Acute cholestasis during long-term treatment with fluvastatin in a nephrotic patient

Sir,
Pharmacologic therapy of nephrotic hyperlipidaemia is needed in some patients because prolonged hyperlipidaemia is a risk factor for accelerated vascular disease and for progression of renal damage. Hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors have become the treatment of choice for nephrotic hyperlipidaemia. However, the long-term efficacy and safety in these patients are unknown. Adverse effects such as liver dysfunction and myopathy may occur.

Case. A 71-year-old man with creatinine 98 μmol/l and high LDL-cholesterol (5.6 mmol/l) secondary to a nephrotic syndrome caused by membranous nephropathy started treatment with fluvastatin (20 mg/day) in September 1996. He received prednisone 20 mg once daily. Six months later, hepatic function was normal, and because of persisting high LDL-cholesterol levels (5.9 mmol/l) the dose was increased to 40 mg/day. In May 1997, anicteric hepatitis with ALT of 210 IU/l (normal <40 IU/l), GGT of 1818 IU/l (normal <40 IU/l) and alkaline phosphatase of 472 IU/l (normal <270 IU/l) was detected. Abdominal ultrasonography was normal. Viral serology was negative. Fifteen days after withdrawal of fluvastatin the patient’s biochemical pattern returned to normal. Fluvastatin was reintroduced with good response. In August 1995 she was admitted for 3 days after withdrawal of fluvastatin the patient's biochemical treated with prednisone, chlorambucil and radiation therapy. Abdominal ultrasonography was normal. Viral serology was negative. Fifteen days after withdrawal of fluvastatin the patient’s biochemical pattern returned to normal. Fluvastatin was reintroduced with good response.

Comment. The acute cholestatic hepatitis initially observed appears to be a dose-dependent effect, even though the new rise of GGT at lower doses, not reproduced with simvastatin, suggests idiosyncratic reaction. We are not aware of other reports of hepatotoxicity during treatment with fluvastatin. To our knowledge the adverse hepatic effects have consisted in a slight rise of transaminases, which in no case was over three times the upper normal limit [1].

Fluvastatin is the only entirely synthetic agent in this class, with high hydrophility and liver extraction during the absorption phase [2]. The hepatotoxicity profile of fluvastatin is such that liver-enzyme testing, required with all HMG coenzyme A reductase inhibitors, is less frequently needed with this agent than with the other inhibitors [3]. Although this agent has been proven safe in clinical trials [4,5], like any other drug, it also carries the risk of adverse effects. A recent study by Marcelino and Feingold [6] suggested that less than half of the patients on a statin had an annual liver panel to monitor for hepatotoxicity. Monitoring of hepatic function in patients on a statin is advisable even when, during the first months, no rise of hepatic enzymes has been detected. Monitoring is particularly indicated when the dose has been increased.

Microscopic polyangiitis associated with non-Hodgkin’s lymphoma

Sir,
Some cases of vasculitis associated with malignant lymphoproliferative processes have been described. They tend to be leukocytoclastic vasculitis with cutaneous but no visceral involvement. We observed a case of microscopic polyangiitis [1] with renal, pulmonary and splenic but not cutaneous involvement in the context of non-Hodgkin’s lymphoma.

Case. The patient was a 40-year-old female who was well until December 1990 when monocyctoid cell lymphoma was diagnosed with involvement of spleen and tonsils and with generalized retroperitoneal and peripheral lymphadenopathy. She was treated with CHOP and remission of the disease was achieved. In February 1992 the disease relapsed and was treated with prednisone, chlorambucil and radiation therapy with good response. In August 1995 she was admitted for evaluation because of another relapse, now with renal insufficiency and microcytic anaemia. Physical examination revealed: BP: 130/70 mmHg, bilateral and multiple supraclavicular, axillary and inguinal lymph nodes (approximately 2 x 2 cm) and palpable spleen. Blood analysis: ESR, 139 mm; creat., 1.7 mg/dl; Hb, 6.4 g/dl; MCV, 72 fl; cholesterol, 171 mg/dl; LDH, 262 IU/l; urine, 100 red blood cells/field; protein excretion, 3693 mg/24 h. A bone biopsy showed paratrabecular and non-paratrabecular focal infiltration due to small cell lymphoma and presence of the three haematopoietic series. The patient was discharged on oral corticoids 30 mg/48 h. Three months later, during follow-up, renal function continued to deteriorate with creat: 2.6 mg/dl and anaemia. Treatment with 2-deoxycophormicin 6 mg/week was started. Three days after the second dose of 2-deoxycophormicin, the patient was admitted presenting with progressive dyspnea and orthopnea without haemoptysis, decreased diuresis and lid oedema. Blood pressure was TA: 160/90 mmHg. The patient was conscious and oriented. She had orthopnea, pale skin and mucous membranes, congested jugular veins, but no malleolar edema. Bilateral basal crackling was noted. Blood analysis: leukocytoysis 15 100/mm³ (91% GR); Hb, 7.2 g/dl; MCV, 74 fl; platelets, 213 000/mm³; PT, 100%; creat., 11.7 mg/dl; urea, 280 mg/dl; Na⁺, 129 mmol/l; K⁺, 5.5 mmol/l; GGT, 105 U/l. Blood gas analysis (FiO₂: 0.21): pH, 7.37; pCO₂, 30 mmHg; pO₂, 55 mmHg; bicarbonate, 18.2 mmol/l; O₂ sat., 87%. Chest X-ray showed a bilateral interstitial pattern with Kerley B lines. Abdominal sonography: discrete splenomeg-
The patient had one dialysis session via femoral catheter. On the second day she developed psychomotor agitation with disorientation, and died of accidental bleeding through the femoral catheter. At post-mortem nodular infiltration of bone marrow by lymphoma was noted as well as fibrosis of lymph nodes with sinusoidal dilation. In addition diffuse proliferative extracapillary glomerulonephritis and necrotizing small vessel vasculitis were found (Figure 1). There was also extrarenal vasculitic involvement concerning the spleen and the lungs (septal capillaritis and alveolar haemorrhage).

Discussion. Vasculitis associated with neoplasias is infrequent and has been described particularly in patients with lymphoproliferative and myeloproliferative diseases, predominantly in leukaemias, less frequently in patients with solid tumours [2]. The most common type of vasculitis is cutaneous leukocytoclastic angiitis, and rarely, systemic vasculitis, develops, mainly in association with hairy cell leukaemia. The types of vasculitis include polyarteritis [3] and Schönlein–Henoch purpura [4]. In patients with lymphoma, Schönlein–Henoch purpura [5] and cryoglobulinemia [6] have been described, but cutaneous angiitis is the most frequent form. Glomerular disease is rare in lymphoma [7]. Membranous, mesangio-proliferative glomerulonephritis, minimal changes, focal glomerulosclerosis and more rarely, focal necrotizing glomerulosclerosis can be observed. The latter, may be associated with cutaneous angiitis [8]. In our case, the patient presented with small vessel vasculitis involving lung and spleen as well as diffuse proliferative extracapillary glomerulonephritis with vasculitis lesions. There was no evidence of renal infiltration by lymphoma at post-mortem. At the time the patient presented with vasculitis, she was treated with 2-deoxyxophormicin. A case of small vessel systemic vasculitis with fatal evolution was described in a patient on 2-deoxyxophormicin, but this may have been only a predisposing factor [9]. There was neither peripheral eosinophilia nor fever suggesting hypersensitivity to the medication. The lesions described correspond to microscopic polyangiitis with pulmonary and glomerular capillaritis in the context of non-Hodgkin’s lymphoma resistant to therapy. This is the first case in which such an extensive vasculitic lesion associated with lymphoma has been demonstrated by histology.

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Hantavirus nephropathy in a child

Sir,

A new case of haemorrhagic fever with renal syndrome (HFRS), is described in an 11-year-old boy from Northeastern Greece, caused by hantavirus infection. This is the first case of the HFRS syndrome in a child detected in Greece.

Haemorrhagic fever with renal syndrome is an acute febrile nephropathy, caused by closely related zoonotic viruses of the genus Hantavirus, family Bunyaviridae [1]. Over the last 15 years, approximately 200 cases of HFRS have been serologically confirmed in Greece [2]. In 1987, a Hantaan-like virus (Porora) was isolated from the urine of a severely ill HFRS patient [3].

Case. An 11-year-old boy, resident of Komotini village, located close to the Greek–Bulgarian borders (Northeastern Greece), was initially admitted to the country hospital and then, on 25 July 1997, was transferred to the 4th Pediatric Department of AHEPA (American Hellenic Educational Progressive Association) Hospital in Thessaloniki, Greece. The patient presented with 7-day illness including fever (39 °C), abdominal pain, back pain and tenderness of the renal area, nausea, vomiting, loose stools, thrombocytopenia (91 000/mm³), anaemia and azotaemia.

On admission, his physical examination was unremarkable, except he was feverish. His laboratory findings were as follows: white blood cell count of 7100 cells/mm³ (54% neutrophiles, 37% lymphocytes and 9% monocytes); haemotocrit of 32%; haemoglobin of 10.9 g/dl and platelet count of 110 000/mm³. The sedimentation erythrocytes rate (SER) was 70 mm and C-reactive protein (CRP) 1.15 g/l (normal value <0.50). Creatinine and urine levels progressively increased to 23 mg/l and 930 mg/l, respectively. No elevation of liver enzymes were observed. The urine output was 250 ml/24 h with proteinuria and microscopic haematuria. The glomerulare filtration rate (GFR) was 47.3 ml/min/1.73 m². No petechiae was observed, nor did internal haemorrhage occur.

On day 12, haematocrit was 36%, hemoglobin 12 g/dl and platelet count 364 000/mm³. Serum creatinine and urea levels were 6.5 mg/l and 325 mg/l respectively, with a urine output 2500 ml/24 h and normal GFR. The patient was discharged after 15 days of hospitalization.

Sera taken on day 9 of illness from the patient were tested at 2-fold dilutions (initial dilution 1:16) by immunofluorescence assay (IFA) with fluorescein-labelled goat anti-human immunoglobulin (GIBCO Diagnostics, Madison, WI) on spot slides containing Vero E6 cells (ATCC CRL 1586), infected with strain 76–118 of prototype Hantaan virus. Titers were recorded as the greatest dilution of serum at which characteristic cytoplasmic immunofluorescence was detected. The IgG and IgM Hantaan virus IFA antibody titers were 1:16 384 and 1:512 respectively. Screening for antibodies to other virus-related HFRS was negative as well as for antibodies to leptospirosis. Management included careful monitoring of electrolytes and fluid intake and output with correction, especially during the oliguric and diuretic phases. Plasma expanders were used as well.

Four months later (November 1997), he remained well and in good condition, with his laboratory findings in normal ranges. Six months later our patient was without any symptoms. The IgG Hantaan virus antibody titer was 1:2048. No IgM antibody titer was quantified. His renal function was normal.

Comment. HFRS is endemic in the Balkan Peninsula and epidemic outbreaks and isolated cases have been reported during the last decades. From a retrospective serological and genetic study of the distribution of hantaviruses in North Greece, it was found that the virus which was responsible for all the PCR positive cases was Dobrava virus, which is endemic in the Balkans [2,4]. The principal rodent host is Apodemus flavicollis, the yellow-necked mouse.

HFRS in the Balkan region ranges from the severe form usually attributable to Hantaan-like infection to mild cases more typical of Puumala-like infection. The mean age of HFRS patients in Greece is 36 years, ranging from 21- to 71-years-old. The clinical course of the HFRS can be divided into five phases (febrile, hypotensive, oliguric, diuretic, convalescent). Some of the patients do not develop all the above phases of the syndrome. Asymptomatic cases of HFRS also seem to be quite common [5].

The exact location at which the boy acquired the hanta-virus infection is not known, but the residency may play a role since the village of Komotini country is thought to be an endemic area. Antoniadis et al. performed a prospective study to determine hantavirus-associated HFRS in this Greek region. HFRS appears more frequently from May to October (our case was admitted in July). Besides, the patient’s parents are farmers and used to take him into the fields or into the woods, where he was possibly infected by inhaling aerosolized rodent excreta or by ingesting material contaminated with rodent excreta. Our patient had never left Greece, suggesting acquisition of an indigenous virus strain. HFRS should be considered in the differential diagnosis of cases with unexplained high fever, even when the patient is very young. Hantavirus infection should be considered even in paediatric patients who have acute renal failure.

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