Renal amyloidosis in intravenous drug users

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Summary
Background: Intravenous drug abuse is associated with a wide variety of acute and chronic medical complications. The increased longevity of drug users has seen the emergence of new diseases as a result of chronic bacterial and viral infection. We recently observed an increase in the number of cases of renal amyloidosis among intravenous drug users in central London.

Aim: To describe here the demographic and clinical characteristics of such patients.

Methods: Patients were identified retrospectively from computerized patient renal biopsy records at University College London and Royal Free Hospitals from 1990–2005. Clinical information was collected from patient hospital records.

Results: We identified 20 cases of AA amyloidosis; 65% occurred between January 2000 and September 2005. All were proteinuric (mean 7.3 g/l, range 0.5–14.8 g/l) and 13 required dialysis within 1 month of diagnosis. Of the remaining seven, four developed end-stage renal failure after mean follow-up of 16 months (range 6–30). Nine died, with median survival of 19 months (range 1–62); all deaths were due to sepsis.

Discussion: Secondary AA amyloidosis is a serious complication of chronic soft tissue infection in intravenous drug users in central London. Affected individuals invariably presented with nephrotic range proteinuria and advanced renal failure. Treatment options are limited and the outcome for such patients on renal replacement was poor. Cross-disciplinary strategies are needed to prevent this serious complication of long-term intravenous drug abuse.

Introduction

The epidemic of intravenous drug use is a major worldwide public health problem. Injection of illicit drugs, mainly heroin, is associated with sudden death from overdose, exposure to blood-borne viruses and a wide variety of medical complications related to the infection risks associated with injection.1 Renal disease related to substance abuse has been reported in association with intravenous drug use.2,3 In the late 1970s, Rao described heroin-associated nephropathy, a disease characterized by nephrotic syndrome and rapid progression to renal failure. This condition was reported almost exclusively in African-American patients with a characteristic renal histological appearance of focal segmental glomerulosclerosis.4 In recent years, heroin-associated nephropathy has been reported much less commonly,5 while reports of renal disease related to HIV, HBV and HCV have increased.6,7 In a recent study from Europe of mainly Caucasian drug users, the most common
renal lesion was hepatitis-C-related membranoproliferative glomerulonephritis (MPGN).\(^7\)

In the late 1970s, nephrotic syndrome due to systemic amyloidosis was first reported in drug addicts in New York.\(^8–10\) This condition, described as ‘skin poppers’ amyloidosis, was associated with subcutaneous drug injection, chronic soft tissue infection and particularly affected African-American patients.\(^11\) Since then there have been a few isolated reports of this condition, while others have reported it as a relatively rare finding in intravenous drug users.\(^5,12,13\) Recently, we observed 20 cases of systemic secondary amyloidosis among intravenous drug users in central London, and we report our clinical experience with this condition in this paper.

**Methods**

Patients with a diagnosis of ‘amyloidosis’ were identified retrospectively from computerized patient records at University College London Hospital (UCLH) and Royal Free Hospital. In addition, we searched a database of renal biopsy specimens from UCLH covering the years 1990–2005. We excluded those with no history of intravenous drug use, those with primary AL amyloidosis and those with another identifiable cause of secondary AA amyloidosis. Clinical details were obtained from review of medical records. The diagnosis of amyloidosis was confirmed by renal biopsy in 14 patients, post mortem examination in one patient and a positive serum amyloid protein (SAP) scan in 17 patients. In five patients, the diagnosis was made on the basis of characteristic clinical findings and SAP scanning without confirmation by tissue biopsy. SAP is a normal plasma protein that binds specifically to amyloid fibrils, and when radio-iodinated, it can be used to localize and quantify visceral amyloid deposits.\(^14\) All SAP scans were performed at the National Amyloidosis Centre. All patients underwent echocardiography to assess cardiac involvement. Renal biopsies were examined after fixation in neutral buffered formalin and paraffin embedding. Sections for light microscopy were stained with haematoxylin and eosin (H&E), periodic acid Schiff (PAS), Jones’ hexamine silver and Congo Red stains. Immunoperoxidase preparations for the detection of immunoglobulins IgG, IgM and IgA, complement components C3 and C1q, fibrin were also examined. The tissue for electron microscopy was embedded in Araldite, thin sections from which were contrasted with uranyl acetate and lead citrate, and examined in a Jeol (JEM 1200) electron microscope. Amyloidosis was diagnosed by Congo Red staining on light microscopy and characteristic amyloid fibrils (9–11 nm in size) on electron microscopy (EM). Immunostaining using anti-AA anti-sera was not routinely performed at UCLH, but was available for seven cases identified at Royal Free Hospital. Serum electrophoresis, serum free light chain and urine immuno-fixation for Bence-Jones protein were performed to exclude paraproteinaemia. Proteinuria was documented either by 24-h urine collections or estimation of the urinary protein/creatinine ratio, and is expressed as g/l.

**Results**

The demographic and risk characteristics of the patients are outlined in Table 1. We identified 20 Caucasian patients (16 male), mean age 40.3 years (range 29–51). Of these 20, two were identified in January 1990–Dec 1994, five in January 1995–December 1999 and 13 in January 2000–September 2005. All had a long history of intravenous drug use, with a mean duration of 18.9 years (range 10–30). Sixteen had a documented history of deep-vein thrombosis. Thirteen reported a history of subcutaneous injection (‘skin popping’) and 18 reported episodes of systemic reaction with fever and chills after injection (‘dirty hits’). All gave a history of skin and soft tissue infections or chronic cellulitis. Seven had a previous history of bacterial endocarditis, two had osteomyelitis and three had been treated for pulmonary tuberculosis.

The renal presentation and laboratory findings are shown in Table 2. All patients were proteinuric (mean 7.3 g/l, range 0.5–14.8 g/l) and 13 presented with end-stage renal failure that required dialysis within 1 month of diagnosis. Of the remaining seven, four developed end-stage renal failure after a mean follow-up of 16 months (range 6–30). In two, renal function has stabilized, with reductions
in proteinuria 19 and 74 months after diagnosis, respectively. Importantly, both of these patients have remained drug-free for most of this time. Nineteen of the 20 patients had antibodies to HCV and six had evidence of prior hepatitis B exposure. One patient was HIV-positive.

In 17 patients, amyloid burden was evaluated by SAP scintigraphy, and was graded by published criteria as moderate or large in all cases. The pattern of organ involvement is shown in Table 3, and a typical appearance on SAP scanning with lung, spleen and renal involvement is shown in Figure 1. Amyloid deposits were detected in kidney and spleen in all cases. Liver involvement, normally an indication of advanced disease, was present in ten cases. One patient had gut involvement confirmed by rectal biopsy. Four patients had adrenal uptake on SAP scanning, but each had normal adrenal function tests. All patients underwent echocardiography; none had evidence of cardiac amyloidosis. Interestingly, in the two patients who remained drug-free with stable renal function, follow-up SAP scan demonstrated a reduction in total amyloid load. The mean C-reactive protein of all patients at presentation was 61.4 mg/l (range 2–200) and mean serum amyloid A protein was 80 mg/l (range 4–474).

Examination of renal biopsies typically found amyloid deposits in tubular basement membranes, glomeruli, the mesangium and in small arterioles. EM demonstrated characteristic amyloid fibrils (9–11 nm diameter) in all cases.

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**Table 2** Biochemical characteristics of patients at presentation

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<table>
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<tr>
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<tr>
<td>End-stage renal failure at presentation</td>
<td>60%</td>
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<tr>
<td>Nephrotic syndrome at presentation</td>
<td>90%</td>
</tr>
<tr>
<td>HCV antibodies (% positive)</td>
<td>95%</td>
</tr>
<tr>
<td>HIV (% positive)</td>
<td>5%</td>
</tr>
<tr>
<td>HBVsAg (% positive)</td>
<td>0%</td>
</tr>
<tr>
<td>HBV exposure</td>
<td>30%</td>
</tr>
<tr>
<td>Mean ± SD proteinuria (g/l)</td>
<td>7.3 ± 4.1</td>
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<tr>
<td>Mean ± SD serum creatinine (μmol/l)</td>
<td>559 ± 370</td>
</tr>
<tr>
<td>Serum creatinine range (μmol/l)</td>
<td>103–1110</td>
</tr>
</tbody>
</table>

a HBV exposure is defined as detection of antibodies to HBV core or surface antigens in the absence of previous vaccination. b Proteinuria was usually assessed by estimation of urinary protein creatinine ratio and is expressed as g/l.

**Table 3** Pattern of organ involvement and markers of systemic inflammation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Involvement</th>
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<tbody>
<tr>
<td>Liver</td>
<td>59%</td>
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<tr>
<td>Spleen</td>
<td>100%</td>
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<tr>
<td>Kidney</td>
<td>100%</td>
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<tr>
<td>Adrenal</td>
<td>24%</td>
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<tr>
<td>Cardiac</td>
<td>0%</td>
</tr>
<tr>
<td>Gut</td>
<td>5%</td>
</tr>
<tr>
<td>Mean ± SD C-reactive protein (mg/l)</td>
<td>61.4 ± 64</td>
</tr>
<tr>
<td>C-reactive protein range (mg/l)</td>
<td>2–200</td>
</tr>
<tr>
<td>Mean ± SD SAA (mg/l)</td>
<td>80 ± 133.2</td>
</tr>
<tr>
<td>SAA range (mg/l)</td>
<td>4–474</td>
</tr>
</tbody>
</table>

SAA, serum amyloid A protein.

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**Figure 1.** Typical SAP scan appearances of AA amyloid with extensive hepatic, splenic and renal involvement.
Of the 17 patients who underwent chronic dialysis, all were non-compliant with their dialysis regimen. Due to widespread venous thrombophlebitis, it was possible to fashion an arteriovenous fistula in only two patients; the remainder suffered recurrent line sepsis. Median overall survival of this group to date is 25 months; nine have died, with a median survival of 19 months (range 1–62), and all deaths were due to sepsis.

Discussion

Secondary AA amyloidosis is a rare condition that can complicate a variety of inflammatory diseases. Amyloid fibrils are derived from the serum amyloid A protein (SAA), a circulating acute-phase response protein. SAA is normally soluble, but during inflammation, circulating levels rise, and can be deposited in an insoluble, fibrillar form. Renal involvement dominates the clinical picture in the majority of cases; common presenting features include proteinuria, nephrotic syndrome and even renal failure. The underlying conditions leading to secondary amyloidosis have changed in the UK over the past several decades. Earlier studies estimated that approximately 50% were due to tuberculosis, but in more recent reports TB has been superseded by chronic rheumatic diseases, which now account for around 70% of cases. Historically, the diagnosis of secondary amyloidosis carried a grave prognosis, with median survival rates of 4–8 years. In a series of 43 patients presenting to a Scottish renal unit, median patient survival was 53 months, with a median renal survival of only 18 months. The rate of decline in renal function was relatively fast, and correlated with the degree of proteinuria. However, in a recent study of patients with AA amyloidosis, 10-year overall survival was >90%, and renal function was preserved among those in whom the SAA concentration was maintained around normal by therapy. Surprisingly, there are relatively few reports of the outcome of patients with secondary amyloidosis on dialysis, and estimates of 2-year patient survival vary from 46% to 62%.

Here we report 20 cases of secondary AA amyloidosis among intravenous drug users in Central London. This condition accounts for 30% of the 48 cases of AA amyloid treated at UCLH in 1985–2005. All patients were Caucasian, and all had a long history of intravenous drug use with recurrent soft-tissue infections. The typical clinical presentation was with nephrotic-range proteinuria and renal failure, and over 50% required dialysis within 1 month. Medical management of the intravenous drug user population is extremely difficult; all patients failed to return for regular medical follow-up, then presented later requiring dialysis. The pattern of organ involvement was characteristic of secondary AA amyloid, with renal and spleen involvement a universal finding. Due to the limitations of SAP scanning in the detection of cardiac amyloid, all patients underwent echocardiography and no patient had clinically significant cardiac involvement. Skin and muscle biopsies were negative in three patients, and four patients had adrenal disease by SAP scintigraphy. Interestingly, liver involvement, which is usually a feature of very advanced disease, was common, and liver involvement may be more common in this patient group. In those who presented early, median renal survival was 16 months (range 6–30). In two patients, renal function stabilized, with a reduction in proteinuria 19 and 74 months after diagnosis. Both have remained drug-free for most of this time.

Our data show that the incidence of this condition is increasing in Central London. In contrast to reports from Continental Europe, none had hepatitis-related glomerulonephritis despite the high rate of hepatitis C infection in this population. In view of the characteristic clinical presentation and ready access to medical care, it is unlikely that an improvement in case ascertainment accounts for this rise. We are unable to say whether a rising population of drug users accounts for the increase, as there are no clear data on the prevalence of intravenous drug use, although estimates suggest it may be as high as 1.8% in inner London. Similarly, there is no evidence to support a role for a contaminant in street heroin. A high proportion of patients (85%) had a history of chronic ulceration that could have contributed to the development of amyloidosis. We are unaware of a direct link between thrombosis and amyloidosis, but venous insufficiency invariably led to chronic ulceration and the use of alternative routes for injection. We speculate that the increasing longevity of users with poor venous access, and the attendant increase in subcutaneous injection and sepsis, is a major contributory factor in the development of amyloidosis. It will be of interest to see if other areas with high prevalence of injection drug users begin to see a similar emergence of this condition.

Although tissue diagnosis remains the gold standard, renal biopsy can be hazardous because of poor patient cooperation and potential bleeding
complications. SAP scanning proved particularly useful for diagnosis, and in the assessment of organ involvement and quantification of amyloid load. The total amyloid burden on SAP scanning and measurement of circulating levels of SAA can be used to predict outcome, and such measurements have also shown that amyloid deposits are dynamic and can regress.15 Unfortunately this group of patients presents with advanced disease with heavy amyloid burden, high levels of SAA and end-stage renal failure. Arresting the progression of systemic amyloidosis depends on reducing inflammation and SAA precursor protein production by treating the underlying condition. Spontaneous resolution and successful treatment with colchicine of renal amyloidosis has been reported in intravenous drug users,24,25 which supports the idea that removal of the inflammatory stimulus, usually chronic skin sepsis, can lead to reversal of the disease. This is consistent with our observation of a reduced amyloid load and reduction in SAA levels in the two patients who remained ‘clean’.

The importance of prevention is underscored by the very poor outcome on dialysis. Median survival of our patients was only 25 months, which compares very unfavourably with reports of a median survival of 52 months for all patients with AA amyloidosis on haemodialysis.18 The delivery of dialysis is fraught with difficulty in these patients. Compliance with dialysis schedule, diet and fluid restriction is very poor. Damage from injection to major veins means creation of permanent vascular access is usually impossible. Tunnelled vascular access catheters are invariably used as portals for drug injection. Poor hygiene leads to serious infection complications, and line-related infection was the cause of death in all of our patients.

Wider recognition of this condition, especially in at-risk groups, ‘skin poppers’ or those with chronic soft tissue infection or cellulitis, is needed. Simple, readily available tests such as urinalysis and CRP could be used to screen for renal disease and chronic inflammation. Further investigation such as measurement of SAA, SAP scanning or tissue biopsy could then be used to confirm the diagnosis. If amyloid is detected, early urgent efforts are needed to institute drug rehabilitation, treatment of infection and reduction in inflammation. The major challenge however will remain the prevention of this disease. In addition to public health measures directed to reducing intravenous drug use, and increasing the availability of single-use needles and syringes, early attention to skin and soft-tissue infection is crucial. In some inner city areas of the US, soft-tissue infection among injection drug users is the commonest non-psychiatric reason for admission to hospital.26 Risk factors for these infections include subcutaneous or intramuscular injection and the use of heroin/ cocaine (‘speedball’) mixtures.27 Active programs using a multidisciplinary approach to soft-tissue infections have been established in some areas,28 and are clearly required to prevent this catastrophic disease.

References


