Primary Systemic Amyloidosis Associated With Multiple Myeloma: A Case Report and Review of the Literature

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GOAL

To understand amyloidosis to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the different clinical types of amyloidosis.
2. Identify criteria for diagnosis of multiple myeloma.
3. Discuss the traditional treatment of primary systemic amyloidosis.

CME Test on page 203.

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Amyloidosis is a broad and complex class of diseases that comprises several etiologies, many manifestations, and a diversity of outcomes. We discuss a patient with primary systemic amyloidosis associated with multiple myeloma that illustrates many of the typical and atypical features of the disease process. Despite more in-depth assessment and accurate classification, survival for patients with primary systemic disease remains poor.

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Cutaneous deposition diseases encompass a variety of unrelated disorders characterized by the deposition of endogenous or exogenous substances within the skin.[1] Amyloidosis, porphyria,

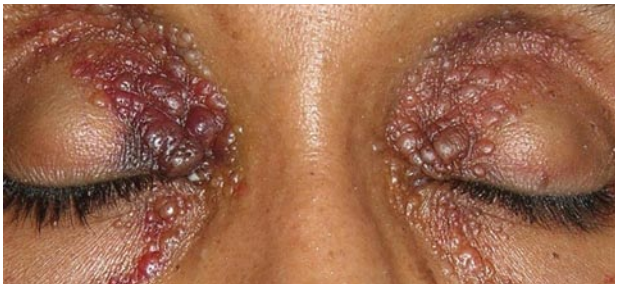

Figure 1. Primary systemic amyloidosis seen as periorbital waxy papules with underlying ecchymoses.

colloid milium, and lipoid proteinosis are included in a differential of metabolic processes involved in endogenous deposition that occur as isolated entities or part of systemic diseases. In the late 1830s, German botanists Vogel and Schleiden[2] first used the term *amyloid* to describe a substance in plants; applied to human disease, amyloidosis refers to the extracellular deposition of various host-synthesized proteins configured as β-pleated sheets, which is a tertiary protein structure that is abnormal in human tissue.[2]

Skin biopsy with ultrastructural immunohistochemical stains can be a tool to determine the clinical type of amyloidosis by detecting the subtype of amyloid fibril protein deposited within the skin.[2-4] We describe a patient with fatal systemic deposition of amyloid light chain (AL) amyloid fibril precursor protein (a protein derived from the variable portion of monoclonal immunoglobulin light chains).[5] Biopsies performed on healthy-appearing skin in patients with primary systemic amyloidosis and myeloma-associated amyloidosis were positive for amyloid in 47% of cases (16/34) in one study[6] and 100% of cases (16/16) in another study.[7] Although positive biopsy results that are characteristic of different types of amyloidosis can be seen, a systemic workup to characterize the presence and extent of involvement of other organs is necessary to differentiate between systemic and localized amyloidosis, which vary in prognosis and treatment.

Case Report

A 43-year-old cachectic-appearing black woman was admitted with progressive shortness of breath over 3 months. She reported that her problems started 6 months prior to admission with increasing tongue size, difficulty swallowing, and fleshy lesions on her face. Additionally, she complained of intermittent fever, history of weight loss, persistent diarrhea, fatigue, and progressive lower extremity weakness. Her past medical history was remarkable for membranoproliferative glomerulonephritis, hypertension, pulmonary hypertension, and anemia of thrombocytosis. Physical examination results revealed bitemporal wasting and numerous waxy papules around both eyes, some with underlying ecchymoses (Figure 1). Additionally, small translucent papules were noted within her nose and around her mouth, as well as on her trunk, neck, and volar wrists. The papules were nontender and nonpruritic. Examination of the oral cavity revealed macroglossia, with a substantially scalloped tongue filling the entire cavity.

A superficial shave biopsy of a typical lesion on the patient's neck revealed an atrophic epidermis and an expanded papillary dermis, with eosinophilic material distributed throughout (Figure 2A). The rete ridges were greatly elongated and encased eosinophilic deposits within the papillary dermis, sometimes forming collarettes. Congo red staining with polarization showed apple green birefringence characteristic of amyloid (Figure 2B). Results of immunohistochemistry showed diffuse staining for λ light chain throughout the dermis but were negative for κ light chain (Figure 3).

Further clinical evaluation showed widespread systemic amyloidosis. Biopsy specimens from the stomach, duodenum, and colon demonstrated amyloid deposition in the mucosa and submucosa. In addition, the results of a gastric biopsy showed evidence of focal intestinal metaplasia (Figure 4). Results of a renal biopsy were negative for Congo red, and the creatinine level was stable at 0.4 mg/dL (reference range, 0.1–0.4 mg/dL) throughout admission. The patient's history of pulmonary hypertension and low-voltage QRS complex on electrocardiogram were consistent with cardiac amyloid infiltration and resultant restrictive cardiomyopathy. Results of a chest x-ray noted bilateral

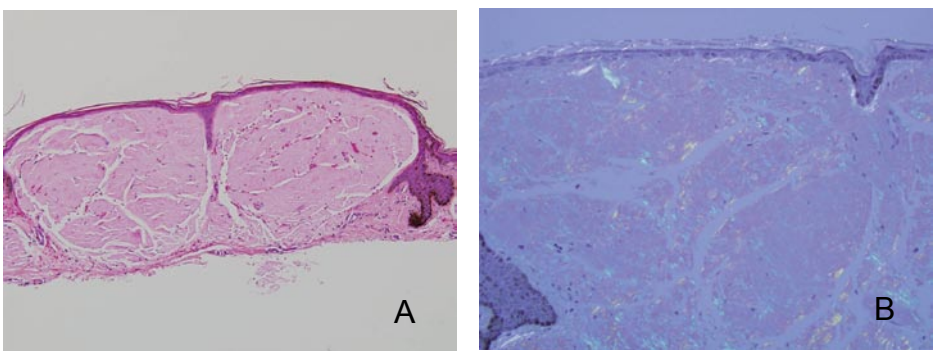

Figure 2. Eosinophilic fissured amyloid deposits in the expanded papillary dermis from a superficial shave biopsy specimen of waxy purpuric lesions on the neck. Note atrophic epidermis and elongated rete ridges (A)(H&E, original magnification ×200). Apple green birefringence in polarized light after staining with Congo red (B)(original magnification ×400).

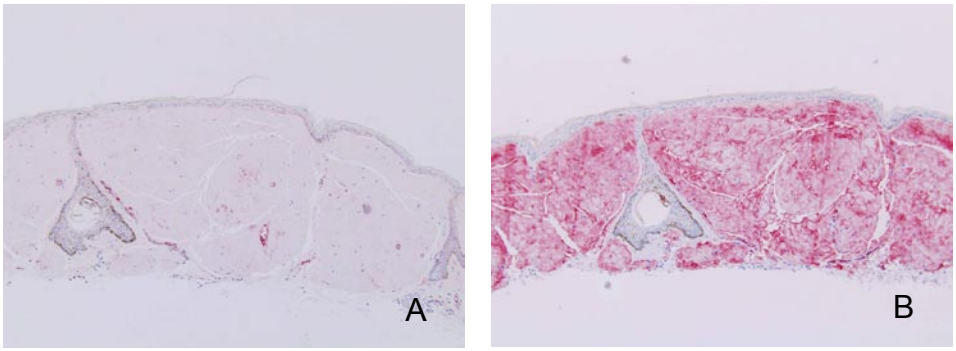

Figure 3. Immunohistochemistry results were negative for κ light chain (A)(immunoperoxidase, original magnification ×400) and showed diffuse staining for λ light chain (B)(immunoperoxidase, original magnification ×400).

pleural effusions consistent with congestive heart failure. Echocardiogram findings suggested diastolic dysfunction with a hyperdynamic ejection fraction of more than 70% and an increased E/A ratio of 15.7 (references, >70% and >1.5, respectively). A fine-needle biopsy of a mediastinal mass compressing the left atrium showed a mixed infiltrate of leukocytes and plasma cells, indicating further systemic involvement.

Urine protein electrophoresis was abnormal, with a 24-hour total urine protein level of 1.229 g/vol (reference range, 0.05–0.10 g/vol) and an M-protein spike (λ light chain) of 33.5 mg/dL (53.4% of total urine protein). The 33.5 mg/dL of urine light chain protein signified a Bence Jones proteinuria, but the amount of light chain protein in the urine fell below the World Health Organization criteria of urinary output of greater than or equal to 1 g urine light chain over 24 hours for the diagnosis of multiple myeloma.[8] An osseous skeletal survey showed no evidence of punched-out lesions or other gross abnormalities. Subsequent bone marrow aspirate and biopsy results found sheets of cytologically atypical plasma cells with prominent nucleoli and occasional multinucleated forms. Quantitatively, the bone marrow showed 75% plasmacytosis, with λ light chain restriction in 75% of the plasma cells. The clinical findings, along with the M protein in the urine and bone marrow plasmacytosis of 75%, are consistent with a clinical diagnosis of multiple myeloma based on the World Health Organization criteria (Table 1).[8]

The evaluation suggested AL amyloidosis and indicated a malignant course with skin, cardiac, and gastrointestinal tract involvement. The patient was started on systemic dexamethasone sodium phosphate at a dosage of 40 mg intravenously daily for 4 days on and 4 days off. A percutaneous endoscopic gastrostomy tube was placed, and the patient was transferred to a smaller community hospital for nutritional rehabilitation prior to starting thalidomide or melphalan therapy. Unfortunately, the patient developed an ileus, continued to experience malnutrition, and was transferred to the palliative care service for pain management. She died approximately 2 weeks later, less than one month after diagnosis.

Comment

Despite the separate classifications of systemic and localized, the different clinical types of amyloidosis look almost identical ultrastructurally. Under the electron microscope, straight, nonbranching, nonanastomosing, irregularly spaced fibrils measuring 7.5 to 10.0 nm in diameter and of indefinite length characterize all forms of amyloidosis.[9] Additionally, all forms of amyloidosis share the same serum amyloid P (SAP) component and ground substance. SAP is an elastase inhibitor and normal constituent of the microfibrillar sheath of elastic fibers; however, as a component of amyloid, SAP is pathological, likely functioning with the β-pleated sheet structure to protect amyloid from phagocytosis and degradation. It is the third component—protein-derived amyloid fibers (AA [amyloid A], AK [altered keratin protein component], AL)—that varies according to deposition subtype.

The type of fibril deposit and the clinical presentation are guidelines to classify various types of amyloidosis (Table 2).[2,9] Three major types of amyloid fibril precursor proteins have been identified: tissue amyloid derived from light chain protein fragments, or AL; a nonimmuoglobulin acute phase reactant, known as serum AA; and AK. In the heredofamilial

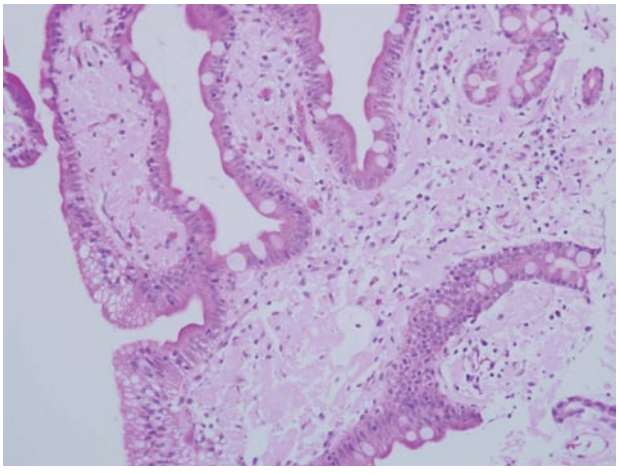

Figure 4. Results of a gastric biopsy showed extensive amyloid deposition and evidence of focal intestinal metaplasia (H&E, original magnification ×200).

Table 1.

Criteria for Diagnosis of Multiple Myeloma Based on WHO Classification Criteria*†[8]

Major Criteria	Minor Criteria
1. Bone marrow plasmacytosis (>30%)	1. Bone marrow plasmacytosis (10%–30%)
2. Biopsy-proven plasmacytoma	2. M protein less than major criteria
3. Monoclonal globulin spike (M protein) on serum or urine electrophoresis	3. Osteolytic lesions
Serum IgG >35 g/L or IgA >20 g/L	4. Decrease of uninvolved polyclonal immunoglobulins in serum
Urine light chain ≥1 g/24 h	IgG <6.0 g/L
	IgA <1.0 g/L
	IgM <0.5 g/L

*WHO indicates World Health Organization; Ig, immunoglobulin.

†The diagnosis of multiple myeloma requires 1 major criterion and ≥1 minor criterion, or 3 minor criteria (including minor criteria 1 and 2), with symptomatic and progressive disease.

forms of familial amyloidotic polyneuropathy (FAP) I, II, III, and IV, other proteins (eg, transthyretin, apolipoprotein A-I, gelsolin) are modified into β-pleated sheets and deposited as amyloid.[2] In addition to the type of protein deposited, amyloidosis is defined as either systemic or localized (Table 3) and varies greatly in terms of prognosis, with cutaneous confinement being more benign.

AL amyloidosis occurs without plasma cell dyscrasia in the minority of cases.[10] In one study of 494 cases of primary systemic amyloidosis, only 13% of cases were associated with multiple myeloma; other monoclonal gammopathies were associated, specifically monoclonal gammopathy of undetermined significance and smoldering myeloma in 15% and 3% of cases, respectively.[10] Sources historically estimated that an average of 15% of patients with multiple myeloma developed amyloidosis.[11,12] As more sensitive diagnostic techniques become available, it is apparent that AL amyloidosis occurs more frequently with plasma cell dyscrasia than previously thought.

Immunoelectrophoresis and/or immunofixation, more sensitive techniques than serum protein electrophoresis, show a serum M-protein spike in 72% (n=430) of cases as well as a urine M-protein spike in 73% (n=429) of cases; combined, of patients who had both urine and serum immunoelectrophoresis and/or immunofixation at the time of AL diagnosis, an M-protein spike was present in 89% of patients (n=408).[10] Of the remaining 11% of patients (n=43) with urine and serum negative for M protein, 20 of 43 patients had bone marrow biopsy results demonstrate a monoclonal plasma cell proliferation or positive immunohistochemical stains.[10] Waxy purpuric mucocutaneous lesions along with carpal tunnel syndrome and macroglossia—all secondary to AL amyloid tissue deposits—may serve as an early marker of plasma cell dyscrasia in general.[9]

Systemic—Systemic amyloidosis is divided into 3 subtypes, with amyloid fibril precursor proteins specific to each type: primary systemic amyloidosis (AL), secondary systemic amyloidosis (AA), and heredofamilial amyloidosis (eg, transthyretin, AA, β_2-microglobulin, apolipoprotein A-I, gelsolin).[9] Systemic amyloidosis has a poor prognosis, with a median survival of 13 to 43 months for primary systemic amyloidosis. Negative prognostic indicators for primary systemic amyloidosis include congestive heart failure, increased septal thickness, urinary light chains, hepatomegaly, and major weight loss (Table 4).[10] Secondary systemic amyloidosis is the result of a chronic inflammatory process caused by a myriad of underlying systemic diseases, with the most common causes varying by country. In the United States and Western Europe, rheumatoid arthritis and chronic inflammatory bowel disease, predominantly Crohn disease, are the most common causes of secondary systemic amyloidosis. In contrast, tuberculosis and leprosy predominate in third-world countries.[13] Amyloidosis is notable for deposition throughout the body of a modified acute phase reactant (AA), with no organ system spared; prognosis varies depending on the ability to effectively treat the underlying disease. The disease course often is irreversible because of the protection from phagocytosis offered by the β-pleated sheet configuration and elastase inhibitor properties of SAP.[2]

Cutaneous symptoms are found in up to 40% of patients with primary systemic amyloidosis[6] and characteristically occur as waxy, smooth, shiny, nontender, nonpruritic nodules or plaques.[9] The papules frequently are distributed on flexural areas (eg, eyelids, axillae, umbilicus), the neck, central parts of the face, lips, tongue, and buccal mucosa, as well as on retroauricular, inguinal, and

Table 2.

Amyloid Fibril Precursor Proteins and Amyloidosis Classification*[2,9]

Amyloid Fibril Precursor Protein	Amyloidosis Type
AL	Primary systemic Lung specific Larynx specific Primary cutaneous nodular
AA	Secondary systemic Familial Mediterranean fever Muckle-Wells syndrome
AK	Primary cutaneous macular Primary cutaneous lichenoid Secondary cutaneous
Transthyretin	FAP I FAP II
Apolipoprotein A-I	FAP III
Gelsolin	FAP IV
β_2-microglobulin	Hemodialysis associated
APCP	Brain specific (senile cerebral/Alzheimer disease associated)
Cystatin C	Brain specific (hereditary cerebral)
Amylin	Pancreas specific

*AL indicates amyloid light chain; AA, amyloid A; AK, altered keratin protein component; FAP, familial amyloidotic polyneuropathy; APCP, amyloid plaque core protein.

anogenital regions.[9] Occasionally, plaques on the head and neck coalesce to produce leonine facies or even to occlude the external auditory meatus, resulting in deafness as a presentation.[9,14]

Other skin findings related to primary systemic amyloidosis are purpura and ecchymosis on the face and neck in 16% of patients, most notably found on the periorbital or perioral regions.[5] The periorbital ecchymoses predominately affect the upper eyelids, which gives the disease the reputation as "black-eye syndrome."[2] Pinch purpura can be induced by gentle skin stretching and is thought to be secondary to blood vessel amyloid infiltration, decreased vitamin K–dependent clotting factors, acquired factor X deficiency, and increased fibrinolysis and antithrombin activities.[2] The "shoulder pad" sign refers to infiltration of periarticular tissues by AL amyloid and often is painful, with resultant decreased joint motility.[2,14] Additionally, patients may exhibit patchy alopecia and nail plate atrophy secondary to amyloid infiltration of follicular and matrix structures, respectively.[9]

β_2-microglobulin and AA amyloid fibril precursor proteins are involved in hereditary inflammatory syndromes associated with secondary systemic amyloidosis—familial Mediterranean fever (AA), Muckle-Wells syndrome (AA), and hemodialysis associated (β_2-microglobulin).[2] Familial Mediterranean fever and Muckle-Wells syndrome, which are recessive and autosomal-dominant disorders, respectively, are associated with fever and renal amyloidosis. Additionally, familial Mediterranean fever is associated with angioneurotic edema and erysipelaslike erythema, arthralgia, and peritonitis, whereas Muckle-Wells syndrome is associated with deafness and urticaria.[9]

FAP rarely has cutaneous manifestations and only has been described in the past 4 decades in pedigrees in Portugal, Japan, and Sweden, as well as in several collections of cases in North America.[15] FAP also is known as familial nephropathic polyneuropathy, with several manifestations that result from deposition of transthyretin, apolipoprotein A-I, or gelsolin amyloid fibril precursor protein in neural tissue. Peripheral neuropathy is the most prominent manifestation, but cardiac disease and autonomic neuropathy also can occur.[4] According to a study of 52 patients with FAP from North America, 43 patients (83%) had peripheral neuropathy and 17 patients (33%) had autonomic neuropathy compared with 5 patients (10%) with renal disease and 14 patients (27%) with cardiomyopathy. The median duration of survival for FAP is 5.8 years, with an approximately 40% mortality from congestive heart failure and cardiac arrhythmia.[15]

Table 3.

Classification of Amyloidosis by Systemic or Localized Involvement

Systemic Amyloidosis
Primary
Secondary (including the following heredofamilial subtypes)
Familial Mediterranean fever
Muckle-Wells syndrome
Familial amyloidotic polyneuropathy
Hemodialysis associated
Localized Amyloidosis
Organ specific
Primary cutaneous
Nodular
Macular
Lichenoid
Secondary cutaneous
Cutaneous tumor associated (benign/malignant)
Psoralen plus UVA associated

Hemodialysis-associated amyloidosis results from dialysis membranes (cellulose, cuprophane) failing to clear β_2-microglobulin proteins from the blood.[2] After an average of 8 to 9 years of dialysis, the deposits become evident in some patients, while other patients with similar deposits remain asymptomatic, prompting thought that the process also must involve a hereditary component.[2,16] Symptomatic β_2-microglobulin deposition most commonly occurs in articular structures and is associated with bilateral carpal tunnel syndrome.[16] Skin manifestations are uncommon, with wrinkling of fingers and lichenoid truncal lesions present in some patients.[2] Peritoneal dialysis and newer dialysis membranes with a β_2-microglobulin absorbent column can filter β_2-microglobulin more effectively than traditional dialysis, and their use can sometimes reverse symptoms of carpal tunnel syndrome and arthralgia related to amyloid deposition.[17]

Localized—Localized amyloidosis includes primary and secondary subtypes. Primary cutaneous amyloidosis is further divided into nodular, macular, and lichenoid forms. Secondary cutaneous amyloidosis often is an incidental finding on biopsy of multiple benign and malignant skin tumors, or is associated with psoralen plus UVA therapy.[2] In both primary cutaneous macular and lichenoid amyloidosis, as well as in secondary cutaneous amyloidosis, the derived amyloid fibers are from keratin protein (AK) and are released following injury to keratinocytes. The lichenoid and macular forms demonstrate features of epidermal damage—necrotic keratinocytes, pigment incontinence, and focal hemorrhage.[4] AK presence within the skin can be evaluated with keratin immunoperoxidase stains and direct immunofluorescence staining of immunoglobulin M, which is passively absorbed by AK deposits.[2]

The degenerated keratin AK amyloid deposits in lichenoid and macular amyloidosis consist of amorphous deposits explained by 2 current theories—Hashimoto fibrillar body theory[18] and Yanagihara secretion theory.[19] The former theory explains that necrotic epidermal cells are transformed by dermal macrophages and fibroblasts into AK amyloid,[18] whereas the latter theory postulates that disrupted basal cells secrete AK amyloid.[19] Lichenoid amyloidosis occurs more commonly among the Chinese population, and macular amyloidosis is more common among Hispanic, Asian, and Middle Eastern populations.[2,4]

Multiple endocrine neoplasia 2, or Sipple syndrome, is an autosomal dominant RET oncogene mutation classically associated with medullary thyroid carcinoma, parathyroid hyperplasia, pheochromocytoma, and both primary cutaneous macular and lichenoid amyloidosis. Pruritus presenting in infancy should include multiple endocrine neoplasia 2 in the differential in terms of its syndromic association with primary cutaneous lichenoid amyloidosis, which can present shortly after birth in this population.[4]

Macular and lichenoid amyloidosis can coexist in the same individual and thus are regarded by some authors as one pathological process; however, lichenoid amyloidosis may be distinguished from macular amyloidosis histologically by hyperkeratosis, acanthosis, and larger deposits of AK amyloid fibril protein. Small hyperkeratotic papules and sometimes larger infiltrated plaques characterize lichenoid amyloidosis, which affects shins bilaterally with rare involvement of the thighs, forearms, and upper back.[2,9] In contrast, primary cutaneous macular amyloidosis typically involves the interscapular upper back, shows salt-and-pepper pigmentation, and displays a rippled appearance when small papules coalesce.[5] The absence of perivascular amyloid in the primary cutaneous macular and primary cutaneous lichenoid forms of amyloidosis largely rules out systemic disease, in which perivascular invasion is characteristic.[4]

Primary cutaneous nodular amyloidosis is unique among the cutaneous amyloidosis subgroup in that its amyloid fibrils are derived from AL, which is the same amyloid present in primary systemic amyloidosis. One study questioned the neoplastic origin of primary cutaneous nodular amyloidosis, citing that the fibril protein studied was polyclonal and could have been secondary to a reactive process.[20] However, histologically, numerous plasma cells suggest localized plasmocytomas are present at the periphery of diffuse amyloid deposits at all levels within the dermis and subcutis.[2,4] Nodules typically are singular, located preferentially in acral areas, and can

Table 4.

Primary Systemic Amyloidosis Findings by Organ System[10]

Organ System	Primary Systemic Amyloidosis Association
Cardiovascular	Left ventricular hypertrophy Congestive heart failure* Orthostatic hypotension Increased septal thickness* Low voltage QRS complex Sudden death secondary to arrhythmias or heart block
Renal	Urinary light chains* Renal failure
Nervous	Peripheral neuropathy
Gastrointestinal	Gastrointestinal tract bleeding Hepatomegaly*
Musculoskeletal	Rheumatoid arthritis–like small joint involvement "Shoulder pad" sign Decreased joint mobility
Integumentary	Waxy purpuric mucocutaneous nodules or plaques Leonine facies Purpura or ecchymoses of face and neck Patchy alopecia Nail dystrophy
Constitutional	Weakness Major weight loss* Fatigue
Miscellaneous	Carpal tunnel syndrome (bilateral) Macroglossia Deafness Sicca syndrome

*Negative prognostic indicators.

be bullous with an atrophic overlying epidermis.[4] Fewer than 50 cases of primary cutaneous nodular amyloidosis have been reported in the medical literature.[3]

Conclusion

The systemic pattern of amyloid involvement in the present case, as well as the underlying diagnosis of multiple myeloma, is consistent with AL amyloidosis secondary to multiple myeloma. Even though the M protein often found in multiple myeloma is the κ light chain, this patient's M protein was λ light chain, which is consistent with two thirds of patients with AL amyloidosis but is inconsistent with multiple myeloma.[10]

Our patient presented with weight loss, fatigue, and weakness, which are notably the most frequent initial symptoms in AL amyloidosis.[5] Of note, this case exhibited 3 negative prognostic indicators of primary systemic amyloidosis: congestive heart failure, urinary light chains, and major weight loss. Primary systemic amyloidosis also can present with a variety of other symptoms that often mimic a variety of diseases—for example, carpal tunnel syndrome, peripheral neuropathy, orthostatic hypotension, gastrointestinal tract bleeding, sicca syndrome, and rheumatoid arthritis–like small joint involvement.[2,20] Macroglossia, as in this case, is found as a presenting symptom in approximately 10% of patients, representing a decreased frequency of up to 40% in the literature, likely because of earlier diagnosis of amyloidosis.[5]

The systemic involvement of amyloid deposition in this patient was typical of primary systemic amyloidosis, which typically involves skin, as well as mesenchymal tissue, the tongue, heart, and gastrointestinal tract.[4,21] In contrast, secondary systemic amyloidosis typically involves parenchymous organs (ie, the adrenals, liver, spleen, kidney, lymph nodes), notably excluding the skin of clinical findings, though amyloid deposits often are found microscopically.[4,5] Renal failure, found in only 8% of patients, is less common in primary systemic amyloidosis compared with renal insufficiency or nephrotic syndrome with secondary systemic amyloidosis, which has a 90% incidence.[4]

Congestive heart failure, which manifested in this patient, and cardiac arrhythmia are common causes of death from primary systemic amyloidosis, which has a 48% to 65% cardiac mortality rate.[4] Amyloid deposits in the myocardium result in left ventricular hypertrophy and congestive heart failure. Amyloid deposits in atrioventricular nodes and branches can result in arrhythmia, heart block, and sudden death; an electrocardiogram workup of amyloidosis characteristically shows low-voltage QRS complex, as seen in this case (A. Kingman, MD, and N.L. Pereira, MD; written communication; January 2006).

Traditional treatment of primary systemic amyloidosis includes a combination of prednisone and the systemic chemotherapy alkylating agent melphalan, with the optional addition of colchicine.[5] Hematopoietic stem cell transplantation after high-dose melphalan has emerged as another therapeutic option and has led to remission in some patients.[22] Additionally, thalidomide combined with prednisone has been tried more recently; synergism between thalidomide and prednisone on myeloma plasma cells was rapidly effective but also was adversely toxic in approximately one half of patients, and symptomatic bradycardia presented in one fourth of patients studied.[23]

Median survival is an average of 43 months for primary systemic amyloidosis,[4] though one study reported a patient survival of 18 years, which is the longest known survival of a patient with primary systemic amyloidosis.[24] This 72-year-old patient had immunoglobulin G κ light chain paraproteinemia and no known myeloma, leading the authors to speculate that κ light chain paraproteinemia could be a positive serum marker for a more benign systemic amyloidosis.[24] The patient we reported displayed a Bence Jones proteinuria and a progressive disease course with a λ light chain paraproteinemia, and died less than one month after diagnosis.

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REFERENCES

1. Vogel T, Schleiden MJ. Ueber das Amyloid, eine neue Pflazensubstanz. *Annalen der Physik*. 1839;122:327-329.
2. Touart DM, Sau P. Cutaneous deposition diseases. part I. *J Am Acad Dermatol*. 1998;39:149-171.
3. Chotzen VA, Gandour-Edwards R, Zang MK, et al. Long-term AL primary amyloidosis. a case report. *Dermatol Online J*. 1995;1:1-5.
4. Errors in metabolism. In: Odom RB, James WD, Berger TG, eds. *Andrews' Diseases of the Skin*. Philadelphia, Pa: WB Saunders Co; 2000:648-652.
5. Daoud MS, Lust JA, Kyle RA, et al. Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol*. 1999;40:507-535.
6. Rubinow A, Cohen AS. Skin involvement in generalized amyloidosis: a study of clinically involved and uninvolved skin in 50 patients with primary and secondary amyloidosis. *Ann Intern Med*. 1978;88:781-785.
7. Wong CK, Wang WJ. Systemic amyloidosis: a report of 19 cases. *Dermatology*. 1994;189:47-51.
8. *EBM Guidelines. Evidence-Based Medicine* [book on CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd; 2005.
9. Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol*. 1988;18(1 pt 1):1-16.
10. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32:45-59.
11. Bluefarb SM. Cutaneous manifestations of multiple myeloma. *Arch Dermatol*. 1955;72:506-523.
12. Bayrd ED, Bennett WA. Amyloidosis complicating myeloma. *Med Clin North Am*. 1950;34:1151-1164.
13. Kyle RA. Amyloidosis. *Circulation*. 1995;91:1269-1271.
14. Kyle RA, Gertz MA. Amyloidosis. In: Schrier RW, Friedman EA. *Atlas of Diseases of the Kidney*. Vol 4. Philadelphia, Pa: Blackwell Publishing; 1999:3.1-3.15.
15. Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. *Mayo Clin Proc*. 1992;67:428-440.
16. Vogelgesang SA, Klipple GL. The many guises of amyloidosis. *Postgrad Med*. 1994;96:119-122, 126-127.
17. Campistol JM, Torregrosa JV, Ponz E, et al. Beta-2-microglobulin removal by hemodialysis with polymethylmethacrylate membranes. *Contrib Nephrol*. 1999;125:76-85.
18. Hashimoto K, Kobayashi H. Histogenesis of amyloid in the skin. *Am J Dermatopathol*. 1980;2:165-171.
19. Yanagihara M, Kitajima Y, Yaoita H, et al. Ultrastructural observation of the relationship between amyloid filaments and half desmosomes in macular amyloidosis [abstract]. *J Cutan Pathol*. 1980;7:213.
20. Inazumi T, Hakuno M, Yamada H, et al. Characterization of the amyloid fibril from primary localized cutaneous nodular amyloidosis associated with Sjögren's syndrome. *Dermatology*. 1994;189:125-128.
21. Gertz MA, Kyle RA. Primary systemic amyloidosis—a diagnostic primer. *Mayo Clin Proc*. 1989;64:1505-1519.
22. Gertz MA, Lacy MQ, Dispenzieri A, et al. Amyloidosis: diagnosis and management. *Clin Lymphoma Myeloma*. 2005;6:208-219.
23. Palladini G, Perfetti V, Perlini A, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood*. 2005;105:2949-2951.
24. Wallis MS, Stough DB IV. Extended survival of patients with primary systemic amyloidosis. *Cutis*. 1992;49:193-195.