Case report

Thiabendazole-induced acute liver failure requiring transplantation and subsequent diagnosis of polyarteritis nodosa

M. Groh[1], P. Blanche[1], Y. Calmus[2], L. Guillevin[1]

[1]*Department of Internal Medicine, Hôpital Cochin, Referral Centre for Rare Autoimmune and Systemic Diseases, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, Paris;*
[2]*Department of Hepatology and Hepatic Transplantation, Hôpital St Antoine, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France.*

Matthieu Groh, MD
Philippe Blanche, MD
Yvon Calmus, MD, PhD
Loïc Guillevin, MD

Please address correspondence and reprint requests to:
Dr M. Groh,
Service de Médecine Interne,
Hôpital Cochin, 27,
rue du Faubourg Saint-Jacques,
75674 Paris, Cedex 14, France.
E-mail: matthieugroh@hotmail.com

Received on February 3, 2012; accepted in revised form on February 28, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S107-S109.

Key words: polyarteritis nodosa, liver transplantation, thiabendazole, eosinophilia

Competing interests: none declared.

ABSTRACT

Polyarteritis nodosa (PAN), a systemic necrotising vasculitis that affects medium- and small-sized arteries, has visceral involvement in 40–60% of the patients. According to the Five-Factor Score (FFS), it is associated with poor outcome. We describe a patient who underwent orthotopic liver transplantation (OLT) for severe ductopenia induced by thiabendazole that was empirically prescribed for chronic hypereosinophilia. Eleven years later, despite immunosuppressive treatment to prevent graft rejection, he developed mononeuritis multiplex; PAN was diagnosed. He also had severe recurrent ischaemic cholangitides because of post-OLT hepatic artery ligation to treat a postoperative severe haematemesis. His outcome was favourable after second OLT, under steroids, cyclophosphamide pulses and tacrolimus. In retrospect, his initial symptoms and hypereosinophilia were probably attributable to PAN.

Introduction

Polyarteritis nodosa (PAN) is a systemic necrotising vasculitis that affects medium- and small-sized arteries with visceral involvement occurring in 40–60% of the patients (1, 2), which is more frequent in hepatitis B virus (HBV)-related PAN. As demonstrated by the Five-Factor Score (FFS) (3, 4), some clinical symptoms are associated with a poor outcome. Liver involvement can be asymptomatic or characterised by elevated aminotransferases and sometimes by more severe manifestations, *e.g.* hepatic aneurysm rupture. To our knowledge, PAN post-orthotopic liver transplantation (OLT) has only been described once in the medical literature (5).

Case report

A 33-year-old man, born in Laos but living in France since childhood was hospitalised in our department in 2010. His medical history included chronic hypereosinophilia 11 years before this admission, associated with cutaneous nodules, labile pulmonary infiltrates, petechial purpura, a massive vena cava thrombosis and biologic signs of disseminated intravascular coagulation (DIVC). Antineutrophil cytoplasm antibodies (ANCA), anti-parasite serologies and tests for thrombophilia were negative. Neither parasites nor haematological malignancy were found. Vitamin B12, tryptase levels and lymphocyte phenotypes were normal. Bone-marrow aspiration and biopsy were also normal, except for homogeneous eosinophil-lineage excess. No karyotype anomaly was found. Polymerase chain-reaction FIP1L1-PDGFRα fusion transcript was absent. Thiabendazole, empirically prescribed for chronic hypereosinophilia, was incriminated for inducing acute liver failure (6) due to severe ductopenia (Fig. 1A). The patient's health improved after orthotopic liver transplantation (OLT), under immunosuppressive (corticosteroids and tacrolimus) and anticoagulant therapy. Six-weeks post-OLT he developed severe haematemesis. Gastric fibroscopy found a perforated 1cm ulcer of the duodenal bulb without active bleeding. During laparotomy, an abscess in the sub-hepatic region in contact with the duodenal bulb and active bleeding of hepatic artery were identified. The duodenal ulcer was sutured, the abscess drained, and the hepatic artery ligated. The patient's condition improved and he was discharged.

Several years later, he developed several successive episodes of cholangitides and hepatic abscesses. Again, his outcome was favourable with percutaneous biliary drainage and cholangioplasty.

Finally, he was referred to us and hos-

pitalised for left orchiepididymitis, abdominal pain, hypereosinophilia (4100 eosinophil granulocytes/mm^3), and recent paresthesias and palsy in both legs. He was still taking tacrolimus (1.5 mg bid.) immunosuppression. The electromyogram showed severe sensory–motor mononeuritis multiplex of the common fibular nerve in both legs and the right tibial nerve. ANCA serology was negative. Post-vaccination anti-HBV antibodies were present. Histologic examination of a neuromuscular biopsy found severe acute sensitive axonopathy suggestive of ischaemia. Abdominal angiography showed microaneurysms in the superior mesenteric artery, both renal arteries and complete occlusion of the ligated-native hepatic artery (Fig. 1B). His glomerular filtration rate and urinalysis sediment were normal, as was computed tomography of the sinuses. Non-HBV-related PAN was diagnosed. Steroids (pulse methylprednisolone 1 g for three days, followed by oral prednisone initially at 1 mg/kg/day) associated with pulse cyclophosphamide (600 mg/m^2 on days 1, 14 and 28, and 700 mg/m^2 on days 49, 70 and 91) were started.

Eleven years after the first OLT, 3 months after PAN diagnosis and after 6 cyclophosphamide pulses, the patient received a second OLT. Histologic examination of the first graft showed ancient thrombosis of the hepatic artery, bile ducts necrosis, recent left portal vein thrombosis, and a zone of ischaemic necrosis in the left liver (Fig. 1C). Anti-graft rejection and PAN maintenance therapy comprised steroids (gradual tapering of prednisone doses), prolonged-release tacrolimus (1.5 mg/day) and azathioprine (100 mg/day). Outcome was favourable: liver function test values normalised and PAN is in complete remission.

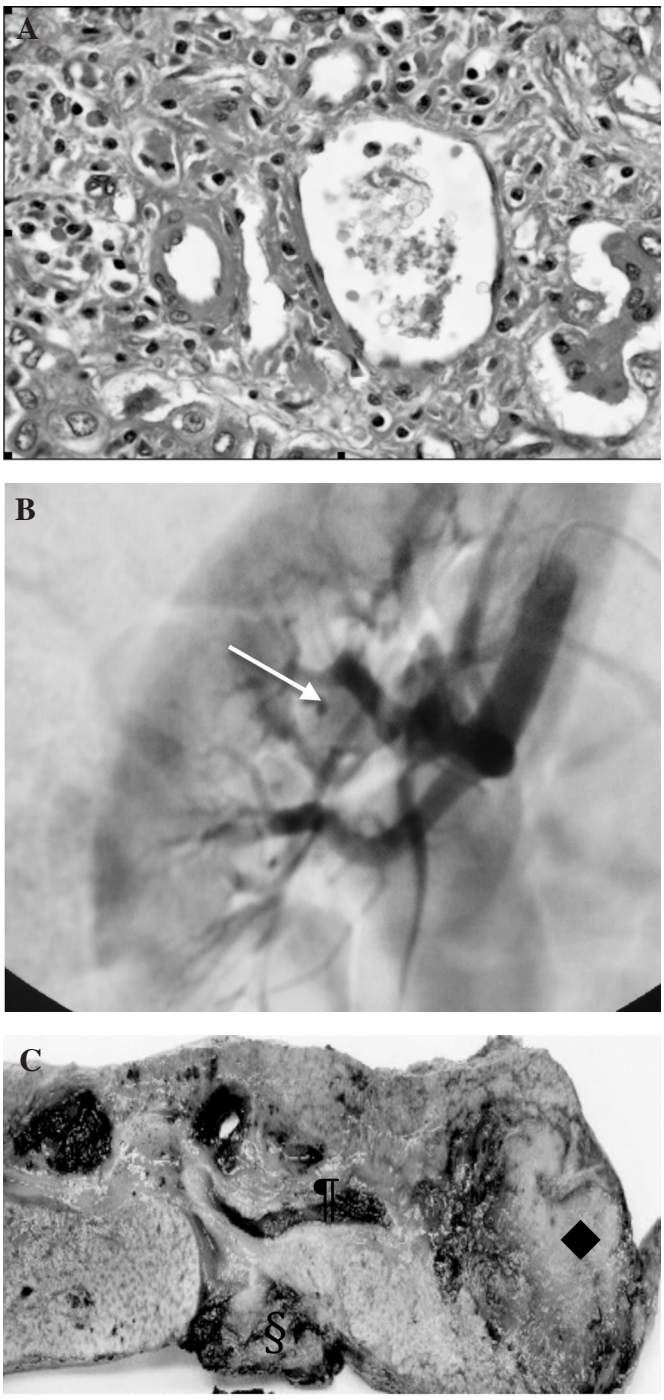

Fig. 1. Documentation of successive stages of disease.
(**A**) Ductopenia in the native liver (after thiabendazole treatment). Optic microscopy view of a portal space: venous portal system and branches of the hepatic arterial system are seen, but no bile ducts.
(**B**) Angiography of a microaneurysm (arrow) in the right renal artery contributing to PAN diagnosis.
(**C**) Macroscopic view of the first liver graft (after the second OLT). Note the necroses of the left lobe, (◆) bile duct (§), and portal vein thrombosis (¶)

Discussion

This case highlights two notable points. First, it seems very likely that the patient's initial symptoms and biologic characteristics (cutaneous nodules, petechial purpura, hypereosinophilia) were already manifestations of PAN. Labile pulmonary infiltrates, a massive venous thrombosis, DIVC and homogeneous eosinophil lineage excess in the bone-marrow aspiration were certainly consequences of his circulating eosinophilia and most probably delayed PAN diagnosis. Indeed, although eosinophilia is strongly associated with Churg-Strauss syndrome, it can also occur in PAN (7). However, because angiography was not done initially, it is impossible to conclude whether the acute haematemesis episode was a PAN-related aneurysm rupture, or a post-operative complication. On the other hand, the patient's several successive cholangitides and hepatic abscesses after the first OLT were most probably ischaemic complications of hepatic artery ligation to treat the acute haematemesis episode, rather than PAN liver infarction.

Second, PAN is known to relapse less frequently than small-vessel vasculitides. Nonetheless, new flares can occur, sometimes after years of remis-

sion. Our patient, despite anti-rejection therapy, relapsed. This event was not totally unexpected in light of the medical literature. Notably, anti-calcineurin therapy is not the gold standard of PAN treatment (8). Indeed, it is not even listed as an alternative therapeutic option in the EULAR recommendations for the management of primary small- and medium-sized-vessel vasculitides (9). Because our patient's angiogram showed diffuse arterial aneurysms, we considered hepatic aneurysm rupture to be a plausible explanation of the initial post-OLT1 haematemesis episode. Because his FFS was one, we prescribed FFS-guided therapy (10) with cyclophosphamide pulses. Although the patient's condition was serious, complete remission of PAN was achieved.

Acknowledgements

The authors thank Dr Bruno Turlin for the photographs and Ms Janet Jacobson for her editorial assistance.

References

1. PAGNOUX C, MAHR A, COHEN P, GUILLEVIN L: Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine* (Baltimore) 2005; 84: 115-28.
2. PAGNOUX C, SEROR R, HENEGAR C *et al*.: Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 2010; 62: 616-26.
3. GUILLEVIN L, PAGNOUX C, SEROR R *et al*.: The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90: 19-27.
4. BOURGARIT A, LE TOUMELIN P, PAGNOUX C *et al*.: Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine* (Baltimore) 2005; 84: 323-30.
5. COOPER SC, OLLIFF SP, MCCAFFERTY I, WIGMORE SJ, MIRZA DF: Polyarteritis nodosa, presenting as life-threatening gastrointestinal haemorrhage in a liver transplant recipient. *Liver Transpl* 2008; 14: 151-4.
6. RAMACHANDRAN R, KAKAR S: Histological patterns in drug-induced liver disease. *J Clin Pathol* 2010; 62: 481-92.
7. KAHN JE, BLETRY O, GUILLEVIN L: Hypereosinophilic syndromes. *Best Pract Res Clin Rheumatol* 2008; 22: 863-82.
8. DE MENTHON M, MAHR A: Treating polyarteritis nodosa: current state of the art. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S110-6.
9. MUKHTYAR C, GUILLEVIN L, CID MC *et al*.: EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; 68: 310-7.
10. GUILLEVIN L: Clinical trials on systemic necrotizing vasculitides. *Presse Med* 2010; 39: 653-9.