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Original Article

Characteristics of AA amyloidosis patients in San Francisco

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SUMMARY AT A GLANCE

Lejmi and colleagues reported a group of patient with AA amyloidosis, which was mainly caused by skin injection of drugs. The high mortality and bad outcome with multiple organs involvement and shortly progressed to dialysis need to caution.

ABSTRACT:

Background: **AA amyloidosis due to subcutaneous injection of drugs of abuse has been described in the USA, but all the existing literature is from more than 20 years ago. There is more recent literature from Europe. We have observed a high incidence of AA amyloidosis in the county hospital in San Francisco.**

Design: **Here, we describe 24 patients who had kidney biopsy-proven AA amyloidosis from our hospital from 1998 to 2013. All the patients were thought to have AA amyloidosis from skin popping of illicit drugs after having exhausted the intravenous route. These patients with biopsy-proven AA amyloidosis were analysed further.**

Results: **All patients were found to have hepatitis C infection, hypertension was not common, most had advanced kidney failure, and acidosis was common as was tubulointerstitial involvement on the kidney biopsy. Other organ involvement included hepatomegaly and splenomegaly in a number of patients; direct myocardial involvement was not seen, but pulmonary hypertension, history of deep vein thrombosis and pulmonary embolism were common. The prognosis of these patients was poor. The mortality rate approached 50% 1 year after biopsy, and most of the patient needed dialysis shortly after diagnosis. Cessation of drug use seemed beneficial but rarely achievable.**

Conclusion: **AA amyloidosis from skin popping is common in San Francisco. Most patients with renal involvement end up on dialysis, and mortality rates are exceedingly high.**

INTRODUCTION

Unlike primary amyloidosis, AA amyloidosis primarily affects the kidneys, spleen and liver. AA amyloidosis can be attributed to systemic inflammatory diseases such as rheumatoid arthritis, osteomyelitis and dermatomyositis in many cases. Interestingly, it has been speculated that many skin conditions also lead to the development of AA amyloidosis. These include (but not limited to) hidradenitis suppurativa, stasis ulcers, basal cell carcinoma and dystrophic epidermolysis. Serum amyloid A protein, the precursor protein for amyloid A protein, is produced by fibroblasts and is seen in connective tissue fibrils of many organs.[1] The dermis is likely to contain the largest number of fibroblasts and thus of serum amyloid A proteins in the body.[2] Another skin condition described to result in AA amyloidosis is skin popping in drug addicts.

Lowenstein in 1970 was the first to describe a drug addict with multiple needle tracts over his arms, endocarditis and nephrotic syndrome who had amyloidosis on the kidney biopsy.[3] Even though skin popping-induced AA amyloidosis appears to be the likely diagnosis, at that time, the kidney disease was attributed to endocarditis. Another report from 1970 described four drug addicts with nephrotic syndrome in New York City who were diagnosed to have lesion-less renal disease.[4] The fact that they did not respond to immunosuppressive therapy suggests that they also likely had AA amyloidosis from skin popping, although the authors did not explicitly make that diagnosis.

The first description of the disease was in 1978 by Jacob *et al.* who described a drug addict with multiple skin abscesses and nephrotic syndrome who had AA amyloidosis on kidney biopsy attributed to skin popping.[5] Since then, several subsequent case reports and case series have been published, almost all of which consisted of patients living in New York City during the late 1970s to 1980s. More recent literature is

exclusively on patients from Europe. To our knowledge, this is the first paper to describe patients with biopsy-proven AA amyloidosis secondary to skin popping in the USA in the last 20 years. We also provide the most complete follow-up data for this devastating disease.

METHODS

The results of all kidney biopsies performed at San Francisco General Hospital (county hospital) between 1998 and October of 2013 were reviewed. There were 24 patients who had AA amyloidosis diagnosed on kidney biopsy during that time period. The AA amyloidosis was confirmed in all of the patients by separate positive staining for serum AA protein on the kidney biopsy. To compare the incidence of AA amyloidosis in San Francisco with that in Chicago, all kidney biopsies performed by one nephrologist (RS) at John Stroger Hospital of Cook County (also county hospital) between 2001 and end of 2007 were also reviewed. The electronic and paper medical records of the patients with AA amyloidosis at San Francisco General Hospital were reviewed. Subsequently, they were analysed for their baseline characteristics, organ involvement and their response to therapy. Complication post-kidney biopsy, including the need for blood transfusions, was also studied. In addition, patient mortality rates from the kidney disease were reviewed. Collected data were analysed using Microsoft Excel statistical-use software (Microsoft Corporation, Redmond, WA, USA) and expressed as average plus/minus standard deviation of the mean.

In addition, because many patients with suspected AA amyloidosis do not have kidney biopsy at our hospital, to determine the true prevalence of AA amyloidosis as a cause of end-stage kidney disease at our hospital, we looked at all our dialysis patients at a single time point. Skin poppers who had nephrotic-range proteinuria and no other likely cause of nephrotic syndrome were thought to have AA amyloidosis. In order to show that this assumption is accurate, we further analysed all biopsies of patients with nephrotic syndrome at our hospital from 1998 to 2013. Of the 129 patients with nephrotic syndrome who had kidney biopsy during this time period (and did not have AA amyloidosis), only five had a documented history of drug use, and out of these, none had extensive skin popping seen in our AA amyloidosis patients. Thus, we feel confident that most of our foregoing dialysis patients had AA amyloidosis causing their kidney disease.

This study was approved by the Local Ethics Committee (Institutional Review Board), and need for informed consent was waived (#13-11935).

RESULTS

There were a total of 425 kidney biopsies performed at San Francisco General Hospital between the years 1998 and October of 2013. Twenty eight (6.6%) patients had amyloidosis on the kidney biopsy, of which 24 (86%) of them were diagnosed with AA amyloidosis. All of the AA amyloidosis cases were in drug addicts who performed skin popping. In contrast, of the 160 patients who had a kidney biopsy at John H. Stroger Hospital of Cook County in Chicago by a single nephrologist (RS) between 2001 and 2007, only one patient was diagnosed with amyloidosis, which was the primary type. Thus, the incidence of primary amyloidosis was similar in Chicago and San Francisco (both county hospitals); however, AA amyloidosis was prevalent in San Francisco and non-existent in Chicago. We chose county hospitals of two big cities in the USA because of similar patient populations.

On pathology, all of the cases showed severe and widespread involvement of the kidney by amyloidosis with high chronicity (Fig. 1). The amyloid accumulated most prominently in the glomeruli and tubular basement membranes, but vessels when sampled and visualized also showed amyloid accumulation in the vascular walls. The interstitium was the least affected of the cortical compartments although often patchy interstitial amyloid was present as well.

Because of the high prevalence of drug abuse and AA amyloidosis at our hospital and the late presentation of these patients, many of them with suspected AA amyloidosis never had kidney biopsies. In order to estimate the prevalence of patients with AA amyloidosis including those who did not have a kidney biopsy, we looked at all of our patients who were receiving dialysis in our system as of September of 2013. There were 287 patients on dialysis at that time; of these patients, 14 (4.9%) were presumed to have end-stage kidney disease because of AA amyloidosis, and only two of these patients actually had a kidney biopsy. Only drug addicts who skin popped with high-grade proteinuria and did not have another likely cause (such as diabetes) for chronic kidney disease and nephrotic syndrome were presumed to have AA amyloidosis. We believe that these patients were highly likely to have had AA amyloidosis as the cause of their renal failure as we did not have any patient with history of extensive skin popping and nephrotic syndrome in whom we performed kidney biopsy and it showed anything other than AA amyloidosis. Thus, among our dialysis patients, only 14% of the patients with presumed amyloidosis actually had a kidney biopsy.

Of the 24 patients found to have biopsy-proven AA amyloidosis due to skin popping, the average age was 44 ± 10.02 years, with an age range of 31–67 years. Thirteen patients were male (54%), and 11 were female (46%). Six patients (25%) were African American, 16 patients (67%) were White and two patients (8%) were Hispanic. All of the patients used heroin, 14 of them used cocaine and three of them used methamphetamine.

Most of the patients with biopsy-proven AA amyloidosis had normal blood pressures; the average systolic blood pressure was 130.6 ± 25.6 mmHg, and that of diastolic blood pressure was 75.3 ± 16.7 mmHg. Only one patient had had severe hypertension with a blood pressure of 221/122. All of the patients had hepatitis C, three of them (13%) had concurrent hepatitis B and three (13%) were positive for HIV.

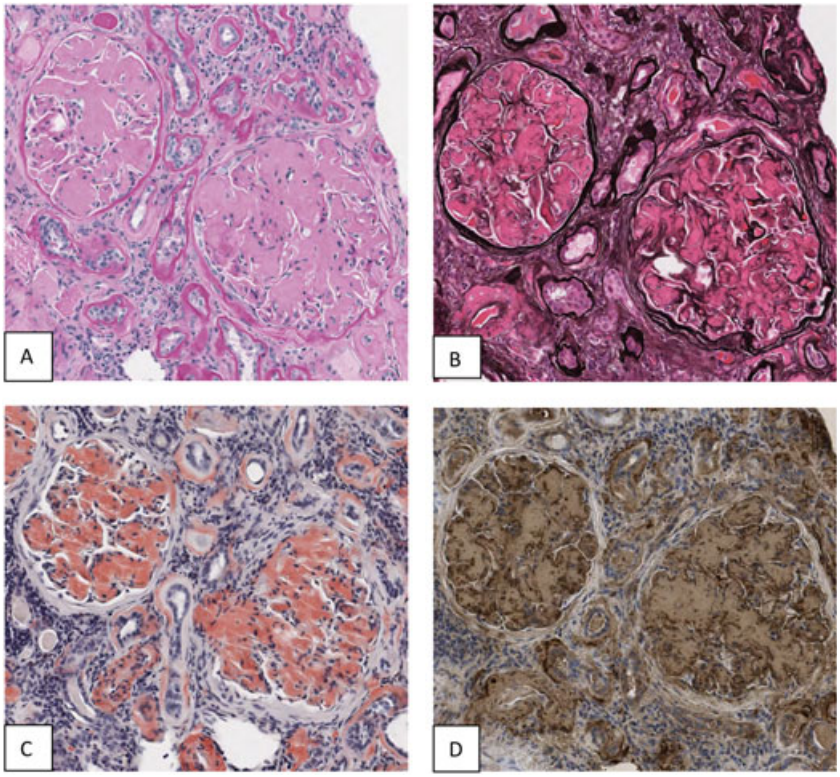

Fig. 1 Representative light micrographs for AA amyloidosis within the kidney on biopsy. Irregular accumulation of material that is negative for periodic acid-Schiff (A) and Jones methenamine silver (B) stains is present within the mesangium, glomerular capillary loops, tubular basement membranes, vessels and focally in the interstitium. (C) This material stains salmon pink on Congo red stain and shows apple-green birefringence under polarized light (not shown), confirming the presence of amyloid. (D) Immunohistochemical stain for serum amyloid A protein is positive. All images taken at 200×.

Furthermore, all of the patients had history of chronic skin infections including ulcers and abscesses.

The serum creatinine, urine protein/creatinine ratio, total serum carbon dioxide, serum potassium and serum albumin levels were also collected at the date of biopsy (Table 1). The average serum creatinine was 4.5 ± 2.2 mg/dL (range from 1.2 to 10.05 mg/dL), average urine protein/creatinine was 24 ± 11.5 g/g (range 7.7–41.5 g/g), average total CO2 was 22.5 ± 4.1 mEq/L (range 14–30 mEq/L), average serum potassium was 4.7 ± 1.1 mEq/L (range 3.1–6.9 mEq/L) and average serum albumin was 2.2 ± 0.8 g/dL (range 1–3.8 g/dL). Nine patients had hyperkalemia (K > 5.1 mEq/L), one patient had hypokalemia (K < 3.5 mEq/L) and 10 patients had metabolic acidosis (total CO2 < 22 mEq/L). Eighteen patients had an ultrasound of their kidneys, and the kidney dimensions were measured bilaterally. The kidney sizes ranged from 8.6 to 14.8 cm with an average size of 12 ± 1.5 cm.

We also looked at the incidence of post-biopsy bleeding in these patients. The average serum haemoglobin prior to biopsy was 10.0 ± 1.4 g/dL; the average serum haemoglobin 24 h post-biopsy was also 10.0 ± 1.4. One patient was transfused prophylactically the day of biopsy (causing the post-biopsy haemoglobin to be falsely elevated). One patient was started on anticoagulation 3 days after biopsy, shortly after he required eight units of red cells. Kidney ultrasound was never carried out, but it is logical to conclude post-biopsy bleeding, although there was question of bloody pleural effusions also.

We also looked at possible organ involvement from the AA amyloidosis. Liver function tests were performed on all patients (Table 2). In these patients who all had hepatitis C, average serum aspartate aminotransferase (AST) was 40 ± 31.06 IU/L (range 10–131 IU/L), average serum alanine aminotransferase (ALT) was 24 ± 52.43 IU/L (range 7–133 IU/L), average International normalized ratio (INR) was 1.1 ± 0.14 (range 0.8–1.4) and average partial thromboplastin time (PTT) was 37.7 ± 6.47 (range 30.9–50.3). Twelve patients had a liver ultrasound performed, of which four patients (33%) had hepatomegaly, one patient (8%) had a nodular liver and

Table 1 Lab values of SFGH patients with AA amyloidosis at time of kidney biopsy

	Serum creatinine (mg/dL)	Urine protein/ creatinine ratio (g/g)	Serum albumin (g/dL)	Serum potassium	Serum total CO2
Average	4.61	24.7	2.2	4.7	21.8
Median	4.44	21.8	2.2	5.0	21.5
Range	1.2–10.05	7.7–54	<1 to 3.8	3.1–6.9 (>5 in nine points)	14–30 (<20 in six points)

SFGH, San Francisco General Hospital.

Table 2 Liver function tests in SFGH patients

	AST (range 10–41)	ALT (range 7–35)	Alkaline phosphatase (range 53–128)	INR (<1.2)	PTT (<37.6)
Average	35	18.4	107.8	1.11	36.25
Median	26.5	16	105	1.1	35.7
Number of patients outside normal range values	5/20 (25%)	2/20 (10%)	3/20 (15%)	8/20 (40%)	6/20 (30%)

SFGH, San Francisco General Hospital.

one patient (8%) had a fatty liver. Only four out of the 12 (33%) patients had splenomegaly. Furthermore, 10 patients (45%) had a deep vein thrombosis, four patients (20%) had pulmonary emboli and three patients (12.5%) had unexplained pulmonary hypertension possibly secondary to undiagnosed pulmonary embolism. Twenty one out of the 24 patients had an echocardiogram. Nine out of 21 (43%) patients had normal findings, 5/21 (24%) patients had left ventricular hypertrophy, 8/21 (38%) had evidence of pulmonary hypertension and 3/21 (14%) had left ventricular systolic dysfunction.

We only looked at the follow-up data on patients who had kidney biopsy before 2013 as the follow-up period would be too short for the more recent patients. Of the 20 patients diagnosed with AA amyloidosis, 15 patients (75%) started dialysis. From these 15 patients, 13 of them (87%) died within 6 years after biopsy (first-year mortality was 47% and 3 year mortality 73%), and two patients (13%) were confirmed alive. We used the national death index to confirm the death of seven of these patients. From the five patients (25%) that did not start dialysis, three of them were lost to follow-up after biopsy, while the other two patients were confirmed alive average of 34 months after biopsy. The cause of death was presumed to be septic shock in three patients, drug overdose in two patients, respiratory failure in two patients, sudden death at home in two patients and sudden cardiac arrest in the hospital in one patient. No patient had autopsy, and in three patients, we were not able to find the cause of death.

Table 3 Baseline characteristics of patients described in the literature

Baseline characteristic	Average (number of patients)
Age	39.4 (80)
Gender	Women 17, men 62
Race	African American 26, White 22
Hepatitis C	33 patients out of 36 patients reported
HIV	12 patients out of 37 patients reported
DVT and/or PE	19 patients out of 26 patients reported
Serum creatinine	3.83 mg/dL (72)
Proteinuria	10.3 g/day (69)
Serum albumin	2.2 g/dL (50)
Serum cholesterol	283 mg/dL (9)
Blood pressure	126/64 (29)

DVT, deep vein thrombosis; PE, pulmonary embolism.

DISCUSSION

Early reports of AA amyloidosis in drug addicts came almost exclusively from New York City mainly in the late 1970s and early 1980s.[6–14] Interestingly, there have not been any recent reports of the disease in the USA, not even from New York City. In recent years, there have been a number of cases of AA amyloidosis in drug addicts described from Europe.[15–20] Table 3 summarizes all the cases described in the literature thus far. Only about a fifth of the 80 patients whom we were able to find in the literature have been woman. Almost all the patients described in the USA have been of African descent, whereas the European patients have been Caucasian. Hepatitis C was highly prevalent, and HIV was seen in about a third. All of these facts may be explained by higher prevalence of drug use in men, high risk of chronic viral infections in long-standing drug addicts and so on. The incidence of hypercoagulability is hard to discern (as it is a hard diagnosis to make), but at least 19 out of the 80 patients had documented deep venous thrombosis and/or pulmonary embolism. Most patients presented with advanced renal failure, severe nephrotic syndrome and were normotensive. The morbidity (requirement for dialysis) and mortality rates were high. All the patients who were reported to improve or stabilize their renal function had stopped using drugs, but unfortunately, this was not a common occurrence.[3,8,13,16,19,20] The data available are from multiple different institutions and at different time periods. Our patients add to the existing data as there are more complete follow-up data available from one single institution.

The incidence of AL *versus* AA amyloidosis has varied tremendously over the years and at different institutions. In Germany in 2009, 53% of patients with renal amyloidosis had primary amyloid, and 40% had AA amyloidosis.[21] At the Mayo Clinic in 1975, out of 236 cases of amyloidosis, 82% had AL amyloidosis, whereas only 8% had AA (although this included all biopsies and not just the kidneys).[22] At our hospital, 86% of renal amyloidosis was AA amyloidosis secondary to skin popping in drug addicts, and this disease caused around 5% of kidney disease in our dialysis patients. By contrast, AA amyloidosis was non-existent in the county hospital in Chicago. The reason for the difference is not clear but may be from the extent of drug use in the two cities. In the older literature from the USA, it has been illustrated that 85% of the drug addicts with AA amyloidosis were African American. In contrast, the majority

of patients at our hospital were White (67%). In addition, our study shows that 46% of patients diagnosed with AA amyloidosis were female, despite the predominance of the male gender in earlier case reports. Hence, gender and race are less likely to be a risk factor but probably reflect the use of drugs in the population.

Of our 24 patients reported to have AA amyloidosis secondary to skin popping, all of them had hepatitis C. Thus, there may be an association between AA amyloidosis and hepatitis C. Nevertheless, we cannot exclude the fact that hepatitis C may be associated solely with use of IV drugs rather than with the presence of amyloidosis. Subclinical liver disease causing decreased clearance of serum amyloid A protein cannot be ruled out as contributing to the amyloid accumulation in the kidneys. However, serum AST and serum ALT in our patients were only mildly elevated despite having hepatitis C. Although the serum albumin was low in our patient with severe nephrotic syndrome, the INRs were on the upper limits of normal.

The incidence of hypercoagulability was high in our patients probably reflecting the high-grade proteinuria and the low serum albumin levels. In fact, these patients are likely just as hypercoagulable as the patients with idiopathic membranous glomerulonephropathy. Prophylactic anticoagulation may be indicated in those with low serum albumin levels.

Although overt liver dysfunction was not seen in our patient who also had hepatitis C, hepatomegaly and splenomegaly were present in a significant number of patient likely secondary to amyloid infiltration of those organs also. Interestingly, even though the amyloid load on the kidney biopsies was extensive, for the most part, the kidneys were not enlarged on ultrasound. Based on the echocardiograms, amyloid infiltration of the heart would be unlikely in any of our patients consistent with other forms of AA amyloidosis. The main abnormality on the echocardiogram was evidence for pulmonary hypertension, which likely reflects the high incidence of undiagnosed pulmonary emboli.

The majority of patients who needed dialysis after their biopsies confirmed the presence of AA amyloidosis. The average time to dialysis from the time of the biopsy was 8.9 months, while the median time to starting dialysis was only 2 months. Of the 15 patients (75%) who underwent dialysis, only two patients (13%) were reported alive after 42 months from biopsy date. The remaining 86% of patients died. From the five patients who did not do dialysis, two of them were still alive, while the remaining three were lost to follow-up. Overall, based on their therapy and follow-up results, it can be concluded that the prognosis for patients with AA amyloidosis due to skin popping is poor.

Of the two patients who did not start dialysis and follow-up is available, serum creatinine stabilized from baseline of 2.9 to 2.3 mg/dL during the course of 2 years. In addition, there was also a decrease in the protein/creatinine ratio in these two patients from 31.4 to 5.01 g/g over a period of 1 year. Both patients stopped intravenous drugs of abuse for at least a prolonged period of time. Thus, it seemed that with cessation of drug use, there is stabilization or improvement of nephrotic syndrome and renal function. However, this is not a common occurrence with our patients currently. Increased effort to encourage drug rehabilitation in these patients is indicated.

In our patients, no one had any treatment for their AA amyloidosis. Measures that can be taken include cleaning the skin before drug use. In one study, drug user who reported cleaning their skin before injecting had a lower rate of abscesses.[23] Therefore, it is an important preventive measure to advice patients to clean the area of skin prior to injection and skin popping. Colchicine has had a role in treating some cases of AA amyloidosis, but there are no good data with drug addicts. Nonetheless, the most effective and best preventive measure is to advise the patient to stop drug use altogether. Newer treatments for AA amyloidosis such as eprodisate have not been studied in this disease.

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