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Amyloidosis Masquerading as Suspected Angioedema: Delay in Diagnosis

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Introduction

Light chain amyloidosis poses a unique diagnostic challenge due to its wide array of nonspecific clinical manifestations. However, making a prompt diagnosis may substantially improve clinical outcomes. Multiple diagnostic pitfalls exist, including markedly low incidence of the disease and variable multi-organ involvement with varying degrees of severity. Light chain amyloidosis typically is a disease of older adults and incidence increases with advancing age. The median age of diagnosis is the seventh decade of life. This disease does have a male predominance, but geographic location and race have not been identified as significant variables.[1] Long term studies have demonstrated a correlation in patients with monoclonal gammopathy of undetermined significance (MGUS) in that they may progress to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, CLL, or plasmacytoma at a rate of 1% per year.[2] Diagnosis is achieved with identification of amyloid fibrils using Congo red staining which results in an apple green birefringence appearance on histologic review. The goal is to collect a biopsy from an affected organ with consideration of safety, procedure complexity, and typical expected yield.

Tissue Sample	Typical Yield
Abdominal fat pad	60-80%
Rectal biopsy	50-70%
Kidney/liver biopsy	Greater than 90%
Bone marrow biopsy	50-55%
Skin	50%

Biopsy site locations and associated diagnostic success rate.[3-5]

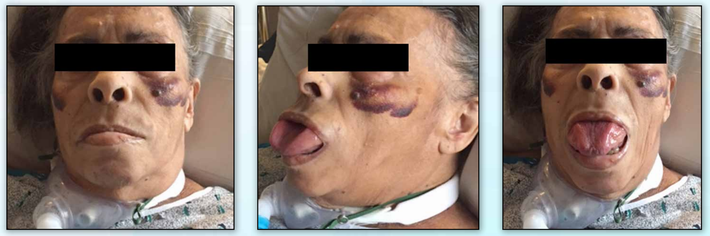
Clinical Case

The patient is a 70 year old female with notable history of mediastinal adenopathy, COPD, dCHF, MGUS (lamda light chain), and suspected chronic tongue angioedema leading to tracheostomy. She presented with acute hypoxic respiratory failure. Findings on admission included fever, periorbital pupura, low-voltage EKG, proteinuria, pulmonary nodules, and polyarthralgia. She was treated with empiric antibiotics for suspected pneumonia, steroids, and an anti-histamine due to concern for angioedema. Her angioedema was not found to be IgE-related or consistent with hereditary angioedema. Direct examination via flexible laryngoscopy did not show laryngeal or tongue base edema. Fat pad biopsy was found to be consistent with amyloidosis. Rather than pursuing cardiac biopsy to demonstrate definitive cardiac involvement of amyloidosis, cardiac MRI was obtained. This study showed diffuse subendocardial delayed gadolinium enhancement in the thickened left myocardium with a markedly hypodense blood pool, a finding that has been described with amyloidosis. Positive identification of amyloidosis with cardiac involvement portends a poor prognosis. The patient also developed progressive polyarthralgia with significant left knee effusion during her hospitalization. This was initially suspected to be crystalline in etiology. Synovial fluid profile status post joint aspiration revealed the absence of crystals and WBC 5860/cmm consistent with inflammatory process. Given her constellation of clinical findings this was suspected to also be related to her amyloidosis. Congo red staining was attempted, however synovial fluid was not successfully stained. She was offered palliative options without bone marrow transplantation for her systemic disease such as melphalan/dexamethasone or a bortezomid-based regimen (such as CyBorD). Unfortunately there were concerns regarding her ability to tolerate these treatments and she ultimately chose not to proceed with these therapies.

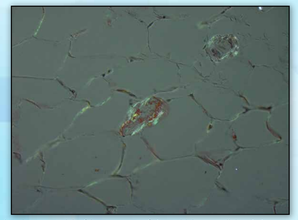
Amyloidosis Manifestations[6-8]	Specific Manifestations Present
Renal disease	Hematuria, proteinuria
Cardiomyopathy	Chronic dCHF, low voltage EKG with poor R wave progression, cardiomegaly, left ventricular thickening
Gastrointestinal disease	Ileus, constipation, hypoalbuminemia , elevated alkaline phosphatase
Neurologic abnormalities	None identified
Musculoskeletal disease	Macroglossia, "shoulder pad" sign, polyarthropathy with effusions
Hematologic/lymphatic abnormalities	MGUS, elevated PT, mediastinal adenopathy
Pulmonary disease	Parenchymal nodules, persistent small bilateral pleural effusions
Skin manifestations	Periorbital purpura

Diagnostic Criteria	Presence
Presence of an amyloid-related systemic syndrome felt to be due to amyloid and NOT another common disease (i.e. DM, HTN)	Yes
Positive amyloid staining by Congo red in any tissue or presence of amyloid fibrils on electron microscopy	Yes: abdominal fat pad biopsy
Evidence that the amyloid is light chain-related established by direct examination of amyloid	Not performed
Evidence of a monoclonal plasma cell proliferative disorder	Yes: MGUS

Diagnostic criteria for light chain amyloidosis developed by the Mayo Clinic and the International Myeloma Working Group. ALL criteria should be present, however this diagnosis may still be established in 2-3% of patients with light chain amyloidosis.[9]



Patient with periorbital purpura and massive macroglossia.



Apple-green birefringence on fat pad biopsy slide status post Congo red staining under polarized light.

Conclusion

The focus of treatment for light chain amyloidosis is control of the underlying plasma cell disorder with chemotherapy to suppress synthesis of immunoglobulin light chains. Promising results have been seen with high-dose chemotherapy in combination with stem cell transplantation, however, as with this patient, safe administration may not be feasible or recommended in patients with widespread disease at diagnosis.[10] The process of diagnosis itself may be a challenge if biopsy tissue samples are not well-chosen in regards to expected tissue yield. The inability to capture positive staining using this patient's synovial fluid was most likely due to the fact that synovial fluid is less than the minimum recommended 6 micron thickness for adequate staining of amyloid fibrils.[11,12] Although the gold standard for diagnosis is biopsy tissue staining in order to demonstrate amyloid fibrils, supplemental studies such as cardiac MRI may be accurate noninvasive methods of providing support for identification of additional organ system involvement.[8]

This patient's multi-system involvement had previously been unexplained and treated as individual entities. The timeframe of her macroglossia alone was suspected to have to progressed over at least three years. Her final diagnosis was unfortunately made when her disease was significantly advanced, thus limiting her treatment options. This case highlights the need to look for the possibility of a unifying diagnosis early in the disease timeline for patients with a constellation of symptoms to provide the best chance for increased overall survival.[13]

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