Cholesterol embolism and acute interstitial nephritis: two adverse effects of streptokinase thrombolytic therapy in the same patient

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Introduction

Thrombolytic therapy with streptokinase is an effective treatment for acute myocardial infarction, but several cases of cholesterol crystal embolization syndrome after streptokinase therapy have been described since 1979 [1]. The pathogenetic mechanism presumably involves dissolution of cholesterol-containing thrombi resulting in the release of cholesterol crystals into the arterial circulation. Furthermore, after streptokinase treatment hypersensitivity reactions have been described by several authors; haematuria and proteinuria are sometimes present, but generally renal injury is mild or moderate. Only one report has described a patient who developed leukocytoclastic vasculitis and severe but reversible renal failure due to tubulointerstitial nephritis [2].

The present report is the first to describe both disseminated cholesterol microembolization with renal failure and tubulointerstitial nephritis in the same patient after thrombolytic therapy.

Case report

A 61-year-old male was admitted to an Internal Medicine division of our hospital because of two episodes of angina pectoris in the previous 48 h and fever. He had a long-standing history of hypertension and ischaemic cardiopathy and was in therapy with nifedipine and nitroglycerin. On admission the serum creatinine was 106 µmol/l, and protein electrophoresis was normal. Chest X-ray was normal. Erythromycin was started, and 3 days later the fever resolved.

Eleven days after admission the patient complained of chest pain, and his EGG revealed acute inferior myocardial infarction. The patient, transferred to a cardiac intensive care unit, received streptokinase 1.5 million units and heparin 25 000 units intravenously in 12 h and aspirin 100 mg orally. Renal function was normal with a serum creatinine of 97 µmol/l. Four days later the patient was transferred to a regular ward. In the meantime serum creatinine rose to 212 µmol/l (creatinine clearance 30 ml/min), and a livedo reticularis rash and cyanotic lesions appeared on both legs. Renal function continued to deteriorate during the next 3 weeks, creatinine levels reaching 760 µmol/l. Antineutrophilic cytoplasmic antibodies (ANCA) were present (1 : 80) with a perinuclear staining pattern, and smooth muscle antibodies were also positive (1 : 320); complement levels (C3, C4) were normal. Serum IgG was increased (22.90 g/l) with two peaks, lambda and kappa. IgM, IgA, and IgE were normal. The leukocyte count reached 13.5 × 10⁹/l with 0.5% eosinophils; fibrin degradation products (FDP) were positive. A 24-h urine collection contained 2 g protein; the urine sediment was normal. Chest X-ray showed reticulonodular densities in the right base and left hylar region. Bronchoscopy and bone-marrow biopsy gave no significant results. Abdominal CT demonstrated normal kidney size and parenchymal thickness for age and gender.

The patient became anuric and was transferred to our Division. Haemodialysis was started with progressive resolution of the chest radiographic manifestations. A renal biopsy (Figure 2) showed predominantly mononuclear cells with occasional granulocytes and an eosinophilic interstitial infiltration with sparing of glomeruli and arteries. The infiltration was focal with occasional features of tubulitis. Other changes in tubules included attenuation or loss of brush borders in proximal tubules, focal oligocellular and/or nuclear enlargement. Focal tubular atrophy and distal tubule dilatation were also seen. The glomeruli showed...
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Fig. 1. Skin biopsy: biconvex needle-shaped cholesterol clefts within the lumen of a dermal arteriole (H&E × 50).

Fig. 2. First renal biopsy: mononuclear interstitial infiltrate (H&E × 120).

Fig. 3. Second renal biopsy: multiple cholesterol clefts in capillary tufts (H&E × 120).

Fig. 4. First renal biopsy: cholesterol clefts in the lumen of a middle-size artery (semithin section of Epon-embedded tissue × 480).

Discussion

Thrombolytic therapy with streptokinase, urokinase, or tissue plasminogen activator may provoke cholesterol embolization by dissolving cholesterol-containing thrombi which release cholesterol crystals into the peripheral circulation. The onset of the cholesterol embolization syndrome (CES) ranges from 7 h to 28 days following thrombolytic therapy [3] although the signs of embolization may develop gradually. Skin, skeletal muscle, kidneys, spleen, intestine, and pancreas are the most frequently affected organs, the most common symptoms being livedo reticularis, digital ischaemia progressing to necrosis, hypertension, and non-oliguric renal failure.

Hypersensitivity reactions have also been described as a complication of intravenous streptokinase administration. In several patients with serum sickness after streptokinase, leukocytoclastic vasculitis was observed subsequently tapered. Currently, 6 months after the start of the symptoms, renal function is stable (serum creatinine 265 μmol/l), but the patient presents distal necrosis of the left fourth toe.

After the renal biopsy methylprednisolone (100 mg on alternate days for 3 doses) and subsequently prednisone (80 mg/day) were started. Renal function improved rapidly, and haemodialysis was discontinued after three sessions. The skin lesions persisted, and a skin biopsy (Figure 1) showed biconvex needle-shaped cholesterol clefts within the lumina of two arterioles in the reticular dermis. The clefts were surrounded by multinucleated foreign body giant cells and fibrin tissue occluding the arterioles.

Thirty days later the creatinine level had stabilized around 309 μmol/l with a creatinine clearance of 30 ml/min. Immunoglobulin levels were within the normal range, and ANCA titres were negative. FDP were absent. A second renal biopsy revealed regression of the tubulointerstitial nephritis. In some glomeruli intracapillary cholesterol microcrystals were observed (Figure 3). A review of the first kidney biopsy demonstrated cholesterol clefts within the vascular lumina of preglomerular and interlobular arterioles (Figure 4).

Steroid therapy was continued for 3 months and subsequently tapered. Currently, 6 months after the start of the symptoms, renal function is stable (serum creatinine 265 μmol/l), but the patient presents distal necrosis of the left fourth toe.
[4], but generally renal function was only moderately impaired. Only recently a case was reported in which a patient developed symptoms compatible with a type III hypersensitivity reaction, the clinical presentation being dominated by severe renal failure [2]. Histological examination of the kidney revealed marked tubulointerstitial inflammation. This patient was treated with high doses of steroids, and renal function returned to normal within 3 months.

Our patient initially presented the classical manifestations of CES, i.e. livedo reticularis, digital cyanosis, and non-oliguric renal failure; however, although CES may mimic other multisystem diseases such as polyarteritis nodosa [5], the signs of an immunological derangement were much more pronounced when compared with the characteristic features of CES (elevated erythrocyte sedimentation rate and eosinophilia). In fact, hypergammaglobulinaemia, antibodies to smooth muscle and p-ANCA were found. This serological picture resembles that described during other drug-induced nephropathies (propylthiouracil, penicillamine), but in those cases ANCA was associated with pauci-immune necrotizing glomerulonephritis or vasculitis [6,7]. In our patient glomeruli and arterioles were normal while the interstitium was infiltrated by mononuclear cells, granulocytes, and eosinophils with some aspects of tubulitis and fibrosis. It should also be emphasized that the presence of p-ANCA in low titre without specificity for either antiproteinase 3 or antmyeloperoxidase would lack diagnostic significance.

The association between acute interstitial nephritis and antineutrophil cytoplasmic antibodies has already been reported in a patient taking the proton pump inhibitor omeprazole [8]. Also in this case neither vasculitis nor necrotizing glomerulonephritis were present, and the significance of ANCA positivity was not clear. In any case, following methylprednisolone therapy, a prompt improvement of renal function and subsequent normalization of immunological indices were obtained. Other studies have suggested the beneficial effect of steroids in drug-induced acute interstitial nephritis [2,8], but the influence of this therapy on CES prognosis is unknown. CES is generally considered to be fatal, specifically when it is associated with renal failure, with a mortality rate ranging from 72 to 90% [9]. Necrotizing glomerulonephritis with crescent formation has been reported as a consequence of CES [10], suggesting some immunological activation, and thus we cannot exclude the possibility that in our patient steroid therapy may have exerted some beneficial effect also with respect to CES.

In conclusion, this is the first reported case of CES combined with acute interstitial nephritis after thrombolytic therapy with streptokinase. The possibility of this association should be borne in mind when acute renal failure occurs after thrombolytic therapy and a thorough search for cholesterol crystals should be performed also when an interstitial nephritis picture predominates. From another point of view when a diagnosis of CES is suggested after thrombolytic therapy by clinical signs and skin biopsy, a kidney biopsy should be considered to exclude the contemporary presence of an acute interstitial nephritis susceptible to steroid treatment.

References