THE AUTOIMMUNE CONSTELLATION IN LICHEN AMYLOIDOSIS

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THE AUTOIMMUNE CONSTELLATION IN LICHEN AMYLOIDOSIS (Abstract): Localized cutaneous amyloidosis is a rare disease among white people, being more common in South-Asia, China and South America. The disease is characterized by deposition of amyloid material in the papillary dermis without visceral involvement. Nevertheless, there is a growing list of immune-mediated disorders that have been linked to cutaneous amyloidosis. We present two cases of concomitant occurrence of lichen amyloidosis and autoimmune thyroiditis/atopic dermatitis in two Caucasian women. Keywords: AMYLOIDOSIS, LICHEN AMYLOIDOSIS, HISTOLOGIC STAINS.

Lichen amyloidosis (LA) is defined as a chronic itchy skin condition, characterized clinically by the presence of hyperkeratotic papules and histologically by the deposition of amyloid in the papillary dermis. It occurs more frequently in males aged 50-60 years and is primarily located on the lower limbs, but the trunk or forearms can also be involved. The condition is the most common subtype of localized cutaneous amyloidosis (LCA), in which the protein is deposited only in the skin, without involving other organs (1).

Amyloidosis refers to the deposition of amyloid in various tissues and all clinical types of amyloidosis share a common amyloid P component: a nonfibrillar protein derived from a precursor known as serum amyloid P. Clinically, Shimizu classified amyloidosis into two major classes (2007):

➢ Systemic amyloidosis with 4 sub-types - systemic AL amyloidosis (AL stands for amyloid light chain), systemic AA amyloidosis, amyloid A being derived form α-globulin called serum amyloid A, familial systemic amyloidosis and hemodialysis-related amyloidosis.

➢ Localized cutaneous amyloidosis (LCA) with 2 major forms:

▪ Primary localized cutaneous amyloidosis: lichen amyloidosis, macular amyloidosis, nodular localized cutaneous amyloidosis (amyloidosis cutis nodularis atrophicans), poikiloderma-like cutaneous amyloidosis, anosacral cutaneous amyloidosis

▪ Secondary localized cutaneous amyloidosis - the deposition of amyloids is associated with another skin disorders (lichen simplex chronicus, verruca vulgaris, basal cell carcinoma, seborrheic keratos, actinic keratos etc).
What does the term amyloid mean? The amyloid was defined in 1854 by Rudolph Virchow as the iodine-stainable starchlike which shares some common features such as eosinophilic amorphous appearance with hematoxylin – eosin stain (2).

LA is a rare, often misdiagnosed disease, which accounts for approximately 10% of cutaneous amyloidoses. In the past, the amyloid was considered to be a single substance regardless of the variation in clinical presentation. Nowadays, using the criteria of Con-gophilia and fibrillar morphology, more than 20 biochemically different forms of amyloid have been identified.

There are some special stains for the amyloid deposits, in addition to the classic Congo red: apple green birefringence, thioflavin T, crystal violet metachromasia, methyl violet, Pagoda red no. 9, amyloid-P component antibody (3).

Although histologically LA involves amyloid deposits only in the papillary dermis, the epidermis is also involved, having as result the appearance of hyperkeratosis and acanthosis. The pathological examination usually shows massive deposits of amyloid in the dermis, highlighted by Congo red staining revealing amorphous appearance (4).

The etiology of LA is still a mystery, viral and genetic factors, feminine gender, atopy or local friction have been listed as possible triggering factors. The most affected areas are the shins or the extensor surfaces of the extremities, but involvement of the abdominal wall, anosacral region, scalp, ears, interscapular region or sites of varicose veins has also been reported (5-7).

**CASE REPORTS**

We present two cases diagnosed and treated at the Dermatology and Pathology Departments of the “St. Spiridon” University Hospital, Iasi, Romania in the interval January - April 2014.

Case 1 was a 50-year-old woman presenting with a history of intermittent pruritic, brownish papules, 4-5 mm in diameter, distributed bilaterally and symmetrically on the extensor area of the pretibial surfaces, (fig.1). Similar but smaller and flatter papules were also noted on the extensor surfaces of the arms. She had no previous skin disease and family history was negative.

Case 2 was a 62-year-old female presenting similar papular and pruritic lesions but confined to the trunk. She had no family history of any similar dermatological disease. Thyroid function tests showed high TSH (thyroid-stimulating hormone) level

![Fig. 1. Hyperkeratotic papules distributed on the pretibial areas](image)
and normal T3 (triiodothyronine), T4 (thyroxine) levels. Anti-thyroid microsomal antibody was positive whereas antithyroglobulin antibody was negative. Routine complete blood cell count, blood chemistry, urinalysis and serum electrophoresis were within normal limits in both patients.

Initial differential diagnosis included: dyschromatosis pigmentosa reticularis, pretibial pruritic popular dermatitis, hyperkeratotic lichen planus, and pretibial thyroid dermopathy (also known as pretibial myxedema).

No evidence of systemic amyloidosis deposition was found.

A punch biopsy specimen of a papule was taken from the pretibial area (case 1) and from the trunk (case 2) for routine microscopic examination.

Results of histological examination showed epidermal acanthosis with hyperkeratosis associated pigment incontinence. Both cases had hematoxylin & eosin (H&E) stains available for review and paraffin blocks for immunohistochemical staining. The H&E slides were reviewed and the diagnoses were made using well-established histopathologic criteria. Special stains were performed: PAS, Congo red, Fontana, methyl violet and van Gieson. The Congo red stain was analyzed in polarizing microscopy.

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded (4 - μm thick) sections using a standard technique (streptavidin– biotin – peroxidase technique) with appropriate positive and negative controls. Novocastra Multi Cyto-keratin (clone AE1/AE3 cocktail ready to use) with Dako’s En Vision system was used for detection.

In papillary and reticular areas an amorphous eosinophilic material was found. The deposits expanded the papillae and the elongated rete ridges were displaced laterally, without involving the vascular or adnexal structure (fig. 2). The amorphous deposits stained positive light red with PAS, Congo red, and methyl–violet (fig. 3), light yellow with van Gieson stain (fig. 4), and appear green to fluorescent yellow in polarizing microcopy (fig. 5). Fontana stain showed melanin pigment associated with the amorphous deposits and the increase pigmentation of the basal layer (fig. 6). Immunohistochemical stain with anti-keratin antibody demonstrated focal reactivity in amyloid deposits (fig. 7).

Based on the clinicopathological and laboratory findings, a final diagnosis of LA was made.

The treatment of LA is often difficult and the condition recurs frequently. Potent topical corticosteroids (with or without occlusive dressings), intralesional corticosteroids, topical calcineurin inhibitors, dermabrasion, PUVA and UVB phototherapy, systemic retinoids, cyclosporine or topical 10% of dimethylsulfoxide have been used for the medical management of LA (8,9).

Fig. 2. Hyperkeratosis, elongation of the rete ridges and dermal papillary deposits of amorphous eosinophilic material, H & E, original magnification, x 200.
In our patients the treatment with oral antihistamine in association with topical applications of corticosteroids had a poor response.

**DISCUSSION**

In literature LA has been associated with a wide range of conditions: atopic dermatitis, dermatomyositis, systemic lupus erythematosus, autoimmune thyroiditis, hyperthyroidism and ankylosing spondylitis; however no association has been supported by statistically relevant data (10-13).
The autoimmune constellation in lichen amyloidosis

The differential diagnosis is often a challenge to many dermatologists, and we must always look for lichen simplex chronicus (affects predominantly females aged 30 to 50 years and clinically appears like chronically excoriated plaques), pretibial pruritic papular dermatitis (with a striking clinical resemblance to lichen amyloidosis but without amyloid deposition), pretibial thyroid dermopathy (a latter manifestation of thyroid disease), prurigo nodularis (hyperkeratotic nodules that vary in size from 0.5 to 3 cm), dyschromatosis pigmentosa reticularis (a rare genodermatosis characterized by generalized hyperpigmentation).

In lichen amyloidosis nerve fibers are localized at the dermoepidermal junction but not in the papillary dermis, suggesting that the pruritus may result from hypersensitivity of the nerve fibers that remain following the unexplained loss of nerves at the dermoepidermal junction. It is also possible that hyperthyroidism, by itching, may induce the occurrence or spread of LA (14).

Pigment incontinence, amorphous material and hyperkeratosis support the diagnosis of pruritic lesion, although non-pruritic variants of lichen amyloidosis have been described (15).

CONCLUSIONS
The histopathological findings in these two cases were similar to those reported in the literature, with amyloid depositing in the papillary and reticular areas and immunohistochemical staining positive for these deposits with antikeratin antibody AE1/AE3.

Lichen amyloidosis, the most common form of primary cutaneous amyloidosis, it is a rare disease among white people, with male predominance.

In our opinion, the occurrence of LA in two women, during a short period of time, in association with two autoimmune diseases is a strong indication that the etiopathogenic process is still unclear and that the genetic profile may be the strongest link to understanding the whole process.

REFERENCES
THE IMPORTANCE OF CYTOKERATIN 19 EXPRESSION IN THE DIFFERENTIATION OF BASAL CELL CARCINOMA AND TRICHOEPITHELIOMA

Basal cell carcinoma (BCC) is the most common skin tumour constituting approximately 70% of all skin malignancies. It occurs mostly in the elderly especially in the head and neck regions in sun-exposed areas. It is a locally aggressive tumour with very rare metastatic rates. With immunohistochemical studies, it has been shown that BCC originates from follicular stem cells and basaloid epithelia of follicular projections of the hair buds. On the other hand, trichoepithelioma (TE) is a rare, benign tumour of skin adnexa originating from follicular germinative cells. They are commonly located on the face and hairy skin. There are three subtypes of TE: desmoplastic, solitary and multiple. Lesions are generally solitary and sporadic papules or nodules in skin color. They show similarities with BCC since they are formed from basaloid islands and cordonal with peripheral palisading in fibrous stroma. In small skin biopsies, if morphological findings of BCC and TE are overlapping, differential diagnosis may be especially difficult. In previous studies, for the differentiation of these two tumours, some immunohistochemical markers such as CD10, bcl2, CK15, and Ber-EP4 have been used. In several studies, cytokeratin 19 (CK19) has been determined to have a high specificity for undifferentiated basaloid cells. CK19 is a small (40 kDa) acidic keratin that is expressed in germinative basaloid cells. In the non-neoplastic skin tissue samples, while positive staining with cytokeratin 19 in the outer root sheath of hair follicles and sweat glands were observed, there was no staining in basal layers. In conclusion, CK19 expression may be helpful in the differential diagnosis of BCC and TE especially in small skin biopsy samples in which morphologic differentiation is difficult (Bedir R, Sehitoglu I, Yurdakul C, et al. The Importance of Cytokeratin 19 Expression in the Differentiation of Basal Cell Carcinoma and Trichoepithelioma. Journal of Clinical and Diagnostic Research. 2015, Vol-9(1):1-4).