Lipoid proteinosis

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Abstract

Lipoid proteinosis (LiP), also known as "hyalinosis cutis et mucosae" or "Urbach-Wiethe disease" is an autosomal recessive disorder that presents in early infancy with hoarseness, followed by pox-like and acneiform scars, along with infiltration and thickening of the skin and certain mucous membranes. So far, over 250 cases have been described throughout the world. Histological and ultrastructural examination reveals widespread deposition of hyaline-like material and disruption/reduplication of basement membrane around blood vessels and at the dermal-epidermal junction. LiP has been mapped to chromosome 1q21 and pathogenetic loss-of-function mutations have been identified in the extracellular matrix protein 1 gene (ECM1). This article reviews the clinico-pathological features, as well as the molecular basis of LiP.

Keywords: genodermatosis, dermal biology, genotype-phenotype correlation

Disease name / synonyms
- Lipoid proteinosis
- Hyalinosis cutis et mucosae
- Urbach-Wiethe disease.

Definition / diagnostic criteria

LiP is a rare, autosomal recessive disorder that presents in early infancy with hoarseness, followed by pox-like and acneiform scars, along with infiltration and thickening of the skin and certain mucous membranes (Hamada T, 2002). Histological and ultrastructural examination reveals widespread deposition of hyaline-like material and disruption/reduplication of basement membrane around blood vessels and at the dermal-epidermal junction (Aroni K et al., 1998, Muda AO et al., 1995). LiP has been mapped to chromosome 1q21 and pathogenetic loss-of-function mutations have been identified in the extracellular matrix protein 1 gene (ECM1) (Hamada T et al., 2002).

Differential diagnosis

Previously, some cases of LiP had been thought to have clinico-pathological features in common with certain types of porphyria (e.g. erythropoietic protoporphyria) as well as some forms of cutaneous amyloidosis (Hofer P, 1973, Parker JM, 1980, Touart DM et al., 1998). Some of the ultrastructural changes seen around blood vessels may also resemble abnormalities seen in diabetic microangiopathy (Hofer P, 1973).
However, demonstration of pathogenetic mutations in ECM1 in LiP now provides a definitive means of establishing a diagnosis of LiP through molecular gene analysis.

**Etiology**

Human ECM1 encodes a glycoprotein of unknown function, the counterpart to an 85-kDa secreted protein first identified in a murine osteogenic stromal cell line, MN7 (Bhalerao J et al., 1995, Johnson MR et al., 1997, Smits P et al., 1997). Previously it has been shown that ECM1 has key roles in bone mineralization, epidermal differentiation and in aspects of angiogenesis (Smits P et al., 2000, Deckers MM, 2001, Han Z et al., 2001). In addition, a key interaction has recently been demonstrated between ECM1 and perlecan, a major heparan sulphate proteoglycan of basement membranes (Mongiat M et al., 2003). Moreover, other recent studies have identified circulating autoantibodies against ECM1 in most patients with lichen sclerosus, a common acquired inflammatory skin disorder, that has several histopathologic features in common with LiP (Oyama N et al., 2003, 2004, Chan I et al., 2004a). These observations may indicate that one of the main functions of ECM1 in the dermis is to act as a form of "biological glue" maintaining dermal homeostasis, including regulation of basement membrane and interstitial collagen fibril macro-assembly as well as growth factor binding (Chan I, 2004).

**Clinical description**

The first clinical sign of LiP is hoarseness, caused by infiltration of the vocal cords. In most cases, it develops soon after birth or in the first year of life or, rarely, after a few years. The hoarse nature of the voice is one of the most striking clinical features in LiP (Nanda A et al., 2001). By contrast, skin lesions usually develop within the first few years of life or may appear later. The classic and most easily recognizable sign is the beaded eyelid papules (Bozdag KE et al., 2000), although the papular infiltration may be quite subtle in some patients. Other cutaneous changes may include waxy, yellow papules and nodules with generalized skin thickening. Hyperkeratosis may appear in regions exposed to mechanical friction, such as the hands, elbows, knees, buttocks and axillae. Skin infiltration can sometimes appear quite verrucous. During childhood, the skin may be easily damaged by minor trauma or friction, resulting in blisters and scar formation. Pox-like or acneiform scars are particularly visible on the face and extremities. Scalp involvement may lead to hair loss, although alopecia is not a significant finding in most cases of LiP. The mucosae of the pharynx, tongue, soft palate, tonsils and lips are also infiltrated and this may lead to respiratory difficulty, especially in association with an upper respiratory tract infection, sometimes requiring tracheotomy (Ramsey ML et al., 1985). Recurrent episodes of inflamed parotid and submandibular glands, poor dental hygiene, and short tongue with a thickened frenulum may all occur (Hofer P, 1973, Disdier P et al., 1994, Aroni K et al., 1998). Indeed, inability to protrude the tongue fully is a useful diagnostic sign. Other extracutaneous features may include epilepsy and neuropsychiatric abnormalities, sometimes in association with calcification in the temporal lobes or hippocampi (Friedman L et al., 1984, Kleinert R et al., 1987, Teive HA et al., 2004). The neuropsychiatric pathology may reflect dysfunction of the amygdala leading to abnormal perception of fear. Life expectancy of individuals with LiP is normal, aside from the risks of respiratory obstruction (Hofer P, 1973, van Hougenhouck-Tulleken W et al., 2004).

**Diagnostic methods**

Histologically, LiP is characterized by periodic acid-Schiff (PAS)-positive, but diastase-resistant, basement membrane thickening at the dermal-epidermal junction, surrounding blood vessels and adnexal epithelia, as well as deposition or accumulation of hyaline material in the dermis (Moy LS et al., 1987). Immunofluorescence labelling with anti-type IV collagen antibody shows bright, thick bands of staining at the dermal-epidermal junction and around blood vessels consistent with basement membrane thickening. (Aroni K et al., 1984). Similar findings are also observed for anti-type VII collagen immunostaining (Hamada T, 2002). Ultrastructural examination reveals concentric rings of excess basement membrane surrounding blood vessels and irregular reduplication of lamina densa at the dermal-epidermal junction (Moy LS et al., 1987). In addition, dermal fibroblasts demonstrate characteristic cytoplasmic vacuole formation (Bauer EA et al., 1981, Moy LS et al., 1987). Abnormal lysosomes with curved tubular profiles in dermal eccrine glands and histiocytes, similar to those seen in Farber disease, have also been demonstrated in patients with LiP, which was thought to reflect an abnormality in a degradation pathway of glycolipids or sphingolipids (Navarro C et al., 1999). However, demonstration of pathogenetic mutations in the ECM1 gene in LiP now provides a definitive means of establishing a diagnosis of LiP through molecular gene analysis. Over 20 pathogenic mutations have been detected, most of which are specific to individual families (Hamada T et al. 2002, 2003, Chan I et al. 2003, Chan I et al. 2004).
2004b, Teive et al. 2004). Mutations have been detected in all exons of ECM1, apart from the alternatively spliced exon 5a, but more than half of the mutations have occurred in exon 6 or the alternatively spliced exon 7 (Chan I et al., 2004b). Individuals with mutations in exon 7 tended to have slightly milder phenotypes but this was not universal. No genotype-phenotype correlation was identified for presence of intracranial calcification or neuropsychiatric abnormalities. Further mutation analysis in LiP patients will be necessary to establish more robust genotype-phenotype correlation. Recently, rapid diagnosis of LiP by skin immunohistochemistry using an anti-ECM1 antibody has been reported (Chan I et al., 2004c). Affected individuals showed reduced or absent skin immunostaining.

Epidemiology
Over 250 cases of LiP have been described so far (Hofer P, 1973). The disorder occurs throughout the world, although it appears to be more frequent in some countries in which consanguinity is common or a founder effect has been suspected. LiP is particularly common in the Northern Cape province of South Africa, including Namaqualand, where propagation of a mutated common ancestral allele dating back to a mid-seventeenth century settler from Germany, has been proposed (Gordon H et al., 1971, Heyl T, 1971, Stine OC et al., 1990). A homozygous nonsense mutation in exon 7 of the ECM1 gene, Q276X, was identified in all patients from this area (Van Hougenhouck-Tulleken W et al., 2004).

Management including treatment
Although there have been many therapeutic trials in LiP, including oral steroids, oral dimethyl sulfoxide (DMSO) and intralesional heparin (Hofer P, 1973, Wong CK et al., 1988), only rarely have there been any sustained benefits. However, carbon dioxide laser surgery of thickened vocal cords and beaded eyelid papules has proved to be helpful in some studies (Haneke E, 1984, Rosenthal G, 1997).

Unresolved questions
Seventy-five years after the original clinical description of LiP (Urbach E et al., 1929), it has been now established that this autosomal recessive disorder is caused by mutations in the ECM1 gene (Hamada T et al., 2002). Identification of mutations in ECM1 in LiP now provides a basis for the development of more rational forms of treatment, including trials of recombinant gene/protein for skin or respiratory mucosa. Further investigations of the protein interactions of ECM1 may also help elucidate its role as a modifier of dermal architecture and epidermal differentiation in normal skin.

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References


