Clubbing associated with oesophageal adenocarcinoma

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Summary: A patient with an oesophageal adenocarcinoma, recent onset of digital clubbing, and evidence of increased oestrogen synthesis is presented. In the discussion, some of the theories of the pathogenesis of clubbing are reviewed, together with previous reports of clubbing in gastro-oesophageal disorders. A possible unifying theory is proposed for our case which we believe is the first report of this triple association.

Introduction

Digital clubbing is a well known finding in a variety of cardiac and pulmonary conditions, and is more rarely seen in liver, and inflammatory bowel disease. We present a case of oesophageal adenocarcinoma without distant spread accompanied by acute bilateral finger and toe clubbing, and with evidence of increased oestrogen excretion.

Case report

A 71 year old Caucasian woman was admitted with a 9-week history of dysphagia and substantial weight loss, but no other disease related to her clubbing. No clubbing was noted on her previous admission for investigation of atrophic vaginitis in 1984.

The patient had a low grade pyrexia, and marked bilateral finger and toe clubbing, and she was confident that her nails had recently changed in shape. The physical examination was otherwise unremarkable.

The patient had a microcytic anaemia (haemoglobin 9.8 g/dl), a neutrophil leucocytosis (white cell count $15.0 \times 10^9/l$), and a thrombocytosis ($778 \times 10^9/l$). The erythrocyte sedimentation rate was 128 mm in the first hour, and the C-reactive protein was 157 mg/l (normal <10). Arterial gas tensions, electrolytes, urea, liver and thyroid function tests were normal. A chest X-ray showed

minimal shadowing at the left lung base. Six sets of blood cultures yielded no growth. An echocardiogram showed possible mitral valve prolapse with no vegetations.

A barium swallow showed severe narrowing of the distal third of the oesophagus, which was biopsied on endoscopy and found to be due to an adenocarcinoma. Computed tomographic scans did not show any hepatic or pulmonary metastases.

Her serum oestradiol was 122 pmol/l (normal <70), with normal post-menopausal gonadotrophin levels. Serum testosterone and sex hormone binding globulin levels were normal. Analysis of steroid metabolites in a 24 hour urine collection by high resolution gas chromatography showed grossly elevated excretion of cortisol metabolites (total cortisol metabolites 58.1 mg/24 h; normal <4.9), suggestive of ectopic ACTH production. Paradoxically, oestradiol was undetectable in the urine on analysis by gas chromatography – mass spectrometry. She had a urinary oestrone level that was high for her age ($15 \mu\text{g}/24 \text{ h}$) and a markedly elevated urinary oestriol ($77 \mu\text{g}/24 \text{ h}$) (normal postmenopausal values <2.7 and <4.3 respectively).¹

Ten days after admission, the patient developed a left sided pleural effusion. The pleural fluid was an exudate (protein = 41 g/l), but no malignant cells were seen. She also complained of pain in her left knee, which was enlarged and tender. An X-ray showed periosteal new bone formation in the proximal tibia consistent with hypertrophic osteoarthropathy although X-rays of the distal arms and legs were normal. She developed a progressive thrombocytosis with a platelet count that peaked at $1231 \times 10^9/l$.

The patient progressively deteriorated and died one month later. A post-mortem examination

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confirmed the presence of a poorly differentiated adenocarcinoma of the lower third of the oesophagus, involving the full thickness of the oesophageal wall, with direct involvement of the left lower lobe and the pericardium. The pleura were intact and there were no discrete metastases. The liver and pelvic organs were normal. The adrenal glands had a normal appearance, and there was no evidence of endocarditis.

Discussion

The onset of generalized clubbing in our patient paralleled the growth of her oesophageal tumour. This was associated with very high levels of circulating oestrogens and the urinary excretion of high concentrations of metabolites of oestrogen and cortisol.

Clubbing has been reported in only one previous case of oesophageal adenocarcinoma,² in one case each of achalasia of the oesophagus,³ and oesophageal leiomyoma,⁴ and in three cases of oesophageal squamous cell carcinoma. Of these, one had coexistent achalasia,⁵ one had hepatic metastases,⁶ and one had hepatic and pulmonary metastases.⁷ Clubbing has also been described in a patient with gastric adenocarcinoma.⁸

The pathogenesis of clubbing remains unknown although many theories have been proposed^{9,10} including the presence in the circulation of unknown vasodilator substances normally inactivated by the lung, or the presence of regional tissue hypoxia. Since diseases causing clubbing occur in organs supplied by the vagus or glossopharyngeal nerves, a further theory² proposes that there is a neurally mediated mechanism initiated by stimuli to the afferent limbs of these nerves. Flavell's finding that, after cutting the vagus nerve, the pain and radiological changes of hypertrophic pulmonary osteoarthropathy (HPOA) were substantially

reduced, showed that an intact vagus nerve is a prerequisite for HPOA to occur.¹¹ Until the nature of the stimulus to the vagus nerve has been identified it is difficult to substantiate the neurally mediated theory.

Clubbing due to pulmonary disease alone has previously been associated with elevated serum oestradiol,¹² and increased urinary excretion of oestrogen metabolites.¹³ Oestrogens may enhance β -adrenergic activity in the lung¹⁴ and by thus relaxing vascular smooth muscle could create arteriovenous connections, allowing a trophic clubbing factor to avoid metabolism and act peripherally. Oestrogens also increase the blood supply to the distal long bones.¹⁵

A further theory proposes that megakaryocytes that are normally trapped by pulmonary capillaries, where they fragment and release platelet clumps, for a variety of reasons, bypass the lung. They then impact peripherally releasing platelet-derived growth factor which causes increased capillary permeability and connective tissue hypertrophy which may produce clubbing.¹⁶

Our patient had no known cause of clubbing except tumour within the vagal territory. Neither oesophageal carcinoma nor high oestrogen levels on their own are normally associated with clubbing. However, in this case elevated circulating oestrogens may have allowed megakaryocytes (present in increased numbers due to recurrent blood loss) to traverse the lungs causing clubbing. This mechanism would be consistent with previous observations and we believe it merits further study.

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