

CASE REPORTS

Disseminated Nodular Primary Localized Cutaneous Amyloidosis

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Abstract. Amyloid is a proteinaceous material that is deposited in the tissues in a large variety of clinical contexts; in the skin it can be found with or without concomitant systemic disease. Primary localized cutaneous amyloidosis encompasses those amyloidoses restricted to the skin without involvement of other systems. The most common forms within this group are macular and lichen amyloidosis. Nodular amyloidosis is extremely rare, and there are notable differences in clinical presentation, prognosis, histology, and pathogenesis between this entity and the macular and lichenoid variants. We report a new case of nodular primary localized cutaneous amyloidosis with disseminated plaques and nodules in which no systemic disease developed in the 3 years following the appearance of the lesions.

Key words: amyloid, nodular primary localized cutaneous amyloidosis.

AMILOIDOSIS CUTÁNEA PRIMARIA LOCALIZADA NODULAR CON PATRÓN DISEMINADO

Resumen. El amiloide es un material proteínico que se deposita en los tejidos en una gran variedad de situaciones clínicas; en la piel puede ser hallado con o sin afectación sistémica concomitante. La amiloidosis cutánea primaria localizada designa a aquellas amiloidosis con afectación exclusivamente cutánea, sin afectación a otros niveles. Las formas más comunes dentro de este grupo son la amiloidosis macular y el liquen amiloideo. La amiloidosis nodular es extremadamente infrecuente y mantiene importantes diferencias clínicas, pronósticas, histológicas y patogénicas con respecto a las variantes macular y liquenoide.

Presentamos un nuevo caso de amiloidosis cutánea primaria localizada nodular con placas y nódulos diseminados, que no desarrolló afectación sistémica tras tres años desde el debut de las lesiones.

Palabras clave: amiloide, amiloidosis cutánea primaria localizada nodular.

Introduction

Amyloidosis is not a single disease; rather this term refers to a group of conditions that have in common the abnormal extracellular deposition in the tissues of amyloid, a fibrillary proteinaceous material. Staining and physicochemical properties of this material, such as congophilia, apple-green birefringence under polarized light, and a beta-pleated sheet structure on x-ray crystallography,^{1,2} are similar regardless of the associated clinical context or pathological process. The classification of amyloidosis is based on the clinical characteristics of the patient and the nature of the amyloid

deposits (Table).¹ The primary cutaneous forms (macular, lichenoid, and nodular) and localized secondary forms^{1,3} are the ones seen most commonly by dermatologists. Nodular primary localized cutaneous amyloidosis (NPLCA) is the least common, with fewer than 100 cases reported in the literature.

We present a case of NPLCA in a 30-year-old woman with multiple lesions principally on the trunk, genitalia, and in the inguinal and axillary folds. After 3 years of follow-up, no evidence of an underlying disorder associated with the lesions has been found.

Case Report

The patient was a 30-year-old woman from Colombia, with no personal or family medical history of interest except for recurrent episodes of bronchiolitis in childhood that had completely resolved on reaching adolescence. She was referred to our outpatient clinic for evaluation of a number

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Table. Classification of Amyloidosis: Clinical Aspects and Amyloid Characteristics

<i>Clinical Aspects</i>	<i>Amyloid Protein</i>
Systemic	
Primary	AL
Myeloma-associated	AL
Secondary	AA
Hereditary/familial	
Familial Mediterranean fever	AA
Muckle-Wells syndrome	AA
Familial amyloid polyneuropathy	Transthyretin
Hemodialysis-associated	β 2-microglobulin
Localized	
Limited to a single organ	
Lung, larynx	AL
Diabetes mellitus-associated	Amylin
Thyroid	Precalcitonin
Cerebral/Alzheimer disease	Amyloid precursor protein
Cerebral/hereditary	Cystatin C
Primary cutaneous	
Nodular	AL
Macular amyloidosis	Altered keratin
Lichenoid amyloidosis	Altered keratin
Secondary cutaneous	
Within skin tumors	Altered keratin

Abbreviations: AA, amyloid protein A; AL, amyloid light chain.

of asymptomatic skin lesions that had appeared progressively over the previous 2 years and that had not resolved after various topical treatments. The lesions had started in the inguinal folds, axillary folds, and on the internal aspect of the thighs and had gradually increased in size at the same time as further lesions appeared on the back, presternal region, lower abdomen, and vulva. The patient had an otherwise good state of general health and no other symptoms were detected. On physical examination, there were maculopapular lesions that coalesced into linear or round plaques of variable size, ranging from a few millimeters up to 6 or 8 cm in diameter, with well-defined but irregular borders, and with a smooth or rough surface depending on the site. The lesions were dyschromic, some being predominantly yellowish-brown and others erythematous-purpuric with areas of a color similar to the adjacent skin (Figure 1). The longer-standing lesions were noted to be more infiltrated on palpation and had a more nodular appearance (Figure 2). In addition, small, shiny, hemispheric papules were observed in the presternal and supraclavicular regions; these were skin colored and had a smooth surface,



Figure 1. Confluent plaques of macules and papules, with marked dyschromia (yellowish-brown color, skin color, and erythematous-purpuric) and variable morphology, situated on the patient's back.



Figure 2. Erythematous nodule, infiltrated on palpation, in the axillary fold.

with a tendency to form a ring pattern (Figure 3). During follow-up, we were able to observe the successive appearance of new lesions on the abdomen, frontal hairline of the scalp, and popliteal fossa.



Figure 3. Shiny papules a few millimeters across with a smooth surface in the supraclavicular region.

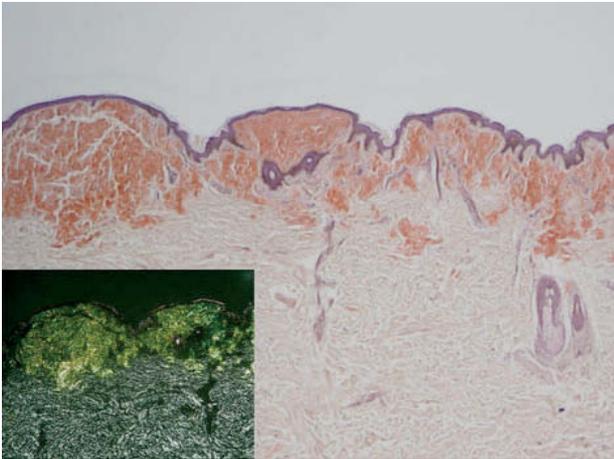


Figure 4. Nodular amyloidosis. Orange-red masses of amyloid in the papillary dermis, extending towards the reticular dermis (Congo red $\times 10$). The inset shows the characteristic apple-green birefringence under polarized light.

Three of the most representative lesions were biopsied, finding similar histological changes. Examination at low magnification revealed a weakly eosinophilic material that was homogeneous but with clefts. This material replaced the normal collagen and fibroblasts, leading to a nodular expansion of the reticular and papillary dermis, as well as extending locally into the subcutaneous cellular tissue and surrounding the skin adnexa. In addition to these findings, there was a perivascular inflammatory infiltrate made up principally of plasma cells. After staining with Congo red, examination with optical microscopy revealed deposits with an intense orange-red color (which persisted after treatment of the sample with potassium permanganate) and apple-green birefringence under polarized light (Figure 4). Immunohistochemistry for amyloid A was negative and the assays performed to detect κ and λ light

chains were weak and nonspecific for κ chains and more intense for λ chains. The complementary tests included electrocardiogram, complete blood count, electrolytes, coagulation, liver and renal function, β_2 -microglobulin, erythrocyte sedimentation rate, serum and urine electrophoresis, chest radiograph, bone scan, and abdominal ultrasound; the results were normal or with no significant changes throughout the follow-up period, finding only a polyclonal increase of immunoglobulin G (2430 mg/dL). There were no abnormalities on bone marrow biopsy. Finally, rectal biopsy did not show the presence of amyloid.

Discussion

Primary cutaneous amyloidosis is a localized form of amyloidosis that only affects the skin; it is subdivided into 3 types: macular, lichenoid, and nodular.⁴ The macular and lichenoid forms are more common and are characterized by the deposition in the papillary dermis of a type of amyloid that appears to be derived from the adjacent keratinocytes.^{1,5} NPLCA is certainly the least common form of primary localized cutaneous amyloidosis,⁶⁻⁸ with fewer than 100 cases published in the literature. It usually occurs in women in their 50s and 60s,⁹ although more recent series have reported higher proportions of men being affected.⁶

Clinically it presents as infiltrated, single or multiple, round or oval, brown or yellowish nodules or plaques with a shiny surface and well-defined borders. Occasionally they appear atrophic, anetodermic or bullous, probably due to destruction of the collagen and elastin fibers.¹⁰ In decreasing order of frequency, the lesions are located on the lower limbs, head, trunk, and upper limbs,^{6,7} with sporadic cases reported on the tongue¹¹ and genitalia.^{9,12} It is not uncommon to find a raised erythrocyte sedimentation rate together with elevated β -globulins and γ -globulins.⁶ Some authors have also established a relationship between NPLCA and Sjögren syndrome¹³⁻¹⁵ or diabetes mellitus.¹⁶

The key to the histological diagnosis of NPLCA is the presence of large hyaline, eosinophilic masses of amyloid that extend from the papillary and reticular dermis into the subcutaneous cellular tissue. There may also be deposits around the skin adnexa, blood vessels, and fat cells.¹ In NPLCA, dermal amyloid deposits are of light chain amyloid (immunoglobulin light chains), as demonstrated on immunohistochemistry by the presence of λ and/or κ light chains.¹⁷ All these findings may be indistinguishable from those of primary systemic amyloidosis or myeloma-associated amyloidosis,^{6,7} but they are not observed in the secondary or hereditary-familial systemic forms, which are characterized by deposits of a specific, nonimmunoglobulin protein called amyloid protein A.¹

Studies of gene rearrangement in a number of patients have identified a clone of amyloid-producing plasma cells

in nodular lesions in the skin, with no signs of a clonal proliferation of plasma cells in the bone marrow.¹⁸ Because of this, some authors suggest that this variant should be considered as an extramedullary plasmacytoma and that the amyloid is produced by the local plasma cells; however, the mechanism through which these cells secrete amyloid locally is unknown.¹⁹⁻²²

NPLCA can only be distinguished from certain types of systemic amyloidosis by performing a detailed physical examination and exhaustive screening studies to exclude the presence of extracutaneous deposits of amyloid.⁷ In our patient, urinary and serum electrophoresis, the bone scan, chest x-ray, abdominal ultrasound, and rectal and bone marrow biopsies did not reveal extracutaneous amyloid deposits or any underlying hematologic disorder; the only finding was a significant polyclonal increase in immunoglobulin G levels, a relatively common finding in this condition,⁶ as has been commented above. Some authors have recommended scintigraphy with serum amyloid P, a precursor of amyloid P contained in all amyloid deposits, as a noninvasive method with an acceptable sensitivity and specificity, and one which could provide evidence of multiorgan disease in patients diagnosed with NPLCA.²³ However, its diagnostic utility is still under evaluation.²⁴

The risk of progression to systemic amyloidosis is uncertain, as the majority of publications on NPLCA are isolated case reports or short series of patients from which it is difficult to extrapolate conclusions. Brownstein and Helwig²⁵ reviewed 39 cases of primary localized cutaneous amyloidosis, of which 10 were NPLCA; of these, 5 (50%) remained stable, without developing other symptoms after follow-up of up to 8 years. With time, the remainder (50%) developed systemic forms of the disease. However, Woollons and Black⁶ found that only 1 of 15 cases (7%) of NPLCA that they reviewed developed systemic amyloidosis after 23 years' follow-up. Although 40% of the patients in that long-term study presented paraproteinemia at the time of diagnosis, the gammopathy remained stable throughout the follow-up period.

The therapeutic management of NPLCA is difficult and there is no individual treatment that is clearly more effective than others.⁶ Various treatments have been proposed in an attempt to improve the cosmetic appearance of the lesions, including surgical excision,²⁶ carbon dioxide laser,^{27,28} cryotherapy,⁵ dermabrasion,²⁹ curettage and electrocoagulation,^{5,30} and, more recently, pulsed dye laser.³¹ However, the recurrence rate in this type of amyloidosis is high as, in contrast to macular and lichenoid amyloidosis, the amyloid deposits reach the reticular dermis and subcutaneous cellular tissue.⁶

At the present time, 3 years after the onset of the condition, we believe that the most correct diagnosis for this patient is NPLCA. It usually presents as a solitary nodule or plaque or a few such lesions; the disseminated

forms, as in our case, are rarer and this makes therapeutic management more difficult. As the prognosis of this disease is unclear, periodic clinical and laboratory follow-up is recommended in order to ensure that there is no disease at other levels.

Conflicts of Interest

The authors declare no conflicts of interest.

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