Pharyngeal Presentation of Goltz Syndrome: A Case Report with Review of the Literature

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Abstract Focal dermal hypoplasia (Goltz syndrome; GS) is an X-linked dominant disorder caused by a mutation in the porcupine homolog (PORCN) gene and is typically embryonically lethal for males. The presence of disease in males is usually the result of post-zygotic mutation, but may also be due to mosaicism. The presentation of this disorder is highly variable, but generally is characterized by cutaneous, skeletal, ocular, oral, dental, and aural defects. Cutaneous manifestations include foci of hypoplastic skin, abnormal pigmentation, and papillomatous growths. We present both the first case of a patient with GS related laryngeal obstruction due to papillary lymphoid hyperplasia in an adult, and the first case in a male patient. Clinical, histologic, and genetic features of the disease are discussed. Operative technique for management of the patient with pharyngeal lesions is detailed, and intraoperative photos are showcased. The challenge in airway evaluation and management is also highlighted as manifestations of GS are rarely encountered in the airway and can cause laryngeal obstruction.

Keywords Goltz syndrome · Papillary lymphoid hyperplasia · Focal dermal hypoplasia · PORCN gene

Introduction

Focal dermal hypoplasia (FDH; Goltz syndrome; GS) is an X-linked dominant disorder originally described by Goltz et al. [1]. It is caused by mutation of the porcupine homolog (PORCN) gene, of which more than 80 mutations have been reported [2]. The presentation of this disorder is highly variable. GS is typically lethal in utero for affected males; however, the presence of disease in males has been documented and is usually the result of post-zygotic mutation.

We present a case of a 38-year-old male with GS who incidentally was found to have laryngeal obstruction due to papillary lymphoid hyperplasia, a rare manifestation of the disease. Review of the literature revealed that this manifestation of GS has only been observed in four pediatric females.

Case Report

The patient is a 38-year-old male diagnosed with GS in 2005 by Dermatology via biopsy of a skin lesion. The skin lesion specimen revealed herniation of adipocytes into the dermis. This patient had no prior family history of the disorder. The patient suffers from masses in left thigh with papillomatous “frog spawn” papules, verrucous changes in the skin, and peripheral hyperpigmentation. Other manifestations of his disease include syndactyly of toes on left and right feet, and Blaschkoid atrophic plaques on the trunk with telangiectasias.

The patient was scheduled to undergo excision of bilateral thigh skin lesions. Upon intubation by the Anesthesiology team, a large papillomatous mass was noted in the oropharynx. Once a secure airway was established, and

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prior to initiating surgery, an intraoperative consultation with the Otolaryngology service was sought for further evaluation of this large pharyngeal mass.

Direct laryngoscopy showed exophytic papillomatous masses arising from the right base of tongue, the left anterior tonsillar pillar and soft palate, and small lesions on the upper and lower lips. A biopsy was performed and a microdebrider was used to remove the obstructing portion of the lesion from the base of tongue, with the goal of providing a more patent airway. All debried material was collected for pathological examination. The patient left the operating room in stable condition.

On an outpatient basis the patient was re-evaluated and informed of his findings. The mutual decision was made to remove the remaining obstructing lesions. The patient returned to the operating room approximately 3 weeks after the first procedure. Intraoperative findings showed an exophytic mass arising from the right base of tongue, obstructing a clear view of the epiglottis and larynx (Fig. 1a). Lesions were also present on the right lateral pharyngeal wall, left anterior tonsillar pillar and soft palate, as well as on the upper lip.

A microdebrider was used to remove the pharyngeal lesions, and all the specimens were sent to pathology for review. The pharynx and larynx were re-examined, showing significant improvement of airway patency (Fig. 1b).

Histologic sections showed papillary structures lined by non-keratinizing squamous epithelium (Fig. 2). The epithelium had no evidence of koilocytic change, dysplasia, or hyperplasia. The papillary cores contained prominent lymphoid proliferation containing lymphoid follicles, which demonstrated features of reactive follicles, including eccentric germinal centers, tingible body macrophages, and variable follicle sizes. There was no evidence of lymphoma or carcinoma. Invaginations of squamous epithelium into the lymphoid component were

present, similar in morphologic appearance to epithelial crypts in the palatine tonsil. These were infiltrated by lymphocytes and demonstrated reactive changes. The combined epithelial and lymphoid elements in the papillary structures were thus strikingly reminiscent of palatine tonsil histology. Based on the combined findings, the specimen was diagnosed as papillary lymphoid hyperplasia. The histologic features of the specimens were identical. At 3 month follow-up, no residual or recurrent pharyngeal lesions were noted.

Discussion

Focal dermal hypoplasia is caused by mutation of the *PORCN* gene, of which more than 80 mutations have been reported [2]. The *PORCN* protein is a protein of the endoplasmic reticulum with *O*-acyltransferase activity, involved in the post-translational processing of the wingless-type mouse mammary tumor virus integration site (*Wnt*) protein, which is involved in ectomesodermal tissue development. The presentation of this disorder is highly variable, but generally is characterized by cutaneous, skeletal, ocular, oral, dental, and aural defects. Cutaneous manifestations include foci of hypoplastic skin, abnormal pigmentation, and papillomatous growths. Skeletal manifestations include syndactyly, polydactyly, microcrania, and facial asymmetry. Other findings may include hypertelorism, microphthalmia, malocclusion, and papillary gingival hyperplasia, as well as sensorineural and/or conductive hearing loss.

GS is typically lethal in utero for affected males. Disease incidence and prevalence estimates are not currently available, however there are approximately 250 reported cases in the literature [2]. Older reports estimated that 90 % of patients with GS were female [3]. The presence of

Fig. 1 **a** Preoperative findings—papillary lesions obstructing a clear view of the epiglottis and larynx. **b** Postoperative appearance—improved patency of the airway after removal of the lesions

Fig. 2 **a** (H&E, $\times 40$ magnification)—papillary structures with thin overlying epithelium and cores containing an exuberant lymphoid proliferation with lymphoid follicles and germinal centers, **b** (H&E, $\times 200$)—invaginations of squamous epithelium are present within the substance of the lymphoid proliferation, similar in morphology to the crypts in the palatine tonsil, **c** (H&E, $\times 400$ magnification)—the squamous epithelium lining the papillary structures is banal, showing no koilocytic change, dysplasia, or hyperplasia

disease in males is usually the result of post-zygotic mutation, but may also be due to mosaicism. Males may also survive in the setting of coexisting Klinefelter syndrome [4]. Familial cases are rare, but in some reports

anticipation has been observed [5–7]. Even in familial cases the presentation can be quite variable [8].

In a more recently developed animal model for GS, mutations of *PORCN* were found to be lethal in utero even for many heterozygous females [9]. In this animal model it was also shown that severe cranial neural tube defects were present in the animals that died in utero, but not in the live births [9]. This correlates to observations of affected humans, in that patients with GS typically do not have neural tube defects and are of normal intellect. The animal study suggests that the lethal nature of neural tube defects in GS is evidence for the low prevalence of such defects in GS patients.

Papillomatous lesions with lymphoid hyperplasia have only been reported in four patients with GS, and all were female children (ages 3, 8, 13, and 14 years) [10–12]. To the authors' knowledge this is both the first case of a patient with GS related laryngeal obstruction due to papillary lymphoid hyperplasia in an adult, and the first case in a male patient. While these lesions are benign, and appear to infrequently cause respiratory complaints in affected patients, they could certainly lead to airway distress as a presenting symptom as well as complicate airway management in the operative setting.

Among the other tissue types previously reported to be affected by GS, there are now several reports of involvement of lymphoid tissues. Lymphoid hyperplasia has a predilection for both pediatric patients and female patients. Notably, there have been no reports of malignancy associated with these hyperplastic lesions.

Conclusion

The authors present a unique case of an adult male with GS encountered as an intraoperative consultation due to the presence of laryngeal obstruction at the time of intubation. Goltz syndrome is a rare disease with airway manifestations of GS being extraordinarily exceptional. Experience with this patient has demonstrated that hyperplastic lymphoid lesions in the setting of GS can cause laryngeal obstruction and potentially complicate airway management.

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