Case and Review

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Systemic Light-Chain Amyloidosis Revealed by Progressive Nail Involvement, Diffuse Alopecia and Sicca Syndrome: Report of an Unusual Case with a Review of the Literature

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Key Words
Light-chain amyloidosis · Nail changes · Alopecia · Sicca syndrome

Abstract
Immunoglobulin light-chain (AL) amyloidosis is a form of systemic amyloidosis in which the fibrils are derived from monoclonal light chains. We report a case of a 66-year-old woman presenting with nail changes, parchment-like hand changes, progressive alopecia and sicca syndrome. Histopathological studies of biopsy specimens of the scalp, the nail, minor labial salivary glands and abdominal skin revealed deposits of AL κ-type amyloid. Urine protein electrophoresis exhibited a weak band of κ-type light chains. Based on this striking case, we here review the characteristic nail and hair manifestations associated with systemic amyloidosis. Knowledge of these signs is important for an early diagnosis of systemic amyloidosis, identification of the underlying disease and patient management.

Introduction

The amyloidoses encompass a complex group of diseases characterized by extracellular deposition of insoluble fibrillary proteins in various tissues and organs that results in progressive organ damage. The fibrils have a characteristic β-pleated sheet configuration that produces apple green birefringence under polarized light when stained with Congo red dye [1, 2]. Amyloidosis can develop as either a limited cutaneous or as a systemic disease. Classification of the amyloidosis depends on the precursor protein that forms the amyloid fibrils. At least 27 different proteins have been identified as causative agents of amyloid diseases [3]. Systemic amyloidosis can be classified into primary and secondary types.

Light-chain (AL) amyloidosis is the most common form of primary systemic amyloidosis. Although AL amyloidosis is often considered a rare disease, its incidence is similar to that of Hodgkin's lymphoma or chronic myelogenous leukemia [4]. It is estimated to affect 5–12 persons per million per year, although autopsy studies suggest that its incidence is even higher [5].

Primary systemic AL amyloidosis is characterized by the pathological production of fibrillary proteins composed of intact or fragments of monoclonal immunoglobulin light chains, more frequently of λ light chain, which accumulate in tissues. It is commonly associated with plasma cell dyscrasia and abnormal immunoglobulin light-chain proteins found in diseases such as multiple myeloma and Waldenström's macroglobulinemia [2]. Amyloid proteins can accumulate in virtually every organ with the exception of parenchymal brain tissue. Cutaneous manifestations, such as purpura, petechiae and ecchymoses, are observed in about 50% of cases of AL amyloidosis and provide important diagnostic clues.

We here report a striking case of systemic amyloidosis of the AL type, which was revealed by the insidious development over years of nail changes in combination with parchment-like hand involvement, diffuse generalized hair loss and sicca symptoms which were first related to a connective tissue disease.

Case Report

A 66-year-old Caucasian woman was referred by the treating rheumatologist for evaluation of a 15-year history of asymptomatic skin changes involving the hands associated with nail changes and hair loss, which were thought to be secondary to a connective tissue disease. During the last 5 years, she had also been suffering from dryness of the mouth and eyes, which was confirmed by Saxon's and Schirmer's tests, respectively. Furthermore, she reported to

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easily develop ecchymoses and hematomas following trauma. Her history was otherwise unremarkable.

On examination, the patient showed a diffuse slightly yellow-orange skin discoloration, predominating on her face and décolleté. A significantly reduced hair density and very thin hair shafts predominantly on the vertex and frontoparietally were found (fig. 1). She had complete loss of her axillary hair and sparse genital hair. The fingernails were markedly atrophic with thinning of the nail plates, loss of nail shine, longitudinal ridging and onychorrhexis (fig. 2); the toenails were similarly involved though much less. The skin of her hands, including the palms and fingers, was parchment-like with a scleroatrophic appearance (fig. 2), while the abdominal skin appeared firmer. The oral mucosa and tongue were dry and appeared atrophic. There was no macroglossia. The rest of the physical examination was unremarkable without evidence of lymphadenopathy, hepatosplenomegaly or neurological deficits.

Biopsy specimens were obtained from the scalp, the nail, minor labial salivary glands and abdominal skin including subcutaneous fat. Light microscopy studies of all specimens showed dense, homogeneous eosinophilic material (fig. 3). The material was strongly periodic acid-Schiff positive and metachromatic in the Giemsa stain. It stained with Congo red and demonstrated apple green birefringence in polarizing microscopy (fig. 4). In the abdominal skin, the amyloid was seen in the papillary dermis and around a vessel in the deep subcutaneous fat. The scalp biopsy revealed miniaturized hair follicles within a broad sheath of amyloid (fig. 4). The lateral longitudinal nail biopsy showed pale eosinophilic material directly under the thinned matrix epithelium, which had developed a broad granular layer as did the nail bed epithelium. The nail plate showed the staining pattern of stratum corneum. The minor salivary gland biopsy revealed a normal labial epithelium and tunica propria. The excretory ducts were surrounded by a broad sheath of eosinophilic Congo red-positive material. The glands were strongly atrophic with only minimal remnants of acini and ductal structures. The immunohistochemical classification of amyloid harbored a strong and even staining of the amyloid deposits with antibodies directed against κ light chain (AK3) and amyloid P component (from Dako, Hamburg, Germany). The amyloid deposits did not immunoreact with antibodies directed against AA amyloid, apolipoprotein AI and transthyretin (all Dako).

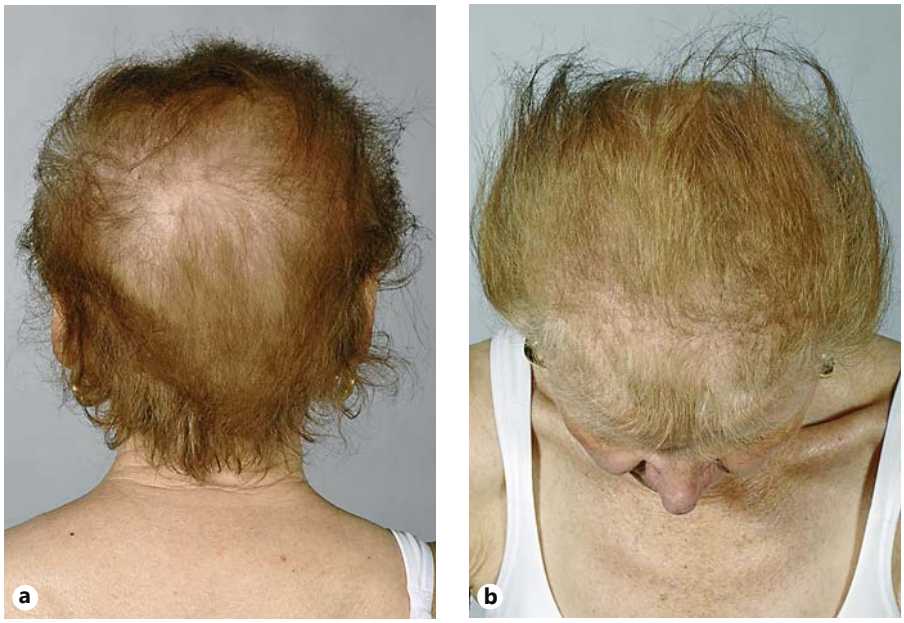

Fig. 1. Marked alopecia. **a** Involvement of the vertex. **b** Frontoparietal involvement.

Full blood cell count, serum chemistry, renal and hepatic tests were within the normal range. Antinuclear antibodies, anti-SS-A (Ro), anti-SS-B (La) and Jo-1 were all negative. Urinalysis showed a slight proteinuria of 0.3 g/l. The patient underwent a thorough investigation for systemic involvement. Serum protein electrophoresis showed a dysproteinemia and hypogammaglobulinemia but no monoclonal immunoglobulin. Urinary protein electrophoresis revealed a weak band of light chains of the κ-type. Chest X-ray, lung function test, ultrasound of the abdomen and echocardiography were within normal limits. A neurological examination showed a small-fiber neuropathy. The patient declined further investigations, including bone marrow and rectal biopsy. Since she was asymptomatic and the laboratory abnormalities not worrisome, the patient was given skin moisturizers. A follow-up occurred regularly. Eighteen months after the initial evaluation, her condition remained stable without significant changes of the clinical presentation and laboratory results, including the amount of light chains in the urine protein electrophoresis.

Discussion

Skin and mucous membrane changes often represent the first manifestations of AL amyloidosis. The most frequent mucocutaneous manifestations include purpura, petechiae and ecchymoses that are commonly found periorbitally, in the flexures and at sites of trauma. Furthermore, waxy papules, nodules or plaques, pigmentary changes, as well as scleroderma-like thickening of the skin and bullous lesions can be found [1, 2, 4, 6–10]. Our patient was peculiar and striking since she presented a systemic amyloidosis of the AL type of very indolent course, in which nail involvement, diffuse hair loss, skin discoloration and parchment-like acral changes with sicca syndrome predominated the clinical presentation over years. The underlying cause remained undiagnosed despite evaluation by different physicians and rheumatologists.

Nail dystrophy is a rare sign of systemic amyloidosis. In contrast to other clinically similar dystrophies, such as in lichen planus or graft-versus-host disease, amyloidosis nails are very soft and thin. The dystrophy usually manifests as brittleness, longitudinal ridging, crumbling, onycholysis and subungual thickening, striations and anonychia. It is caused by amyloid deposi-

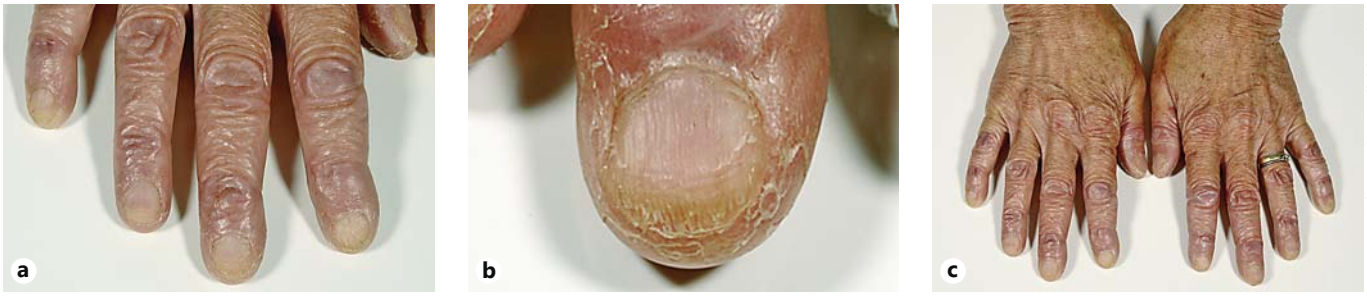

Fig. 2. Hand and nails. **a**, **b** Brittle nails with longitudinal striations and onychorrhexis. **c** Parchment-like skin with scleroatrophic appearance.

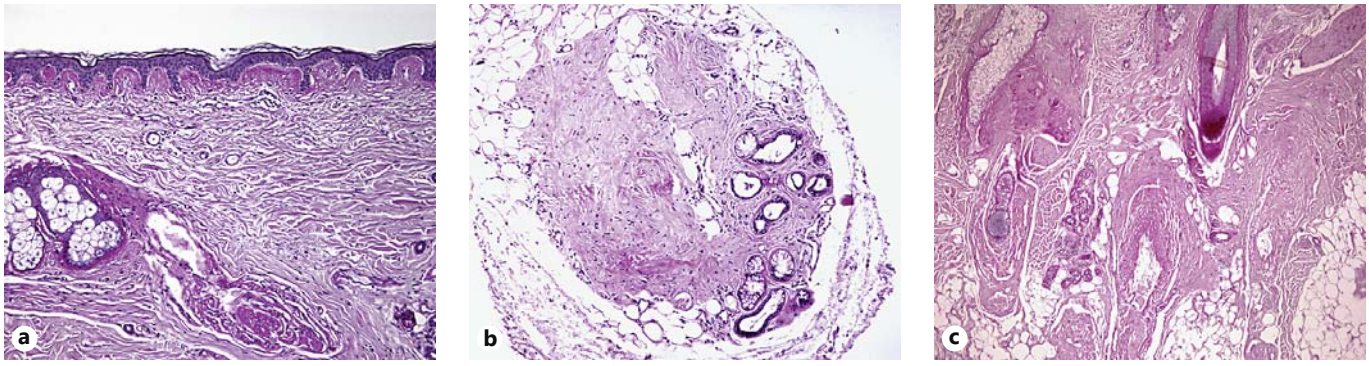

Fig. 3. Histopathology of the skin, minor labial gland and scalp. **a** There is atrophy of the epidermis and a dense homogeneous periodic acid-Schiff-positive substance in the papillary dermis in the abdominal skin. **b** The salivary gland is highly atrophic with only minimal secretory acini and amyloid deposits around the salivary ducts and in the connective tissue. **c** Miniaturized hair follicles with a broad sheath of amyloid are seen in the scalp biopsy.

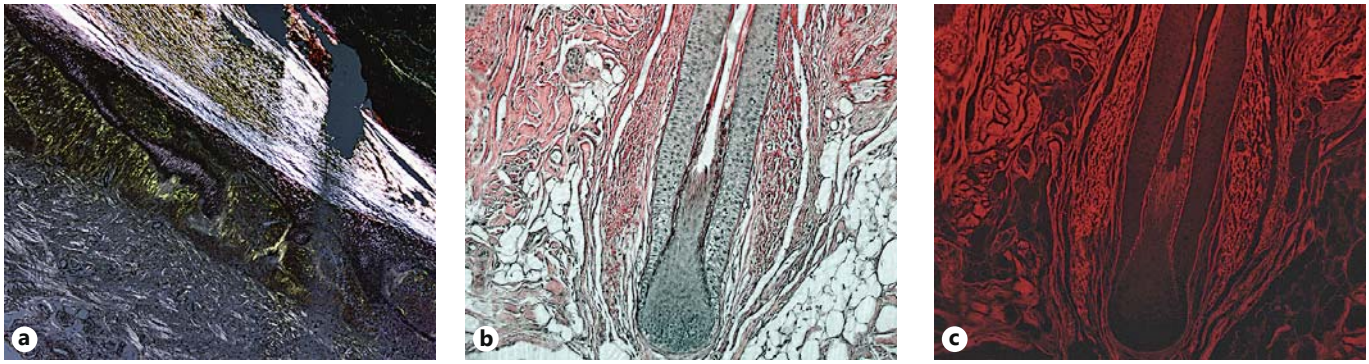

Fig. 4. Congo red staining. **a** Polarization microscopy of the nail biopsy shows subepithelial apple green birefringence consistent with amyloid deposition; the nail keratin is strongly birefringent. **b**, **c** Congo red stain of the scalp biopsy demonstrating amyloid deposits surrounding a hair follicle. **b** Light microscopy. **c** Fluorescence microscopy.

Table 1. Features of patients with nail changes

Age/sex	Nail changes as first manifestation/presence prior to diagnosis, months	Cutaneous involvement at time of diagnosis	Underlying disease	Reference
68/M	yes/36	only nail changes	no underlying disease	7
49/M	yes/24	only nail changes	multiple myeloma	8
70/M	yes/36	only nail changes	no underlying disease	9
65/F	yes/24	diffuse thickening of the skin, papules, purpura, sparse hair and nail changes	multiple myeloma	10
54/M	yes/13	purpura, waxy plaques, scleroderma-like thickening of the skin on the fingers, macroglossia, nail changes	monoclonal gammopathy	11
65/F	no	generalized hair loss, macules, purpura, macroglossia, skin thickening, nail changes	multiple myeloma	12
70/M	no	papules, alopecia, sparse hair axillary and genital, nail changes	monoclonal gammopathy	13
75/M	no	scleroderma-like infiltration of the face and abdomen, macroglossia, nail changes	multiple myeloma	14
81/M	no	ecchymotic macules, nail changes	monoclonal gammopathy	15
67/M	no	ecchymoses, thickened skin over hands and fingers, macroglossia, nail changes	multiple myeloma	16
81/F	yes/18	only nail changes	multiple myeloma	17
79/M	no	purpura, diffuse hair loss, sicca symptoms, nail changes	monoclonal gammopathy	18
68/M	yes/48	alopecia, sparse body hair and eyebrows, macroglossia, nail changes	monoclonal gammopathy	19
63/F	no	alopecia, sparse axillary and genital hair, scleroderma-like infiltration of the fingers, nail changes	monoclonal gammopathy	20
73/F	no	scleroderma-like skin changes, nail changes	multiple myeloma	21
61/M	yes/48	only nail changes	multiple myeloma	22
62/M	yes/24	purpura, nail changes	no underlying disease	23
69/F	no	nonhemorrhagic bullae on the hands and forearms	multiple myeloma	24
72/F	no	alopecia, petechiae, nail changes	multiple myeloma	25
66/F	no	alopecia, complete loss of axillary hair, sparse genital hair, scleroderma-like infiltration of the fingers, nail changes	monoclonal gammopathy	our case

tion in the matrix, nail bed and nail fold with consecutive defective nail production. Nail changes may exceptionally represent the initial cutaneous manifestation of systemic amyloidosis [7]. They tend to slowly worsen over the course of several years [8, 9]. To our knowledge, 20 cases of systemic amyloidosis associated with nail changes, including the present case, have been reported in the literature so far [7–25]. A summary of these cases is given in table 1. Ten patients were diagnosed as myeloma-associated systemic amyloidosis. In 6 cases, there was an underlying monoclonal gammopathy, while in 3 patients, no underlying hematological disease was found. Whereas in 5 of these cases, nail involvement was the only cutaneous sign of systemic amyloidosis at the time of diagnosis, the other patients including our case presented additional skin or mucosal manifestations characteristic for amyloidosis. In 9 cases, the nail lesions represented the first manifestation of the disease. Noteworthy, in 5 of these patients, nail changes were the sole cutaneous sign for at least 24 months prior to the diagnosis of systemic amyloidosis. Therefore, the recognition of nail changes as a manifestation of systemic amyloidosis is important because it can occasionally lead to an early diagnosis.

Our patient also presented a severe diffuse alopecia with generalized hair loss. Light microscopy studies of the scalp biopsy specimen revealed that the follicles were surrounded and virtually suffocated by the dense and broad perifollicular amyloid layer. Alopecia is a rare complication of systemic amyloidosis. A literature search revealed only 14 cases in which development of an alopecia was highlighted [10, 12, 13, 18–20, 25–28]. In 3 of the cases the alopecia has been reported as initial leading sign of occult amyloidosis [20, 27, 28]. Lutz and Pittelkow [20] described a case of systemic amyloidosis, in which alopecia constituted the initial manifestation of the disease, preceding the other signs and symptoms by 6 years. Alopecia may develop in either a patchy or in a diffuse distribution. Based on a serial analysis of biopsy specimens from a patient with systemic amyloidosis, Hunt et al. [28] suggested that vascular impairment with inhibition of anagen restoration is responsible for amyloidosis-induced alopecia.

Our patient was first thought to suffer from either systemic sclerosis or dermatomyositis based on the presence of parchment-like skin changes of the hands with a slightly scleroatrophic appearance. The term 'scleroderma amyloidosum' was coined by Gottron in 1932 to describe sclerosing skin changes resembling scleroderma in patients with primary systemic amyloidosis. Since then, scleroderma-like lesions have been described in patients with systemic amyloidosis and multiple myeloma. Scleroderma-like skin changes may be observed in association with other disorders such as overlap syndromes, scleredema, scleromyxedema, endocrine disorders, nephrogenic systemic fibrosis, graft-versus-host disease, or from exposures to a variety of drugs (such as bleomycin, pentazocine) and toxins (e.g. organic solvents, petroleum distillates). These conditions should therefore always be considered and eventually excluded [29].

Finally, another rare manifestation of systemic amyloidosis, which was observed in our case, is sicca syndrome. The latter results from amyloid deposits within the minor salivary and lacrimal glands leading

to severe loss of functional acini. Sicca syndrome is defined as the occurrence of xerostomia and xerophthalmia. It is commonly associated with Sjögren's syndrome and the presence of anti-SSA and anti-SSB antibodies. Nevertheless, there are several other conditions that can secondarily lead to sicca syndrome such as systemic scleroderma, sarcoidosis, lipoproteinemias, myeloproliferative disorders, autoimmune liver disease, hyperglobulinemic renal tubular acidosis and hemochromatosis [30]. Therefore, patients presenting with sicca syndrome have to be evaluated carefully for an underlying disease by a detailed clinical history and physical examination. In our patient presenting with dry eyes and xerostomia with amyloid deposits in the minor salivary glands, search for anti-SSA and anti-SSB antibodies was negative, a finding that should make the clinician consider other causes than Sjögren's syndrome. In analogy to previous similar cases described by Yokota et al. [31], Gogel et al. [30] and Richey and Bennion [32], our observation reminds us that systemic amyloidosis should be included in the differential diagnosis of sicca syndrome and warrants an adequate laboratory workup including labial biopsy [33].

The organs most commonly involved in AL amyloidosis are the kidneys with proteinuria and renal failure, the heart with diastolic heart insufficiency and the gastrointestinal tract with abdominal pain, diarrhea, constipation up to motility abnormalities. Less frequently, cholestatic hepatopathy, peripheral neuropathy, autonomic neuropathy and infiltration of soft tissues including macroglossia, a pathognomonic finding in 15% of cases, can be found [34]. No treatment that specifically targets the amyloid deposits is available yet. Therapy therefore aims at suppressing the underlying plasma cell, lymphoplasmocytic or lymphoproliferative disorder responsible for the secretion of the amyloid precursor. All treatments which have been found effective in multiple myeloma or in lymphoproliferative disorders can be used [35, 36]. The prognosis of AL amyloidosis is generally poor with death usually resulting from cardiac or renal failure if the disorder causing AL amyloidosis remains untreated. Patients with systemic AL amyloidosis have a median survival of 1–2 years, while fewer than 5% of all AL amyloidosis patients survive 10 or more years after the diagnosis has been made [6].

In conclusion, our observation reminds us that progressive nail changes, diffuse hair loss with parchment-like skin changes and sicca symptoms may represent the leading signs and symptoms of systemic amyloidosis of the AL type. Knowledge of these manifestations is essential for prompt diagnosis of the disease with potential multiorgan involvement and its management.

Disclosure Statement

The authors declare no competing financial interests.

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