LETTERS

Hypertrophic osteoarthropathy associated with gastrointestinal stromal tumour

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Hypertrophic osteoarthropathy (HOA) is a condition characterised by digital clubbing, polyarthralgias, periostitis, occasionally arthritis,^{1–2} and cutaneous signs of autonomic disorders (sweating, flushing, blanching).³ HOA is classified as either primary (hereditary or occasionally idiopathic in adults) or secondary (often associated with neoplastic or infectious diseases).⁴ In the industrialised world, 90% of cases are associated with an underlying malignancy, usually a pulmonary neoplasm,¹ but also cardiovascular and gastrointestinal diseases.⁴ Here, we describe the case of a patient presenting with HOA as the first manifestation of a gastrointestinal stromal tumour (GIST).

A 47 year old white man consulted the rheumatologist in January 2005 with a 2 month history of fatigue and bilateral ankle and knee arthritis. Physical examination was normal, except for arthritis in knees and ankles. Blood and urine routine tests were normal, including haemoglobin, liver and renal function tests. The erythrocyte sedimentation rate was 59 mm/1st h and the C reactive protein 63.3 mg/l. Rheumatoid factor, antinuclear and anti-cyclic citrullinated peptide antibodies were negative. Serological tests for *Yersinia*, *Borrelia*, *Mycoplasma*, *Brucella*, *Salmonella*, and parvovirus B19 were negative. An x ray examination of knees and

ankles was normal. Non-steroidal antinflammatory drugs, sulfasalazine, and low-dose oral prednisone did not significantly improve the symptoms.

Three months later, the patient was re-evaluated. By this time, clubbing of the fingers was noted on physical examination (fig 1A). Radiographs showed periostitis along the long bones in both legs (fig 1B). Chest radiographs were again normal. Abdominal ultrasound scan, barium x ray and computed tomography (CT) scan (fig 1C) showed a large solid mass in apparent communication with the gastric fundus. An endoscopy showed a lobulated lesion in the fundus, but biopsies were not diagnostic. A percutaneous biopsy of the tumour confirmed the diagnosis of GIST (fig 1D). After 3 months of treatment with imatinib, the tumoral mass had a 50% reduction and the arthritis had vanished, suggesting a true relationship between the GIST and the HOA.

To our knowledge, this is the first description of HOA associated with GIST. Our patient presented with the classic findings of HOA (digital clubbing, polyarthralgias, and periostitis).^{1–5} Secondary HOA can be associated with pulmonary and non-pulmonary conditions (table 1).^{2–8} As our patient exemplifies, HOA can be an early manifestation of an occult and serious disease. About 12% of children with

Figure 1 (A) Digital clubbing; (B) Periostitis at the femoral diaphysis (arrow); (C) CT scan showing a solid tumour containing areas of necrosis, adjacent to the gastric fundus; (D) puncture of the tumour disclosed a hypercellular smear showing clusters of spindle cells with strong cytoplasmic immunoreactivity for c-kit ($\times 400$).

Table 1 Causes of secondary HOA

<i>Pulmonary</i>
Benign conditions
Bronchial carcinoid
Cystic fibrosis
Sarcoidosis
Bronchiectasis
Tuberculosis
Chronic infections
Pleural methothelioma
A-V fistulae
Lipid pneumonia
Plasma cell granuloma of the lung
Lung mass of xanthogranulomatous inflammation
Pulmonary alveolar microlithiasis
Primary pulmonary malignancies
Small cell carcinoma of the lung
Adenocarcinoma
Large cell carcinoma
Squamous cell carcinoma
Hodgkin's disease
Fibrosarcoma
Carcinosarcoma of the lung
Pulmonary metastatic disease
<i>Extrapulmonary malignancies</i>
Nasopharyngeal carcinoma
Oesophageal carcinoma
Oesophageal leiomyoma
Breast cancer
Thymic carcinoma
Soft tissue sarcoma
Malignant fibrous histiocytoma
Hodgkin's disease
Undifferentiated thyroid cancer
Renal cell carcinoma with pulmonary metastasis
<i>Cardiovascular disease</i>
Cyanotic congenital heart disease
Subacute bacterial endocarditis
Patent ductus arteriosus
Aneurysms
Aortic prosthesis
<i>Hepatic</i>
Biliary atresia
Primary sclerosing cholangitis
Wilson's disease
Primary biliary cirrhosis
<i>Benign gastrointestinal lesions</i>
Gastrointestinal polypoid
Crohn's disease
Ulcerative colitis
Regional enteritis
Gastro-oesophageal reflux and oesophagitis
Achalasia
<i>Miscellaneous</i>
Graves' disease
Thalassaemia
Infected graft with endotoxin: infected aortic graft
AIDS
Neurogenic origin: vagotomy, hemiplegia
Docetaxel chemotherapy for breast cancer

HOA have a neoplastic disease, but in adults the figure reaches 92%.⁹

Among the gastrointestinal causes of HOA, gastric tumours are an uncommon possibility. GISTs are most often located in

the stomach and proximal small intestine, but can occur in any portion of the digestive tract containing smooth muscle within its wall. GISTs are identified by c-kit immunoreactivity or by the presence of activating mutations of KIT or PDGFRA.¹⁰

Some criteria are useful for distinguishing benign and malignant GISTs, including the size of the tumour, the level of mitotic activity, the site of origin (better long term outcomes for gastric GISTs), and some imaging characteristics on CT or endoscopic ultrasound. The most effective treatment of HOA is that of the underlying condition. Tumour ablation or chemosuppressive therapy of an associated malignancy often results in prompt resolution of symptoms.⁴ In the case of GISTs, small lesions (<1 cm), with benign endoscopic ultrasound findings, may be followed conservatively. The tyrosine kinase inhibitor imatinib can provide a dramatic clinical benefit for patients with advanced or unresectable GIST, resulting in tumour response and long term disease control. Thus, surgical resection has been postulated as a feasible option after imatinib treatment in some patients with initially unresectable (but not metastatic) disease.

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