The Interesting Case

A dialysis patient with unexplained peripheral neuropathy

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Case presentation

A 68-year-old female started chronic ambulatory peritoneal dialysis (CAPD) in November 1992 for treatment of end-stage renal failure secondary to bilateral staghorn calculi and chronic interstitial nephropathy. Between 1981 and 1985 she underwent four operations attempting to remove the kidney stones, and received several blood transfusions. When starting CAPD she was found to have antibodies against the hepatitis C virus (HCV) and a two- to threefold elevation in serum aminotransferases. A transjugular liver biopsy performed in September 1993 disclosed only minimal nonspecific changes and no clinical or laboratory signs or symptoms of hepatocellular failure ever developed. The patient denied alcohol or drug abuse and there was no history of toxic exposure. In May 1994, the patient complained of symptoms consistent with the 'restless leg' syndrome, followed by increasing paraesthesias and weakness in both legs, severe enough to make her unable to walk, and she became bedridden. She was admitted for investigation. Physical examination was remarkable for diminution to pinprick and temperature sensation below both knees, bilaterally hyporeflexic ankle and knee jerks, muscle atrophy, and marked motor weakness in both legs. There was a positive Tinel's sign over the right superficial peroneal and sural nerves. Pretibial skin ulcers, 3 cm in diameter and with sharp borders were noted in both legs. No purpuric lesions were seen.

Investigations, treatment, and outcome

Electrodiagnostic studies (nerve conduction/EMG examination) on admission demonstrated a bilateral and symmetric sensory motor polyneuropathy predominantly axonal (values obtained were on the average 20% of normal). Underdialysis was ruled out as the cause of the peripheral neuropathy because weekly Kt/V was 2 and creatinine clearance was 80 litres/week, indicating good dialysis efficacy. Other laboratory values on admission were: haemoglobin 9.8 g/dl, WBC count 9000/mm³, platelets 392 000/mm³, prothrombin time 105% of control, serum calcium 2.55 mmol/l, serum phosphorus 1.48 mmol/l, serum alkaline phosphatase 263 IU/l, serum iPTH 22 pmol/l (normal 1.2–5.6), serum aluminium 4 μg/l, and serum gamma glutamyltranspeptidase 63 IU/l. Other serum enzymes (ASAT, ALAT, LDH), serum glucose, bilirubin, cholesterol, triglycerides, total proteins, and serum protein electrophoresis were normal. A determination for cryoglobulins was positive, with an 8% cryocrit. Cryoglobulins were subsequently identified by immunofixation as mixed polyclonal (type III), composed of IgM, IgG, and IgA. Hepatitis C virus RNA was demonstrated by nested PCR 5' in the cryoprecipitate, that had been previously purified by centrifugation and serial washings with saline. Results were confirmed by the Amplicor PCR amplification kit (Roche Diagnostic Systems, Madrid, Spain). A biopsy was taken from the border of one of the skin ulcers. It showed intensely PAS-positive thrombi within the arteriolar lumen (Figure 1). Immunoperoxidase studies demonstrated the existence of kappa and lambda light chains in these thrombi, thus establishing their immunoglobulin origin related to cryoglobulinaemia. With a diagnosis of peripheral neuropathy secondary to HCV-induced cryoglobulinaemia, it was decided to start plasmapheresis and alpha interferon treatment. The patient underwent six sessions of plasmapheresis, exchanging 3 litres of plasma in each one and reposing with 5% albumin. Alfa interferon was administered subcutaneously, at a dose of 3 million U thrice weekly. No serious side-effects were observed.

One month later, determinations for serum cryoglobulins were negative, skin ulcers had healed, and the signs and symptoms of peripheral neuropathy had improved markedly, as had the results of nerve conduction velocities. She was discharged from the hospital walking by herself and interferon treatment continued for 6 months. Her clinical condition steadily improved and now she is stable and fully ambulatory on CAPD. Nerve conduction velocities remain improved, and HCV antibodies continue to be detectable in serum. Serum cryoglobulins, which had remained negative up
to 6 months after discontinuation of interferon treatment, have recently reappeared in serum at low titres and she has restarted interferon treatment.

Discussion

Overall, 17.7% of dialysis patients in Mediterranean countries carry HCV [1]. Liver disease is a major cause of morbidity among them, but until now extrahepatic disease related to this virus was thought to be rare. However, in the non-dialysis population, HCV infection can induce a long list of extrahepatic manifestations that Gumber and Chopra have recently reviewed [2] (Table 1). It is now well established that mixed cryoglobulinaemia is frequently due to HCV infection, and the cryoprecipitate has been shown to contain the virus RNA. [3]. Mixed cryoglobulinaemia is a cause of peripheral neuropathy similar if not identical in its characteristics to the one our patient had [4]. Vasculitis has been demonstrated by nerve biopsy in epineurial blood vessels in cases with cryoglobulinaemic polyneuropathy [5]. We believe that HCV-induced cryoglobulinaemia, demonstrated by the existence of RNA from the virus in the cryoprecipitate, caused severe and reversible peripheral neuropathy in our patient. This hypothesis is further supported by the absence of other factors (and in particular absence of underdialysis) potentially responsible for polyneuropathy, by the demonstration of PAS-positive intraluminal deposits containing immunoglobulin fragments in the skin ulcers, and by the simultaneous improvement of the signs and symptoms of peripheral neuropathy, including nerve conduction velocities, and the temporal disappearance of cryoglobulins from serum after treatment with plasmapheresis and interferon. Physicians taking care of dialysis patients should be aware of the possibility of HCV-induced cryoglobulinaemia and polyneuropathy, since it can cause significant morbidity, and be reversible with treatment.

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References


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