Case Report

Henoch–Schönlein purpura, cryofibrinogenaemia, and peripheral gangrene

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Introduction

Henoch–Schönlein purpura (HSP) is a systemic vasculitis syndrome involving skin, joints, gastrointestinal tract, and kidneys. Vascular IgA-dominant immune complexes lead to small-vessel leukocytoclastic inflammation, usually taking a benign self-limited course [1]. HSP is regarded as a hypersensitivity vasculitis and has been associated with inciting agents such as upper respiratory tract infection, foods, and drugs.

Compared to children the course in adults is often more severe and renal involvement is more common (25–50%) [2,3]. End-stage renal disease is seen in 5–15% [4]. As to striking morphological similarities to IgA nephropathy, some authors regard the two conditions as phenotypic variations of the same disease [5].

Cryofibrinogen is a plasma complex of fibrin, fibrinogen, fibronectin, and other plasma proteins characterized by reversible precipitation in cold. It is found primarily or in association with an underlying disorder such as neoplasm, acute infection, collagen vascular, or thrombembolic disease [6]. Cryofibrinogenaemia may be asymptomatic but sometimes leads to small-vessel obstruction followed by necrosis affecting mainly skin, lungs, and myocardium. Therapeutic measures include plasma pheresis, fibrinolysis, and immunosuppression. More recently, good results have been reported with stanozolol [7].

We present the case of a young polytoxicomaniac with severe courses of cryofibrinogenaemia and HSP with renal involvement, and discuss therapeutic and prognostic consequences.

Case

A 29-year-old patient sought medical advice in March 1998 for painful and swollen fingers. A week before hospital admission he had noticed progressive rash on the extremities, arthralgia of hips and shoulders and blue patches of skin on the dorsal fingers. He had a 10-year history of heroin addiction and was currently on methadone substitution. In addition he frequently consumed cocaine, marihuana, benzodiazepines, and about 20 cigarettes per day. The medical history was remarkable for acute endocarditis in 1996, chronic otitis media, and chronic hepatitis B and C.

On physical examination he had symmetric palpable purpura, predominantly on the dorsal areas of the extremities, mild oedema of hands and fingers, and necrotizing skin on the dorsal fingers and toes (Figure 1). Blood pressure was 220/110 mmHg with good peripheral pulses, body temperature was 37.4°C.

Laboratory investigation showed a microcytotic anaemia (haemoglobin 10.5 g/dl, mean corpuscular volume 71.3 fl) with leukocytosis (16.3 × 10⁹/l) and

Fig. 1. Initial presentation: palpable purpura on the lower arms, diffuse oedema and blue areas of necrotic skin with haemorrhagic blisters on the dorsal aspect of the fingers.
mild thrombocytosis (458 x 10^9/l) (Table 1). Serum creatinine was elevated (132 μmol/l) as were C-reactive protein (CRP 34 mg/l), creatine kinase (416 U/l), and uric acid (540 μmol/l). There were no laboratory signs of impaired function of liver or pancreas. Serum IgG (19.3 g/l) and IgA (4.9 g/l) were increased.

No ANCA, ANA, anti-staphylococcal, or cryoglobulins could be detected, Anti-streptolysin L and anti-DNase B were slightly elevated (171 IU/ml, 600 U/ml), complement C3 was reduced (85.9 mg/dl).

Serological studies confirmed the diagnosis of chronic hepatitis B (positive HBV-DNA, HBs antigen 10 000 IU/ml) and C (HCV-RNA 11 900 copies/ml). HIV antibodies and Treponema pallidum haemagglutination test (TPHA) were negative.

Plasma fibrinogen, partial thromboplastin time (PTT), and prothrombin time (PT) were normal. There was evidence for antiphospholipid antibodies with elevated anticardiolipin antibodies (71.6 U/l) and two positive screening tests (kaolin clotting time, diluted viper venom test). Cryofibrinogen was detected as precipitant in edetic acid (EDTA) plasma refrigerated at 4°C after warm centrifugation as described by Cwazka et al. [8]. Urinalysis revealed microscopic haematuria and proteinuria of 1.2 g/g creatinine. The patient’s stool screened positive for blood.

Purpura, arthralgia and gastrointestinal bleeding were consistent with HSP. The diagnosis was confirmed by a skin biopsy from the lower leg showing leukocytoclastic vasculitis and IgA deposition.

Despite several negative cultures of blood, urine, and sputum, the patient appeared to have a bacterial infection. White-cell count and CRP rose to 28.3 x 10^9/l and 74 g/l respectively within the first 3 days of hospitalization. The site of infection appeared to be the skin and we started antibiotic therapy with penicillin, later changed to vancomycin plus ciprofloxacin and metronidazole.

The patient’s high blood pressure was hard to control and we were concerned about his renal function. Drinking 3 litres per day he had a daily output of about 1.8 l. Despite increasing oedema of the extremities he was unwilling to reduce his input.

Serum creatinine rose to 260 μmol/l within 5 days in the first week of hospital treatment and urinary protein excretion reached 5.7 g/g creatinine (mainly albumin and IgG). According to sonography both kidneys were normal sized (120 mm) with prominent medullary pyramids. Because of the rapid progressive clinical course we performed a kidney biopsy. One-half of the specimen was fixed in buffered formalin (4%) for routine histology on paraflin sections (H & E, PAS and Goldner staining). Cryostat sections cut from the other half were stained immunohistochemically using FITC-labelled polyclonal antibodies directed against human IgA, IgG, IgM, complement C3 and C4 and fibrinogen (rabbit-anti human antibodies, Dako, Hamburg, Germany).

Histological examination revealed mesangio-proliferative crescentic glomerulonephritis with crescents in two of four glomeruli (Figure 2). Large amounts of IgA were detected immunohistochemically within the mesangial matrix of the affected glomeruli, leading to the diagnosis of an IgA nephropathy. Additionally, deposits of fibrinogen were found focally within the crescents and in areas of capillary wall necrosis.

Considering the patient’s overall condition we refrained from therapy with cytotoxic agents and administered methylprednisolone 500 mg i.v. with a rapid reduction to 0.75 mg/kg day. Within 1 week, serum creatinine dropped to the initial level and urinary output slowly increased.

The purpura was regressive, the ischaemia of the fingers and resulting pain, however, worsened despite anticoagulation (dalteparin 5000 IU s.c. b.i.d.). The skin of the fingers and toes detached in blisters and progressive gangrene developed. A local infection with Stenotrophomonas maltophilia was noted.

Knowing of the patient’s cryofibrinogen we suspected plugging fibrin thrombi and started stanozolol 5 mg b.i.d. About 2 weeks later, the perfusion of the vital areas of fingers and toes looked improved and the patient reported striking pain-relief. However, due to necrosis, amputation of a total of eight fingers and three toes at the proximal interphalangeal joint was necessary. The wounds healed well and without delay.

Table 1. Abnormal laboratory values on admission

<table>
<thead>
<tr>
<th>SI unit</th>
<th>Alternative unit</th>
</tr>
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<tbody>
<tr>
<td>Haemoglobin</td>
<td>6.5 mmol/l</td>
</tr>
<tr>
<td>MCV</td>
<td>71.3 fl</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>16.3 x 10^9/l</td>
</tr>
<tr>
<td>Platelet count</td>
<td>458 x 10^9/l</td>
</tr>
<tr>
<td>Creatinine</td>
<td>132 μmol/l</td>
</tr>
<tr>
<td>CRP</td>
<td>34 mg/l</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>6.9 μkat/l</td>
</tr>
<tr>
<td>Uric acid</td>
<td>540 μmol/l</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>19.3 g/l</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>4.89 g/l</td>
</tr>
<tr>
<td>Complement C3</td>
<td>0.86 g/l</td>
</tr>
</tbody>
</table>
Vessels from the removed tissue showed vascular fibrin thrombi and no signs of vasculitis.

The patient was discharged after 7 weeks with stable levels of creatinine (165 μmol/l) and CRP (10 mg/l) on prednisolone 7.5 mg/day and stanozolol 5 mg b.i.d. On follow-up after 2 months his renal function was unchanged and he was negative for cold precipitating proteins.

Discussion

The patient presented with HSP meeting the criteria of the American College of Rheumatology [1]. Taking intravenous drugs he suffered from recurrent bacteraemia and a chronic hepatitis B, disorders that have been associated with this disease. A connection with cocaine snorting has also been reported and entering of antigens through mucosal barriers is thought to be important in the pathogenesis of HSP [9].

In our case, therapeutic options were limited due to underlying infections and low patient compliance. Despite rapid deterioration of the kidney function we restricted therapy to steroids, antibiotics, and antihypertensives. When purpura, gastrointestinal bleeding, and arthralgia slowly regressed and the renal function improved, progressive ischaemia of fingers and toes was suggestive of a separate disorder. As cryofibrinogen was detected in our patient’s plasma, we assumed the formation of fibrin thrombi with consecutive plugging of small vessels.

In 1977 Cwazka et al. [8] suspected that in some patients with HSP cryofibrinogen and not immune-complex-mediated tissue injury may be primarily responsible for major disease manifestations. In their patient exacerbation of HSP correlated closely with the presence of cryofibrinogenemia.

There are numerous reports on ischaemic necrosis in HSP. The lesions are often confined to the gastrointestinal tract, but other locations can be affected. Examining 57 adults with HSP and skin manifestations Tancrede-Bohin et al. [3] found necrosis and blistering in 60%. In another report necrosis necessitated the amputation of two fingers of a child with HSP [2]. However, screening for cryofibrinogen was not performed and it is questionable whether the ischaemia was solely due to vasculitis.

In our case, more evidence for cryofibrinogen-induced vascular occlusion came from the histological work-up of amputated tissue and from the response to stanozolol. This androgen is believed to have fibrinolytic activity and is usually administered for several months without major side-effects. As in our patient, disappearance of plasma cryofibrinogen accompanied by pain-relief and healing of skin ulcers has been reported [7]. Perhaps earlier treatment could have saved his fingers and toes.

Ischaemic necrosis can also arise from cocaine ingestion causing vascular spasms. This mainly affects larger arteries on upper arms and legs not involved in our patient. Lupus anticoagulants may lead to similar symptoms, although venous thrombosis is often predominant and aPTT and PT are usually affected. Furthermore, the local infection with stenotrophomonas may have led to an exacerbation.

The severity of our patient’s renal involvement was remarkable. Nagy et al. [10] detected cryofibrinogen in 37 of 50 patients with IgA nephropathy. On follow-up, none of the 19 patients with persisting cryofibrinogenemia achieved clinical remission, 13 even had a progression of renal disease. Moreover, the authors revealed a close relationship between plasma levels of cryofibrinogen and tubulointerstitial fibrin/fibrinogen deposits which have been implicated in the progression of fibrosis. Predictive factors for the deterioration of kidney function in HSP have been identified, e.g. hypertension, proteinuria >1.5 g/day, and crescent formation [3,4]. Unfortunately, the comorbidity with cryofibrinogenemia has not been examined in detail yet.

Our screening for cryofibrinogen is basic and does not allow precise qualitative or quantitative statements. There is, however, evidence for sufficient sensitivity and specificity [8,10].

Aetiology and pathogenesis of HSP remain to be resolved in detail. Synthesis of deficient IgA as well as antigen mimicry by bacterial (streptococcus, mycoplasma) and viral (HBs, HIV) antigens have been suggested. Cryofibrinogenemia may also be initiated by infection. Perhaps, a genetic predisposition provided, there is a common trigger for both disorders or an interaction between cryofibrinogen and complexed IgA.

In summary, our case indicates that cryofibrinogenemia might worsen the course of HSP and require specific treatment. Therefore patients with renal involvement or gangrene in HSP should always be tested for this disorder.

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References


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