CASE REPORT

Interferon α sensitisation induced fatal renal insufficiency in a patient with chronic myeloid leukaemia: case report and review of literature

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Renal dysfunction as a sequel to extended interferon alfa (IFN α) treatment in chronic myeloid leukaemia (CML) has been reported previously in six patients. An additional patient is presented with Philadelphia chromosome positive (Ph+) CML and nephrotic syndrome in whom initial renal insufficiency developed after only one month of low dose IFN α therapy. The renal biopsy showed a focal segmental mononuclear cell infiltration, basal membrane thickening, and deposits of immunoglobulins (IgG; IgAGM IC3). In spite of discontinuation of IFN α , renal function deteriorated and the patient died six months later. This case represents an instance of fatal kidney insufficiency as an untoward effect of sensitisation to the IFN α , confirmed by modified Coombs assay.

The nephrotic syndrome has been reported in association with some lymphoproliferative disorders such as Hodgkin's lymphoma and chronic lymphocytic leukaemia.¹ Interferon alfa (IFN α) is recommended as an effective treatment for chronic myeloid leukaemia (CML). It induces a haematological response in 40–80% of patients with CML. IFN α is associated with significant toxicity, including renal damage which consists of mild non-nephritic proteinuria in 15% to 20% of treated patients. Several cases of acute renal failure and nephritic syndrome in patients with CML have also been reported.² The association of nephrotic syndrome and CML has been previously reported as a complication of long term IFN α therapy.^{3–5} We present a patient with CML in whom a fatal nephritic syndrome developed after a short period of IFN α treatment.

CASE REPORT

A 56-year-old man had been diagnosed as having Philadelphia chromosome positive (Ph+) CML by the middle of 2003, with the appearance of malaise and sweating. The initial full blood counts showed leucocytosis which led to repeated antibiotic treatment. There was no clinical response and the patient was directed to our institution under suspicion of myeloproliferative disorder. In June 2003, two benign colonic polyps were surgically removed. Physical examination showed splenomegaly (+16 cm), but other findings were within the normal range. Laboratory analyses showed a haemoglobin of 155 g/l, a platelet count of 194×10^9 /l g/l, and a leucocyte count of 28×10^9 /l with 16% myelocytes, 4% metamyelocytes, 7% bands, 4% eosinophils, 55% segmented neutrophils, 7% monocytes, and 7% lymphocytes. Renal function test showed a urea of 4.7 mmol/l, creatinine 0.127 μ mol/l, and uric acid 322 mmol/l. The creatinine clearance was normal, calculated using the Cockcroft and Gant method [$Cr_{clear} = (140 - \text{age}) \times \text{weight in}$

kg/72 $\times$ serum creatinine]. Urine analysis was normal. Proteinuria was not found. Total plasma proteins were 78 g/l, with albumin 42 g/l.

On cytogenetic analysis he was found to be 46XY, t⁹22(q34;q11). Bone marrow aspirate was hypercellular, congruent with the chronic phase of CML, with 3% eosinophils, <1% basophils, and 1% blasts. The bone marrow trephine confirmed a histopathological pattern characteristic of CML. The patient was treated with 3 MIU of IFN α (Roche, Basel, Switzerland) subcutaneously daily and cytosine-arabinoside 20 mg subcutaneously for 10 days. After normalisation of the leucocyte count, the dose of IFN α was reduced to 3 MIU on alternate days. One month after the start of IFN α , facial oedema developed, with delayed and scarce voiding. He received diuretics and human albumin at the Regional Medical Centre. His diuresis was reinstated to approximately 1200 ml/daily. Because of developing signs of nephrotic syndrome he was treated in the nephrology department. By the beginning of March 2004 he had only periorbital oedema, the remaining physical findings being normal.

His laboratory data at that time were: Hb 143 g/l, platelets 235×10^9 /l, leucocytes 15.6×10^9 /l, urea 34.7 mmol/l, creatinine 321 μ mol/l, total proteins 33 g/l, albumin 10 g/l, fibrinogen 5.6 g/l, C reactive protein 34.5 mg/l, cholesterol 9.28 mmol/l, triglycerides 4.16 mmol/l, calcium 1.69 mmol/l, phosphorus 1.34 mmol/l, serum iron 6.0 μ mol/l, total iron binding capacity 15 μ mol/l, lactate dehydrogenase 784 IU/l, C3 0.84, and C4 0.30. There was a massive proteinuria (16.9 g/24 h) with large numbers of fresh, pale erythrocytes and the presence of coarsely granular cylinders in the urinary sediment. Electrophoresis of the plasma proteins showed albumin 40.4%, α 1-globulin 6.0%, α 2-globulin 22.0%, β -globulin 21.6%, and γ -globulin 10.0%. On immunoelectrophoresis, IgG concentration was 3.68 g/l, IgA 1.2 g/l, and IgM 0.9 g/l. Thrombin time was 16 s and activated partial thromboplastin time, 42 s. Tests for hepatitis B surface antigen, hepatitis C virus, and HIV were negative. Modified Coombs assay showed that the patient's serum induced haemolysis in the presence of IFN α (Roferon®, Roche) compared with healthy control serum. Additional analyses for Landsteiner antibodies excluded the presence of non-specific haemolysis. Chest x ray showed a right pleural exudate. On abdominal ultrasound, the liver and spleen had normal diameters. The right kidney size was 13 $\times$ 5 cm, with a pronounced parenchymal echo of 17 mm diameter. The left kidney size was of 14 $\times$ 5.9 cm with an 18 mm diameter parenchyma. Renal biopsy showed neutrophils and mononuclear infiltrates in the glomeruli (fig 1, panels A and B). The mesangial matrix was pronounced and the glomerular basal membrane often perimesangially thickened

Abbreviations: CML, chronic myeloid leukaemia; IFN, interferon

Figure 1 (A) Hypercellular glomeruli with moderate infiltration of polymorphonuclear cells, narrowed volume of capillaries, and local circumscriptive glomerular capsular adhesion (haematoxylin and eosin (H&E) stain, original magnification $\times 400$). (B) Enlarged glomeruli with tubules of different lumen size and necrotic desquamated epithelial cells in the lumen (H&E stain, original magnification $\times 400$). (C) Marked expansion of mesenchymal matrix with interposition of glomerular basal membrane (silver impregnation by Jones, original magnification $\times 400$). (D) Hypercellular glomeruli with dilated tubules and atrophic epithelium, giving a microcyst-like appearance, with protein in the lumen (original magnification $\times 200$).

(fig 1C). A solitary infiltrate of mononuclear cells and incipient fibrosis was noticed. Mild vasculitis was also present. Immunofluorescence showed IgG; IgAGM IC3 as a slight granular phosphorescence in the mesangium and in some of the glomerular capillaries (fig 1D). Nephrotic syndrome with initial renal insufficiency was diagnosed as a probable consequence of IFN α therapy. Despite treatment with pulsed doses of methylprednisolone, diuretics, and albumin, the renal disease deteriorated and the patient died two months later from severe renal failure.

DISCUSSION

We present a patient with CML in whom the treatment with IFN α resulted in severe renal insufficiency and subsequent death. That IFN α may induce renal damage has been described previously in six patients treated for hepatitis C.⁶ These patients developed nephropathy following IFN α treatment; four had membranoproliferative glomerulonephritis, one had membranous nephropathy, and the last one had focal segmental glomerulosclerosis, all as a result of deposited immune complexes. While renal damage may be less severe in some patients, it can result in an end stage renal dysfunction in others, particularly those treated with high dose IFN α for hepatitis C.⁷ A patient with both pre-existing hepatitis C and CML treated with IFN α developed nephrotic syndrome,⁸ which may have been precipitated by either the hepatitis C or the IFN α therapy. This patient's renal function worsened rather than improved with IFN α treatment, arguing in favour of IFN α treatment rather than the underlying CML as a precipitating factor.

Patients with malignant diseases treated with IFN α as a potentially curative or adjuvant therapy who developed secondary renal toxicity have been described.^{9–10} Three patients with CML developed minimal change nephropathy^{11–12} and rapidly progressing glomerulonephritis.¹³ To

examine the impact of IFN α on the pathological findings in the kidney, we investigated the induction of haemolysis by patient's serum and IFN α in vitro, in a modified Coombs test. Serum from a healthy person was used as a control. We obtained haemolysis of healthy red blood cells with the patient's serum plus IFN α . Control serum and IFN α did not induce haemolysis. This was indirect proof of sensitisation induced by IFN α , which may have caused deposition of antibodies and immunoglobulins in the glomerular basal membranes and consequent nephrotic syndrome. To exclude non-specific haemolysis we carried out a Landsteiner antibody test, which was negative. The dose of IFN α seems to be of no importance for the toxic changes observed in the kidneys, which are related to hypersensitivity to this agent. The resistance to steroid therapy in our patient is particularly baffling as a favourable response to steroids has been described in most patients treated for IFN α induced glomerulosclerosis.^{14–15} For either steroid dependent or steroid resistant patients, other agents such as ciclosporine A, azathioprine, cyclophosphamide, and mycophenolate mophetil have been used with varying degrees of success.^{16–17}

The first line treatment of CML is currently imatinib mesylate (Glivec, Gleevec®) rather than interferon. In patients with CML on IFN α therapy, nephritic changes represent a rare untoward effect, but one which demands early recognition and treatment.^{18–19} So far six instances of this therapeutic complication have been reported in CML.^{2–6, 9, 18–20} Nephrotic syndrome is extremely rarely associated with CML.^{7, 18–21, 22}

We believe that our patient is the first reported case of acutely developing renal insufficiency in a patient with CML treated with low dose IFN α for a brief period of time, and which proved resistant to treatment and fatal for the patient. The possibility of an idiosyncratic type of sensitivity reaction was corroborated by a positive indirect Coombs test in the presence of IFN α .

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