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ORIGINAL ARTICLE

Lipoid proteinosis: A case report with recurrent parotitis and intracranial calcifications

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Abstract Lipoid proteinosis is an autosomal recessive disease of abnormal deposition of glycoprotein in various tissues. Symptoms may include a hoarse voice, lesions and scarring on the skin, easily damaged skin with poor wound healing, dry, wrinkly skin, and beading of the papules around the eyelids. Calcifications of brain tissue can lead to epilepsy and neuropsychiatric abnormalities. In this paper we will review the current literature on the disease and report a case of a 15 year old Saudi female with lipoid proteinosis that presented initially with recurrent parotitis.

1. Review of the literature

Lipoid proteinosis (also named hyalinosis cutis et mucosae, lipoidosis cutis et mucosae, or Urbach-Wiethe disease) is an autosomal recessive disease of abnormal deposition of glycoprotein in various tissues, most notably skin and mucous membranes, although the brain and other internal organs may also be affected (Gorlin, 1969; Hamada et al., 2002; Chan et al., 2007). The disease is caused by reduced expression of the extracellular matrix protein 1 gene, ECM1, on chromosome 1q21 (Hamada et al., 2002; Chan et al., 2007). There is an increase in mRNA for Type IV procollagen resulting in underproduction of fibrous collagens and overproduction of basement membrane collagens, which tend to deposit in the skin and various organs, which is the characteristic feature of the disease (Rajendran and Sivapathasundharam, 2009).

It is described in the literature as rare (Uchida et al., 2007; Javeria et al., 2008; Santana et al., 2010), however there is a higher prevalence of the disease in populations where it is common to have consanguineous parents (Baykal et al., 2007; Chan et al., 2007; Al-Aboud and Al-Natour, 2008; Al-Natour 2008; Javeria et al., 2008), which may explain the frequent finding in the Saudi population. The South African population also has a relatively higher prevalence of the disease due to the *founder effect* after the introduction of the mutation into the country by a German settler (Chan et al., 2007).

In clinical practice, lipoid proteinosis is rarely a life-threatening condition, and although autopsy studies have shown it to be a generalized disorder with microscopic deposits of hyaline material in practically every organ, symptoms related to the viscera have not been described (Di Giandomenico et al., 2006). Although its features are variable, the disease is characterized

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predominantly by hoarseness of the voice and flesh-colored papules and nodules involving the skin and mucosa (Gorlin 1969; Hamada et al., 2002; Di Giandomenico et al., 2006; Chan et al., 2007).

Hoarseness of the voice, which is usually the first sign of the disease, may present as an inability of infants to cry at birth, or may develop soon after birth, but occasionally may develop after some years. The hoarseness is due to nodules being deposited in the epiglottis and larynx. Rarely, severe cases may develop dyspnea, leading to death in some cases (Leonard et al., 1981; Ozbek et al., 1994; Bazopoulou-Kyrkanidou et al., 1998; Di Giandomenico et al., 2006). The classic and most easily recognizable sign of intradermal nodules is beaded eyelid papules. The involvement of the eyelids may be followed by loss of cilia. Deposition of the nodules may also involve the skin of the face, neck, hands, axilla, scrotum, perineal areas and intergluteal cleft. Hyperkeratotic lesions may present on areas exposed to extension and flexion such as the hands, knees, elbows, and proximal interarticular surfaces of the fingers (Gorlin 1969; Hamada et al., 2002; Chan et al., 2007; Uchida et al., 2007). Rarely, the hyaline deposits may also cause ophthalmic abnormalities (Chan et al., 2007; Mandal et al., 2007), and obstruction of the nasolacrimal duct (Ostrovsky et al., 2007). Photosensitivity may also be associated with this condition (Chan et al., 2007). In some cases the mucocutaneous lesions may manifest as vesiculobullous lesions, which later become erosive, and may heal by scarring (Rao et al., 2008; Bahhady et al., 2009).

Intraorally, the deposits are usually very marked, involving much of the oral mucosa (Chan et al., 2007), and usually appear before puberty and gradually increase in severity. The lips may be thickened due to the deposits and the tongue may be thick and firm to palpation with loss of the dorsal papilla (Gorlin 1969; Neville et al., 2002). Infiltration of the lingual mucosa causes thickening of the sublingual frenum, limiting tongue movements and causing speech difficulties (Di Giandomenico et al., 2006; Chan et al., 2007). The buccal mucosa may have a cobblestone appearance and be firm to palpation.(Gorlin 1969; Hamada et al., 2002; Neville et al., 2002) Other oral manifestations may include gingival hypertrophy, xerostomia, and dysphagia (Bazopoulou-Kyrkanidou et al., 1998; Di Giandomenico et al., 2006; Chan et al., 2007; Uchida et al., 2007), as well as congenital absence of the teeth and enamel hypoplasia (Gorlin 1969; Neville et al., 2002). Recurrent ulceration associated with the xerostomia in lipoid proteinosis has been reported (Sargenti Neto et al., 2009). The findings of a hoarse voice and an inability to fully protrude the tongue are the most reliable clinical diagnostic features of lipoid proteinosis (Chan et al., 2007).

Recurrent inflammation of the parotid and submandibular glands may also occur, due to stenosis of the parotid duct by the surrounding deposits, and there have been reports of reduced salivation and dryness of the mouth associated with lipoid proteinosis (Chan et al., 2007; Neville et al., 2002). Some of the patients developed progressive dryness of the mouth in the fourth and sixth decades of life (Disdier et al., 1994; Aroni et al., 1998), while others have noticed it earlier on in childhood (Bazopoulou-Kyrkanidou et al., 1998).

Intracranial and neural involvement are other frequently encountered features of lipoid proteinosis. Bilateral, circumscribed, and symmetrical calcifications in the medial temporal regions, lateral to the sella turcica, are common (Leonard et al., 1981; Ozbek et al., 1994; Siebert et al., 2003; Thornton et al., 2008). However the incidence of such calcifications is difficult to estimate as only a limited number of affected subjects undergo brain imaging (Chan et al., 2007). High-resolution CT examination of the intracranial calcifications in two affected siblings revealed a bony structure consisting of cortical and medullar components (Ozbek et al., 1994), therefore it was suggested that the term "ossifications" should be used instead of "calcifications". The osseous nature of these lesions is supported by the fact that the ECM1 gene is thought to have a role as a negative regulator of endochondral bone formation, inhibiting alkaline phosphatase activity and mineralization (Hamada et al., 2002).

Although this disease is well documented in the medical literature, it is not widely recognized in the dental field. Furthermore, although recurrent parotitis is a common feature of this disease (Chan et al., 2007) we have been unable to find a documented description of the CT appearance of the parotid gland or sialography findings in affected individuals with repeated parotitis. Therefore, we report the clinical findings in Saudi siblings with lipoid proteinosis, and the panoramic, CT, and sialography findings from one of the siblings whose chief complaint was recurrent parotitis.

2. Case report

2.1. Clinical features

2.1.1. Sibling 1

A 15 year old female was referred to the Oral and Maxillofacial Radiology (OMFR) clinic by a maxillofacial surgeon for sialography of the left parotid gland to investigate glandular function after repeated episodes of acute infection of the gland. The patient had a history of three episodes of acute infection occurring within a six month period, and the latest was associated with suppuration which was drained intraorally by probing Stensen's duct. Afterward, a localized swelling developed in the left cheek. The swelling was incised and found to contain saliva.

When the patient presented to the OMFR clinic, the initial presenting feature was hoarseness of the voice. A scar was noted in her left cheek and pus could be expressed from the left Stensen's duct. Reduced, viscous saliva was expressed from the right duct. The patient also had dermal papules in her eyelids and widespread submucosal nodules in the mucous membranes of the buccal mucosa, tongue, and lips (Fig. 1a and b). Multiple missing teeth were noted with bad oral hygiene and high carious activity in the existing teeth. Antibiotics and saline mouth rinses were prescribed to control the acute phase of the infection prior to attempting sialography.

2.1.2. Sibling 2

The patient was the offspring of consanguineous parents, and there was a history of mucosal abnormalities in her older sister and younger brother, as well as a maternal uncle. Therefore, the family was requested to undergo clinical examination, however only her younger brother was brought in for examination because the parents stated that only the younger brother exhibited marked mucosal abnormalities. The older sister had a history of hoarseness of the voice which resolved after endoscopic removal of nodules on the vocal cords. According