

Histopathological Findings in Patients with Lipoid Proteinosis

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Abstract

Objective: Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis characterized by the accumulation of amorphous hyaline substance in the skin and mucous membranes. In this study, the histopathological findings of the patients who were admitted to our clinic and diagnosed with LP were examined. **Materials and Methods:** This prospective study included 18 patients who presented to our clinic between January 2014 and December 2018 and were confirmed by histopathological examination. A punch biopsy including epidermis, dermis, and subcutaneous tissues was obtained from the lesional skin of each patient evaluated clinically, and the material was stained with hematoxylin and eosin stain and periodic acid–Schiff (PAS) stain. These preparations were evaluated by a pathologist experienced in dermatopathology. **Results:** The most common histopathological findings in the epidermis were hyperkeratosis (88.8%) and pigmentary incontinence (83.3%) in the basal layer. The most common histopathological findings in the dermis were amorphous substance accumulation (100%), perivascular PAS positivity (33.3%), and PAS positivity around eccrine glands (11.1%). **Conclusion:** The findings of our study were similar to the histopathological findings of late-term skin lesions in LP patients previously described in the literature. In order to better understand the histopathological findings of skin lesions of LP patients, studies with a large number of patients including early skin lesions of LP are needed.

Keywords: Histopathology, hyaline substance, lipoid proteinosis

INTRODUCTION

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis characterized by the accumulation of amorphous hyaline substance in the skin and mucous membranes. It affects both sexes equally. Although the incidence is not known exactly, about 350 patients have been reported in the literature. LP is more common in our country due to the frequent consanguineous marriages compared to the world countries.^[1-6]

LP develops as a result of decreased expression in the ECM1 gene. ECM1 gene is located on 1. chromosome and plays an important role in angiogenesis, epidermal differentiation, and wound healing. The loss of normal function of ECM1 in LP results in infiltration with hyaline-like material in the skin, mucosa, and internal organs. On histopathological examination of the skin lesions of LP patients, diffuse dermal accumulation of hyaline material, basal membrane thickening

of the dermoepidermal junction, and epidermal hyperkeratosis can be seen.^[7-10] In this study, the histopathological findings of 18 patients who were admitted to our dermatology clinic and were diagnosed with LP and confirmed by histopathological examination were examined.

MATERIALS AND METHODS

This prospective study included 18 patients who were admitted to our dermatology and venereal diseases clinic between January 2014 and December 2018, who were clinically diagnosed with LP and confirmed by histopathological examination. The sociodemographic characteristics (age and gender) and clinical findings (hoarseness and skin lesions) of the patients were recorded.

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A punch biopsy including epidermis, dermis, and subcutaneous tissue was obtained from the lesional skin of each patient evaluated clinically, and the material was stained with hematoxylin and eosin stain and periodic acid–Schiff (PAS) stain. These preparations were evaluated by a pathologist experienced in dermatopathology. Histopathological findings of the epidermis and dermis were recorded.

Statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) package program. Continuous data were calculated as mean \pm standard deviation and categorical data as frequency (%). The study was approved by the local ethics committee of Faculty of Medicine, Harran University (date: May 13, 2013, number: 5).

RESULTS

Of the 18 patients included in the study, 13 (72.2%) were female and 5 (27.8%) were male. The ages of the patients ranged between 3 and 33 years, and the mean age was 15.6 ± 8.2 years. All patients included in the study had the complaint of hoarseness. Atrophic scars were seen on the skin of all patients, especially on the face. Six patients had hyperkeratotic verrucous plaques on their knees and elbows. Three patients had hair loss and nail anomalies, two had palmoplantar hyperkeratosis, one had tongue thickening, and one had pearly papules on the eyelids. No patients had vesicles, pustules, blisters, and hemorrhagic crusts.

Hyperkeratosis in epidermis in 16 (88.8%) patients, pigment incontinence in basal layer in 15 (83.3%) patients, and atrophy in epidermis in 1 (5.5%) patient were seen [Table 1].

In the dermis, 18 (100%) patients had amorphous accumulation, 6 (33.3%) patients had perivascular PAS positivity, 2 (11.1%) patients had PAS positivity around eccrine glands, 2 (11.1%) patients had fibrosis, 2 (11.1%) patients had inflammatory cells in papillary dermis, 1 (5.5%) patient had papillomatosis, 1 (5.5%) patient had the presence of melanophage, and

1 (5.5%) patient had flattening of the rete ridges [Table 1, Figures 1 and 2].

DISCUSSION

LP is a rare autosomal recessive genodermatosis characterized by amorphous hyaline material accumulation in the skin, mucosa, and visceral organs.^[11] Hoarseness caused by infiltration of the larynx mucosa in LP is a characteristic finding. This symptom is often mistaken by clinicians for more common diseases such as chronic laryngitis. The cause of hoarseness is the deterioration of wave formation due to accumulation of subepithelial hyaline material and incomplete closure of vocal cords with air leakage during vocalization. In the following years, the skin and mucosal changes become clinically evident. Tongue thickening, epiglottis and vocal cord thickening, and frenulum sclerosis result in limited tongue movements. Infiltration of the gums and salivary glands can lead to tooth loss and recurrent parotid attacks. Dental anomalies are hyperplasia or aplasia of upper incisors, premolars, and molars.^[12] Nearly, in half of the cases, intracranial calcifications and epilepsy have been reported. Memory problems, behavioral disorders, and mental retardation are among the other reported neurological and psychiatric symptoms. On computed tomography, sickle-shaped calcifications in the bilateral temporal lobe or hippocampus–amygdala complex are pathognomonic and are responsible for accompanying behavioral disorders.^[13,14] The disease typically has a stable or slow progression and has a normal life span, unless there is airway obstruction or deadly epileptic seizures.^[4,5]

Cutaneous findings in LP usually occur in the first 2 years of life. At first, recurrent vesicles in variable size, pustules, bullae, and hemorrhagic crusts are seen. Lesions are often seen in traumatic areas such as face and distal extremities, and they heal with atrophic scar. Then, a thickened skin is formed which often creates a wax appearance due to the dermal accumulation of amorphous hyaline substance in the facial skin, eyelids, axils, and scrotum. Finally, hyperkeratotic, verrucous papules and plaques are seen on the surfaces exposed to friction such as elbows, knees, and hands. Thickened scalp, hair loss, and nail anomalies can be seen. The yellowish, wax-colored papules, called “Moniliform blepharosis,” are lined up along the eyelids.^[6,8,10,11,14]

Diseases such as erythropoietic protoporphyria, papular mucinosis, amyloidosis, and xanthoma disseminatum should be considered in the differential diagnosis of LP. The treatment approach in LP is symptomatic. Despite the presence of various treatment alternatives including dimethyl sulfoxide, acitretin, D-penicillamine, and surgical intervention, there is no single effective treatment for LP.^[2,4-8,10]

The exact pathogenesis of LP is not understood. The overproduction of basal membrane type IV collagen by epithelial or endothelial cells and the increased synthesis of noncollagen glycoproteins by fibroblasts appear to be important

Table 1: Histopathological findings in patients with lipid proteinosis

Histopathological findings	n (%)
Epidermis	
Hyperkeratosis	16 (88.8)
Pigmentary incontinence in basal layer	15 (83.3)
Atrophy	1 (5.5)
Dermis	
Amorphous substance accumulation	18 (100)
Perivascular PAS positivity	6 (33.3)
PAS positivity around eccrine glands	2 (11.1)
Fibrosis	2 (11.1)
Inflammatory cells in papillary dermis	2 (11.1)
Papillomatosis	1 (5.5)
Presence of melanophage	1 (5.5)
Flattening of the rete ridges	1 (5.5)

PAS: Periodic acid-Schiff

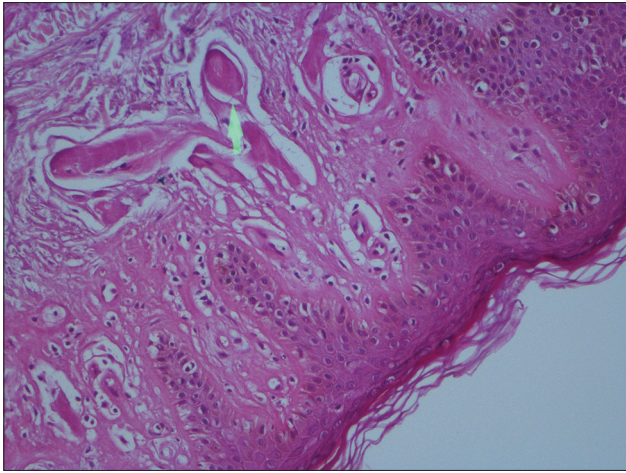


Figure 1: Eosinophilic hyaline material (indicated by arrow) is observed in the papillary dermis and around the blood vessels (H and E, $\times 200$)

in pathogenesis.^[15,16] The major clinical manifestations of LP are associated with the accumulation of amorphous material around blood vessels and connective tissue. Concentric layers of basement membrane-like material contain collagen and laminin, whereas amorphous deposits contain mainly noncollagen proteins. In addition, accumulations are PAS positive, indicating the presence of neutral mucosaccharides.^[3]

Hematoxylin and eosin-stained sections of early skin lesions of LP show pink hyaline-like thickening of capillaries in the papillary dermis. Ko and Barr found that intra-epidermal bullae formation with large nondyskeratotic acantholysis in the early lesions of LP and possibly LP was an acantholytic dermatosis.^[17] Rao *et al.* found intra-epidermal bullae without acantholysis in the early lesions of LP.^[18] Gutte *et al.* detected subepidermal bulla consisting of fibrin and extracellular erythrocytes in the early lesions of LP.^[19]

Kaya *et al.* found atrophy of the epidermis and a homogeneous pink material in the papillary dermis in a patient with an early erosive vesicular stage of LP. The amorphous material is deposited in thick bundles around the blood vessels, perpendicular to the skin surface. The ends of the dermal papilla are extremely narrowed and are mostly eroded by the amorphous material. A possible sudden increase in amorphous mass may be the cause of epidermal atrophy. In addition, as a result of perivascular deposits, erosions and ulceration may occur due to obstruction of the capillary circulation in the papillary dermis.^[20]

The old skin lesions of LP show hyperkeratosis, sometimes papillomatosis, and a thickened dermis with pink hyaline bundles in a diffuse pattern. These bundles are often aligned vertically to the dermoepidermal junction. There is less scattered hyaline accumulation in the lower dermis. Hyaline mantle may encircle hair follicles, sebaceous glands, and rarely erectile pili muscle.

Elmas *et al.* found accumulation of eosinophilic material around small vessels in superficial dermis and slightly papillomatous changes in histopathological examination of skin

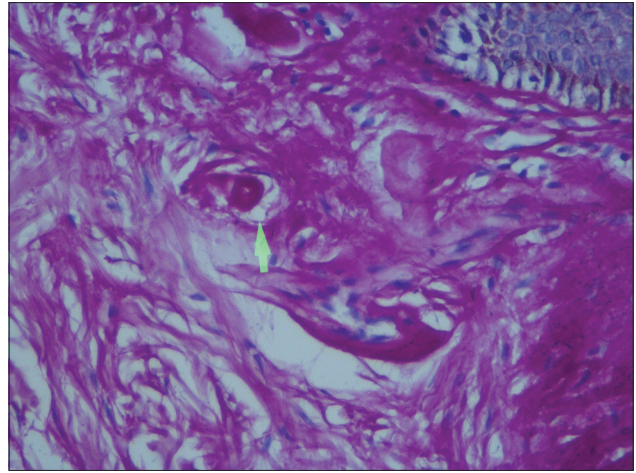


Figure 2: Periodic acid-Schiff-positive eosinophilic hyaline material observed around the papillary dermis and blood vessels (indicated by arrow) (PAS, $\times 400$)

lesions of a patient with LP.^[21] Akoglu *et al.* found epidermal hyperkeratosis and eosinophilic material accumulation around blood vessels in the papillary dermis, adnexal epithelium, and eccrine glands in the skin biopsies of three LP patients. The material was PAS positive, diastase resistant, and amyloid negative.^[22]

In a study conducted by Dertlioğlu *et al.* on nine LP patients, minimal hyperkeratosis and acanthosis; eosinophilic PAS positivity in the papillary dermis; and diastase-resistant, amyloid-negative material accumulation around blood vessel, adnex epithelium, and eccrine glands were seen.^[4]

CONCLUSION

In our study, hyperkeratosis, epidermal atrophy, papillomatosis, pigmentary incontinence in the basal layer, presence of melanophage and flattening of rete ridges, inflammatory cells in the papillary dermis, amorphous substance accumulation in the dermis, perivascular PAS positivity, PAS positivity around eccrine glands, and fibrosis were observed. Because the skin lesions of our patients were not early lesions, histopathological examination of the lesions did not reveal any findings such as acantholysis and intra-epidermal or subepidermal blisters. The findings of our study were similar to the histopathological findings of late-term skin lesions in LP patients, previously described in the literature. In order to better understand the histopathological findings of skin lesions of LP patients, studies with a large number of patients including early skin lesions of LP are needed.

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Conflicts of interest

There are no conflicts of interest.

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