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Case Report

A Case of Finger Clubbing Associated with Nasopharyngeal Carcinoma in a young girl, and review of Pathophysiology

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Abstract

Hypertrophic osteoarthropathy is characterized by clubbing of the digital tips and periosteal reaction of long bones. Most of the cases are associated with malignancy or other conditions such as congenital heart disease, liver cirrhosis, pulmonary fibrosis, biliary atresia and gastrointestinal polyps. Hypertrophic osteoarthropathy associated with malignancy is rare in children.

A few cases of hypertrophic osteoarthropathy in children with nasopharyngeal carcinoma have been reported. This is a case of hypertrophic osteoarthropathy associated with nasopharyngeal carcinoma with lung and bone metastasis in a 16 year old girl. In this case, lung metastases progressed after intensive chemotherapy and hypertrophic osteoarthropathy (Clubbing) persisted.

Introduction

Hypertrophic osteoarthropathy (HOA) is a condition characterized by periosteal reaction of tubular long bones, characteristic bulbous deformity of the digital tips, and synovial effusion.¹ HOA in malignancy is very rare in children. To date, very few cases of HOA in association with childhood neoplasia have been published.^{2,3} Most of the patients had abnormalities of the lung, mediastinum, or pleura during the course of the disease but only six had no abnormalities. We experienced a case of HOA, associated with nasopharyngeal carcinoma with lung and bone metastasis in 16 year old girl, which progressed after intensive chemotherapy. Here we report our case with a short review of the pathophysiology.

Case Report

A sixteen year girl was diagnosed in February 2006, to have T3N3aM0 large cell nasopharyngeal carcinoma. She received 5FU, cisplatin chemotherapy three cycles followed by concurrent chemo radiation therapy to the nasopharyngeal fields and received 6660 cGy dose of Radiation therapy in December 2006. Follow up CT scan showed complete resolution of the left neck large node and slight asymmetry of left Para pharyngeal space. She was kept on follow up. She started noticing clubbing of fingers in mid 2007 (Fig 1 & 2). CT scan of chest, head and neck showed mediastinal lymphadenopathy and few nodes in right neck.

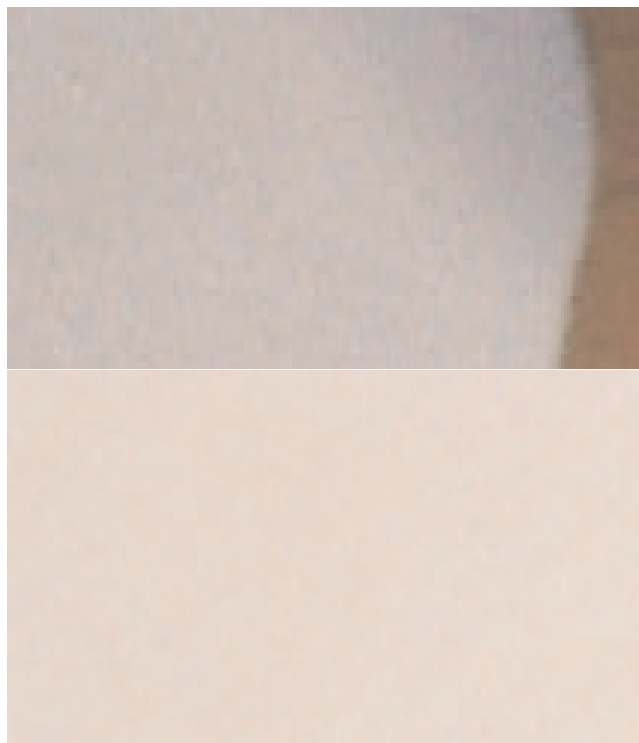


Figure 1: Clubbing of fingers.

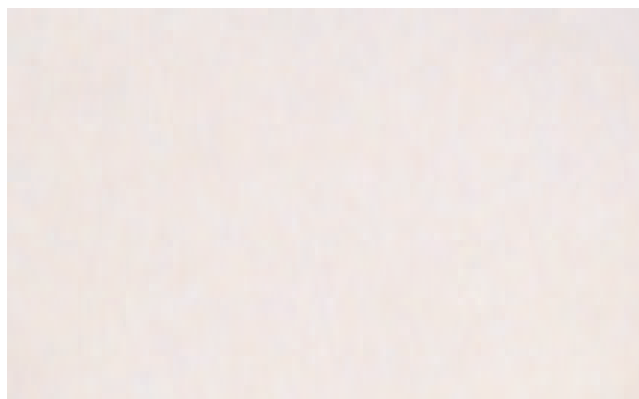


Figure 2: Clubbing of toes.

After confirmation of the recurrent disease in neck and development of lung and bone metastases she was offered second line chemotherapy. In January 2008 her CT chest showed progression of mediastinal nodal metastases and progression of pulmonary nodules. At the time of writing this

report she is continuing her palliative chemotherapy.

Discussion

Hypertrophic Osteoarthropathy (HOA) is a rheumatic disorder characterized by digital clubbing, periostosis of tubular bones, and synovial effusions, which are most prominent in large joints. Periostosis is usually accompanied by tenderness of the involved area. It can be divided into primary HOA, which is not associated with any other medical conditions and secondary HOA, which can be further divided into pulmonary and non-pulmonary causes.⁴ Primary HOA is known as pachydermoperiostosis and is transmitted as an autosomal dominant trait.²

In secondary HOA, common pulmonary causes include cystic fibrosis, pulmonary fibrosis, primary or metastatic carcinoma, and mesothelioma. The most frequently associated non-pulmonary causes include congenital heart disease, liver cirrhosis, infective endocarditis, inflammatory bowel disease, gastrointestinal polyps, Grave's disease, and thalassemia. In children, 12% of those with HOA have a neoplastic disease while in adults the figure is 92%.⁵ HOA may precede the discovery of recurrence or metastasis of primary malignancies by 1 to 18 months.

Although the pathophysiology of clubbing remains a controversy, two different theories have been forwarded. The neurologic theory that stimulation of the vagal neural arc as an etiologic factor is suggested by reversal of the syndrome after vagotomy.⁶ On the other hand, the humoral theory is to explain HOA on the basis of circulating factors in the venous circulation, which are usually removed or inactivated by the lungs.⁷ In diffuse pulmonary fibrosis or lung cancer, a growth factor derived from abnormal tissue enters the systemic circulation and induces clubbing. The fibroblast growth factor could be the etiologic factor of the syndrome.⁸ In the cases of right- to-left shunts of blood, megakaryocytes escape the normal fragmentation in the lung and reach the distal extremities, activating endothelial cells, releasing fibroblast growth factors (e.g., platelet-derived growth factors).^{9,10} The vascular component is thought to be primarily neurogenic, while abnormalities in osteogenesis are believed to be humorally mediated.⁷

The megakaryocyte/platelet theory of the pathogenesis of clubbing has been supported by several subsequent studies. Patients with cyanotic heart disease and secondary HOA had a lower platelet count and higher mean platelet volume than control subjects, indicating larger platelets and less fragmentation of megakaryocytes in the lungs.¹⁰ Necropsy of clubbed fingers showed more platelet

microthrombi than in control subjects, indicating more platelet activation.¹¹ Patients with primary and secondary HOA had greater PDGF levels than control subjects and patients with lung disease without HOA.¹²

In a series of HOA reported previously, development of finger clubbing has been incriminated as a marker for distant metastases. The most common site of distant metastases with finger clubbing is lungs; however, metastasis in bone has also been reported. The mechanism by which pulmonary metastases results in clubbing might be due to anoxia, but why bulky metastases from sarcoma and breast cancer cases do not develop clubbing is unclear. In the case presented, we found secondaries in the lung. There are anecdotal reports of painful osteoarthropathy controlled by local external radiotherapy.¹³

Conclusion

Our case of nasopharyngeal cancer developed finger clubbing and HOA as a part of their paraneoplastic manifestation following radical radiotherapy. The symptomatology described in this report preceded the development of lung metastases in this case. As the development of HOA precedes the progression of the disease, close follow up is necessary for early detection and management of this problem.

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