Hyalinosis Cutis et Mucosae: Diagnosis Based on Oral Manifestations – Report of a Case

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Hyalinosis cutis et mucosae is a rare, autosomal recessive disorder characterized by diffuse deposition of a hyaline-like material in the skin and mucous membrane of the oral cavity, upper respiratory tract, and internal organs. In the first weeks of life it begins with typical hoarseness due to hyaline deposits in the larynx. Rough, yellowish-white papular deposits in the skin and the oral mucosa usually develop during childhood. The etiology and pathogenesis are unknown and the treatment is only symptomatic.

A 14-year old boy developed several typical clinical features of the disease since birth and remained undiagnosed until he was referred by his dentist to our department for oral evaluation. The clinical, histopathological and immunological aspects of the patient are discussed in detail. Oral and systemic manifestations of the disease are also reviewed.

The oral mucosa appeared nodular, diffusely enlarged and thickened because of infiltration with waxy-yellowish-white plaques and nodules. The patient also exhibited a thickened, furrowed appearance of the skin with several skin scars, eyelid nodules, loss of eyelashes and voice hoarseness. The clinical diagnosis of hyalinosis cutis et mucosa was confirmed histologically.

Keywords: *hyalinosis cutis et mucosae, lipoid proteinosis, hyaline oral mucosa, infiltration*

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INTRODUCTION

Hyalinosis cutis et mucosae (HCM), also known as lipoid proteinosis (LP), was first described by a Viennese dermatologist and an otorhinolaryngologist, Urbach and Wiethe, in 1929.[1]

It is an uncommon, autosomal recessive inherited disorder, characterized by deposition of a hyaline-like material primarily in the mucous membranes of the larynx and pharynx, in the skin and several internal organs.[2,3]

Lipoid proteinosis appears to be more frequent in some countries where consanguinity is common. More than 250 cases of HCM disorder have been described in the literature.[4,5] Familiar aggregation of the disorder has been reported in a group of LP cases in South Africa.[6] Parental consanguinity has been implicated in the etiology of the disorder; however, there is insufficient evidence to support this opinion.[4,7]

Hoarseness is among the initial clinical signs of LPS, caused by infiltration of the laryngeal mucosa with a hyaline-like material and starts either at birth or during the first years of life. Bead-like papules along the margins of the eyelids are typical of this disorder. Dental abnormalities, recurrent parotitis and nail dystrophy are also common findings in the LP patient.[8,9]

The disease occurs with equal frequency in both genders, and the age of diagnosis ranges from 6 months to 67 years. It has recently been shown that the loss of functional mutations in the extracellular matrix protein 1 gene on chromosome 1q21 is the main cause of the disorder. This protein plays an important physiological and biological role for epidermal differentiation, skin adhesion, wound healing, binding of dermal collagens and proteoglycans, and regulation of angiogenesis.[10,11,12]

A 14-year old boy developed several typical clinical features of the disease since birth and remained undiagnosed until he was referred by his dentist to our department for oral evaluation. The clinical, histopathological and immunological aspects of the patient are discussed in detail. Oral and systemic manifestations of the disease are also reviewed.

CASE REPORT

His dentist referred a 14-year-old boy for an oral evaluation to the University of Athens School of Dentistry's Oral

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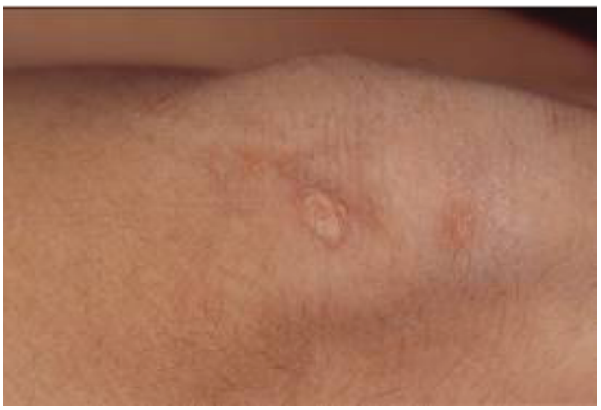

Figure 1. Multiple scars. (Knee)

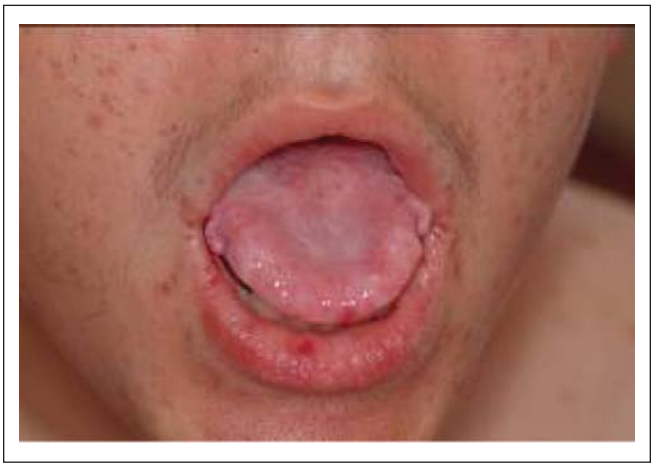

Figure 2. Restriction of the mouth opening.

Diagnosis and Radiology Clinic. There was no chief complaint. His parents reported the presence of a hoarse cry during infancy and hoarseness of his voice during early childhood. The medical history revealed recurrent episodes of both, parotitis and "ocular infection" during childhood. In addition, bullous skin eruptions following minor trauma with resulting scar formation were reported.

The patient was submitted to thorough radiographic, extraoral and intraoral clinical examinations including a panoramic radiograph.

The clinical examination revealed marked voice hoarseness. The skin of the face and neck was pale, thick and indurated with deep expression furrows.

Beads of small nodules and loss of eyelashes along the free margin of the lower eyelids were also identified. The skin of the body appeared pale, thick and indurated with deep furrows and multiple scars (Figure 1). Additionally, the patient presented a diffuse firm thickening of the extremities skin with hyperkeratosis in the knees, elbows and the back of the hand. A cluster of nodules forming wart-like lesions was noticed on the buttocks.

The patient's mouth opening was restricted (Figure 2). Radiating fissures were present at the commisures. The buccal mucosa was thick and indurated, infiltrated with waxy plaques. The Stensen's ducts appeared indurated. Both lips were rigid, thick and large, waxy and yellowish-white colored (Figure 3). The hard and soft palate mucosa and the uvula were thickened and indurated, infiltrated with waxy yellowish-white nodules and plaques. The tongue was thick and indurated, displaying mobility restriction due to lingual frenum induration. The tongue's surface was smooth and glossy with loss of papillae and presence of plaques in the dorsal central area.

The radiographic examination showed normal findings for this age group.

The patient was referred to the Department of Oral Pathology for further evaluation including a biopsy of the intraoral soft tissues.

The biopsy specimens were taken from the lower labial mucosa and light microsopic examination revealed extensive deposits of pink-grey homogeneous hyaline-like material in the perivascular and intramuscular area of the oral mucosa (Figure 4). Infiltration and replacement of the minor salivary gland parenchyma with a hyaline-like material and periduc-

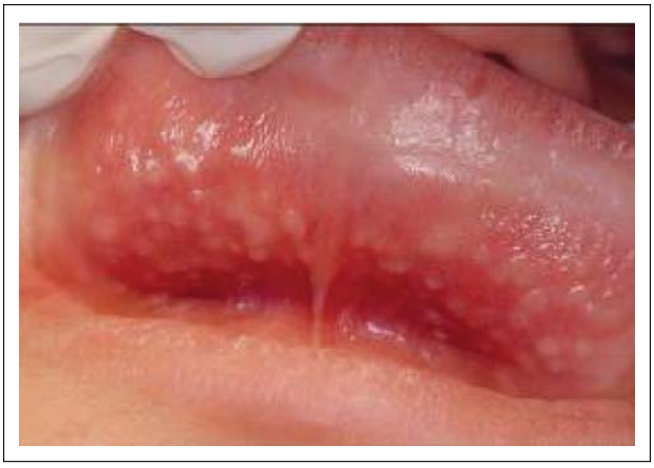

Figure 3. Thickened and indurated mucosa of the lips infiltrated with waxy, yellowish-white nodules and plaques

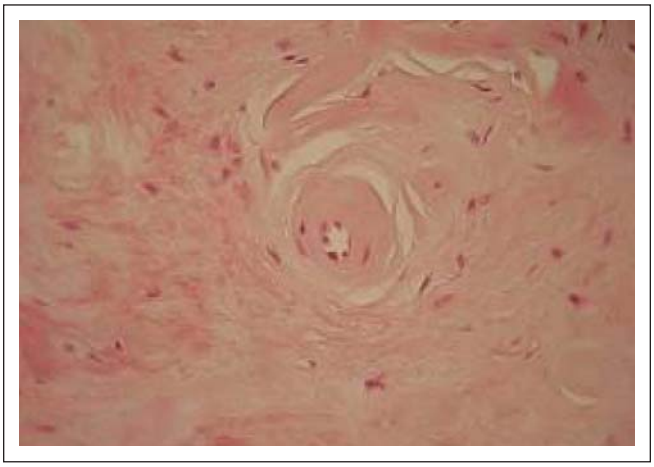

Figure 4. Perivascular deposition of a Hyaline-like substance. (H-E x 400)

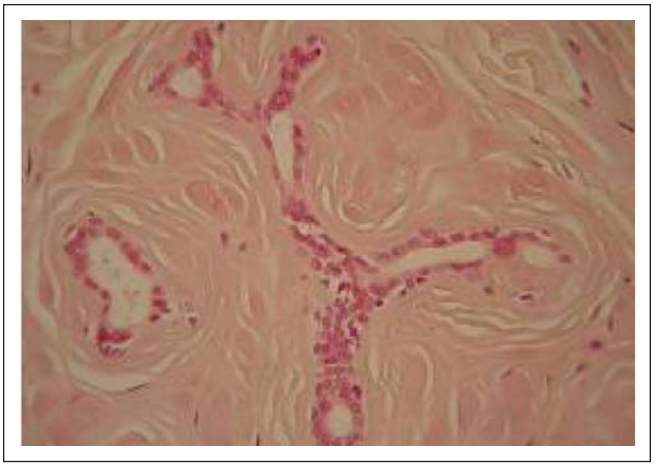

Figure 5. Infiltration and replacement of salivary gland parenchyma with hyaline-like material and periductal deposition of the substance. (H-E x 400).

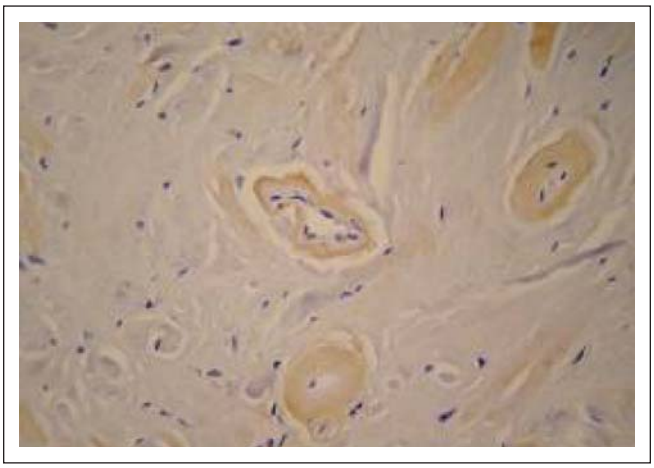

Figure 6. Collagen IV positivity of hyaline-like material. (ABC x 400)

tal deposition of the substance were also noticed (Figure 5).

The hyaline-like substance stained positive for periodic acid-Schiff reaction (PAS), resisting digestion by diastase and stained positive for collagen IV and laminin (Figure 6).

The histopathological and immunohistochemical findings established the diagnosis of Hyalinosis cutis et mucosae. The parents denied any history of consanguinity or any family history associated to this condition. The patient was referred to a dermatologist.

DISCUSSION

In the patient here described, the intraoral and extraoral clinical features were typical of HCM. These typical features of the disorder however, were undetected and the patient remained undiagnosed.

The clinical manifestations of HCM reported in the literature vary widely and depend on the organs involved and the extent of hyaline accumulation. In most cases, the initial clinical sign of HCM is hoarseness caused by hyaline material infiltration of the laryngeal mucosa and vocal cords or epiglottis.[5,6] The hoarseness may be present at birth or develop during the first years of life. In the present clinical case, the pediatrician had attributed the patient's hoarse voice to "an anatomical abnormality" of his vocal cords. In some cases, the infiltrative mucosal process may also involve the pharynx and esophagus resulting in dysphagia as well as, the vulva and rectum.[3,7,10]

The skin lesions include yellowish, waxy infiltrated papules, plaques and nodules, and are occasionally preceded by bullous eruptions.[11,12] Other typical signs include bead-like papules along the margins of the eyelids and facial acneiform or pock-like scars. Hyperkeratosis may occur in sites of chronic trauma, such as hand, elbow, knee, buttocks etc.[4,8] In this clinical case, there were eyelid papules and bullous skin eruptions following minor trauma, resulting in scar formation, as well as hyperkeratosis in all the typical sites of chronic trauma.

The oral cavity is the area most extensively involved. Mouth opening is restricted. The oral mucosa is thick and indurated, infiltrated with waxy plaques. The tongue becomes firm and woody, thickened, large and bound to the floor of the mouth and sometimes the dorsum loses its papillae and ulcers may develop. Furthermore, the infiltrates in the tongue and frenum limit mobility and cause speech difficulties. All these signs were present in our patient. Gingival involvement is uncommon.[13,14,15] Congenital absence of teeth and severe enamel hypoplasia have also been reported.[2] Parotid pain and recurrent swelling may indicate obstruction of Stensen's duct by infiltration of the buccal mucosa with hyaline material resulting in retrograde parotitis.[4,13] In this case, the recurrent parotitis was falsely diagnosed in the past as sialolithiasis.

Mucosal signs are present at birth or develop within the first years of life. Hoarse cry during infancy indicates early laryngeal involvement, as in the present case. The oral mucosal abnormalities usually become evident during the second decade of life.[16]

Characteristic deposits have been reported virtually in every organ of the body, even in the central nervous system, which results in epilepsy and neuropsychiatric abnormalities. "Beam-shaped" intracranial calcification located above the pituitary fossa in the hippocampus falx cerebri or temporal lobes has been reported in at least 70% of the cases older than 10 years of age. The intracranial calcification is pathognomonic and sometimes responsible for epilepsy or behavioral defects later in life.[4] The absence of neurological manifestations in our patient was probably due to his young age.

It has recently been shown that this disorder results from loss of functional mutations in the extracellular matrix protein 1 gene (ECM1) on 1q21 chromosome, leading to defective protein binding. ECM1 has an important physiological and biological role for epidermal differentiation, skin adhesion, wound healing, binding of dermal collagens and proteoglycans, and regulation of angiogenesis.[11,16,17]

In HCM, the lack of ECM1 could result in increased type IV collagen expression and typical histopathological changes.

Although various therapeutic modalities have been used for the management of this disorder, such as systemic administration of steroids, retinoids, dimethyl sulphoxide (DMSO) and intralesional heparin injections, their effectiveness is limited. CO_2 laser treatment of the vocal cords and beaded eyelid papules has been proved be helpful for some patients.[4] According to some authors, retinoid treatment should be avoided in childhood because of possible side effects on bone development.[10]

The success of surgical treatment is questionable because, according to some authors, trauma might increase hyaline deposition in the skin and mucous membranes.[10] Dermabrasion appears to have excellent topical results, long-lasting effects and no side effects.[10]

The detection of mutations in ECMI in LP cases provides the basis for the development of a more rational form of treatment including trials of recombinant ECMI protein and the development of somatic gene therapy for skin and respiratory mucosa.[4]

Some HCM cases have been reported to have common clinicopathological features with certain types of porphyria (e.g. erythropoietic protoporphyria) as well as some forms of cutaneous amyloidosis. However, the demonstration of pathogenic mutations in the ECMI gene in LP now provides a definitive mean of establishing a diagnosis of LP through molecular gene analysis.[11,17]

Generally, most patients presenting the HCM disorder have a normal life span. Prognosis is good and mortality is low, aside from the risk of respiratory obstruction because of stenosis of the larynx. However, the appearance of the skin and the vocal hoarseness may influence the quality of life of the affected patients.[4]

CONCLUSION

The role of the dentist in detecting oral signs of this disorder is important. Early detection of the oral signs of the HMC disorder may promote an early diagnosis and therefore, an optimal management.

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