Thrombotic Microangiopathy Associated with α-Interferon Therapy for Chronic Myeolid Leukemia

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ABSTRACT

The association of interferon therapy with hemolytic uremic syndrome in patients with chronic myeloid leukemia (CML) has beeen reported infrequently. The pathogenesis of the renal lesion in such cases remains unclear. We report the case of a patient with chronic myeloid leukemia who developed nephrotic syndrome and renal failure while being treated with hydroxyurea and interferon- α. Renal biopsy showed features of chronic thrombotic microangiopathy. The discontinuation of interferon- α, and a prompt institution of plasmapheresis and steroids resulted in improvement of the nephrotic syndrome and renal function. These findings suggest that long-term interferon- α therapy can induce thrombotic microangiopathy and hemolytic uremic syndrome in patients with chronic myeloid leukemia.

Key words: chronic myeloid leukemia, interferon, nephrotic syndrome, renal failure, thrombotic microangiopathy.

INTRODUCTION

Therapy for chronic myeloid leukemia (CML) constists of cytoreduction (typically with hydroxyurea) and interferon-α: only a minority undergo bone marrow transplantation. Only, a few reports of renal thrombotic microangiopathy has been described in patients with CML. In almost all cases these patients were receiving interferon-α (1-6). The interferons are a family of glicoproteins with antiviral, antitumor and immunomodulatory activities. Interferon-α is used particularly in the treatment of chronic myeloid leukemia, and other haematological malignanices as well as in hepatitis C. Various adverse effects associated with interferon-α have been reported previously, including cardiac and renal dysfunction (7). In patients with chronic hepatitis C, interferon-α therapy is rarely associated with renal side effects (8). In patients receiving high doses of interferon-α for malignancy, a wide range of renal side effects have been reported, including proteinuria, acute interstital nephrititis and membranoproliferative glomerulonepfritis (9-12). In some cases, the discontinuation of treatment led to the recovery of renal function, but irreversible renal failure may occur (4-6). Many authors have observed various renal toxicities with interferon-α therapy, but the incidence of renal complications remains unknown and the causal link between interferon-α and thrombotic microangiopathy is still underappreciated.
We described a case of haemolytic uremic syndrome that occured in a patient with CML receiving interferon-α and hypotheses regarding the potential mechanisms underlying this association are discussed.

CASE REPORT

A 45-year-old man was admitted in July 2001 because of increased leukocytes and plateletes. Previous medical history was unremarkable. Physical examination showed hepatosplenomegalia. The peripheral blood leukocytes count was $43x10^9$/L, Hb 111 g/L, platelets $1209x10^9$, serum creatinine was 88μmol/L, urinalysis was normal. The bone marrow biopsy was diagnostic of CML and the presence of th Philadelphia chromosome.Treatment included hydroxyurea (50mg/kg/day) and interferon-α (Roferon) $9x10^6$ IU

subcutaneously/day and allopurinol 100mg/day. One year later his peripheral leukocytes count had decreased to $18.1x10^9$, and platelets to $457x10^9$. Hepatosplenomegalia had regressed. In August the patient was referred to Nephrology department for edema and a recently discovered impairment of renal function (serum creatinine 450μmol/L).
On admission he was pale, had high blood pressure (190/120 mmHg), bibasal lung crackeles, hepatosplenomegaly, and marked lower limb edema. Urinary dipstick showed protein ++, trace red cells, microscopy showed a few granular casts only. Ultrasound showed normal sized kidnyes with echogenic cortex. Severe anemia with a hemoglobin level of 49 g/dl was present, hematocrit was 0.33, mean corpuscular volume 0,93fl and reticulocyte count was 1,2%. He had the following results: WBC $4.9x10^9$ platelets $128x10^9$, total bilirubin 17 μmol/L (reference range 3.4-20.5 μmol/L μmol/L) lactate dehidrogenase (LDH) 2845 U/L (reference range 170-430 U/L), Coombs test-indirect was positive, normal liver enzymes, creatinine 450 μmol/L (reference range 64-120 μmol/L). The following tests were negative or normal: antinuclear antibody (ANA), hepatitis B, surface antigen (HbsAg) hepatitis B core antibody (HbcAb) human immunodeficiency virus antibody (HIV), protrombin time (PT) partial thromboplastin time (PTT), serum fibrinogen, fibrin split products and serum haptoglobin. Serum C3 were depressed at 0,57 (reference range, 0.9-1.8g/L) serum C4 was 0.12g/L (reference range 0.1-to 4.0 g/L). A peripheral blood smear revealed moderate schistocytosis. Serum protein electrophoresis was normal, proteinuria was 16.2 g/day (normal value <0.2g/day). Bone marrow biopsy revealead a CML. Fundoscopy detected a stage II retinopathy

Percutaneous renal biopsy disclosed typical changes of thrombotic microangiopathy: by light microscopy all glomeruli (20 glomeruli) were globally enlarged. The remainder showed increased mesangial matrix cells and pronounced thickening of peripheral capilary loops (Figure 1). Diffuse subendothelial swellings of the glomerular capillary walls coexisted with focal thrombi of the capillay lumen and of the arterioles whose intima was extensively swollen.
The latter finding was associated with marked «double contour» formation (duplication of the basement membrane) and with interposition of cell elements within the thickened capillary walls. Many of the glomerular capillaries were occluded by the thickened walls and swollen endothelial cells. Significant interstitial fibrosis was also present. The smaller arteries and arterioles showed marked fibrocellular proliferation with myxoid change and focal hyline deposition, often resulting in significant narrowing of vessel lumen. Immunofluorescence microscopy showed large granular deposits of immunoglobulin M (IgM) and fibrin. Electron

microscopy showed extensive capillary wall changes with degenerative change of the endothelium and loss of fenestrae; there was widening of the subendothelium space by electron-lucent material and by cellular projections and formation of the new basement membrane under displaced endothelial cells (Figure 2). The light and electron microscopy findings were highly suggestive of thrombotic microangiopathy.
A diagnosis of HUS was made and the patient was started on daily plasmapheresis (7 days). The patient was also given corticosteroids, aspirin and antihypertensivs. Renal function improved and stabilized with serum creatinine of 200μmol/l. His Hb incresed to 100g/L. Interferon-α was withdrown and oral hydroxyurea was continued for menagement of the CML. The patient was seen for his outpatient control one and two months latter. His renal function was improving (creatinine 170μmol/l) and CML in stable phase.

DISCUSSION

The mechanisms by which interferon-α therapy may initiate HUS are unknwn, but several mechanisms are possible. Intereferon- α has been shown to increase leukocytes adherence to vascular endothelium, and this may initiate endothelial cell damage and subsequent release of large multimers of the von Willebrand factor, causing endothelial cell swelling, patelet aggregation and intraluminal microthrombi formation. Unusually large multimers of von Willebrand factor are probalby cleaved by metalloprotease-ADAMTS 13 directly on the surface of endothelial cells. Some of the patients with hemolytic-uremic syndrome have a deficiency or defect of complement factor H (13). It will be useful to measure antibodies of ADMTS 13 and antibodies of H factor, wich could better illustrate the mechanism of HUS in our patient, but we could not measure it. Some autors suggested that activated leukocytes and/or their products, such as TNF, IFN, IL-1 and free radicals can participate in tissue injury and endothelial cell damage with the resulting deleterius effects (14). Indeed, in an experimental model of HUS a central role for leukocytes or leukocyte products had been suggested and in vivo neutralisation of TNF or IFN with a specific antiserum protected mice from an HUS-like reaction (15). Therefore, IFN-induced free radicals production by activated phagocytes may result in the pathogenesis of HUS. Another report showed incresed IFN production in two patients with HUS associated with adenovirus infection and a possible nephrotoxic role from elevated IFN levels was speculated (16).

Possible nephrotoxic effects of IFN have been previously reported. Exogenous interferons could cause similar effects.

The possible role of interferon-α inducing this toxic effect is increasingly suspected as more case reports are described. In our patient, the clinical presentation and laboratory findings are consistent with the diagnosis of thrombotic mycroangiopathy and renal dysfunction and the presence of schistocytes in the blood smear were detected**.** Platelets in our patient were slightly decreased (platelets $128x10^{9)}$.

Because renal failure was predominant feature at presentation of our patient this disorder was considered to be the haemolytic-uremic syndrome. The clinical distinction between thrombotic thrombocytopenic purpura and haemolytic-uremic syndrome is not always clear (14). Treatment with interferon-α was probably the only factor involved in the development of HUS. No other known causes could be suspected in our patient.

The subsidence of HUS after the cessation of interferon therapy strongly supports the view that interferon caused HUS in our patient.

HUS has already been reported during tretment with a number of cytotoxic agents (mitomycin, methyl-carmustin, bleomycin, daunomycin, cisplatin, and deoxycoformycin) but has never to date been described with hydroxyurea, suggesting a role for interferon- α.

The association of interferon-α therapy with hemolytic uremic syndrome and thrombotic thrombocytopenic purpura has been reported infequently. Only sporadic cases of HUS have been reported in association with interferon tretment in CML (1-6).

HUS is a rare side effect that occurs in only small subgroup of patients given interferon- α for CML. There is a possible genetical predisposition in these patients. Several studies have demonstrated genetic predisposition in non-shigatoxin-associated hemolytic uremic syndrome, involving regulatory proteins of the complement alternative pathway: factor H and membrane co-factor protein (CD46) (17).

The associaton of malignant disorders and cancer chemotherapeutic agents with hemolytic uremic syndrome (HUS) and thrombotic microangiopathy (TTP) has been previously described (18, 19). Most cases occur in patients with adenocarcinomas, gastric adenocarcinoma being the most common, but also with small lung carcinoma, squamous carcinoma and Hodgkin disease. CML has been uncommonly associated with microangiopatic disorders (20, 21, 22). In HUS, renal endothelial cell injury, with endothelial cell swelling and the resulting narrrowing of the glomerular capillary lumen, is belived to be the initiating event. HUS is commonly preceded by bloody diarrhea caused by infectious orgnanisms, such as Shigella dysenteriae or E. coli. The toxins secreted by these organisms, are capable of

binding the predominanat membrane globotrisyl ceramide (Gb3). Gb3 is expressed on the membrane of renal endothelial cells and other endothelial cells. Other agents can up-regulate Gb3 expression on the endothelial cells and therefore potentiate the effects of the toxins. These include the cytokines interleukin (IL-1) or alfa or beta tumor necrosis factor (TNF)-alfa or beta (18).

The pathogenesis of HUS in Shigella infection is similar to HUS caused with interferon- α. The damage of glomerular endothelial cells by Shiga toxin 1 and 2 is potentiated by the monocytes and neutrophils that invade glomeruli in response to the secreted interleukin-8 and the production of monocytes chemoattractant protein 1 by renal cells. Interleukin-8-activated neutrophils release oxygen-derived free radicals, hydrogen peroxide, elastase and other protease that potentiate the damage to the kidneys. In fact, neutrophilia increases the likelihood of irreversible renal injury. The death and desquamation of endothelial cells in the kidneys may also promote, by means of glycoproteins Ibα, the adhesion of platelets to unusually large multimers of von Willibrand factor in the subendothelium. Subsequent binding of fibrinogen to activated platelet glycoprotein IIb/IIIa complexes induces the aggregation of platelets under conditions of high flow as occur in the glomerular microcirculation

In summary, HUS is a rare side effect of interferon-α therapy in patients with CML. The mechanisms contributing to its pathogenesis are poorly understood but interferon-α can through modulatory effects on endothelial receptors make these cells more susceptible to the effects of bacteria toxins. They may also mediate free radical production by activating phagocytic cells and as a result cause endothelial cell injury. The release of platelet-aggregating agents from the damaged endothelial cells is probably the event resulting in intraluminal thrombus formation and organ damage, as seen in HUS. This rare but definite complication of interferon-α therapy should be recognised early when clinical and laboratory findings are suggestive so interferon-α therapy can be discontinuated immediately and appropriate therapeutic measures can be initiated.

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Figure 1. Haemolytic-uremic syndrome. A large glomerulus with inconscpicous mesangium because of mesangiolysis. Capillaries are dilated, some filled with thrombi and some have splitet, double contoured basement membranes. P.A.S. method. 400x

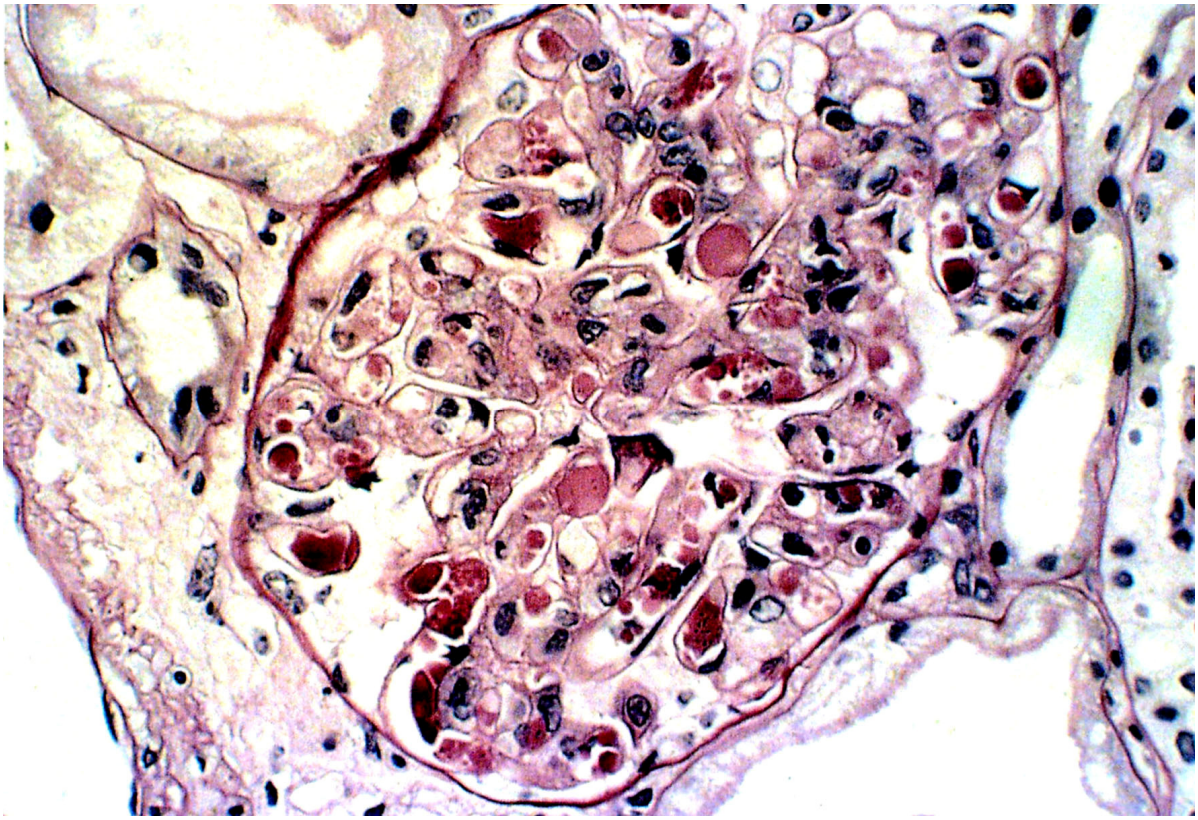
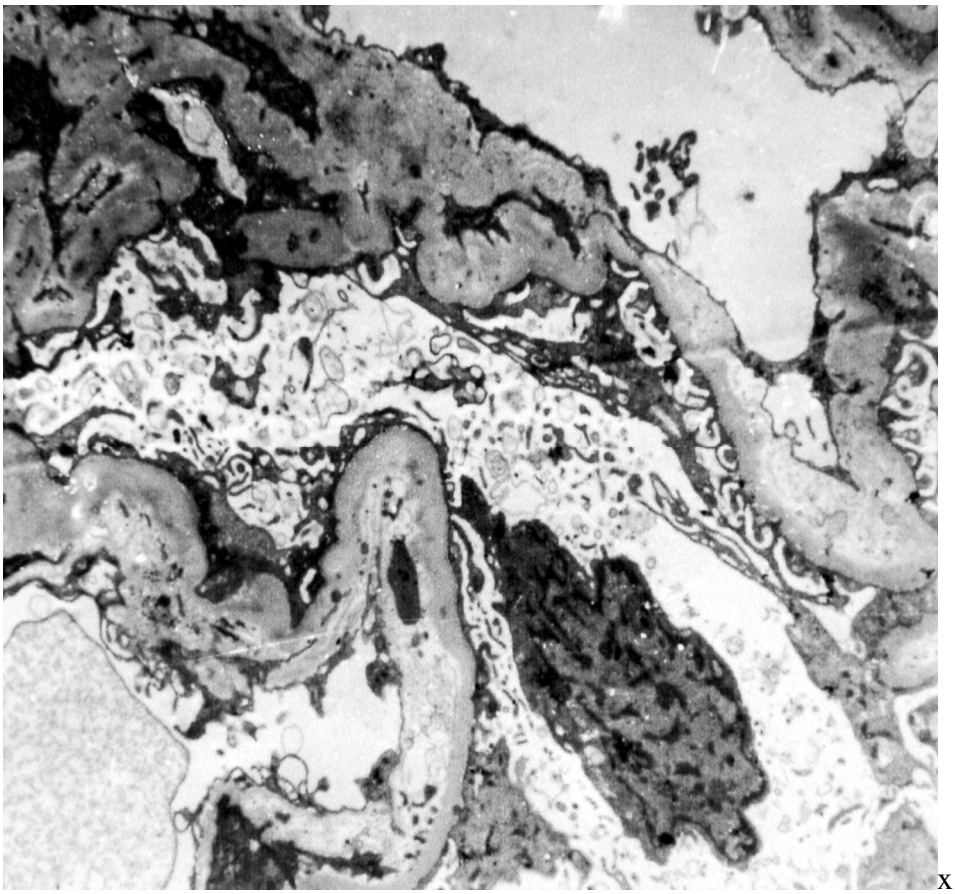


Figure 2. An ultrastructural detail of a glomerulus. One can see the detachment of endothelial cells from GBM with formation of the clear space filled with some fluffy material. Uranyl-acetate and lead cytrate. 24500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