

A Rare Occurrence of Biphasic Pulmonary Blastoma in an Elderly Male

ANAND SHARMA^{1*}, KIERAN O'GORMAN^{1*}, COONAR AMAN², DORIS RASSL³,
WARIA MOHAMID⁴ and ANDREAS POLYCHRONIS¹

¹Mount Vernon Cancer Centre, Northwood, Middlesex, U.K.;

Departments of ²Thoracic Surgery and ³Histopathology, Papworth Hospital
NHS Foundation Trust, Papworth Everard, Cambridge, U.K.;

⁴Department of Histopathology, Lister Hospital, Stevenage, Herts, U.K.

Abstract. *Pulmonary Blastoma (PB) is a rare primary lung malignancy usually occurring in young to middle aged adults. Surgery is the primary mode of treatment, but survival is poor with the mean 5-year survival being approximately 16%. We report on a case of PB arising in a 63-year-old man. Computed tomography, magnetic resonance imaging and positron emission tomography confirmed the mass to be of pulmonary origin. The morphological appearance combined with the immunoprofile of the tumour was consistent with a poorly-differentiated biphasic pulmonary blastoma. Two months after the surgical resection the patient relapsed with multiple sites of metastasis. The patient was treated with four cycles of cyclophosphamide-, doxorubicin- and vincristine-(CAV)-based chemotherapy, achieving a partial response to treatment. He is currently on a two-monthly review and is recovering from chemotherapy-related toxicities.*

Biphasic pulmonary blastoma is a very rare intrathoracic tumour thought to account for 0.25-0.5% of pulmonary malignancies (1). It is an aggressive primary lung neoplasm derived from foetal lung tissue. This tumour type usually presents in young and middle-aged adults with a history of smoking, and very few cases have been reported in the elderly population. Unlike the pleuropulmonary blastomas of childhood, the adult presentation has a mixed histological picture with both epithelial and mesenchymal malignant components.

*These Authors contributed equally to this study.

Correspondence to: Dr. Anand Sharma, Department of Medical Oncology, Mount Vernon Cancer Centre, Rickmansworth Road, Northwood, Middlesex, HA6 2RN, U.K. Tel: +44 1923844526, Fax: +44 1923844138, e-mail: drandy2003@gmail.com

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This aggressive malignancy is uniformly fatal, and spread can be both local and distant. Even early disease, with nodal metastases only, has a very poor prognosis (2). Current management advocates for surgery as a successful intervention in early disease.

We present a case of pulmonary blastoma seen in a 63-year-old male who underwent primary surgical resection and was subsequently treated with cyclophosphamide, adriamycin and vincristine chemotherapy (CAV) following disease recurrence.

Case Report

A previously healthy 63-year-old white Caucasian male presented to the Emergency Department with right-sided chest pain, dyspnoea and a dry cough, which had worsened over the previous three months. He also complained of haemoptysis and lethargy in the 10 days preceding admission.

The patient denied any fever or weight loss, had a 40 pack-year history of smoking and consumed 10 units of alcohol per week. His past medical history included appendicectomy and an inguinal hernia repair. Physical examination revealed reduced breath sounds on the right side of his chest, with an oxygen saturation of 94% on air, and normal abdominal examination. He was afebrile, with a heart rate of 130 beats per minute, a respiratory rate of 24 breaths per minute and blood pressure of 110/75 mmHg.

A full blood count revealed haemoglobin of 14g/dl, thrombocytosis with a platelet count of 682 (150-400) $\times 10^3$ per mm³, leucocytosis with a white blood cell count of 10,500 (4-11,000) cells/cu.mm and a neutrophil count of 80% of the total white blood cells. Other blood tests, including biochemical and blood cultures, were normal.

Chest X-ray demonstrated a 15.5 cm opacity in the right hemi-thorax (Figure 1). Computed tomography (CT) showed a soft tissue mass measuring 15.8 \times 9.5 \times 10.3 cm in the right lower lobe abutting the postero-lateral pleura, with no enlarged mediastinal or hilar lymphadenopathy. The lungs showed

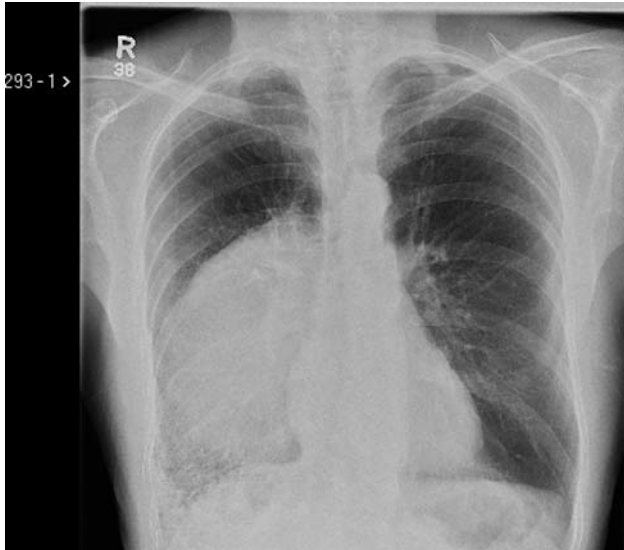


Figure 1. Chest X-ray demonstrated 15.5-cm opacity in the right hemithorax.



Figure 2. Computed tomography of the chest showed a soft tissue mass measuring 15.8×9.5×10.3 cm in the right lower lobe abutting the postero-lateral pleura.

background severe emphysematous changes with large bullae (Figure 2). Magnetic resonance imaging (MRI) of the chest showed a large heterogeneous mass located against the posterior chest wall on the right side, which was bright on the T1, T2 and Software for Tomographic Images (STIR) (Figure 3). There was no evidence of bone marrow edema in any of the ribs, in the costovertebral junction or in the vertebral body. No neural foramina involvement was seen.

A biopsy of the lesion showed fragments of necrotic material with occasional degenerated nuclei. In view of the symptomatic deterioration and uncertain diagnosis, the patient underwent a right lower lobectomy, and was discharged on the seventh postoperative day.

The microscopic examination of the resected specimen revealed a largely necrotic, centrally-cavitating and focally haemorrhagic tumour with a rim of viable tumour tissue at the periphery, which in areas appeared biphasic in nature with small nests of malignant epithelial cells within a malignant undifferentiated stromal component. The epithelial foci were composed of focal nests of squamoid cells and infrequent tubular structures formed by relatively uniform cells with round hyperchromatic nuclei and some eosinophilic cytoplasm. The malignant mesenchymal stroma was composed of medium-sized oval cells displaying pleomorphic, hyperchromatic nuclei with variable visible nucleoli. The stromal component was mitotically active, and very small, well-defined morular structures with a cartilaginous appearance were identified. The tumour invaded focally and appeared to breach the pleura.

Immunohistochemistry showed the tubular epithelial nests, to be positive for Epithelial membrane antigen (EMA),

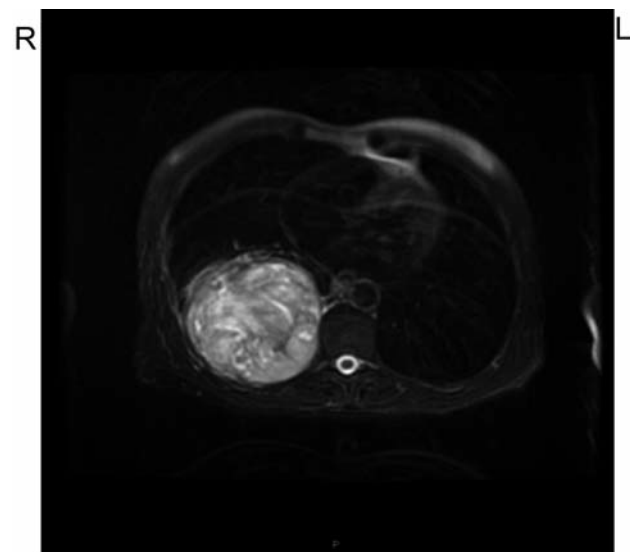


Figure 3. Magnetic resonance imaging of chest showing a large heterogeneous mass located against the posterior chest wall on the right side.

Creatine kinase 7 (CK7) and MNF 116 (Molls number- an epithelial marker), with variably patchy staining for Thyroid transcription factor 1 (TTF1). The squamoid nests were variably positive for CK 5/6 and MNF 116, and very focally stained for S100 protein. The mesenchymal component was negative for epithelial markers, but variably positive for vimentin, with patchy staining for CD56 (neuroendocrine

marker), Cytoplasmic B-cell lymphoma 2 (BCL2), Cytoplasmic Wilms tumour gene 1 (WT1), and CD99 (weak), and very focal staining for synaptophysin. The tumour was negative for chromogranin, Carcinoembryonic antigen (CEA), Smooth muscle actin (SMA), CD34 and Leucocyte common antigen (LCA).

The morphological appearance combined with the immunoprofile of the tumour were consistent with a poorly differentiated biphasic pulmonary blastoma (Figure 4).

The tumour had invaded the visceral pleura, but showed no lymph node involvement; and hence the pathological staging was pT3N0M0. There was a large pleural defect over the superior postero-lateral aspect of the lobe and completeness of excision in this area could not be guaranteed. The patient presented two months later with a painful subcutaneous swelling measuring 4×6 cm adjacent to the surgical scar on the right side of his chest posteriorly. He went on to have a Positron emission Tomography (PET) CT scan, which revealed multiple Fludeoxyglucose (FDG) avid pleural nodules, soft tissue recurrence and possible right adrenal metastases (Figure 5). A skin biopsy was performed, which confirmed a recurrent tumour, morphologically similar to the original resection specimen.

The patient was treated with four cycles of cyclophosphamide, doxorubicin and vincristine (CAV) based chemotherapy, achieving a partial response to treatment. He is currently on a two-monthly review and is recovering from chemotherapy-related toxicities.

Discussion

Pulmonary blastoma, originally described as an embryoma by Bernard in 1952 (3), is a rare and often difficult to diagnose tumour, usually found in the periphery of the lung. It presents with a wide variety of symptoms and signs including dyspnoea, chest pain, haemoptysis, cough, fever and pleural effusions. Approximately 40% of cases are asymptomatic, with the tumours being found incidentally on chest x-rays (4). The radiographic appearance tends to be that of a well-circumscribed lesion. In children, the mass can be large enough to take up most of the hemithorax, leading to mediastinal shift (5). The typical CT image is a cystic lesion with a necrotic centre.

Since 1988, childhood pleuropulmonary blastomas have been considered as a different pathological entity and are excluded from the adult classification. In adults, this tumour is usually seen in the younger age group, with a median age of presentation of 35.5 years (6-8). Adult pulmonary blastoma has been proposed to consist of two different tumor types: classic biphasic pulmonary blastoma (CBPB), characterized by both epithelial and mesenchymal malignant components in which the mesenchymal cells are derived from low-grade foetal lung adenocarcinoma, and well-differentiated foetal adenocarcinoma

(WDA); and the blastomatoid variant of carcinosarcoma, which originates from high-grade adenocarcinoma of foetal lung type (H-FLAC) which resembles foetal lung at 10 to 15 weeks of gestation (4). Molecular studies of gene mutations of p53 and β -catenin have provided evidence that both the epithelial and mesenchymal components of these tumors are monoclonal, and it has been suggested that the occurrence of a biphasic pattern is a later event that takes place within the epithelial component through the process of epithelial-mesenchymal transition (9).

Preoperative diagnosis tends to be difficult; cytology usually only identifies adenocarcinoma, although a diagnosis of CBPB should be suspected when a fine needle aspiration biopsy shows separate populations of epithelial and stromal cells (10).

Approximately 80% of CBPBs are found in adults (6) and the two peaks in age are the first and fourth decades of life, with a few cases which have been reported up to the age of 80 years. There is a slight male predominance and there is also an association with cigarette smoking (4).

Surgery is the first-line treatment for classical pulmonary blastoma; however, prognosis is poor, with a five-year survival rate of approximately 16% (4). To date, there is no standard therapy for metastatic disease. However, Zaidi *et al.* (11) reported a series of adults with pulmonary blastomas who were treated with neo-adjuvant chemotherapy with vincristine, dactinomycin, ifosfamide, etoposide, doxorubicin and platinum. These patients with advanced disease had a median survival of 30 months. A role for adjuvant chemotherapy is yet to be clearly defined and this is unlikely to occur considering the rarity of this condition. Data have been extrapolated from experience in treating primary pulmonary blastoma in children, which have shown varying responses to chemotherapeutic agents (cisplatin, cyclophosphamide, etoposide, vincristine, actinomycin D and adriamycin) (12).

We treated our patient with CAV chemotherapy, considering his age as well as issues related to tolerability. There have been reported disease responses with CAV chemotherapy in childhood pulmonary blastomas (13). Radiotherapy is reserved for incomplete resections and symptom palliation.

For our patient, we used a regimen with a proven activity in pulmonary blastoma, and achieved good clinical and radiological response. He is currently in clinical follow-up.

This case illustrates the need for clinicians to consider the diagnosis of pulmonary blastoma in patients with an uncertain histology on lung biopsy, and for initiating multimodality treatment in this highly aggressive disease with an uncertain outcome.

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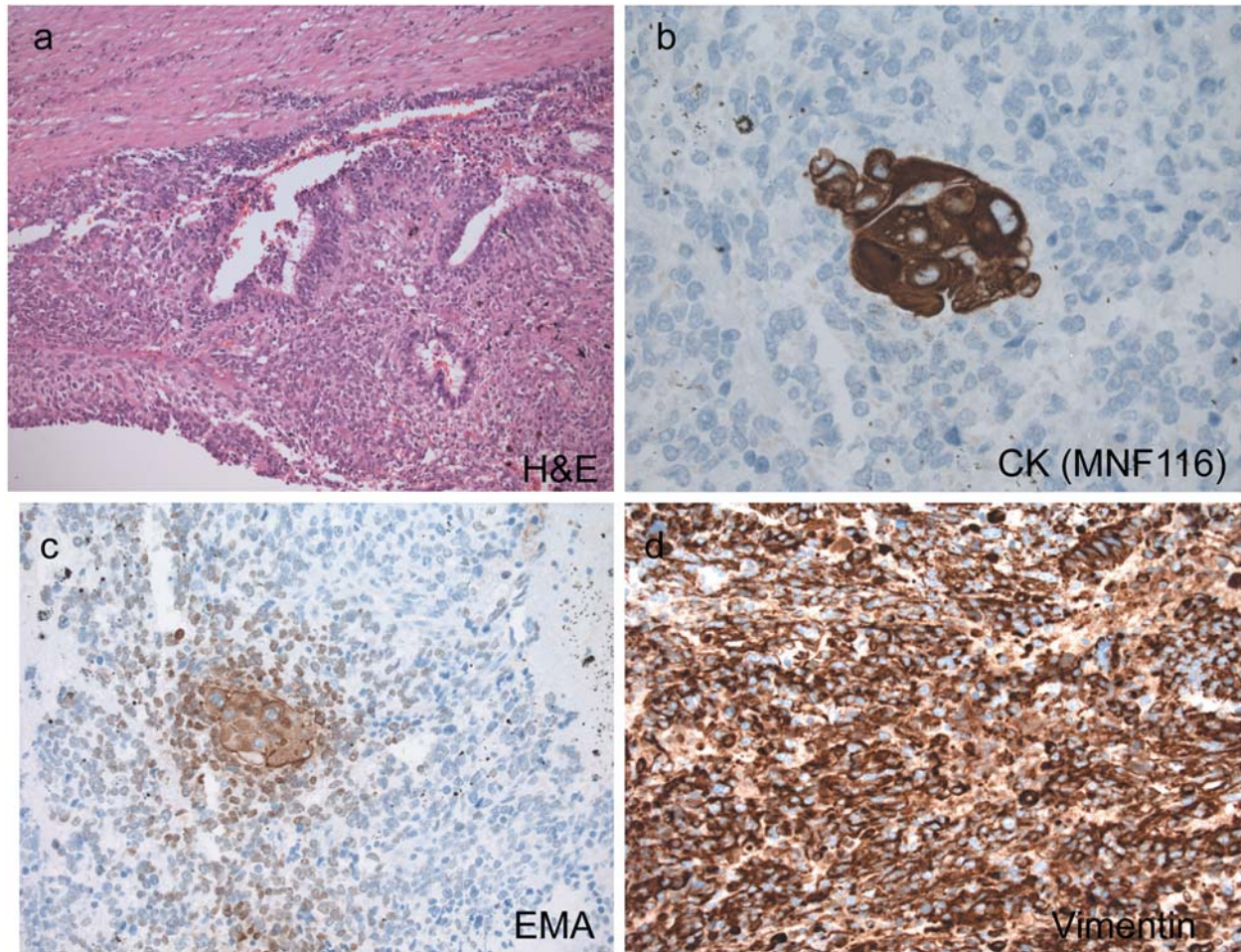


Figure 4. Histological images of the lung lesion. a) Malignant epithelial elements set in undifferentiated mesenchymal stroma (H&E $\times 100$) b) cytokeratin-positive epithelial island (MNF116 $\times 400$) c) EMA-positive epithelial nest ($\times 200$) d) Vimentin-positive malignant mesenchymal stroma $\times 200$.

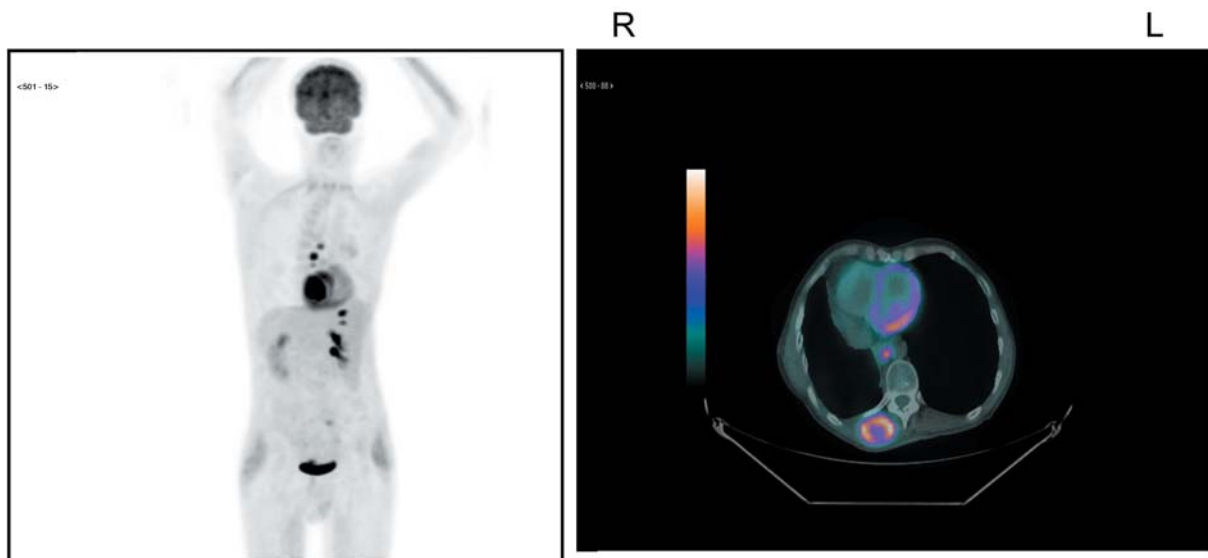


Figure 5. Positron emission tomography scan, which revealed multiple fluorodeoxyglucose avid pleural nodules, soft tissue recurrence and possible right adrenal metastases.

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