Austin Journal of Clinical Immunology

Open Access

Austin Publishing Group

Case Report

B2 Microglobulin and Bence Jones Proteinuria Guide the Diagnosis of Idiopathic AA Amyloidosis: A Journal to Diagnosis

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Received: October 04, 2021; **Accepted:** October 30, 2021; **Published:** November 06, 2021

Abstract

Amyloidosis is a disease caused by the extracellular deposition of pathological insoluble fibrillary protein in multiple tissues and may result in severe organ dysfunction.

There are two major forms of amyloidosis: AL amyloid and AA amyloidosis, which complicates any chronic inflammatory condition, including rheumatologic, chronic infections, and certain neoplasms.

In small but increasing numbers, the chronic inflammatory state underlying AA amyloidosis remains obscure, despite extensive investigations, which are known as idiopathic.

In the current case, the first extensive evaluation to determine the inflammatory disease was negative. The patient had B2 microglobulin elevation and Bence jones proteinuria, which are non-specific findings, but are not conclusive, for malignancies.

The diagnosis of Idiopathic AA amyloidosis was guided by understanding the pathophysiology of B2 microglobulin and Bence jones proteinuria along with excluding all other etiologies. Unfortunately, the development of restrictive cardiomyopathy and ESRD within 3 months indicates a rapid progression and poor prognosis in this patient.

Clinicians may not be familiar that B2 microglobulin and Bence jones proteinuria are also found in amyloidosis, which may delay the diagnosis. Inflammatory process and kidney injury due to AA amyloidosis caused previous markers positivity in our patient.

It is plausible that delays in diagnosis may be multi-faceted and heavily influenced by the average age of the patient, the complexity and the rareness of the disease. Also, non-disease-specific symptoms may reduce the likelihood of a prompt diagnosis. Therefore, establishing the diagnosis is difficult, and early diagnosis requires high clinical suspicion.

Keywords: AA amyloidosis; B2 microglobulin; Bence jones proteinuria

Introduction

Amyloidosis is a disease caused by the extracellular deposition of pathological insoluble fibrillary protein in multiple tissues and may result in severe organ dysfunction. Despite the etiological heterogeneity of systemic amyloidosis, the clinical manifestations of the different forms of amyloidosis largely overlap and depend upon the affected organ. Signs and symptoms that should raise suspicion for the potential diagnosis of amyloidosis are usually nonspecific; therefore, establishing the diagnosis is difficult, and early diagnosis requires high clinical suspicion [1].

There are several major forms of amyloidosis: AL amyloid is due to the deposition of protein derived from immunoglobulin light chain fragments. AA amyloidosis is a potential complication of chronic diseases in which there is ongoing or recurring inflammation. Other major forms of amyloid seen clinically include dialysis-related amyloidosis, heritable amyloidosis, age-related systemic amyloidosis and organ-specific [2].

Case Presentation

A 57-year old patient was admitted to the Nephrology Department of Al Assad University Hospital due to edema, malaise and weight loss for 3 months. His story began ten years earlier complaining of arthritis in both knees with frequent use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and developed to generalized arthralgia later. Also, he had several tests, which showed anemia and elevated inflammatory markers. The patient was studied in the hematologic department before 3 months.

In the Hematologic Department, laboratory tests showed in (Table 1). Serum Protein Electrophoresis (SPEP) showed low albumin with slightly elevated alpha 1, alpha 2, beta, and gamma. Echocardiography and bone marrow biopsy were normal. Peripheral

Citation: Alsultan M, Bakr A, Hassan Q and Alshaar D. B2 Microglobulin and Bence Jones Proteinuria Guide the Diagnosis of Idiopathic AA Amyloidosis: A Journal to Diagnosis. Austin J Clin Immunol. 2021; 7(1):1044.

Table 1:

WBC	9	Ur	59	HBs Ag	Neg	IgM	82 N
HB	9.4	Cr	1.4	Anti HCV	Neg	ANA	Neg
MCV	96	Ca	7.8	RF	14 N	24h urine /protein	1150 mg
PLT	213	CRP	13	Anti CCP	Neg	ANA	Neg
ESR	95	B 9	3.9 N	C4	32 N	B2 M	13.3
Iron	47	B 12	433 N	C3	40 L	Bence jones	Pos
Ferritin	1816	Brucellosis IgM, IgG	Neg	IgA	352 N	Kappa light chain	126 L
ALB	1.7	TP	4.2	IgG	802 N	Lambda light chain	157 N

WBC: White Blood Count; HB: Hemoglobin; PLT: Platelets; Ur: Urea; Cr: Creatinine; TP: Total Protein; ALB: Albumin; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; Ca: Calcium; HBs Ag: Hepatitis B Surface Antigen; Anti HCV: Anti-Hepatitis C Antibodies; RF: Rheumatoid Factor; Anti CCP: Cyclic Citrullinated Peptide Antibodies; C: Complement; ANA: Antinuclear Antibodies; B2M: B2 Microglobulin (Up To 2.2); N: Normal; L: Low; Neg: Negative; Pos: Positive.

Table 2:

HB	7.3	UA	10.6	CRP	7.7
Ur	180	PTH	156	ESR	67
Cr	7.7	24h urine /protein	5350 mg	Ca	5.5
ALB	1.6	24h urine /Cr	243 mg	P	9.9

Ca: Calcium; P: Phosphorus; UA: Uric Acid; PTH: Parathyroid Hormone.

blood smear showed normochromic normocytic anemia. CT scan of the whole body along with upper and lower gastrointestinal endoscopy with biopsies were done and no tumors were found. A rheumatologic consult was requested for bone Densitometry (DEXA) and ophthalmic examination. DEXA showed generalized osteoporosis and ophthalmic examination was normal. During admission, the patient developed septic arthritis and was treated with antibiotics. The patient was discharged on low dose prednisone with calcium supplementation and referred to obtain kidney biopsy later.

In Nephrology department, the physical exam showed a cachexic patient with grade IV edemas. Laboratory tests (Table 2) revealed anemia, stage V Chronic Kidney Disease (CKD) and nephrotic syndrome.

How to find the diagnosis? DDX?

The status is compatible with autoimmune disease or malignancy, which causes elevated inflammatory markers, osteoporosis, cachexia and anemia of chronic disease.

Starting from the previous hematologic study, we start from positive laboratory findings, which include B2 Microglobulin (B2M) elevation and positive Bence Jones Proteinuria (BJP), and put deferential diagnosis to this case.

B2M elevation is found in End-Stage Renal Disease (ESRD), amyloidosis, rheumatologic disorders, and lymphoproliferative disorders, which include Multiple Myeloma (MM), lymphoma and waldenstrom macroglobulinemia [3].

BJP is found in MM, waldenstrom macroglobulinemia, amyloidosis, and acute or chronic kidney injury [4].

All markers of autoimmune diseases were negative and the status was not compatible with any diagnostic criterions of rheumatologic disorders. Also, no malignancy or metastases were found in hematologic and imagining investigations, which consisted of bone marrow biopsy, blood smear, SPEP, immunoglobulin assays, CT scan, and gastrointestinal biopsies.

Depending on all previous investigations and by the crossing of previous etiologies, the diagnosis was confined to amyloidosis and CKD. However, the basal Creatinine (Cr) before hematologic admission was normal and the clinical course consisted of idiopathic inflammatory process, which caused all other manifestations.

Due to clinical suspicion of amyloidosis, we tested Serum Amyloid A (SAA) and came back positive 41.7 (normal range up to 6.4), however, kidney biopsy could not be done due to ESRD.

By noticing the rapid deterioration of renal function in 3 months, we repeated echocardiography because of the probability to affect after this period. The echocardiography showed dilation of both arteria and thickness walls of ventricles with increased cardiac echogenicity or as known sparkling appearance. To confirm the diagnosis, congo red of previous gastrointestinal biopsies were performed, which showed a positive stain in vessels walls with green birefringence under polarized light (Figure 1).

The patient was diagnosed with idiopathic AA Amyloidosis (AAA) and treated with high dose prednisone and melphalan, however, he died a month later.

Discussion

AA amyloidosis

AA amyloidosis may complicate any chronic inflammatory condition, including rheumatologic, autoinflammatory, chronic infections, and certain neoplasms. The most common organ involved in AA amyloidosis is the kidney, although other organs are also affected such as the gut and heart [5].

Chronic disorders underlying AA amyloidosis have changed; arthritis has become the most common underlying disease, replacing chronic infections, especially tuberculosis and osteomyelitis due to the widespread availability of antimicrobial agents. It is anticipated that advances in rheumatologic treatments with biologic agents will result in a decrease proportion that developing to amyloidosis [5].

In a study of the changes in causation over 25 years, uncharacterized inflammatory disease was found in 19% of patients at diagnosis of AA amyloidosis, and unknown etiology of AA amyloidosis has also risen from 10% to 27% [6]. Also, idiopathic AA amyloidosis have been reported in 21-29% of patients from two large centers in the United States [7].

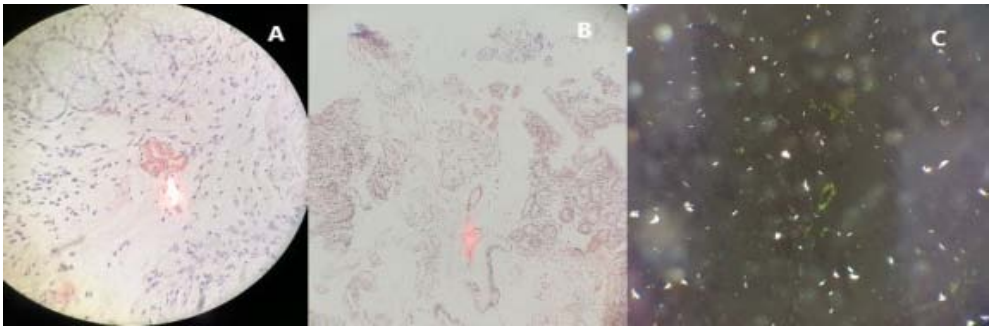

Figure 1: Duodenum biopsies show positive congo red stain in vessels walls (A,B); C: Green birefringence under polarized light.

Idiopathic AA amyloidosis (journey for diagnosis)

In small but increasing numbers, the chronic inflammatory state underlying AA amyloidosis remains obscure, despite extensive investigations to determine inflammatory or infectious causes [8].

In three single-center series from the United States, approximately 20% of patients with AA amyloidosis were found to be idiopathic at diagnosis, and a small percentage revealing a known disease later in the course [5]. In two large series in the United Kingdom and Italy, the underlying disease of AA amyloidosis remained unknown in 19% and 32%, respectively [9].

Broad etiologies of AA amyloidosis consider a diagnostic challenge, and increasing numbers of idiopathic cases need to exclude all possible reasons. So the journey to diagnosis looks like very hard and lead to delay diagnosis and treatment. In most cases, organ damage is irreversible; therefore, rapid treatment initiation is necessary to receive the optimal treatment benefit.

A published survey showed that delayed diagnosis is common in amyloidosis, with a median time of 7 months, 37% over a year and 10% were diagnosed more than 3 years since symptoms started [10].

Cardiac involvement in almost all types of amyloidosis is the major factor influencing prognosis and is associated with very poor prognosis. In AA amyloidosis, cardiac involvement is very rare, occurring in about 2% of patients. However, echocardiography plays an essential role in the diagnosis, classical features of cardiac amyloidosis are present only in advanced disease [11].

However, renal AA amyloidosis progresses insidiously to ESRD, some patients show a rapid progression to ESRD. This has been reported in a study of 57 patients who developed ESRD in approximately 6 months and the need for renal replacement therapy occurred in 1 year [12].

In the current patient, the first extensive evaluation to determine the inflammatory disease was negative but had B2M elevation and BJP, which are non-specific findings, but are not conclusive, for malignancies [3,4].

The diagnosis of Idiopathic AA amyloidosis was guided by understanding the pathophysiology of B2M elevation and BJP along with exclude all other etiologies.

Unfortunately, the development of restrictive cardiomyopathy and ESRD within 3 months indicates a rapid progression and poor prognosis of AA amyloidosis in this patient.

Clinicians may not be familiar that B2M elevation and BJP are also elevated in amyloidosis, which may delay the diagnosis. Inflammatory process and kidney injury due to AA amyloidosis caused previous markers positivity in our patient.

It is plausible that delays in diagnosis may be multi-faceted and heavily influenced by the average age of the patient, the complexity and the rareness of the condition. Also, non-disease-specific symptoms may reduce the likelihood of a prompt diagnosis. The onset of disease often occurs at any age when individuals are at increased risk for other more common, chronic conditions.

Finally, first-line clinicians may not be familiar with such a rare condition and may not initially consider it when making decisions related to differential diagnoses.

Unnecessary biopsies and the use of diagnostic testing with low sensitivity can lead to delays in diagnosis and treatment initiation. Despite previous reports of diagnostic delays and their detrimental impact on patient prognoses, there are limited data to describe patients' journey to diagnosis [13].

Acknowledgment

We thank Dr. Alaa Younis for helping in photos of the microscopic preparations.

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