Clinical Reports

Portal hypertension secondary to azathioprine in myasthenia gravis

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Summary: A 52 year old man with myasthenia gravis and normal liver function was treated with neostigmine, prednisolone and azathioprine. Three years after starting azathioprine he developed clinical evidence of portal hypertension. A liver biopsy showed nodular regenerative hyperplasia (NRH).

The development of NRH following azathioprine treatment in a patient with myasthenia gravis strengthens the case for a causal role of azathioprine in producing in producing NRH and portal hypertension.

Introduction

Portal hypertension association with nodular regenerative hyperplasia of the liver (NRH) secondary to immunosuppressive therapy has been previously described, usually after renal transplantation.^{1,2} A patient with myasthenia gravis who recently developed NRH following treatment with azathioprine has recently been reported.³ We report a further case in a patient with myasthenia gravis who was treated with azathioprine.

Case report

A 52 year old man presented with diplopia, ptosis and dysphonia. A diagnosis of myasthenia gravis was made on the basis of a positive edrophonium test. Acetylcholine receptor antibodies were present. There was no past history of jaundice and he did not abuse alcohol. There were no signs of liver disease and the liver and spleen were impalpable. He was treated with neostigmine. He underwent thymectomy and 3 months later was started on prednisolone, which was tapered to a maintenance dose of 20 mg on alternate days. Due to continuing weakness he was started on azathioprine 150 mg daily, 6 months later. At the time of initiation of azathioprine the following investigations were carried out: haemoglobin 15.6 g/dl, MCV 94 fl,

white cell count $9.9 \times 10^9/l$, urea 5.5 mmol/l (normal range 3.0-6.5), total protein 66 g/l (60-80), albumin 44 g/l (30-50), bilirubin $15 \mu\text{mol/l}$ (5-17), aspartate transaminase (AST) 14 U/l (5-40), alkaline phosphatase (ALP) 75 U/l (35-130).

Over the next 2 years his myasthenia improved and he remained in good general health. His MCV rose to 115 fl and platelet count fell to $110 \times 10^9/l$. These changes were considered to be the result of azathioprine therapy.

Three years after starting azathioprine the spleen was found to be enlarged 4 cm in the mid clavicular line below the costal margin, on routine physical examination. He had no other symptoms or signs suggestive of liver disease. Investigations: haemoglobin 12.1 g/dl, white cell count $3.4 \times 10^9/l$, MCV 113 fl, platelets $103 \times 10^9/l$; urea 4.3 mmol/l, bilirubin $70 \mu\text{mol/l}$; AST 40 U/l; ALP 107 U/l; gamma glutamyl transferase (GGT) 125 U/l (10-48); amylase 85 U/l (0-220). Ultrasound: small liver, portal vein and splenic vein enlarged. Spleen grossly enlarged with several prominent vessels around the hilum. Liver biopsy (3 cylinders each 1 cm) showed nodular regenerative hyperplasia, characterized by small hyperplastic nodules with intervening atrophy but no substantial degree of fibrosis (see Figure 1).

Azathioprine was stopped and cyclophosphamide commenced but he developed haemorrhagic cystitis and cyclophosphamide had to be discontinued. Six months after discontinuation of azathioprine splenomegaly persists but his MCV has fallen to

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Accepted: 7 June 1988

Figure 1 Liver biopsy: (a) nodules not surrounded by fibrous tissue. Reticulin fibres are compressed. Gordon and Sweets' reticulin method $\times 80$. (b) Same field as in (a), haematoxylin and eosin stain $\times 80$.

94 fl and bilirubin to 21 $\mu\text{mol/l}$ although GGT remains elevated at 127 IU/l.

Discussion

The development of portal hypertension in this patient appears to be related to treatment with azathioprine. Biopsy confirmed that the increased portal venous pressure was associated with nodular regenerative hyperplasia.

Hepatic dysfunction is not uncommon in patients treated with azathioprine. This usually manifests as a reversible acute cholestatic hepatitis⁴ or occasionally as acute focal hepatocellular necrosis⁵ or veno-occlusive disease.⁶ Nodular regenerative hyperplasia leading to portal hypertension has previously been described in patients taking azathioprine^{1,2} but most of the patients described were on another immunosuppressive therapy as well. The largest

proportion of patients with this complication have had renal transplantation.¹ As renal disease and transplantation is associated with an increased incidence of vascular events, azathioprine, while suspected of being the cause of liver changes, could not be conclusively incriminated. Myasthenia gravis is not associated with recorded increased risk of occlusive vascular disease, nor are treatment with steroids and neostigmine. Azathioprine therefore is likely to be the sole agent responsible for the development of portal hypertension in this patient and strengthens the case for a causal role of azathioprine in producing these effects.

Acknowledgement

We wish to thank Professor P.J. Scheuer for his valuable help and guidance.

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