www.nephropathol.com DOI:10.12860/JNP.2013.31 J Nephropathology. 2013; 2(3): 196-200

Journal of Nephropathology

Serum amyloid A renal amyloidosis in a chronic subcutaneous ("skin popping") heroin user

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ARTICLE INFO

Article type:
Case Report

Article history:
Received: 1 December 2012
Revised: 20 December 2012
Accepted: 29 January 2013
Published online: 1 July 2013

Keywords:
Renal amyloidosis
Acute tubulointerstitial nephritis
Heroin
Skin popping

ABSTRACT

Background: Systemic AA amyloidosis is a long-term complication of several chronic inflammatory disorders. Organ damage results from the extracellular deposition of proteolytic fragments of the acute-phase reactant serum amyloid A (SAA) as amyloid fibrils. Drug users that inject drug by a subcutaneous route ("skin popping") have a higher chance of developing secondary amyloidosis. The kidneys, liver, and spleen are the main target organs of AA amyloid deposits. More than 90% of patients with renal amyloidosis will present with proteinuria, nephrotic syndrome, or renal dysfunction.

Case presentation: A 37 year-old female presented to the hospital with a one-week history of pain and redness in her right axilla. Her relevant medical history included multiple skin abscesses secondary to "skin popping", heroin abuse for 18 years, and hepatitis C. The physical examination revealed "skin popping" lesions, bilateral costovertebral angle tenderness, and bilateral knee swelling. The laboratory workup was significant for renal insufficiency with a serum creatinine of 5 mg/dL and 14.8 grams of urine protein per 1 gram of urine creatinine. The renal biopsy findings were consistent with a diagnosis of renal amyloidosis due to serum amyloid A deposition and acute tubulointerstitial nephritis.

Conclusions: AA renal amyloidosis among heroin addicts seems to be associated with chronic suppurative skin infection secondary to "skin popping". It is postulated that the chronic immunologic stimulation by one or more exogenous antigens or multiple acute inflammatory episodes is an important factor in the pathogenesis of amyloidosis in these patients. Therefore, AA renal amyloidosis should always be considered in chronic heroin users presenting with proteinuria and renal impairment.

Implication for health policy/practice/research/medical education:
Systemic AA amyloidosis is a long-term complication of several chronic inflammatory disorders. Organ damage results from the extracellular deposition of proteolytic fragments of the acute-phase reactant serum amyloid A (SAA) as amyloid fibrils. AA renal amyloidosis should always be considered in chronic heroin users presenting with proteinuria and renal impairment.

Please cite this paper as: Cooper C, Bilbao JE, Said S, Alkhateeb H, Bizet J, Elfar A, Davalos O, Meza AT, Hernandez GT. Serum amyloid A renal amyloidosis in a chronic subcutaneous ("skin popping") heroin user . J Nephropathology. 2013; 2(3): 196-200, DOI: 10.12860/JNP.2013.31

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Case Report

Introduction

Amyloidosis is a group of diseases characterized by extracellular deposition of insoluble polymeric protein fibrils as beta-pleated sheets in tissues and organs (1). Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits. This classification is described according to whether it is systemic or localized, acquired or inherited, and by their clinical patterns. The accepted nomenclature is AX. The A indicates amyloidosis and the X represents the protein in the fibril. AA amyloid type, also known as secondary amyloidosis, is composed of an acute phase reactant serum amyloid A protein that develops between protein and due to a chronic inflammatory process. AA amyloidosis may complicate chronic diseases in which there is ongoing or recurring inflammation, such as rheumatoid arthritis (RA), spondyloarthropathy, inflammatory bowel disease, or chronic infections (2). Once the polymers reach, a critical size, they become insoluble and deposit in the extracellular tissues. These deposits interfere with organ function that may become toxic to the target cells once cellular uptake is initiated. Renal involvement will cause proteinuria that can be as much as 30 g/d, resulting in hypoalbuminemia.

The diagnosis of amyloidosis can be confirmed only by tissue biopsy, although the presence of amyloidosis may also be suspected by the history and clinical manifestations. In the systemic form of amyloidosis, the involved organ can be biopsied; however, amyloid deposits can be found in any tissue of the body. The structure of the beta-pleated sheet exhibits a green birefringence when examined under light microscopy with Congo red stain. The protein type is identified with immunohistochemistry or immunoelectron microscopy. Therapy for AA amyloidosis involves treatment of the underlying inflammatory or infectious disease. Once treatment is initiated, the level of SAA protein concentration begins to decrease.

Case

A 37-year-old white female presented to the hospital with a one-week history of pain and erythema on her right axilla due to an abscess involving her right breast and axilla. Other complaints included bilateral leg edema for two weeks. She had a history of subcutaneous heroin abuse for 18 years, cocaine abuse, and multiple skin abscesses. Her medical history also included hepatitis C, gonorrhea, bronchitis, depression, and previous deep venous thrombosis. Her last admission to the hospital was two weeks prior due to a left breast axilla abscess. Associated symptoms included shortness of breath, fever, flank pain, dysuria, and urinary frequency. At the time of the present admission, she denied having any fever, chills, nausea, vomiting, weakness, dizziness, chest pain, or abdominal pain. Pertinent findings on the physical examination were multiple scar-like lesions over all her extremities and trunk area secondary to "skin popping." She also demonstrated bilateral lower extremity edema up to her knees. There was no lymphadenopathy.

Pertinent laboratory workup on admission was significant for hemoglobin of 8.5 g/dL, hematocrit of 26.7%, Blood Urea Nitrogen (BUN) of 33mg/dL, and creatinine of 5.01 mg/dL. The initial urinalysis on admission had more than 300mg/dL of protein. Reactive phase proteins showed a C Reactive Protein (CRP) of 5.47 mg/L and an Erythrocyte Sedimentation Rate (ESR) of 137 mm/hr. Complement levels of C3 and C4 were within the normal range. Antinuclear Antibody (ANA), Anti-neutrophil Cytoplasmic Antibody (ANCA), cryoglobulin, and Anti-double stranded DNA were negative. A rapid

streptococcal test was negative. The Urine Protein Electrophoresis (UPEP) and Serum Protein Electrophoresis (SPEP) revealed no monoclonal proteins. The culture from her right breast axilla abscess was positive for Methicillin Resistant Staphylococcus Aureus (MRSA). Blood cultures during this admission were negative. The hepatitis C viral load was 412,000 IU/mL.

The patient was started on methadone and systemic antimicrobial therapy. A percutaneous renal biopsy was percutaneous.

The renal biopsy findings were consistent with a diagnosis of renal amyloidosis secondary type (serum amyloid A protein) and acute tubulointerstitial nephritis (Figures 1-4). Microscopic examination of the biopsy specimens revealed expansion of the glomerular mesangial matrix by eosinophilic amorphous material which was weakly positive upon periodic acid Schiff's (PAS) staining. The glomerular capillary basement membranes were thickened. The tubulointerstitial compartment exhibited mild to moderate inflammation. The inflammatory cells were mostly lymphocytes and scattered eosinophils. The Congo Red stain was positive as well as the amyloid A immunohistochemical stain. The immunofluorescence (IF) studies revealed diffuse and generalized positivity for Immunoglobulin M (IgM) deposits. Transmission electron microscopy (TEM) findings correlated with the light microscopy and immunofluorescence (IF) analysis.

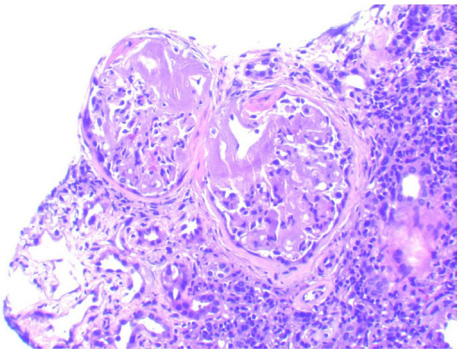

Figure 1. Low magnification H&E stained light micrograph showing two glomeruli with segmental deposits involving the capillary walls and mesangium with obliteration of some of the capillary lumina and interstitial lymphoplasmacytic infiltration.

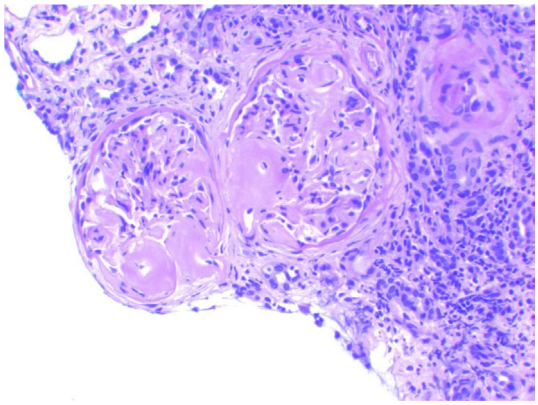

Figure 2. Light micrograph showing amorphous deposits that are weakly positive with the periodic acid schiff (PAS) stain.

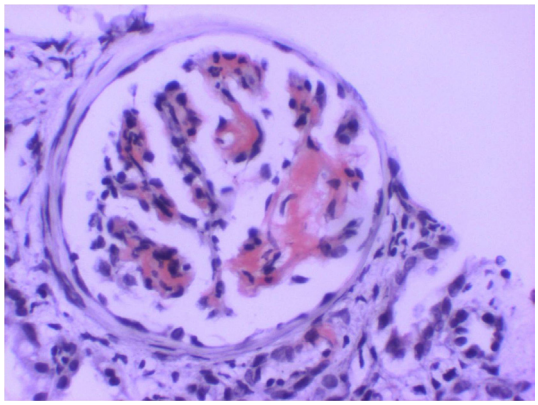

Figure 3. Light micrograph showing deposits with positive staining with Congo Red.

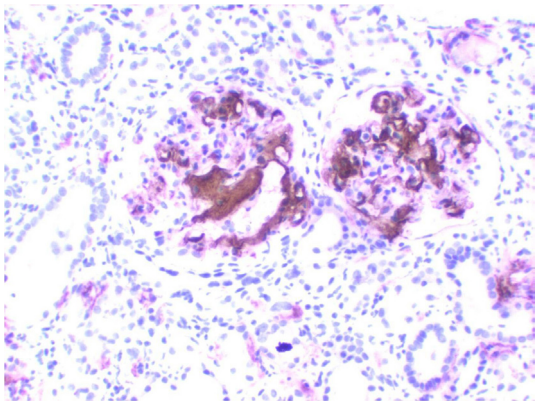

Figure 4. The involvement of two glomeruli by serum amyloid A protein-related amyloid is revealed by immunohistochemical staining with antiserum specific for serum amyloid A protein.

After the diagnosis was confirmed, the patient was advised on the importance of avoiding intravenous (IV) and subcutaneous drug use to prevent further deterioration of her renal function. Unfortunately, after discharge from the hospital the patient failed to follow-up to establish outpatient care.

Discussion

In the United States and Europe, serum amyloid A protein-related amyloidosis occurs in less than 2% of patients with amyloidosis. Rheumatoid arthritis accounts for up to 40% of cases. Other causes associated with AA amyloidosis are ankylosing spondylitis, psoriatic arthritis, chronic pyogenic infections (bronchiectasis, osteomyelitis, chronic skin or decubitus ulcers, intravenous drug users, paraplegics, or tuberculosis), inflammatory bowel disease, primarily Crohn's disease, cystic fibrosis, neoplasms such as renal cell carcinoma and Hodgkin lymphoma, and familial Mediterranean fever (3). Patients who abuse heroin will typically present with chronic suppurative skin infections, edema, nephrotic syndrome, benign urinary sediment, and normal-sized or enlarged kidneys. Chronic suppurative skin infection, consequent to repeated subcutaneous injections, appears to be an underlying cause (4). Amyloid typically appears after the wounds have healed and is not associated with any particular infectious organism.

The deposition is limited in AA amyloidosis and usually starts with renal involvement. As the disease progresses it affects the liver, spleen, autonomic nervous system and rarely cardiac tissue. SAA is an acute phase apoprotein synthesized in the liver and transported by high density lipoprotein, HDL3 in the plasma (5). There is an increased synthesis of SAA with inflammation, which may be due to elevated levels of proinflammatory cytokines. After several years of the inflammatory disease being active, the SAA rises to a high enough level in which the tissue deposition begins to occur. at amyloidosis can result from fibrillar deposition of serum amyloid A (SAA) or deposition of immunoglobulin light chains from amyloid L (AL). Secondary amyloidosis usually presents as asymptomatic proteinuria or nephrotic syndrome. Complications associated with renal amyloidosis are nephrogenic diabetes insipidus and both proximal and distal renal tubular acidosis (6). Approximately, 40-60% of patients that develop nephrotic syndrome will eventually need dialysis.

Biopsy of the kidney or liver is diagnostic in about 90% of cases. Light microscopy in renal amyloidosis typically reveals diffuse glomerular deposition of amorphous hyaline material, initially in the mesangium and then in the capillary loops after these weakly stain with PAS and methenamine silver stain because they are composed mostly of amyloid fibrils and not extracellular matrix as in diabetes mellitus (7). Immunofluorescence will confirm light microscopy findings and will also be negative for immunoglobulins and complement in AA amyloidosis. In contrast, AL amyloid will be positive for lambda or kappa light chains. Histological characteristics of renal amyloidosis are correlated with clinical outcome (8).

AA amyloidosis usually leads to end stage renal failure in patients that have persistently high circulating levels of serum amyloid A. Those patients who do progress to End Stage Renal Disease (ESRD) can be treated with either dialysis or renal transplantation. SAA concentration should be strictly monitored over time to assess biochemical response to treatment (9). Renal amyloidosis is associated with chronic active interstitial inflammation. Certain features that make amyloidosis more common in a heroin user is the du-

ration of subcutaneous heroin use and a history of recurrent minor infections such as cutaneous suppurative lesions (10). Renal amyloidosis has emerged as an important differential diagnosis when heroin users are admitted to the hospital with proteinuria and nephrotic syndrome. Early diagnosis and rapid control of the underlying inflammatory disease are of utmost importance to prevent irreversible organ damage and to improve survival in patients with AA amyloidosis. Once clinically overt kidney damage due to AA amyloidosis occurs, the prognosis is dictated by the effective control of the underlying inflammatory condition.

Conclusions

AA renal amyloidosis should be considered in chronic heroin users presenting with proteinuria and renal impairment.

Authors' contributions

CC, SS and HA prepared the primary draft. JEB reported the pathology. JB, AE,OD and ATM provided extensive intellectual contribution. GTH prepared the final manuscript.

Conflict of interest

The author declared no competing interests.

Funding/Support

None declared.

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