Case Presentation 9

Dermatopathology

Weill Cornell Medical College

LIGHT CHAIN ASSOCIATED AMYLOIDOSIS PRESENTING WITH NEPHROTIC SYNDROME AND SPONTANEOUS UPPER TORSO PURPURA

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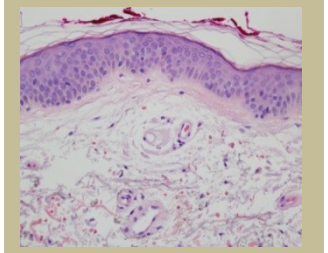

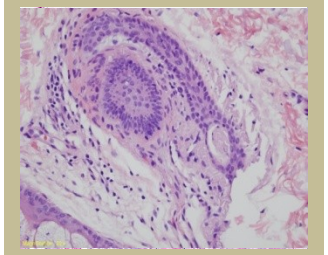

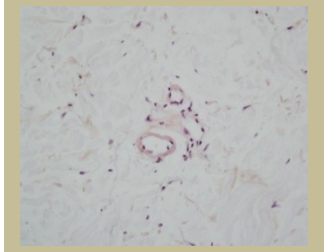

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Clinical History

The patient was a 50 year old male who presented with symptoms of nephrotic syndrome for the past 2.5 years. Investigations revealed a monoclonal gammopathy. More recently in the last several months, the patient developed spontaneous purpura affecting the anterior chest and neck and periorbital skin(figure 1). Due to worsening of the spontaneous ecchymoses, he sought an additional opinion regarding his skin condition. Dr. P felt that the clinical presentation was highly suspicious for amyloidosis. Three biopsies were performed and were interpreted as representing palisading and granulomatous dermatitis. The case was subsequently seen by CM in consultation.

Review of these slides were interpreted as being characteristic for light chain associated amyloidosis based on subtle but highly distinctive findings. The patient had subsequent confirmatory biopsies including electron microscopy showing classic features of amyloidosis as will be discussed presently.

The patient has now been staged. He has evidence of cardiac and renal involvement with amyloidosis and also radiographic studies show splenomegaly. The bone marrow biopsy shows a kappa light chain restricted plasma cell infiltrate along with evidence of amyloid deposition in the marrow although without diagnostic features of multiple myeloma. Radiographic studies of his long bones does not disclose any discrete lytic or sclerotic lesions typical of multiple myeloma. The aspirate smear demonstrates an increase in atypical plasma cells averaging 9% of the differential count. The plasma cells were described as manifesting voluminous cytoplasms resulting in a distinctive pseudo-Gaucher's like appearance albeit without an increase in plasmablasts.

He is about to commence treatment with Bortezomib, dexamethasone, and cyclphosphamide. Due to the extent of organ dysfunction, he is not held to represent an adequate candidate for autologous or heterologous stem cell transplantation.

Pathology Findings

A total of 4 skin biopsies were performed.

The initial set of biopsies showed a distinct pattern of eosinophilic deposition consistent with amyloidosis localized to the adventitial dermis of the eccrine coil and hair follicle. In addition there was concomitant deposition of the material within the capillaries and venules of the perifollicular and perieccrine adventitial dermis. The angiocentric deposits were associated with focal red cell extravasation. The deposits were amorphous glassy and almost cartilage-like hence defining a hyaline like appearance. A Congo red was not performed on this particular set of biopsies.. In a subsequent biopsy striking deposits of pink material consistent with amyloid were noted throughout the vessels of the dermis including the superficial vascular plexus and were associated with significant red cell extravasation diagnostic of amyloid angiopathy(figure 2). The congo red stain showed the congophilic nature of the deposits(figure 3); a characteristic apple green birefringence was noted under polaroscopic examination. The highly unusual but distinctive pattern of adventitial dermal deposition of amyloid is illustrated in figure 4a while the congophilic nature of the deposits is illustrated in 4b.

Electron microscopy showed long bands and aggregates of closely packed fibrillar material which were haphazardly arranged with a solid cross section ranging in measurement form 9 to 12 nanometers in thickness diagnostic of amyloid(figure 5). The amyloid deposits were seen surrounding the dermal adnexa, capillaries and also in the interstitium between fibroblasts, separating bundles of collagen.

Discussion

The patient presents with classic systemic light chain associated amyloidosis. One of the cardinal hallmarks of this subtype of amyloidosis is cutaneous amyloid angiopathy manifesting clinically as pinch and or spontaneous purpura and/or purpura induced by minimal trauma. The propensity for this subtype of amyloid to deposit within the cutaneous vasculature is unclear. In addition the mechanism by which amyloid incorporation within the vessel wall leads to vascular compromise remains elusive although toxic effects by the amyloid on the cellular components of the vessels seems plausible. In the same vein, the sequelae of amyloid deposition within the heart is one of an irreversible cardiomyopathy and renal dysfunction with the commonest manifestation of the latter being that of nephrotic syndrome. There are various stains that can highlight amyloid including congo red, thioflavin T, and alcian blue. In regards to the latter, glycosaminogylcans intrinsic to amyloid appears blue. In this case while later biopsies showed classic changes of an amyloid angiopathy, the earlier biopsies demonstrated subtle changes albeit highly characteristic for light chain associated amyloidosis. There was amyloid deposition in the adventitial dermis of the hair follicle and eccrine coil. In prior reports this particular propensity to involve the adventitial dermis of the hair follicle is unique to light chain associated amyloidosis and oftentimes is accompanied by discernible hair loss clinically with a distinctive form of nonscarring alopecia involving the scalp, axillary and pubic hair. In this case the adventitial dermal involvement was not accompanied by hair loss at least according to the patient's history.

Our patient had an abnormal kappa light chain restricted plasma cell infiltrate although qualitatively and quantitatively the findings were insufficient to warrant categorization as multiple myeloma. Roughly 15 to 20% of cases of light associated amyloidosis are related to underlying multiple myeloma which confers a worse prognosis. Conversely 30% of patients with light chain associated amyloidosis will develop a B cell malignancy. In systemic myeloma the morbidity and mortality is more directly linked with myeloma infiltration of bones and the kidney while in light chain associated amyloidosis the morbidity and mortality reflects organ dysfunction caused by the abnormal protein.

There are various forms of systemic amyloidosis; the three principle subtypes are light chain associated (L) amyloidosis(AL), amyloid associated protein(AA) amyloidosis and familial amyloidosis . The commonest form of amyloidosis is AL and is the most severe because of its propensity to target the heart resulting in severe cardiac dysfunction. A small plasma cell clone is not of the magnitude to warrant categorization as multiple myeloma however the clonally restricted plasma cells synthesize an unstable misfolded light chain which is susceptible to aggregate and form amyloid fibrils. The second most common one is that associated with acute phase proteins namely amyloid associated protein also falling under the designation of AA amyloidosis. In AA amyloidosis there is a pre-existing inflammatory disorder which may or may not have an immunological basis. Various diseases are associated with AA amyloidosis including systemic lupus erythematosus and other autoreactive conditions including rheumatoid arthritis and ankylosing spondylitis. It may also occur in association with long standing inflammation with variant conditions including a lung abscess, tuberculosis and osteomyelitis. Persistent acute inflammation induces not only the synthesis of the amyloid precursor protein but also the appearance of a substance termed amyloid enhancing factor which is critical for the induction of amyloid deposition. An additional factor is the deposition of apoprotein E and the structural constituents of basement membranes. Transthyretin amyloidosis is a form of familial amyloidosis and reflects a mutation in this protein. Transthyretin is normally secreted by the liver and serves as a carrier of thyroid hormone and as a retinal binding protein.

Independent of the type of amyloidosis, the pathogenic protein is similar being that of one showing fibrous properties exhibiting a beta pleated sheet arrangement consisting of beta strands connected bya hydrogen bond. The B pleated sheets are organized into stacks representing fibrils. The protein deposition causes systemic toxicity and devastating organ dysfunction. The basic effect of amyloid is to interfere with the acquisition of cell nutrients resulting in their atrophy and ultimately death. Hence its deposition in the blood vessels does not enhance the structural integrity of the vessel but rather leads to endothelial cell injury and smooth muscle necrosis by virtue of interfering with nutrient uptake and biosynthesis. The kidney involvement is primarily in regards to nephrotic syndrome while amyloid deposition in the heart leads to results in progressive cardiomyopathy. One of cardinal hallmarks diagnostically of amyloid cardiomyopathy is low voltage on the electrocardiogram. The striking amyloid angiopathy leads to vascular compromise resulting in protean manifestations include gastrointestinal hemorrhage, skin hemorrhage, and hemoptysis.

continued

Involvement of the tongue results in tongue enlargement (i.e. macroglossia). Regardless of the type of amyloidosis, patients with systemic amyloidosis, suffer from significant renal and cardiac dysfunction

There are now sensitive biomarkers than can detected at a point in the course of the clinical illness when organ damage is at a subclinical level. The most sensitive of these is the amino terminal pro-natriuretic peptide type- B . It is a highly specific biomarker of cardiac amyloid. Its availability as a serologic test add to its utility. A concentration in excess of 332ng/L defines a very sensitive marker of cardiac amyloidosis in the absence of discernible echocardiographic evidence of amyloid deposition.

Interventional therapy at an apparently asymptomatic phase may prevent organ damage and hence prolong long term survival. Assessment of the extent of amyloid associated organ damage is critical in the management of patients with systemic amyloidosis. Echocardiograpy including Doppler and strain imaging defines baseline cardiac function. Cardiac MRI is useful in diagnosing and monitoring amyloid deposits. The two most important parameters for assessing renal function are glomerular filtration rate and the extent of albuminuria. . The key in prolonged survival although not specifically cure is early diagnosis before irreversible organ damage occurs. In this regard while therapies have improved overall survival, the early death rate has remain unchanged with patients dying a few weeks after presenting with significant cardiac dysfunction.

As far as treatment, the extent of organ dysfunction is a critical determinant in establishing reasonable treatment protocols. Autologous stem cell transplantation should be considered in low risk patients given the long term survival in responders. Higher risk patients are treated with combination therapy with cyclophosphamide, bortezomib, and dexamethasone. Our patient in fact is receiving salvage chemotherapy and due to the extent of organ involvement is not considered a reasonable candidate for autologous/heterologous stem cell transplantation.

Case References

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Figure Legend

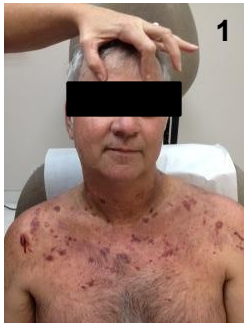


Figure 1 : The patient presents with spontaneous hemorrhagic echymotic areas involving upper chest and face. In addition there was spontaneous purpura upon gentle compression.

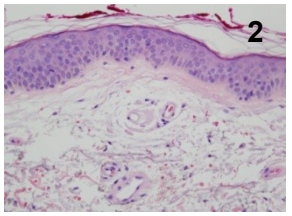


Figure 2 : There is expansion of the cutaneous vasculature by homogenous pink refractile deposits associated with conspicuous red cell extravasation.

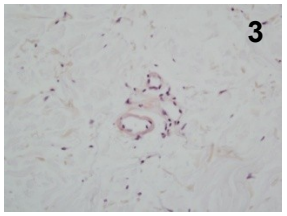
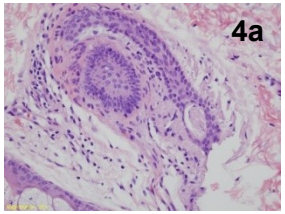
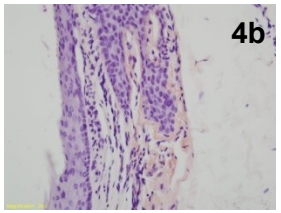


Figure 3 : The congo red stain highlights the deposits. Under polaroscopic examination a green birefringence would be apparent.





Figures 4a & 4b : A rare finding in light chain associated amyloidosis is the deposition of amyloid in the adventitial dermis of the hair follicle. This particular finding can be associated with alopecia, a finding not apparent in this case despite the degree of follicular based amyloid deposition

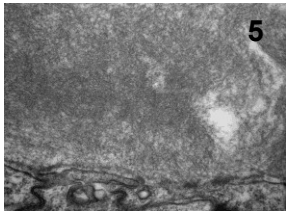


Figure 5: Electron microscopy shows the nonbranching narrow fibrils typical for amyloid.

Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 250 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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