

# Lipoid proteinosis

**Author: Doctor Takahiro Hamada<sup>1</sup>**

**Creation date: December 2003**

**Update: February 2005**

**Scientific editor: Doctor Jemima Mellerio**

<sup>1</sup>Department of Dermatology, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka, Japan, 830-0011. [hamataka@med.kurume-u.ac.jp](mailto:hamataka@med.kurume-u.ac.jp)

[Abstract](#)

[Keywords](#)

[Disease name / synonyms](#)

[Definition / diagnostic criteria](#)

[Differential diagnosis](#)

[Etiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Epidemiology](#)

[Management including treatment](#)

[Unresolved questions](#)

[References](#)

## 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.

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).

## 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.*,

## 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 (Bozdogan 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.*

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 sulphoxide (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.

### Acknowledgements

I am especially grateful to J. McGrath and I. Chan for their help in the identification of the gene responsible for LiP and subsequent molecular and mutation studies.

### References

- Aroni K**, Lazaris AC, Papadimitriou K *et al.* Lipoid proteinosis of the oral mucosa: case report and review of the literature. *Pathol Res Pract* 1998; 194: 855-9.
- Bauer EA**, Santa-Cruz D, Eisen AZ. Lipoid proteinosis: in vivo and in vitro evidence for a lysosomal storage disease. *J Invest Dermatol* 1981; 76: 119-25.
- Bhalerao J**, Tylzanowski P, Filie JD *et al.* Molecular cloning, characterization and genetic mapping of the cDNA coding for a novel secretory protein of mouse. Demonstration of alternative splicing in skin and cartilage. *J Biol Chem* 1995; 270: 16385-94.
- Bozdag KE**, Gul Y, Araman A. Lipoid proteinosis. *Int J Dermatol* 2000; 39: 203-4.
- Chan I**, El-Zurghany A, Zendah B *et al.* Molecular basis of lipoid proteinosis in a Libyan family. *Clin Exp Dermatol* 2003; 28: 545-8.
- Chan I**. The role of extracellular matrix protein 1 in human skin. *Clin Exp Dermatol* 2004; 29: 52-6.
- Chan I**, Oyama N, South AP *et al.* Characterization of IgG autoantibodies to extracellular matrix protein 1 (ECM1) in lichen sclerosus. *Clin Exp Dermatol* 2004a; 29: 499-504.
- Chan I**, Sethuraman G, Sharma VK *et al.* Molecular Basis of Lipoid Proteinosis in Two Indian Siblings. *J Dermatol* 2004b; 31: 764-6.
- Chan I**, Oyama N, South AP *et al.* Rapid diagnosis of lipoid proteinosis using an anti-extracellular matrix protein 1 (ECM1) antibody. *J Dermatol Sci* 2004c; 35: 151-153.
- Deckers MM**, Smits P, Karperien M *et al.* Recombinant human extracellular matrix protein 1 inhibits alkaline phosphatase activity and mineralization of mouse embryonic metatarsals in vitro. *Bone* 2001; 28: 14-20.
- Disdier P**, Harle JR, Andrac L *et al.* Specific xerostomia during Urbach-Wiethe disease. *Dermatology* 1994; 188: 50-1.
- Friedman L**, Mathews RD Swanepoel PD. Radiographic and computed tomographic findings in lipid proteinosis. A case report. *S Afr Med J* 1984; 65: 734-5.
- Hamada T**, McLean WHI, Ramsay M *et al.* Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (*ECM1*). *Hum Mol Genet* 2002; 11: 833-40.
- Hamada T**. Lipoid proteinosis. *Clin Exp Dermatol* 2002; 27: 624-9.

- Hamada T**, Wessagowit, South AP *et al.* Extracellular matrix protein 1 gene (*ECM1*) mutations in lipid proteinosis and genotype-phenotype correlation. *J Invest Dermatol* 2003; 120: 345-50.
- Han Z**, Ni J, Smits P *et al.* Extracellular matrix protein 1 (*ECM1*) has angiogenic properties and is expressed by breast tumor cells. *FASEB J* 2001; 15: 988-94.
- Gordon H**, Gordon W, Botha V *et al.* Lipoid proteinosis. *Birth Defects Orig Artic Ser* 1971; 7: 164-77.
- Hofer P**. Urbach-Wiethe disease (lipoglycoproteinosis; lipid proteinosis; hyalinosis cutis et mucosae. A review. *Acta Derm Suppl (Stockh)* 1973; 53: 1-52.
- Haneke E**, Hornstein OP, Meisel-Stosiek M *et al.* Hyalinosis cutis et mucosae in sibilings. *Hum Genet* 1984; 68: 342-5.
- Heyl T**. Lipoid proteinosis in South Africa. *Dermatologica* 1971; 142: 129-32.
- Johnson MR**, Wilkin DJ, Vos HL *et al.* Characterization of the human extracellular matrix protein 1 gene on chromosome 1q21. *Matrix Biol* 1997; 16: 289-92.
- Kleinert R**, Cervos-Navarro J, Kleinert G *et al.* Predominantly cerebral manifestation in Urbach-Wiethe's syndrome (lipoid proteinosis cutis et mucosae): a clinical and pathomorphological study. *Clin Neuropathol* 1987; 6: 43-5.
- Mongiat M**, Fu J, Oldershaw R *et al.* Perlecan protein core interacts with extracellular matrix protein 1 (*ECM1*), a glycoprotein involved in bone formation and angiogenesis. *J Biol Chem* 2003; 278: 17491-9.
- Moy LS**, Moy RL, Matsuoka LY *et al.* Lipoid proteinosis: ultrastructural and biochemical studies. *J Am Acad Dermatol* 1987; 16: 1193-201.
- Muda AO**, Paradisi M, Angelo C *et al.* Lipoid proteinosis: clinical, histologic, and ultrastructural investigations. *Cutis* 1995; 56: 220-4.
- Nanda A**, Alsaleh QA, Al-Sabah H *et al.* Lipoid proteinosis: report of four sibilings and brief review of the literature. *Pediatr Dermatol* 2001; 18: 21-6.
- Oyama N**, Chan I, Neil SM *et al.* Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. *Lancet* 2003; 362: 118-23.
- Oyama N**, Chan I, Neil SM *et al.* Development of antigen-specific ELISA for circulating autoantibodies to extracellular matrix protein 1 in lichen sclerosus. *J Clin Invest* 2004; 113: 1550-9.
- Parker JM**. Erythropoietic protoporphyria. *Cutis* 1980; 26: 247-50.
- Ramsey ML**, Tschen JA, Wolf JE Jr. Lipoid proteinosis *Int J Dermatol* 1985; 24: 230-2.
- Rothenthal G**, Lifshitz T, Monos T. Carbon dioxide laser treatment for lipid proteinosis (Urbach-Wiethe syndrome) involving the eyelids. *Br J Ophthalmol* 1997; 81: 252-4.
- Smits P**, Ni J, Feng P *et al.* The human extracellular matrix gene 1 (*ECM1*): genomic structure, cDNA cloning, expression pattern and chromosomal localization. *Genomics* 1997; 45: 487-95.
- Smits P**, Poumay Y, Karperien M *et al.* Differentiation-dependent alternative splicing and expression of the extracellular matrix protein 1 gene in human keratinocytes. *J Invest Dermatol* 2000; 114: 718-24.
- Stine OC**, Smith KD. The estimation of selection coefficients in Afrikaans: Huntington disease, porphyria variegata, and lipid proteinosis. *Am J Hum Genet* 1990; 46: 452-8.
- Teive HA**, Pereira ER, Zavala JA *et al.* Generalized dystonia and striatal calcifications with lipid proteinosis. *Neurology* 2004; 63, 2168-9.
- Touart DM**, Sau P. Cutaneous deposition diseases. Part I. *J Am Acad Dermatol* 1998; 39, 149-71.
- Urbach E**, Wiethe C. Lipoidosis cutis et mucosae. *Virchows Arch Path Anat* 1929; 273: 285-319.
- Van Houghenouck-Tulleken W**, Chan I, Hamada T *et al.* Clinical and molecular characterization of lipid proteinosis in Namaqualand, South Africa. *Br J Dermatol* 2004; 151: 413-23.
- Wong CK** and Lin CS. Remarkable response of lipid proteinosis to oral dimethyl sulphoxide. *Br J Dermatol* 1988; 119, 541-4.