RENAL INVOLVEMENT IN A SYNDROME OF VASCULITIS COMPLICATING HBsAg NEGATIVE CIRRHOSIS OF THE LIVER

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Summary

Six HBsAg negative patients with cirrhosis of the liver (CL) presented with recurrent bouts of palpable purpura in the legs due to small vessel leucocytoclastic vasculitis. In addition, all patients had renal failure, proteinuria and microhaematuria.

Renal biopsy disclosed either diffuse proliferative (3 cases) or focal necrotising glomerulonephritis with crescents (2 cases). One patient had IgM-IgG mixed cryoglobulinaemia (type II).

Four patients died of complications of their CL. Hepatocellular carcinoma was found in 1 case. In the patient without renal biopsy renal function improved following steroids and cyclophosphamide. The pathogenesis of this syndrome of cutaneous vasculitis with severe glomerular involvement in CL is unknown but could be immune-complex mediated.

Introduction

Hypersensitivity vasculitis is characterised pathologically by inflammation of small vessels and includes a heterogeneous group of clinical disorders. In recent years we have seen 6 HBsAg negative patients with cirrhosis of the liver who developed a syndrome of cutaneous vasculitis accompanied by severe renal involvement. This report describes the features of the syndrome.

Methods

The patients are five males and one female, aged 50 to 74 years. All patients were HBsAg negative and had histologically documented cirrhosis of the liver, of either alcoholic (4/6) or cryptogenic (2/6) origin.

In addition to the features of liver disease, the clinical presentation of the syndrome was similar in all cases and consisted of the appearance of recurrent bouts of palpable purpura in the lower extremities closely associated in time...
with the development of renal failure, proteinuria and microhaematuria. To further investigate these abnormalities five patients underwent skin biopsy and renal biopsies were also performed in five.

Most patients had advanced liver disease. Their serum albumin ranged from 16 to 32g/L (mean 24.8 ± 5.5g/L, ± = SD) and their serum bilirubin from 0.4 to 7.2mg/dl (mean 2.5 ± 2.6). Initially, only two patients (cases 2 and 3) had moderately prolonged prothrombin times with respect to controls (3 and 5 seconds respectively). Platelet counts were greater than 110,000/mm³ in every instance and averaged 181,000 platelets/mm³.

Results

All cases but patient Number 1 had skin biopsies of purpuric lesions and they uniformly showed small vessel leucocytoclastic vasculitis with subepidermal haemorrhage (Figure 1). No drug or offending antigen could be identified in any case.

Figure 1. Skin biopsy showing inflammatory perivascular infiltrate, thrombosis of dermal vessels and subepidermal haemorrhage (H&E x 100 – reduced for publication)

Coincident in time with the cutaneous vasculitis, the patients also developed significant renal failure associated with proteinuria and microscopic haematuria
(Table 1). Two patients (cases 3 and 4) required dialysis. Cases 2 and 3 had transient episodes of arthritis and otherwise vasculitic involvement of other organs was lacking.

**TABLE I. Summary of the main features of the syndrome**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Sex</th>
<th>Skin biopsy</th>
<th>Peak serum creatinine (mg/dl)</th>
<th>Proteinuria (g/24hr)</th>
<th>Microscopic Haematuria</th>
<th>Renal biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>NP</td>
<td>8.5</td>
<td>3.2</td>
<td>Yes</td>
<td>Diffuse proliferative GN</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Vasculitis</td>
<td>2.8</td>
<td>0.8</td>
<td>Yes</td>
<td>Diffuse proliferative GN</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>M</td>
<td>Vasculitis</td>
<td>9.4</td>
<td>1.5</td>
<td>Yes</td>
<td>Focal necrotising GN with 60% crescents</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>Vasculitis</td>
<td>9.6</td>
<td>2.4</td>
<td>Yes</td>
<td>Focal necrotising GN with 75% crescents</td>
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<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>Vasculitis</td>
<td>2.7</td>
<td>3.4</td>
<td>Yes</td>
<td>Diffuse proliferative GN</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>M</td>
<td>Vasculitis</td>
<td>8.8</td>
<td>1.2</td>
<td>Yes</td>
<td>NP</td>
</tr>
</tbody>
</table>

M = Male, F = Female, NP = Not performed, GN = Glomerulonephritis

![Image](image.png)

*Figure 2. Renal biopsy: glomerulus showing focal necrotising glomerulonephritis and extracapillary proliferation (Masson's trichrome x 1000 - reduced for publication)*
Renal biopsy results were as follows: case 1 had a diffuse endocapillary proliferative glomerulonephritis with mesangial IgA and C3 deposits; case 2 had a mild diffuse proliferative glomerulonephritis with negative immunofluorescence, and cases 3 and 4 both had a severe focal necrotising glomerulitis (Figure 2) with extracapillary proliferation in 60 per cent and 75 per cent of glomeruli respectively. Immunofluorescence in cases 3 and 4 showed only fibrinogen within the crescents. Finally, patient Number 5 had endocapillary diffuse proliferative glomerulonephritis with granular capillary C3 deposits and type II mixed essential cryoglobulinaemia (monoclonal IgM-Kappa against polyclonal IgG). No inflammatory lesions of the renal arteries or arterioles were seen in any case.

Cryoglobulins were negative in all patients but case 5, and antinuclear antibodies were absent in all cases. Serum C3 was low in patients 1, 2, 4 and 5, normal in case 6 and not performed in case 3. Alpha 1 fetoprotein was raised in patient 2, later found to have hepatocellular carcinoma, and normal in the remaining cases. Unfortunately, serum IgA and circulating immune complexes were not measured in a meaningful number of patients.

In patient 6 no renal biopsy was performed, but he was treated with steroids and cyclophosphamide and his serum creatinine came down within two months of initiating treatment. After a follow-up of three years he is now off therapy, without skin lesions and with a serum creatinine of 2.1mg/dl.

Four patients (cases 1 to 4) died during the acute phase of the disease. Causes of death included sepsis, gastrointestinal bleeding and hepatocellular failure in various combinations. In addition, patient 2 was found to have hepatocellular carcinoma at autopsy. Of the patients who died only case 3 had been treated with steroids, cyclophosphamide and a short course of plasmapheresis.

Patient 5 was not treated and is now clinically stable with a serum creatinine of 2.2mg/dl after six months of follow-up.

Discussion

The present work identifies a syndrome of cutaneous vasculitis with glomerular involvement developing in HBsAg negative patients with cirrhosis of the liver. Both the types of glomerular disease encountered, diffuse proliferative and focal necrotising glomerulonephritis with crescents are consistent with vasculitic inflammation of the glomerular capillaries [1]. To our knowledge this report is the first to describe serious renal disease in this syndrome. However, Grau Junyent et al have recently described a predominantly cutaneous vasculitis in nine cirrhotic patients, eight of whom had their visceral organs spared [2]. Hypersensitivity vasculitis has been reported to occur in other forms of liver disease, such as primary biliary cirrhosis [3] acute viral hepatitis, chronic active hepatitis [4] and alpha 1 antitrypsin deficiency with liver disease [5].

The development of an immunologically mediated disease like vasculitis within the framework of liver cirrhosis is not particularly surprising since antinuclear antibodies, rheumatoid factor, Raynaud's phenomenon, necrotising pulmonary vasculitis and other clinical signs of systemic disease have been noted in post-necrotic cirrhosis of the liver [6].
Apart from the patient with cryoglobulinaemia, no other aetiological agent for vasculitis could be identified. The relation of cryoglobulinaemia with liver disease is well known [7].

It is generally believed that hypersensitivity vasculitis represents an immunological response to antigenic material which leads to antibody formation and immune complex deposition in the vessel wall [8]. The nature of the antigenic material in this group of patients is unclear, but we could speculate firstly, the patients with cirrhosis of non alcoholic origin might be suffering from chronic undetected viraemia, perhaps due to the non A non B hepatitis virus. Secondly, impaired clearance by the diseased liver of absorbed intestinal antigens could be an alternative explanation. Finally, release of tumoral antigens [9] may provide the antigenic stimulus in those cases with superimposed hepatocellular carcinoma, such as our patient Number 2.

References

2 Grau Junyent JM, Urbano Marquez A, Rozman C et al. Med Clin (Barc). In press
3 Gilliam JN, Smiley JD. Ann Allergy 1976; 37: 328
5 Bandrup F, Ostergaard PA. Arch Dermatol 1978; 114: 921
9 ibid. Pages 116–122

Open Discussion

SIMOES (LISBON) A very interesting paper. Did you exclude the action of drugs in these patients? Some of these histological reactions, vasculitis in the skin and lesions in the kidney, I assume could be produced by hypersensitivity?

MONTOLIU As I said before in the three months immediately preceding admission, these patients were not receiving any drugs and specifically were not taking diuretics. We were also unable to identify any specific infection or antigenic stimuli responsible for the development of vasculitis.

DAL CANTON (Naples) Did you carry out immunofluorescence studies in your renal biopsies? I enquire about that because we have recently observed a quite similar case and we have found diffuse deposits of IgA.

MONTOLIU Yes, all renal biopsies were studied by immunofluorescence. Of the patients with diffuse proliferative glomerulonephritis, one had mesangial IgA deposits, another one negative immunofluorescence and the patient with cryoglobulinaemia had isolated capillary C3 deposits. The two patients with focal necrotising glomerulonephritis had negative immunofluorescence except for fibrinogen in the necrotic areas and within the crescent. I might add that in our
experience IgA deposition in glomerular disease associated with cirrhosis of the liver is not as common as generally believed.

VERROUST (Chairman) Perhaps I could ask you if you have any information on the serum IgA of these patients?

MONTOLIU As I said before serum IgA levels were measured in few patients, exactly three. They were raised in two patients, one of them with glomerular IgA deposits. This was a retrospective study and we could not obtain more data.

VERROUST Can you exclude also, apart from the one with mixed cryoglobulinaemia, that other patients did not have monoclonal bands in their serum?

MONTOLIU All I can say is that cryoglobulins were negative in all patients but one and that the admission serum electrophoresis did not show a monoclonal component in any patient.