Paraneoplastic arthropathy as manifestation of pulmonary metastases in phyllodes tumour of breast

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ABSTRACT

Phyllodes tumours are rare, representing less than one percent of all breast malignancies. Phyllodes tumor arises from the fibro-epithelial component of the breast tissue and is capable of a diverse range of clinical behaviour. It can behaves like a fibro-adenoma in the least aggressive form to an aggressive tumour with tendency for distant metastases. We report the case of 38-year-old lady with phyllodes tumour affecting the left breast who presented with polyarthralgia as a paraneoplastic manifestation of pulmonary metastases.

Keywords: Breast cancer, phylloides tumour, manifestation, paraneoplastic manifestation

INTRODUCTION

Phyllodes tumours are rare, representing only 0.5 percent of breast malignancies. [1] They arise from the fibro-epithelial component of breast tissue and are capable of a diverse range of clinical behaviour. They behave like fibroadenoma in least aggressive form to aggressive tumour with tendency for distant metastases. We report the case of a 38-year-old lady with phyllodes tumour of the left breast who presented with polyarthralgia as a manifestation of pulmonary metastases.

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CASE REPORT

A 38-year-old previously healthy lady with no comorbidities presented with history of progressive left breast mass for the past four years. The breast lesion was biopsied and this confirmed a diagnosis of a malignant phyllodes tumour which was unresectable due to locally advanced stage. She was treated with neoadjuvant chemotherapy consisting of Ifosfamide and Adriamycin for two cycles followed by palliative mastectomy two months later. A large tumour measuring 21 x 23 cm was removed and plastic reconstruction was carried out. She had good post-operative recovery.

A follow up computed tomography (CT) scan three months after surgery noted a

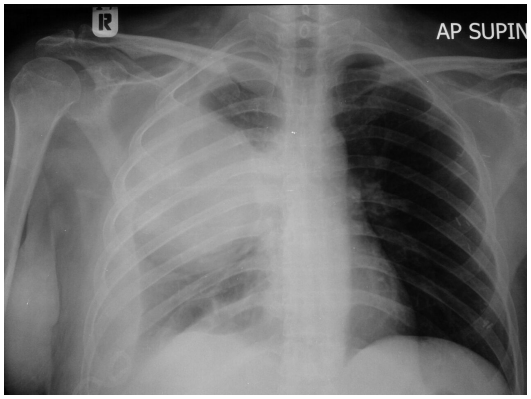

Fig. 1: A chest radiograph showing a right sided pleural effusion with a mass in the right hilar area.

2.0 x 2.5 cm lesion at the right hilar region of the lung with unknown nature. No biopsy was carried out and she was followed up and monitored. She was admitted to our service in in four months later with a history of intermittent multiple joint pains lasting for the past two months that was associated with intermittent low grade fever. She required frequent analgesia as the joint pain was limiting her mobility. She also reported a mild dry cough. She denied any associated bowel or urogenital symptoms. On examination her vital signs were stable with no documented fever but gross clubbing of both hands were noted with swollen proximal inter-phalangeal joints of the right 2nd, 3rd third and 4th fingers with reduced range of movements. Her chest examination revealed reduced breath sounds at the base of the right lung.

Investigations revealed a haemoglobin of 7.9 gm/dL (Normal range 10.9-14.3), mean cell volume 90.1 fL (75.5-95.3), red blood cell 2.83 x 10^{12}/L (3.63-4.92), white cell count 23.6 x 10^{9}/L (3.8-11.8), C-reactive protein 22.32 mg/dL (<10), and alkaline phosphatase 211 U/L (40-150) and a normal renal function profile. Chest radiograph (Fig. 1) showed a pleural effusion on the right side with a large mass in the right lung at suprahilar region, later confirmed on CT scan of thorax as right sided suprahilar mass up to 9.2 x 8.8 cm size. Her pleural fluid analysis showed a cloudy fluid with RBC 8,960 mm^3, WBC 230 mm^3, a protein of 48 gm/L, glucose 6.67 mmol/L, lactate dehydrogenase (LDH) 422U/L. Pleural fluid culture and smear for Acid Fast Bacilli (AFB) were negative so as blood and urine cultures with culture for AFB from pleural fluid. Fasting blood sugar was 5.9 mmol/L (3.5-6.0). Autoimmune work up (antinuclear antibody, double stranded DNA antibodies and Rheumatoid factor) were all negative. Erythrocyte sedimentation (ESR) rate of 102mm/hr (0-10) was noted. She was empirically treated with antibiotics for possible infected pleural effusion until all cultures found to be negative.

Echocardiogram did not show any evidence of infective endocarditis. She undergone biopsy of the lung mass which was reported as metastases from malignant phylloides tumour, however the cytology examination from pleural fluid remained negative for malignant cells. A review from rheumatologist suggested an episode of polyarthritis.

She was discharge well with mild joint pains off and on managed with analgesics. Currently she is undergoing chemotherapy for metastatic phylloides tumour and remained well so far as of last follow-up.

DISCUSSION

Due to it rarity, phylloides tumours of breast are not well studied. The treatment response is poor or unfavourable if there is metastatic

disease. Paraneoplastic hypertrophic pulmonary osteoarthropathy (HPOA) in association with malignant phyllodes has been reported in literature. In our case the marked clubbing with an episode of polyarthritis preceded the presentation of pulmonary metastatic disease for which other causes were ruled out.

Phyllodes tumours were originally called "cystosarcoma phyllodes" by Johannes Muller in 1838 [2] but the terminology evolved with time. Despite their first description of phyllodes tumours as cystic and sarcomatous, they rarely have cystic components or true sarcomas by cellular origin or by their clinical behaviour. Similar to breast carcinoma the vast majority of cases occur in women, in whom the median age at presentation is 42 to 45 years old.

Clinically similar to that of fibroadenoma but they grow more rapidly. On physical examination most patients have well localised smooth, multi-nodular, well-defined, firm mass that is mobile and painless similar to fibroadenoma. Tumour size is variable, with reported sizes ranging between one and 41 cm. [3]

Phyllodes tumours generally do not metastasize to the lymph nodes. Despite palpable axillary lymphadenopathy in up to 20 percent of patients, metastatic involvement of lymph nodes is rarely seen. [4]

Most phyllodes tumours resemble fibroadenoma on mammography and approximately 20% of phyllodes tumours are only identified on screening mammography. [5] On ultrasonography phyllodes lesions are primarily solid, hypo-echoic and well circumscribed. Cystic areas within the mass may increase the level of suspicion for phyllodes tumours but this change not commonly seen. [5] Imaging with magnetic resonance imaging (MRI) is not helpful. [6] A small retrospective study of 30 patients with proven phyllodes tumours showed that malignant phyllodes tumors represent well-circumscribed tumours with irregular walls, high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. [7] Cystic change are demonstrable with MRI, however such changes are not commonly found per se. A rapid enhancement pattern with benign rather than malignant phyllodes tumours is interesting as it represents opposite of the pattern seen with adenocarcinomas of the breast which enhance more if malignant in nature. [8]

As fine needle aspiration cytology is associated with diagnostic difficulty, a core needle biopsy is the preferred method for making a diagnosis as it provides a better tissue specimen for microscopic details. [9] A Core biopsy has some features that are helpful in distinguishing phyllodes tumours and fibroadenomas. The features distinguishing phyllodes tumours from fibroadenoma include increased cellularity, mitosis, stromal overgrowth, and fragmentation (stroma with epithelium at one or both ends of the fragment).

Histologically phyllodes tumours may be classified in to benign, borderline and malignant. So far more than 50% of phyllodes tumours that have been reports in case series have been classified as benign based on histology. [10] Nearly 25% of phyllodes tumours are malignant. Benign phyllodes tumours are represented by increased stromal cellularity with mild to moderate cellular atypia, well

defined tumour margins and low mitotic rate in the range of four or less mitoses per 10 high power fields and scant stromal overgrowth. Borderline tumours show a more stromal cellularity and cellular atypia, mitotic rate ranges from four to nine mitosis per 10 high power fields, microscopic margins are involved by the tumour cells, and lack of stromal overgrowth seen. Malignant tumours have marked stromal cellularity and atypia, margins involvement by tumour cells, high mitotic rate of more than 10 mitosis per 10 high power fields, and marked stromal overgrowth. [11, 12]

As data are limited due to rarity of phyllodes tumours, treatment principles are based mainly on retrospective series and case reports. Due of their clinical behaviours and prognosis, phyllodes tumours are generally treated as primary breast sarcomas rather than carcinomas of breast. [13]

Para-neoplastic syndromes are defined as clinical syndromes due to non-metastatic systemic effects caused by malignant disease. Recent advancement in medicine helped understanding, diagnosis, and treatment of paraneoplastic syndromes. These syndromes are caused by the secretion of hormones, peptides, or cytokines or from immune cross-reactivity between malignant and normal tissues, which is directed towards various organ systems. Para-neoplastic syndromes may affect endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems. The most commonly associated cancers manifesting Paraneoplastic syndromes include small cell lung cancer, breast cancer, gynecologic tumours, and hematologic malignancies. [14]

HPOA is one of the syndromes targeting the skeletal system and is characterised by periostosis and subperiosteal new bone formation along the shaft of long bones and phalanges (causing clubbing), joint swelling, and pain, [15] vascular endothelial growth factor, platelet-derived growth factor, and prostaglandin E2 are involved in pathogenesis of HPOA. [16] It has been documented that that nearly 90% of cases of HPOA are paraneoplastic, with the remaining cases found in association with pulmonary fibrosis, endocarditis, Graves' disease, and inflammatory bowel disease. [17] HPOA as a primary disorder has been described , termed as pachydermoperiostosis. [15] HPOA, manifesting as digital clubbing is noted in up to 10% of patients with lung tumours, especially carcinoma of lung. In patients presenting with symptoms of long bone involvement, nuclear bone scans may demonstrate symmetric and concentrate tracer uptake. [15] Symptoms of paraneoplastic HPOA may resolve or diminish with successful cancer therapy. The treatment options for symptomatic control include bisphosphonates, opiate analgesics, non-steroidal anti-inflammatory drugs, and localised palliative radiation, especially for pain control. [17]

Generally, phylllodes tumours are uncommon and their clinical behaviour has not been studied in detail. However, HPOA has been reported with these tumours [18] However it is uncommon to see digital clubbing. Clinician need to be vigilant when dealing with patients with history of underlying malignancy as unexplained symptoms may point towards paraneoplastic origin.

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