsequent to his article in the European literature in 1952.[11] The syndrome is attributed to anomalous development in the late first trimester of structures related to the formation of the first and second branchial arches, namely the ear, maxilla, mandible, and central face. GS has variable expressivity and is mostly