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Lipoid proteinosis of the larynx

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Abstract
Lipoid proteinosis is a rare disease that presents with hyaline deposits in many tissues. It involves predominantly the skin and upper aerodigestive tract, presenting with small yellowish papules and hoarseness. It may involve the central nervous system and cause intracerebral calcifications. Laryngeal lesions may resemble singer's nodule or chronic laryngitis. The pathogenesis of the disease is not clear although several studies suggest a defective collagen production and/or lysosomal storage disease. In this article two cases with skin and larynx involvement are reported.

Key words: Larynx; Hyalin; Dysphonia

Introduction

Lipoid proteinosis, hyalinosis cutis et mucosa, or Urbach-Wiethe disease is a rare disease that displays many systemic manifestations. About 300 cases are reported in the literature. Although many different systemic manifestations are possible, the disease predominantly involves the skin and upper aerodigestive tract. The association of early hoarseness with unusual skin eruptions suggests the diagnosis. Laryngeal changes resulting in hoarseness may be present at birth and are often the first sign of the disease. Papular, bead-like infiltration of the eyelids, acne-like lesions of the skin and alopecia areata are other common findings. Although rare, calcifications in the temporal lobes of the brain leading to neuropsychiatric problems and seizures are considered to be pathognomonic.[1] The disease is characterized by diffuse deposition of hyaline material and lipids in the mucosa and dermis, hence the name lipoid proteinosis. Recent reports suggest that the deposition is due to impaired collagen production and/or defect in lysosomal storage.[2–4] Although neither the exact pathogenesis nor the defective gene(s) have been identified, autosomal recessive inheritance has been documented by the studies of Gordon *et al*.[5]

Case reports

Case 1

A nine-year-old girl with hoarseness was referred to our clinic from the dermatology department. The family stated that hoarseness was present at birth. The patient had a weak cry and the hoarseness had progressed with time. Speech started at the age of two, but the patient tired easily while talking. At the age of 30 months inflammation and plaque developed at the coronal region of the scalp. Later the inflammation disppeared leaving an area of alopecia. The patient presented at the dermatology clinic with this complaint. Dermatological examination revealed atrophic alopecia plaques, as well as yellowish papules and ice-pick scars on the forehead and along the rims of the eyelids.

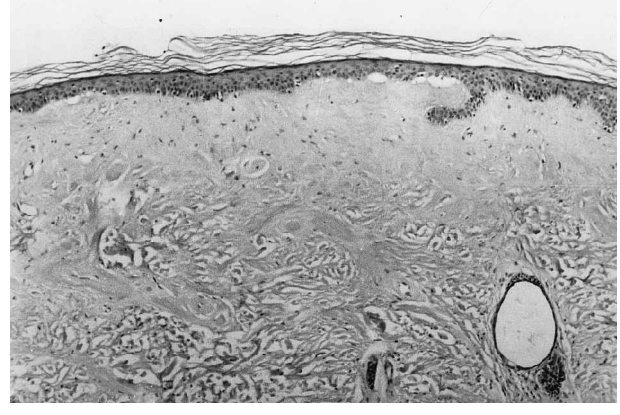

Fig. 1
Skin biopsy demonstrating hyaine deposits around blood vessels and skin appendages. ((H & E; ×100).

Biopsy from the lesions revealed atrophy, elongation and anastomosis of rete ridges and hyaline material, concentrating around the blood vessels and skin appendages, that stained with periodic acid-Schiff (PAS) and was diastoresistant. The deposits did not stain with Congo red (Figure 1).

The patient was referred to the ENT department for evaluation of the larynx and upper aerodigestive tract. Physical examination revealed hypertrophied gingiva and frenulum. The tongue was enlarged and its mobility was reduced. There were several yellowish plaques on the posterior wall of the pharynx. The teeth were yellow in colour. The voice was hoarse and the patient tired easily while talking. There were articulation problems secondary to the reduced mobility of the tongue and soft palate. Videolaryngoscopy revealed thickening of the epiglottis, arytenoids and irregularities along the rims of the vocal folds due to yellowish papules (Figure 2). The changes

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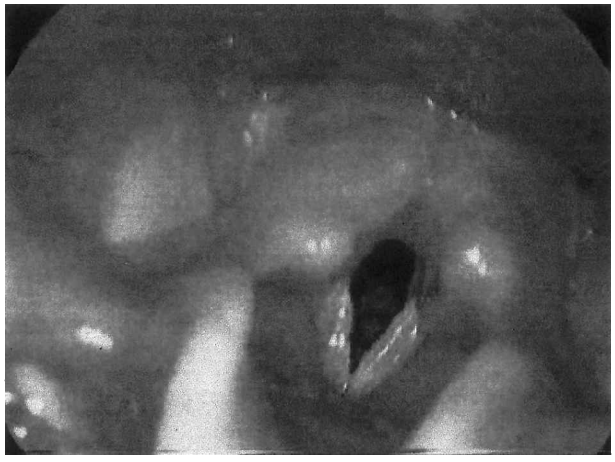

FIG. 2

Endoscopic view of the larynx of *Case 1*. Papules can be observed along the borders of the vocal folds.

resulted in incomplete closure of the vocal folds and thus hoarseness. Impaired mobility and wave formation were observed on videostroboscopy.

Direct laryngoscopy and biopsy were performed under general anaesthesia. Diffuse thickening of the epiglottis and endolarynx was observed. The vocal folds had irregular, bumpy surfaces with yellowish papules. The biopsy taken from the left vocal fold showed a deposition of hyaline, eosinophilic material in the submucosa and around the blood vessels. These deposits showed a positive reaction to the PAS stain and a negative reaction to the Congo red stain (Figure 3).

The patient did not have any neurological problems. Skull films and computed tomography (CT) of the cranium did not reveal any pathological changes. Neurobehavioural analysis did not reveal any problems in the cognitive and memory functions of the patient. The child psychiatry department found the patient normal except for depression in both the child and the parents.

After the evaluation was complete the patient was given 20 mg/kg/day etretinate orally. The patient was informed about the possible side-effects of the drug. No response to the treatment was observed at the end of nine months of follow-up.

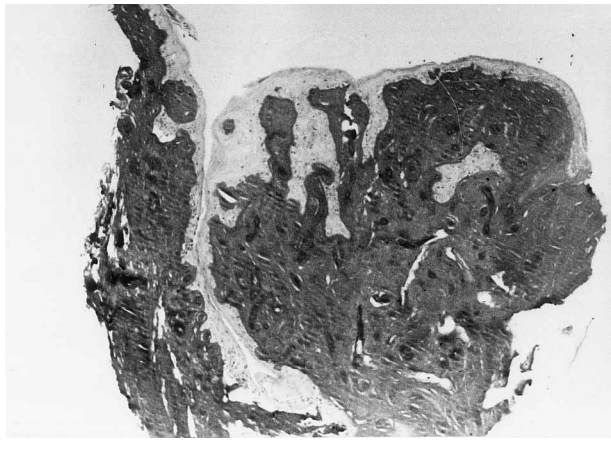

FIG. 3

Biopsy from the vocal fold of *Case 1*. Diffuse submucous hyaline deposits that stain PAS(+). (PAS stain; ×100).

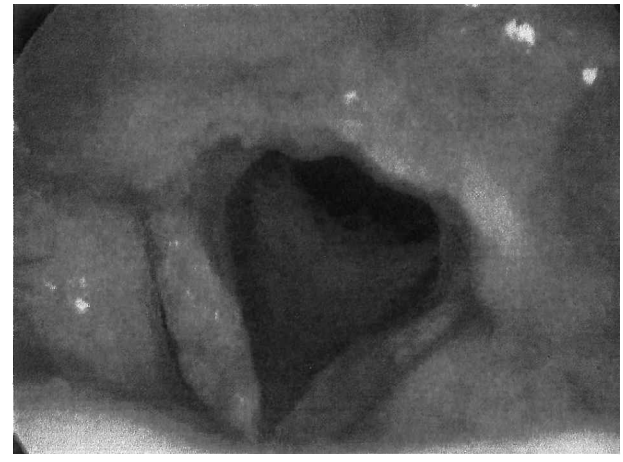

FIG. 4

Endoscopic view of the larynx of *Case 2*. Papules coalesce to form a mass on the right vocal fold.

Case 2

A 21-year-old woman presented to our clinic with hoarseness. The hoarseness was not present at birth. Speech had started at 16 months of age. She tired easily while speaking. At about age 12, hoarseness started. As a child she had received several antibiotics for recurrent laryngitis. The voice did not improve with this therapy. The family accepted her voice and she was not evaluated until the age of 21. Six months ago she applied to an otolaryngology department of a social insurance hospital. After she was treated with oral antibiotics for three weeks, the patient was diagnosed as having vocal fold nodules and referred to our clinic. Videolaryngoscopy revealed numerous yellowish papules, which caused incomplete closure of the vocal folds, as well as thickened aryepiglottic folds (Figure 4). Impaired wave formation due to these papules was detected by videostroboscopy. Twenty-four hour double probe pH monitoring was performed. Intermediate degree laryngopharyngeal reflux was detected and lansoproazole 30 m b.i.d. was given. After one month of follow-up the vocal folds were biopsied under general anaesthesia. Histopathological examination revealed submucosal hyaline material that concentrated around the blood vessels (Figure 5). These deposits did not stain with Congo red and showed a positive reaction with the PAS stain. The patient was thoroughly examined and yellowish

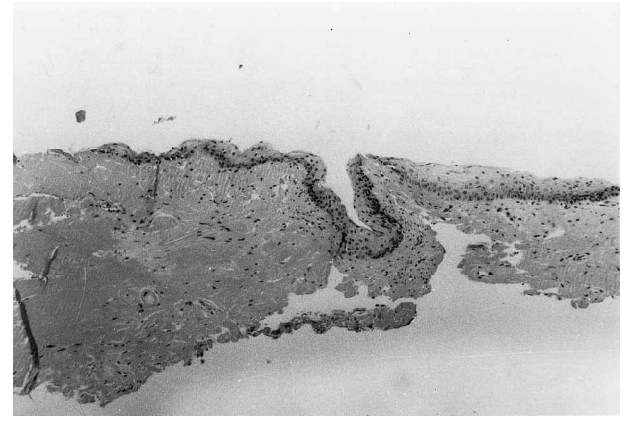

FIG. 5

Biopsy from vocal fold of *Case 2*. Diffuse submucous deposits. (H & E; ×100).

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papules on the rims of the eyelids and along the border of the soft palate were noted as well as mild plaque formation on the lips. A biopsy was taken from the lower lip. Hyaline material around the blood vessels and skin appendages was noted. The material was PAS(+) and diasto-resistant. Psychiatric evaluation was normal except for mild depression. The patient did not have any neuropsychiatric problems. Cranial computed tomography (CT) was not performed because of economic problems.

The patient has an uncle and a niece who have similar symptoms. They were not accessible because they live in another country. No therapy was given to the patient because there were no prominent skin symptoms.

Discussion

Urbach and Wiethe first described lipoid proteinosis in 1929. Since then approximately 300 cases have been reported in the literature. Almost a quarter of the reported patients are residents of South Africa. The disease was demonstrated to be familial. Gordon *et al*. reported numerous cases in an inbred South African community demonstrating the autosomal recessive inheritance.[5] Newton *et al*. reported an affected brother and sister of Lebanese origin whose parents were second cousins.[1] Costagliola *et al*. performed ultrastructural evaluation on the lesions of six lipoid proteinosis cases from the same family.[6] Although no other affected family member is known for *Case 1*, *Case 2* has possible affected family members: an uncle and a niece.

The earliest manifestation of the disease is hoarseness. A hoarse or weak cry is usually present at birth, but may present in later ages as in *Case 2*. Hofer *et al*. reported hoarseness at birth in 26 of 27 cases in 1974.[7] Hoarseness is very consistent and may progress with age. There are no worsening factors although some cases are badly affected by damp weather. Physicians not familiar with this disease may mistake the laryngeal findings for more common diseases such as chronic laryngitis or singer's nodule, especially in the absence of skin lesions. *Case 2* was misdiagnosed as recurrent laryngitis and vocal fold noldules. Thus the disease is easily overlooked. It is possible that the disease occurs more frequently than the reported 300 cases.

Laryngeal lesions range from small irregularities along the rims of the vocal folds to vegetative lesions in the larynx necessitating tracheotomy. Changes in the vocal folds are described in 75 per cent of the reported cases. Epiglottic changes are reported in 45 per cent.[7] The two cases had irregular vocal folds due to yellowish papules but did not have any visible pathology on the epiglottis. The cause of hoarseness was impaired wave formation due to subepithelial hyaline material deposits as well as incomplete closure of the vocal folds with air leakage during phonation.

Skin manifestations are usually not present at birth. They may appear at any age or not at all. The most typical lesion is bead-like papules along the rim of the eyelids (moniliform blepharosis). Such lesions and scars due to these lesions were present in both cases. Acne-like lesions are usually present on the forehead and elbows and axilla.[8] The lesions usually heal with ice-pick scars. Alopecia, which was the prominent symptom of *Case 1*, may be present due to plaque formation in the scalp.

Patients with lipoid proteinosis may display neuropsychiatric problems. Meenan *et al*. indicated that bilateral intracranial calcifications are found in at least 70 per cent of cases.[9] Emsley *et al*. reported that calcifications are located in the temporal lobes.[10] These calcifications may cause seizures as well as memory defects and rage attacks. Adolphs *et al*. studied a 30-year-old woman with lipoid proteinosis, that had caused a nearly complete bilateral destruction of the amygdala.[11] This unusual patient had lost the ability to recognize emotions of the human face. Our cases did not have any neuropsychiatric symptoms nor any neuropsychiatric problems. There are also rare manifestations of the disease such as intestinal changes[12] and xerostomy,[13] that were not present in our cases.

The pathogenesis of the disease is not clear. Recent studies indicate two different, or maybe related, pathological changes. Hyaline material that is concentrated on junctional zones of the epidermis and mucosa, dermal and mucosal vessels and appendages such as eccrine sweat glands in the skin and minor salivary glands in the mucosa are demonstrated to be rich in type IV collagen[3,14] and lipid-containing epithelial cells.[2,4] Olsen *et al*. demonstrated an increased amount of alpha 1 (IV) collagen mRNA in cultured fibroblasts of patients with Urbach-Wiethe disease.[3] Navarro *et al*. reported accumulation of ceramide and more complex lipids accumulating in epithelial cells.[2] A recent article by Costagliola *et al*. reported a decreased amount of mucopolysaccharides, sialic acid and hexosamine in the affected regions of the skin suggesting a defect (possibly enzymatic) in glycoprotein synthesis.

There is no proven treatment for Urbach-Wiethe disease. Life expectancy is normal for these patients. Surgical interventions such as tracheotomy for airway obstruction may be necessary. Oral dimethyl sulphoxide (DMSO) treatment was reported to be beneficial in one patient after three years of use,[15] but a more recent study reported DMSO not effective in three patients.[16] Oral etretinate has been shown to produce a clinical response after three months treatment.[17] We administered etretinate to *Case 1* at a dose of 20 mg/day. We did not observe any beneficial effects in six months of follow-up.

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