



Malta Medical Journal, 32 (3): Pages (2020) http://mmsjournals.org/index.php/mmj

Joints, bones and congenital heart disease... A forgotten association?

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A 20 year old Caucasian male, with a history of uncorrected cyanotic congenital heart disease, presented with a one year history of bone pains in his thighs, legs and forearms. The diagnosis of hypertrophic osteoarthropathy (HOA) was picked up on bone scintigraphy. HOA is usually associated with lung disease and the link with congenital heart disease has become a less frequently encountered association.

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INTRODUCTION

Gout, as a result of increased red cell turnover and hyperuricaemia, is the most commonly recognised cause of joint disease in patients with cyanotic congenital heart disease. We describe a case of hypertrophic osteoarthropathy (HOA), a far less common cause of bone disease in patients with congenital heart disease. It is now becoming increasingly rare to see HOA in these patients, as surgical correction of most congenital heart defects is now successfully being performed earlier on in life.

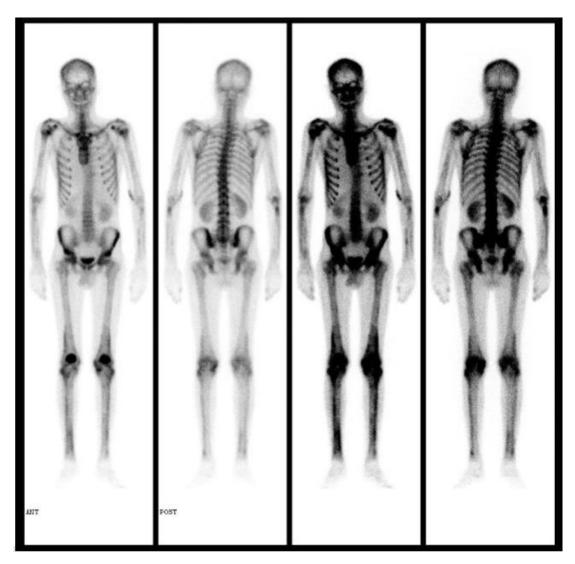
CASE PRESENTATION

A 20 year old male was referred to the Rheumatology Department complaining of bone pains in the upper thighs, legs and forearms over the past year. The pain was present throughout day and was not affected by activity. He denied nocturnal pain, joint swelling, systemic upset, rashes, fever, mouth ulcers or sicca symptoms.

Figure 1

Whole body bone scan

Increased tracer uptake along the diaphyseal and metaphyseal surfaces of the femoral bones and tibiae and to a lesser degree the radius and ulna bilaterally.



He was born with complex congenital heart disease, in the form of dextrocardia, double outlet right ventricle and subvalvular pulmonary stenosis. At the age of one year, he underwent a palliative Blalock-Taussig shunt in view of worsening cyanosis but over time developed pulmonary vascular disease and subsequent Eisenmenger syndrome. He had been established on advanced pulmonary vasodilators for several years.

On examination, the patient had an oxygen saturation of 62% on room air. He had clubbing of the digits and central cyanosis. There was no evidence of synovitis or joint deformities, but thickening of the distal part of both tibiae was noted. There was no overlying erythema or tenderness. Blood investigations were normal, apart from a high haemoglobin of 20.2 g/dL (14.1 - 17.2 g/dL) with a high haematocrit level of 59.3% (40.4 - 50.4%), slightly elevated uric acid of 507 umol/l (202 - 416 umol/l) and high alkaline phosphatase of 225 U/l (40 - 104 U/l). Autoimmune screen including antinuclear antibody, rheumatoid factor and anti-cyclic citrullinated peptide antibody was negative. Plain X-rays of hands and lower legs showed no abnormalities. Whole body bone scan, Figure 1, showed increased tracer uptake along the diaphyseal and metaphyseal surfaces of both femoral bones and tibiae and to a lesser degree the radius and ulna bilaterally. These findings are in keeping with HOA. The patient was treated with paracetamol and nonsteroidal agents. He is being followed up regularly at rheumatology out-patient clinic for evidence of progression of disease.

DISCUSSION

HOA is characterised by triad of severe disabling arthralgia and arthritis, digital clubbing and periostosis of tubular bones with or without synovial effusion. HOA was first described by Eugen von Bamberger and Pierre Marie in 1890.¹ In rare cases it is inherited as an autosomal dominant condition, known as pachydermoperiostosis. In 95-97% of cases, it is secondary to pulmonary or extrapulmonary diseases, Table 1. The majority of these cases are of pulmonary origin, when it is known as hypertrophic pulmonary osteoarthropathy (HPOA). 90% of these are associated with malignancy. Non-small cell lung cancer (NSCLC), specifically adenocarcinoma, is the most common cause (0.7-17%). Although lower in absolute incidence, a higher percentage of pleural tumours result in HPOA, 22% of solitary fibrous tumours of pleura as compared to 5% of NSCLC.¹

Three pathways for the mechanism of development of HOA have been proposed:

- Vascular pathway due to secretion of vasoactive agents by the tumour or due to arteriovenous shunting within the pulmonary circulation,
- Neurogenic pathway triggered by vagal innervation, resulting in vasodilatation and increased blood circulation to the extremities,
- Hypoxaemia driven surge of circulating growth factors e.g. platelet-derived growth factor, vascular endothelial growth factor (VEGF) and prostaglandin E2.

The latter is the proposed mechanism in patients with cyanotic congenital heart disease.²

Table 1Causes of generalised HOA

Pulmonary	Cardiac	Gastrointestina l	Hepatobiliary	Miscellaneous
Bronchogenic carcinoma/ metastatic disease	Congenital cyanotic heart disease	Polyposis	Cirrhosis	Thymoma
Mesothelioma	Atrial myxoma	Malignancy	Biliary atresia	POEMS syndrome
Cystic fibrosis	Infective endocarditis	Inflammatory bowel disease	Primary biliary cirrhosis	Myelofibrosis
Pulmonary tuberculosis		Achalasia	Wilson disease	Haematological malignancy
Chronic infections		Laxative abuse	Hepatobiliary carcinoma	
Pulmonary arteriovenous malformations			Primary sclerosing cholangitis	
Sarcoidosis				
Solitary fibrous tumours of the pleura				

POEMS: polyneuropathy, organomegaly, endocrinopathy, myeloma protein and skin changes.

Patients with HOA share common features: pleomorphic platelets, giant macrothrombocytes with aberrant volume distribution curves, glomerular enlargement with entrapped megakaryocytic nuclei and high circulating levels of von Willebrand factor antigen.² All these lead to the activation of platelets and endothelial cells, with the subsequent release of growth factors. Electron microscopy shows structural damage to vessel integrity with prominent Golgi complexes, activated endothelia, duplicated capillary basement membranes and perivascular infiltrate. At the level of joints the pathologic changes are dominated by arterial wall thickening.³

There are no specific serological markers of HOA and as a result, the diagnosis of HOA is often delayed. Bone formation markers such as alkaline phosphatase, osteocalcin or aminoterminal propeptide of type 1 pro-collagen may be increased.

Imaging is the mainstay of diagnosis. X-rays typically show symmetrical periostosis of the shafts of tubular bones in the absence of cortical destruction or fracture. The tibia, fibula, radius and ulna are most commonly affected sites. Magnetic resonance imaging shows a low to intermediate signal intensity on T1 and T2 weighted images, highlighting periosteal elevation and reaction.⁴ There are cases where HOA was diagnosed on positron emission tomography by increased fluorodeoxyglucose (FDG) uptake, however there is the risk of an erroneous diagnosis of metastatic disease.⁵ Bone scintigraphy with technetium 99m (99mTc) methylene diphosphonate (MDP) is the gold standard and is the most sensitive test.

The differential diagnosis of HOA includes thyroid acropachy, hypervitaminosis A and a rare autosomal dominant disease known as Camurati Engelmann disease. Voriconazole has been reported to cause periostitis that mimics HOA.

Management of HOA includes treatment of the underlying cause and appropriate analgesia. Other treatment options described include: unilateral vagotomy, in cases of inoperable primary lung malignancies. The procedure was first carried out in the 1950s and was revisited in 2006, however not many cases have been reported in the literature.⁶ Adrenergic blockade with propranolol or phenoxybenzamine was trialled once in 1976.⁷ This option has not been used favourably. NSAIDs, currently the most widely used treatment option, work by blocking the prostaglandin pathway. In fact, opioids are less effective. Octeotride, a VEGF inhibitor, has been shown to limit endothelial proliferation and is highly effective in pain relief.⁸ There are several case reports regarding the symptomatic and therapeutic effects of bisphosphonates, also VEGF inhibitors.9 Therapeutic trials are currently being carried out with bevacizumab, a VEGF inhibitor and erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, which could show promising results.¹⁰

CONCLUSION

Bone pains in patients suffering from malignancy, chronic lung disease, liver disease or cyanotic heart disease should raise the suspicion for HOA. Likewise, a new diagnosis of HOA should always trigger a search for the primary cause.

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