International Journal of Women's Dermatology 2 (2016) 18–22

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Amyloidosis: A story of how inframammary erosions eclipsed inconspicuous periorbital ecchymoses☆,☆☆

Andrew Kelsey, MD, Diane H. Smith, MD, Joyce Meng, MD, Michael Murphy, MD, Marti J. Rothe, MD *

Department of Dermatology, University of Connecticut Health Center, Farmington, Connecticut

ARTICLE INFO

Article history:
Received 5 September 2015
Received in revised form 27 November 2015
Accepted 28 November 2015

Key words:
apple-green birefringence
amyloid
amyloidosis
Congo red
inframammary erosions
periorbital ecchymoses
pinch purpura
plasma-cell dyscrasia
serum protein electrophoresis

ABSTRACT

Systemic amyloidosis is a rare disease that can be rapidly progressive due to widespread organ involvement. There are well-described renal, cardiac, pulmonary, neurological, and dermatologic findings. Here, we outline one patient's experience with the condition from presentation to making the diagnosis. She presented with pathognomonic dermatologic findings including pinch purpura and ecchymoses found in the skin folds.

Introduction

Amyloid is a term selected by the pathologist Rudolf Virchow in 1954 to describe the microscopic depositions he observed as being "cellulose-like" (Seldin and Skinner, 2012). Amyloidoses are a large group of diseases in which multifolding of excess proteins renders these proteins insoluble and results in deposition within organs and tissues (Falk et al., 1997; Merlini and Bellotti, 2003). Although localized and systemic forms exist, in the United States less than 10% of cases are the localized form. There are no known racial, occupational, geographic, or environmental predispositions to this condition (Lachmann and Hawkins, 2012). The incidence of amyloidosis is unclear, but it is thought to be increasing. From 1950 to 1969, there were 6.1 cases per million, which increased to 10.5 cases per million between 1970 and 1989 (Lachmann and Hawkins, 2012).

At least 26 unrelated proteins are known to form amyloid fibrils. While there is a great variety in the precursor protein fibril, diffraction studies have shown that all amyloid proteins share a similar pattern of antiparallel β-sheets with a propensity for aggregation (Lachmann and Hawkins, 2012; Merlini and Bellotti, 2003). In addition to the disease-specific protein, all amyloid deposits also contain a proteoglycan, serum amyloid P, laminin, collagen IV, entactin, and apolipoprotein E (Kisilevsky, 2000). The misfolded proteins are highly organized, which is thought to be responsible for the proteins' stability and resistance to proteolysis (Lachmann and Hawkins, 2012).

The most common form of amyloidosis is amyloid light chain (AL amyloidosis), in which proteins originate from misfolded monoclonal antibody light chains. Plasma cell dyscrasia leads to the overproduction of these immunoglobulins. In these patients, 5 to 10% of bone marrow cells are plasma cells (Falk et al., 1997). Not all immunoglobulin light changes result in amyloidosis; in fact, only 12 to 15% of patients with myeloma have AL amyloidosis (Falk et al., 1997). However, more than 80% of patients with clinically significant AL amyloidosis have some form of monoclonal gammopathy (Lachmann and Hawkins, 2012). These protein depositions consist of 23-kDa monoclonal Ig light chains or 11-18-kDa fragments. Although both lambda and kappa subtypes have been described, the lambda subtype is most common (Seldin and Skinner, 2012).

Case Summary

A 66-year-old woman was referred by her cardiologist to the department of dermatology with a 2-month history of nonhealing, inframammary lesions (Fig. 1). These lesions initially presented as

☆ Financial disclosure: None
☆☆ Disclosures of interest: None
* Corresponding Author.
E-mail address: rothe@uchc.edu (M.J. Rothe).

http://dx.doi.org/10.1016/j.ijwd.2015.11.001

erythematous patches that progressed to erosions. They were intermittently productive of a grey exudate. The lesions were asymptomatic with the exception of mild burning when applying nystatin powder, which failed to produce clinical improvement. The patient denied pruritus. The patient was in her usual state of good health until 3 to 4 months before her presentation, when she started to experience worsening shortness of breath with exertion. She was found to have a host of arrhythmic issues such as paroxysmal atrial fibrillation, atrioventricular nodal reentrant tachycardia (treated with catheter ablation), and sick sinus syndrome. The patient suffered from severe diastolic heart failure with New York Heart Association class III symptoms that was increasingly unresponsive to diuretic therapy. She was found to have severe left ventricular hypertrophy on her echocardiogram without any clinical history of hypertension. Her electrocardiogram showed slightly diminished voltage in the limb leads.

On exam, the patient had three oval-shaped erosions, two located in the left inframammary region and one in the right inframammary region, ranging in size from approximately 2 cm × 1 cm to 4 cm × 3 cm. The bases were bright red and without exudate. Purpura were present adjacent to the ulcers but were present and more prominent on the adjoining skin of the breasts. The skin at the inframammary crease was clear, and no satellite lesions were appreciated (Fig. 1). The patient was also found to have purpura of the medial half of the left upper eyelid (Fig. 2). Further questioning revealed a 2-month history of intermittent eyelid purpura that occurred bilaterally but with a predilection for the left eyelid.

Laboratories included b-type natriuretic peptide 1457 pg/mL, troponin I 0.28 ng/mL (Positive 0.05-0.49 ng/mL), Blood Urea Nitrogen (BUN) 49 mg/dl, creatinine 1.4 mg/dl, and albumin 3.5 g/dl. No monoclonal protein was detected in the serum; however, serum immunofixation identified three precipitin bands, one against immunoglobulin-G heavy chains and 2 against lambda light chains.

Hemotoxylin and eosin staining of two punch biopsies revealed amorphous, faintly eosinophilic material in the dermis, which was suspicious for amyloidosis (Figs. 3 and 4). The diagnosis of amyloidosis was confirmed by apple-green birefringence on polarization and positive staining for Congo red (Figs. 5 and 6).

The patient has completed a chemotherapy regimen, which included cyclophosphamide, dexamethasone, and bortezomib to treat her multiple myeloma and AL amyloidosis. She has had a good response. Her lambda light chain has decreased from 1099 mg/L to normal range approximately 5 months after treatment. She still experiences substantial fatigue and shortness of breath with exertion. She continues to have periodic episodes of purpura affecting the eyelid and the inframammary region but rarely develops erosions.

Discussion

Diagnosis

The diagnosis of amyloidosis is based on clinical suspicion and a tissue biopsy showing protein deposition. The recommendation is a punch biopsy of subcutaneous abdominal fat or minor salivary glands (Desport et al., 2012). Staining with Congo red will be positive in 85% of patients and apple-green birefringence will be exhibited when exposed to polarized light (Falk et al., 1997; Merlini and Bellotti, 2003). If the biopsy is positive, then the type of amyloidosis should be determined. AL amyloidosis is the most common type, and a search for plasma cell dyscrasia should be considered. This workup may include serum protein electrophoresis (SPEP) to detect light chains.

SPEP reveals a monoclonal protein expansion in 50% of AL amyloidosis patients when serum alone is tested and may show expansion in 86% of patients when serum and urine are tested simultaneously (Kumar et al., 2013). If the SPEP does not reveal a spike in light chains and clinical suspicion remains high, one would then consider immunofixation and a bone-marrow biopsy. If there is no evidence of plasma-cell expansion, then consideration should be given to other forms of amyloidosis (Falk et al., 1997). Nevertheless, it is not always possible to identify a monoclonal protein, and diagnosis of AL amyloidosis is therefore occasionally based on the clinical presentation (Kumar et al., 2013).

Presentation

AL amyloidosis most frequently affects patients after the age of 50 years old, is rapidly progressive, and can present with widespread symptoms (Lachmann and Hawkins, 2012). The kidneys are the most frequently affected organ. Renal involvement presents with nephrotic-range proteinuria, hypoalbuminemia, secondary hypercholesterolemia, and edema. Occasionally, amyloid is deposited in the tubules rather than the glomerulus, resulting in azotemia without proteinuria (Seldin and Skinner, 2012).

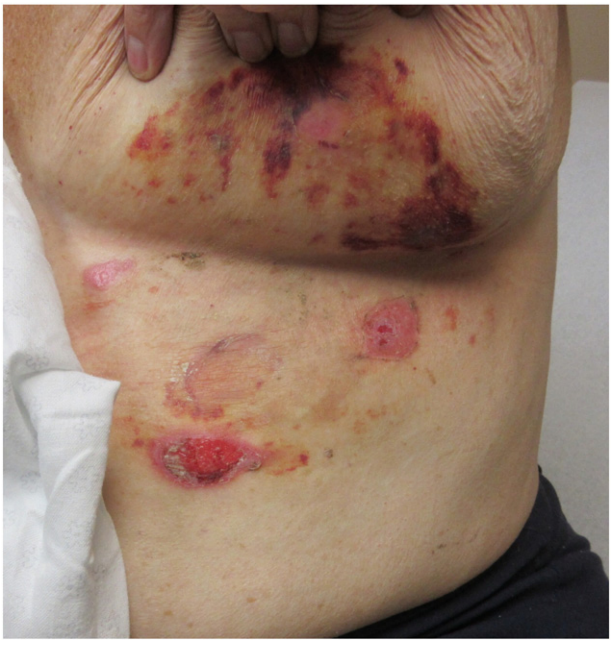

Fig. 1. Ecchymoses and erosions in the inframammary region. Note how the skin at the inframammary crease is intact whereas skin where friction is likely to be applied is most affected.

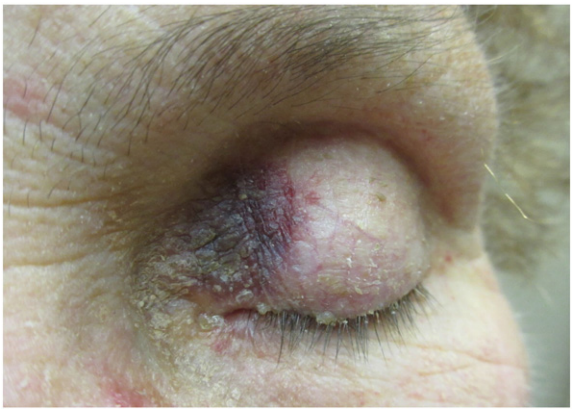

Fig. 2. Waxy ecchymosis on the medial portion of the left upper eyelid. With the appropriate history, this may represent a pinch purpura classically described as a waxy, indurated, plaque after minor trauma.