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Painful hypertrophic osteoarthropathy successfully treated with octreotide. The pathogenetic role of vascular endothelial growth factor (VEGF)

SIR, Hypertrophic pulmonary osteoarthropathy (HPOA) is a syndrome defined by digital clubbing and distal periostitis in tubular bones [1]. It is associated with a number of medical conditions, mainly lung cancer, congenital cyanotic heart disease and other systemic illnesses with pulmonary involvement. Symptoms may include bone pain, occasionally severe. The pathogenesis of this syndrome is elusive. A possible role for some unknown growth factor(s), probably platelet or tumour-derived, not cleared by the lungs, has been proposed [2]. As hyperaemia and neoangiogenesis have been identified as common pathological features, a hypothetical role for vascular endothelial growth factor (VEGF) in subperiosteal bone inducing periosteal thickening, is gaining acceptance [3, 4]. This hypothesis would be reinforced if VEGF inhibition improved HPOA-related symptoms.

We recently assisted a patient with painful HPOA, associated with Fallot's tetralogy, who dramatically responded to octreotide, a potent VEGF inhibitor.

A 34-yr-old man was admitted with bilateral leg pain. He had Fallot's tetralogy with pulmonary artery atresia. A left-to-right bypass from the ascending aorta to the right pulmonary artery,

and later two Blalock–Taussig procedures to attach the left subclavian to the left pulmonary artery had been performed in the past, with only transient success. The patient had been offered no further surgical interventions and was rejected for cardiopulmonary transplantation.

He had grade III dyspnoea. In the last 2 months, progressive, severe pain along both legs and ankles developed, which had not responded to usual analgesics and impeded his sleep. The pain was alleviated partially by immersion of his legs in cool water.

The patient was cyanotic. Prominent digital clubbing of his fingers and toes and mild ankle oedema were present. Intense tenderness was elicited along the distal two-thirds of both tibial shafts and around the ankles, without signs of cellulitis or arthritis. Polycythaemia and severe hypoxaemia were prominent. X-rays showed typical, bilateral periosteal thickening in the distal tibiae and fibulae (Fig. 1).

Paracetamol, ketorolac, amitriptyline, indomethacin and dexamethasone were sequentially tried in combination, without relief. After informed consent had been obtained, subcutaneous octreotide, 100 µg twice daily, was added. After 3–4 days, complete pain relief was achieved and the other drugs could be withdrawn. No adverse events were recorded. After 2 weeks, octreotide was tapered to 100 µg daily and the patient was discharged. After about 1 week, the pain reappeared and the patient was readmitted. His poor cardiorespiratory status was then rapidly deteriorating. Octreotide was increased to 100 µg twice daily but, owing to untreatable dyspnoea, multiple other palliative measures were needed, including morphine (thus precluding the evaluation of a specific response to octreotide), and the patient finally died.

Our patient fulfilled HPOA criteria [1], in this case associated with advanced Fallot's tetralogy, with pain resistant to combined analgesia. Octreotide induced and maintained complete pain relief in monotherapy. Moreover, the pain reappeared as the dose was tapered. This case is the second reported in HPOA-related pain responding to octreotide, and the first in HPOA associated with congenital cyanotic heart disease.

Complete pain relief with octreotide was reported in a patient with lung cancer-related HPOA [5]. These and other authors [6] related this effect to some hormone-inhibiting or intrinsic analgesic actions of octreotide. As more recent data are accumulating on



FIG. 1. Bilateral periosteal thickening in the distal tibiae and fibulae.

VEGF involvement in the pathogenesis of HPOA, the effect of octreotide could be explained by VEGF inhibition.

The pathological hallmark of HPOA is neoangiogenesis, plus oedema and osteoblast proliferation in distal tubular bones, leading to subperiosteal new bone formation. VEGF, a powerful endothelial cell-stimulating factor, is very likely to play a central role in the pathogenesis of HPOA for several reasons [3, 4]. Firstly, abnormal platelet function seems to be involved in diseases with right-to-left shunting and VEGF is a platelet-derived factor that can also be ectopically produced by some tumours or locally induced in response to hypoxia. Secondly, VEGF receptors are expressed in subperiosteal bone-forming cells. Finally, both increased VEGF plasma levels and/or tissue expression have been reported in virtually all the medical diseases associated with HPOA, correlating with disease activity [4].

Recently, octreotide has been shown to inhibit the production of VEGF and endothelial proliferation [7]. Interestingly, bisphosphonates, also effective for pain relief in HPOA (an effect previously attributed to its action on osteoclasts) [8], are also potent VEGF inhibitors [9].

Our case confirms the effectiveness of octreotide in HPOA associated with different underlying medical conditions. It also demonstrates that HPOA-related symptoms can be blunted by different VEGF inhibitors, strongly supporting the central role of VEGF in the pathogenesis of this syndrome. Perhaps the use of an anti-VEGF monoclonal antibody, such as bevacizumab, will more specifically confirm this hypothesis.

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Rupture of the splenic arterial aneurysm due to Behçet's disease

SIR, We present a patient with Behçet's disease who developed intra-abdominal haemorrhage due to rupture of a splenic artery aneurysm. The patient underwent urgent open surgical intervention. Aneurysmectomy and splenectomy were performed successfully; the patient recovered completely and was discharged on the sixth postoperative day. Our case is the first splenic artery aneurysm and its rupture due to Behçet's disease in the literature.

Behçet's disease was described by Hulusi Behçet, a Turkish dermatologist. The aspects of the disease are oral and genital aphthous ulcers and iridocyclitis. But it is now evident that the disease affects many systems, such as the central nervous system, the eyes, the skin and the locomotor, gastrointestinal, cardiovascular and genitourinary systems [1]. The aetiology of the disease is not clear yet. The disease has been found to be associated with HLA-B51 [1]. The prevalence is high in the Far-Eastern and Mediterranean countries, such as Japan, China, Iran and Turkey.

Arterial complications represent a fatal course and thus are very important in Behçet's disease [2, 3]. The approach to the diagnosis and treatment of aneurysms in Behçet's disease has been discussed. Furthermore, cerebral, carotid, subclavian, aortic (thoracic and abdominal), pulmonary, brachial, ulnar, iliac, renal, femoral and popliteal arterial aneurysms have been reported [4]. The case presented here is the first reported case of splenic artery aneurysm and its rupture due to Behçet's disease in the literature.

On the second day of admission, the patient was diagnosed with acute abdomen secondary to rupture of the aneurysm. Urgent upper abdominal ultrasonography revealed a 15 × 5 × 5 cm haematoma between the spleen and portal hilus, adjacent to the aneurysm of the splenic artery. The patient had urgent surgical intervention, and aneurysmectomy plus splenectomy was performed. The patient was discharged uneventfully on the sixth postoperative day.

The patient was a 46-yr-old Turkish man who had an 11-yr old history of Behçet's disease with ocular and neurological involvement. On the admission day, epigastric tenderness was found by physical examination. Blood pressure was 120/80 mmHg, the pulse rate 80/min and fever 38.8°C. The first laboratory findings were as follows: white blood cells 15 000/mm³, haemoglobin 10.3 g/dl, haematocrit 30.3%, platelets 263 000/mm³, ESR 103 mm/h and CRP 143 mg/dl. Nine aphthous ulcers on the corpus and antral mucosa of the stomach were observed on gastroscopy. A 5 × 5 cm mass was detected near the spleen by abdominal ultrasonography. Abdominal CT (Fig. 1) and portal system Doppler ultrasonography revealed that the mass was an aneurysm of the splenic artery.

The incidence of vascular complications in Behçet's disease has varies widely, from 8 to 60% [5]. Four different vascular complications have been described: arterial occlusion, arterial aneurysm, venous thrombosis and variceal formation [5, 6]. The basic mechanism in the pathogenesis of all vascular complications is 'vasculitis'. A number of consecutive immunological processes, inflammatory cell infiltration, impairment of endothelial cell function and coagulation disorders result in thrombosis, leading to collateral venous circulation. Furthermore, vena cava superior occlusion leads to downhill oesophageal varices [5, 7].

Venous involvement is more frequent (15–25%) than arterial lesions (1.5–3%) [7, 8]. The prevalences of arterial aneurysms and arterial occlusions are similar to each other in most studies (1–2%) [4, 5, 8].

Splenic arterial aneurysms can occur in atherosclerosis, mycotic infection, blunt abdominal trauma, essential hypertension, portal hypertension, chronic pancreatitis, diabetes, polyarteritis nodosa,