

## Case Report

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# Primary Amyloidosis (A Rare Disorder): Clearing Myths and Fallacies

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## Introduction

Primary (or AL amyloidosis) is a rare disorder. It is a clonal disorder characterised by the deposition of the insoluble fibrillar AL amyloid protein in organs resulting in their dysfunction [1,2]. When the composition of these fibrils consists of the precursor serum amyloid A protein (persistently elevated in response to a chronic inflammatory stimulus) it is labelled as secondary or AA amyloidosis [3] and is the second most common type of amyloidosis. A relatively rare type of amyloidosis called LECT2 – where the protein is leucocyte chemotactic factor protein is the fibril precursor – is the third most common amyloid type in northern India [3]. Congo red staining with exhibition of an apple-green birefringence is the gold standard for a histopathologic diagnosis of amyloidosis [4]. This amyloid protein requires further typing by immunohistochemistry [5] to subtypes of amyloidosis such as AA (secondary) or AL (primary) or LECT2.

Immunohistochemistry is very reliable for diagnosis of amyloid subtypes in majority of the cases (Figure 1). Unfortunately, even the minimum panel AA/AL staining is not readily available in India. Additionally, interpretation remains difficult and a positive and negative control must be included on each slide – a high level of quality assurance if needed. A number of practices have hence evolved without use of full panel of immunohistochemistry. However, this has serious limitations and is perilous to making a diagnosis. These include: A) practice of relying only on kappa/lambda immunohistochemical staining and presence serum free light chains to classify as primary or secondary amyloidosis has developed in a number of Indian centres. The kappa and lambda light chain epitopes that are recognised by antisera are lost while processing the biopsy samples, giving an accuracy of just ~ 50% by the use of this modality [6]. B) The notion that a monoclonal excess of a serum free light chain (FLC) or paraprotein is specific for primary / AL amyloidosis. This assay is not specific for the diagnosis of AL amyloidosis. Monoclonal FLC are present in one half of patients with uncomplicated MGUS, and in virtually all patients with multiple myeloma [6]. In the presence of renal failure, it can be further more difficult to rely upon these figures. C) The myth that plasmacytosis of the bone marrow in a patient with amyloidosis implies that it is AL or primary amyloidosis is also incorrect [6]. Bone marrow plasmacytosis is only surrogate and not 100% specific evidence for AL amyloidosis. The typing of amyloidosis as primary / AL or secondary / AA is important as the treatment is entirely different. Systemic primary/AL amyloidosis is managed with chemotherapy including the use of thalidomide, lenalidomide, bortezomib and in those who are fit to proceed onto autologous haematopoietic stem cell transplantation [7-10]. On the other hand AA amyloidosis is treated by immunosuppression of treatment of the underlying disorder. It has been shown in the past that monoclonal gammopathy itself cannot be used as a marker to differentiate between AA and AL amyloidosis [11].

We highlight below 3 recently detected cases of systemic amyloidosis at our institution where immunohistochemical staining on the amyloid tissue in the biopsy completely altered the management plans for the patient in his best interest. Also, the myths outlined above are well demonstrated in these cases.

## Case 1

A 36 year old male, who has undergone renal transplant for unexplained chronic renal failure 5 years back, presents to our department of Nephrology with progressive chronic renal failure. He is also noted to have episodes of haematochezia. As a part of evaluation, renal biopsy and colonoscopic rectal biopsy show diffuse deposition of amyloid. He has no past history of tuberculosis, but has recurrent episodes of exacerbation of chronic bronchitis since childhood. The serum immunofixation electrophoresis shows a small suspicious spike in lambda region. He was then referred to the department of Clinical Haematology for further workup. Bone marrow aspiration and biopsy are performed. The aspirate reveals 12% plasma cells and the biopsy reveals amyloidosis. Kappa/lambda staining on the renal biopsy shows preferable kappa light staining. Due to presence of disease in the bone marrow and the presence of a monoclonal light chain spike and kappa light chain staining on the renal biopsy, he is presumed (in the absence of availability of AA/AL (immunohistochemical staining) to have primary amyloidosis, and systemic chemotherapy with bortezomib and dexamethasone was commenced, but the patient appeared to show no response over the ensuing 6 weeks. Meanwhile his bone marrow and renal biopsies are referred to the National Amyloidosis Centre, Royal Free Hospital for immunohistochemistry; and this reveals that he has AA (that is secondary) amyloidosis. Henceforth, chemotherapy is abandoned and he is now managed conservatively.

## Case 2

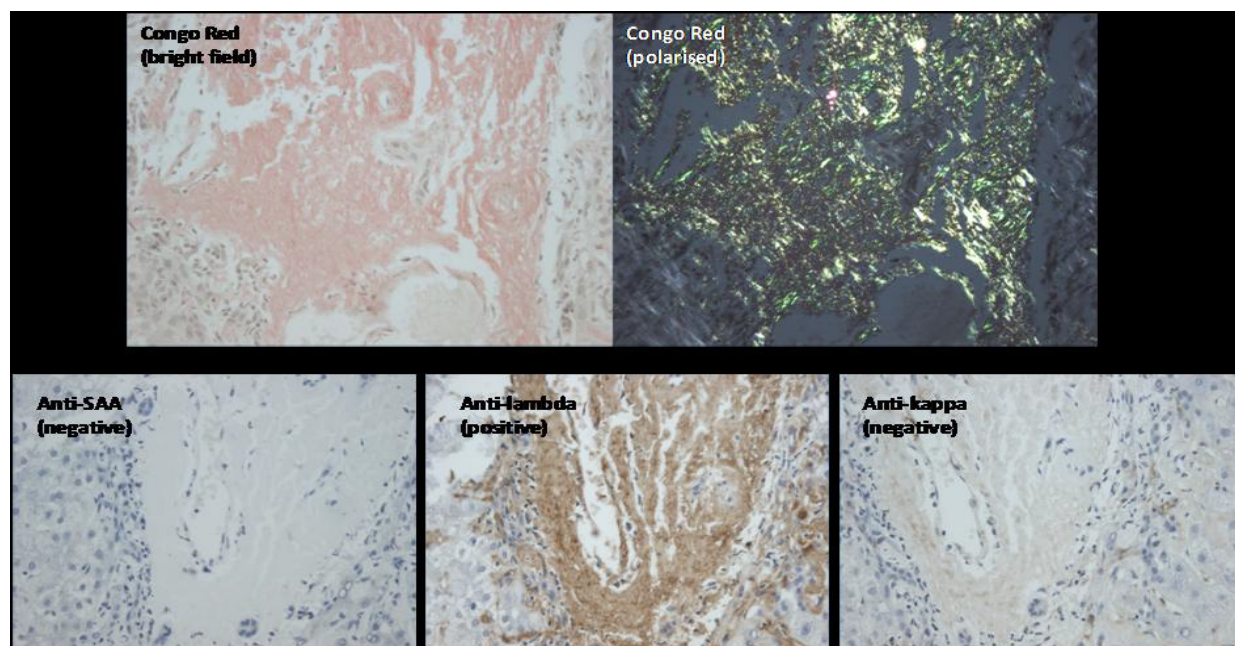
A 63 year old lady with recently diagnosed chronic renal failure thought to be secondary to chronic glomerulonephritis is noted to have a suspicious monoclonal spike on serum protein electrophoresis. She had been admitted 2 months back in critical care with fever, chest infection and altered sensorium; when she had not responded to the usual line of antimicrobials and improved only on empirical anti-tubercular treatment. The kidney biopsy as a part of workup for the renal failure shows cast nephropathy, which stains positive for amyloid. Bone marrow aspiration reveals 13% plasma cells and the bone marrow biopsy do not show any evidence of amyloidosis. In the absence of availability of AA/AL (immunohistochemical staining), she is presumed to have primary (AL) amyloidosis on the basis of presence of monoclonal paraprotein and increased plasma cells on bone marrow

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**Figure 1:** Immunohistochemistry of amyloid subtypes.

aspirate. However, the renal biopsy is sent for immunohistochemistry to the National Amyloidosis Centre, Royal Free Hospital and the amyloidosis is detected to be AA/secondary in type. She is continued on anti-tubercular treatment; chemotherapy abandoned, and is doing reasonably well over the next few months.

### Case 3

A 58 year old male presents to the liver transplant team of our hospital with cirrhosis of the liver. He had been diagnosed to have rheumatoid arthritis 20 years back but presently it is quiescent. Also, he had been treated for pulmonary tuberculosis 12 years back. His liver biopsy shows amyloidosis; and further evaluation reveals that he also has nephrotic syndrome. Serum protein electrophoresis, serum free light chain measurement and bone marrow examination are non-contributory. Keeping the past history in mind, and in the absence of availability of AA/AL (immunohistochemical staining), he is presumed to have secondary amyloidosis. However, the liver biopsy is reviewed at the National Amyloidosis Centre, Royal Free Hospital and reveals AL/primary amyloidosis. The patient is commenced on CTD (combination of cyclophosphamide, thalidomide and dexamethasone) chemotherapy and his nephrotic range proteinuria improves but unfortunately he succumbs to a large ischaemic stroke.

### Discussion

The above 3 cases demonstrate the following:

AA/AL (immunohistochemical staining) is the modality of choice to differentiate between primary and secondary amyloidosis. The detection of the correct histopathological subtype in all the above 3 cases lead to a change in management plan.

The presence of a monoclonal paraprotein or serum free light chains are not exclusively diagnostic of the primary nature of the amyloidosis; as high plasma cell burden in secondary amyloidosis can also lead to secretion of these. Cases 1 and 2 though AA amyloidosis

had evidence of a serum paraprotein. Case 3, even though AL/primary amyloid did not show any serum paraprotein or definite clonal increase in any serum free light chain.

Bone marrow involvement with amyloidosis can also be seen in secondary amyloidosis. It is not a hallmark of primary amyloidosis; and similarly primary systemic amyloidosis can exist without bone marrow involvement. Cases 1 and 2, despite being AA/secondary amyloidosis had evidence of bone marrow amyloidosis; whereas, case 3 (AL/primary amyloidosis), did not show bone marrow involvement.

Kappa/lambda staining on histopathologic specimens is not recommended as it is postulated that a major proportion of these fibrils are destroyed while processing, making it a nonspecific technique for the diagnosis of primary and / or secondary amyloidosis. This is clearly exhibited by case 1.

Hopefully, this article shall lead to change in our understanding and practice of this rare disorder (primary amyloidosis). As of now in India, immunohistochemical staining to subtype as AA or AL in amyloidosis is not being practised. In the coming future, we shall hopefully be able to set up immunohistochemical (AA/AL) staining at our centre and hence lead us to better selection of patients for chemotherapy. There have been major advances in treatment of AL amyloidosis. Younger patients with successful ASCT may survive for over a decade. A number of treatments directly targeting the amyloid fibril precursor are on the horizon offering hope to patients with this rare, rapidly progressively, poorly understood and difficult to treat disease.

### Conclusion

This series of cases well demonstrates the importance of immunohistochemical staining on amyloid tissue biopsies to stratify them as AA or AL being the key to their management plan. This modality appears to have far more benefit in planning management rather than bone marrow testing or serum free light chain / protein electrophoresis analysis in the laboratories.

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