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Classic Biphasic Pulmonary Blastoma: A Case Report and Review of Literature

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Abstract. Pulmonary blastoma is relatively a rare aggressive tumour on adults with poor prognosis that usually presents at an early age than the non-small cell lung cancer. Pulmonary blastomas are subdivided in three subtypes: Well-differentiated foetal adenocarcinoma, classic biphasic pulmonary blastoma and pleuropulmonary blastoma. Classic biphasic pulmonary blastoma is composed of immature epithelial and/or mesenchymal tissues with similarity to an early embryonic lung. Pulmonary blastoma most commonly manifest as a solitary parenchymal mass on chest radiograph and Computerized Tomography. Symptoms are evident in 60% of cases due to the large tumour size. The World Health Organization differentiates pulmonary blastoma from pleuropulmonary blastoma and the well-differentiated foetal adenocarcinoma is included as a histological variant of adenocarcinoma. This report is the first case of classic biphasic pulmonary blastoma of a 16 years old female diagnosed at our department and treated by surgical intervention followed by chemotherapy. As for our knowledge, this is the first case reported in the Kingdom of Saudi Arabia. Extensive literature review of this category of lung malignancy is provided encompassing the clinical and pathological features, as well as the prognosis of this group of malignancy.

Keywords: Biphasic pulmonary blastoma, Pathology of lung blastoma, Immunohistochemistry of lung blastoma.

Introduction

Pulmonary blastoma (PB) is a rare and aggressive malignant tumour formed of immature neoplastic epithelium with or without neoplastic

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mesenchymal components with similarity to foetal lung[1]. Pulmonary blastoma first described by Barrett and Barnard[2], and it has been divided into three subgroups; classic biphasic pulmonary blastoma (CBPB), well-differentiated foetal adenocarcinoma (WDFA) and pleuropulmonary blastoma (PPB) of childhood[3]. Histologically, CBPB and WDFA are similar but they have distinct clinical and prognostic features. The best treatment of pulmonary blastoma is surgery in the early stages of the disease[4]. This report presents the first case of CBPB in Saudi Arabia.

Case Presentation

A 16-years-old female admitted to King Abdulaziz University Hospital complaining of cough and shortness breath for the last 4 years. Previously, she was diagnosed with psychiatric stressful symptoms. A year prior to admission, her symptoms got worse and persistent. On seeking de-novo medical attention; she was diagnosed with bronchial asthma. On admission, the patient primary complaint was cough, shortness of breath and headache; no other complains were documented. Patients' family history was negative for any significant illness.

Chest X-ray and computed tomography (CT) of the chest were performed and revealed a 6 x 5.8 cm right upper lobe lung mass (Fig. 1A & B) with no mediastinal lymph nodes enlargement. Several attempts to obtain a tissue diagnosis failed due to the patient health conditions (developing tachycardia and palpitation). An open chest surgery was performed and total tumour excision achieved. The surgical specimen was delivered to the pathology department.

Gross examination of the specimen revealed fragmented pieces of brownish firm tissue measuring 11 x 10 x 3 cm in aggregates and weighting 150 grams (Fig. 1C). On cut sectioning, the tissue was firm and revealed white areas. Microscopic examination revealed an ill-defined neoplastic growth showing biphasic pattern (epithelial and primitive mesenchymal) (Fig. 1D). The epithelial component was composed predominantly of irregular, closely packed variable size and shape glands. The glands were lined by pseudo-stratified bland-looking epithelium and some glands contained cytoplasmic mucin (Fig. 1E). The glands exhibited sub-nuclear, supra-nuclear and intra-cytoplasmic vacuolisation as well as cilia in some cells. The glands were surrounded by dense fibrotic stroma infiltrated by lymphoplasmacytic cells. Focal

nodular pattern with squamoid differentiation was seen (morule formation) but no mitotic activity observed in the glands. The second component was primitive mesenchymal component and was composed of round to spindled blue cells with granular chromatin and scanty

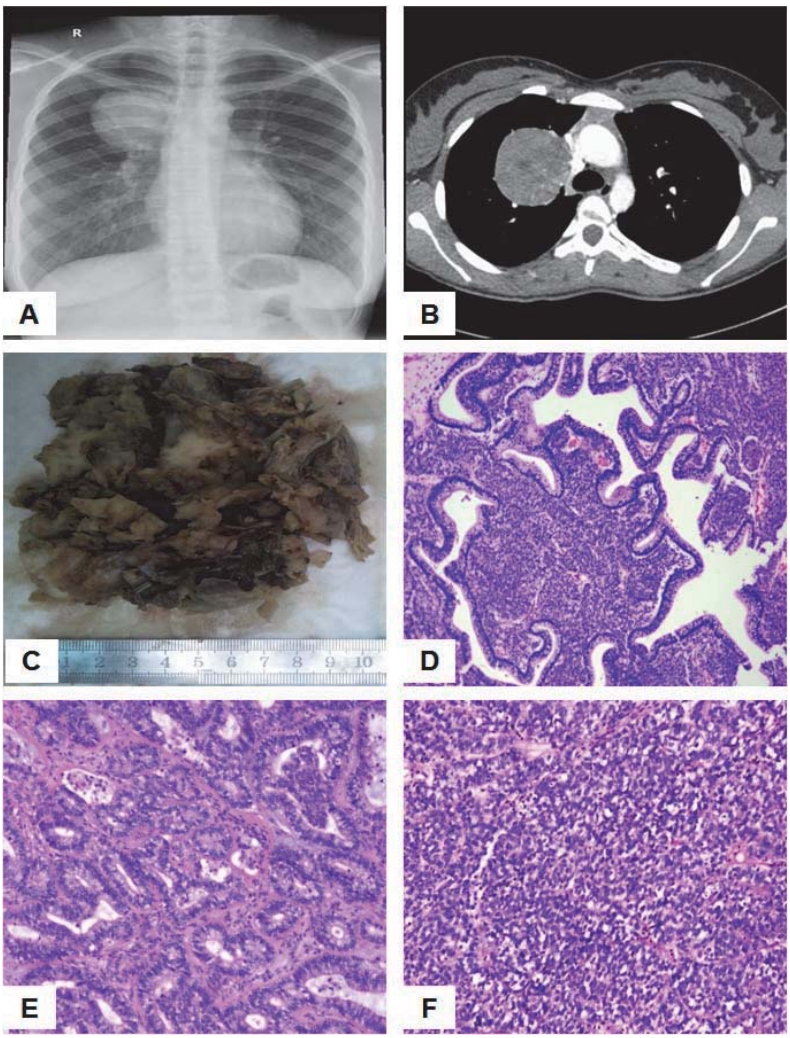

Fig. 1. ***A&B*** **represents radiological appearance of the tumour showing right upper lobe lung well circumscribed large mass.** ***C,*** **The gross appearance of the tumour revealed fragmented pieces of brownish firm with firm with white areas. In** ***D,*** **histopathological examination shows a mixture of glandular elements resembling foetal pulmonary tissue and an immature mesenchymal component (H&E). In** ***E,*** **the glandular elements consist of branching tubules lined by columnar cells with a clear**

cytoplasm and little nuclear atypia (H&E). In *F,* the stromal component is composed of round to spindled blue cells (H&E).

cytoplasm (Fig. 1F). This component formed large islands and sheets of cells with frequent mitotic activity, pyknotic nuclei and multiple rosettes formation. The mesenchymal component undermined the less malignant glandular component and the tumour grows with an infiltrative pattern into the adjacent lung tissue. Normal bronchial and lung tissue adjacent to the tumour was identified. A panel of immunohistochemistry stains were performed including; Pan-cytokeratin, TTF-1, vimentin, CK7, CK20, CK5/6, LCA, S-100, synaptophysin, chromogranin, NFP, GFAP, WT-1, EMA, calretinin, and actin. The Pan-cytokeratin and TTF-1 were diffusely positive in glandular areas, CK7 showed focal positivity in glandular areas, and vimentin was positive in mesenchymal areas (Fig. 2 A-D). The remaining of the immunohistochemistry stains were negative.

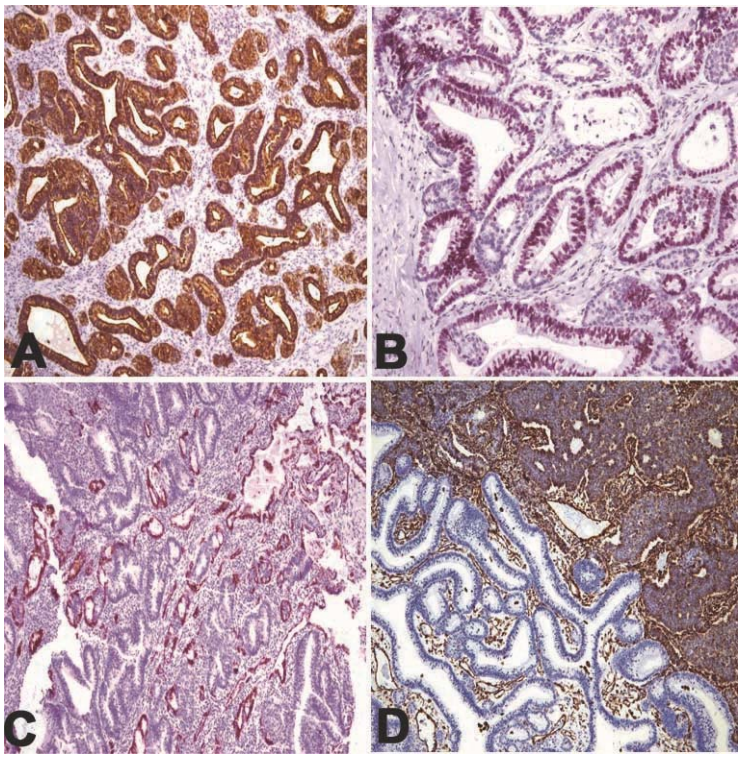

Fig. 2. Immunostaining of the tumour; *A*, the glandular component shows Pan-cytokeratin diffuse positivity. *B*, TTF-1 is diffusely positive in glandular cells. *C*, CK7 showed focal positivity in glandular areas, positive immunoreactivity *D*, Vimentin is positive in the mesenchymal cells. Immunohistochemical labelling using the primary

antibodies stated, with diaminobenzidine as the chromogen and haematoxylin counter stain.

The diagnosis of biphasic pulmonary blastoma (with foetal type invasive adenocarcinoma and malignant mesenchymal blastema component) was entertained. Patient is doing well until current time (three months after surgery) and she underwent chemotherapy treatment.

Discussion

Most of the published literature about pulmonary blastoma came from case reports or the experience of multiple centres over several decades[4]. The present study reported a case of CBPB and provided a review of recent issues regarding pulmonary blastoma.

Pulmonary blastoma forms only about 0.25–0.5% of malignant lung tumours[5]. This tumour was first recognised by Barrett and Barnard in 1945[2]. Later on, this tumour was termed embryoma of the lung, due to histological similarity to foetal lung tissue[3]. In 1961, Spencer had introduced the term blastoma to denote that the origin of pulmonary blastema similar to other tumours developing from foetal tissue as nephroblastoma[6]. Pulmonary blastoma is subdivided traditionally in three categories: Well-differentiated foetal adenocarcinoma (WDFA), PPB and classic biphasic pulmonary blastoma (CBPB)[5]. Well-differentiated foetal adenocarcinoma (WDFA) (formerly monophasic epithelial tumour) was identified by Kradin *et al*. in 1982 and consisted only of epithelial component[7,8]. Monophasic pulmonary blastoma composed only of malignant mesenchymal component was designated as PPB[8,9]. Classic biphasic pulmonary blastoma (CBPB) often viewed as a special type of carcinosarcoma in which the epithelial and/or mesenchymal components resemble foetal lung[10]. In 1999, the WHO classification of lung tumours designated the WDFA and PPB as variants of adenocarcinoma and soft tissue sarcoma, respectively[11]. However, in 2001, the WHO classification incorporated PB under the category of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements based on clinical, pathological and molecular data.

The well-differentiated foetal adenocarcinoma (WDFA) was considered as a histological variant of adenocarcinoma and was no longer regarded as a monophasic pulmonary blastoma. This change was due to the WDFA having a much better prognosis and the lack p53 mutations

seen in PB. Pulmonary blastoma can be distinguished histologically and clinically from pleuropulmonary blastoma. Pulmonary blastoma is observed in adults, whereas PPB is a cystic and/or solid sarcoma (included in soft tissue tumours) arising in children 6-years-old[12]. In the 2004, WHO classification of lung tumours, the WDFA was designated as a variant of adenocarcinoma of the lung and histologically composed of glandular elements with tubules formed of glycogen-rich, non-ciliated cells that resemble foetal lung tubules[13]. In a recent multidisciplinary classification of lung carcinoma, the well differentiated foetal adenocarcinoma is still considered as a variant of lung adenocarcinoma[14]. Therefore, it is inferred that WDFA is a variant of lung adenocarcinoma, and the term of PB is applicable to the CBPB.

Approximately 80% of CBPB cases occur in adults[5] with an average age of 43 years and unimodal age peak in the fourth decade[1]. 39 years old was the average age for CBPB occurrence in another study[4]. Other reports showed cases with age incidence below 48 years[1,5]. However, bimodal age distribution was described in different reports; in the first and in the seventh decades of life[16], and in the first and fourth decades, and some cases reported age range from 0 to 80 years[16]. Pulmonary blastoma usually presents at an earlier age, than the non-small cell lung carcinoma[17].

Sex prevalence is controversial. Reports support female prevalence[18,19]. While others showed male predominance[7,16,20], yet other reports found equal incidence among males and females[1,15,19]. Interestingly, series of cases showed the CBPB favoured men by 1.5:1, while the WDFA favouring woman with a ratio of 3:1[4]. In view of the current literature, there is no prognostic difference regarding gender.

Pulmonary blastoma usually presents as a large well-circumscribed lesion at the periphery of the lung[1]. The average size reported in the literature revealed different sizes; 10.1 cm [4], and 9.1 cm in largest diameter[1]. The large size of the tumours was also documented in radiological examination[21,22]. Mediastinal lymph nodes involvement was observed in about 80% of cases, which may explain the grim prognosis of PB[9].

These tumours present with cough, chest pain and haemoptysis, but in 40% they can be asymptomatic and discovered in routine chest X-ray; this occurs in cases with small tumour size[1]. WDFA consists only of

immature epithelium mimicking that is seen in the foetal lung (first trimester foetal lung), while CBPB is a biphasic neoplasm composed of immature epithelium and a malignant mesenchymal component[1,23]. PPB consists only of immature mesenchyme[9].

In CBPB, the epithelial component corresponds to low-grade adenocarcinoma of foetal lung type/well WDFA. It shows complex endometrioid glands, which resemble foetal lung and lined with glycogen-rich, and non-ciliated cells. It might show squamoid morules exhibiting rounded polygonal cells with ample eosinophilic finely granular cytoplasm and clear nuclei[1,24]. The stroma consists of loose undifferentiated mesenchyme that may be embryonic or blastema type and has variable degrees of nuclear atypia. The primitive stroma may differentiate toward osteosarcoma, chondrosarcoma, rhabdomyosarcoma, or combination of these tissues, or differentiate toward neuroendocrine cells[1,16,23,24].

Immunostaining is useful in the diagnosis of CBPB. And a combination of epithelial and mesenchymal markers should be used to exclude adenocarcinoma, carcinosarcoma, metastasis from endometrial carcinoma, and endometrioid adenocarcinoma of the ovary. The glandular cells are strongly reactive for cytokeratin, carcinoembryonic antigen and milk fat globulin and often chromogranin. Mesenchymal markers such as vimentin, actin, desmin, myoglobin, chromogranin, neurone specific enolase (NSE)[8,23,25] are also helpful in confirming the diagnosis. No serum tumour marker is specific for PB[26]. The histological origin of pulmonary blastoma remains unclear and is still under investigation[4,8,27].

It was speculated that CBPB may develop from a pluripotent blastema cells that give rise to the epithelial and mesenchymal tumour components[28]. These pluripotent cells may be stimulated through genetic and/or environmental influences to differentiate into both, epithelial and mesenchymal components. This view is supported by the positive immunostaining of cytokeratin and vimentin in the blastomatous component[29]. Simultaneous, expression of cytokeratin and vimentin in the blastomatous component was observed[28]. Origin of both cell populations by a single clone has been supported by expression of some molecules in both epithelial and mesenchymal components.

Mutations in p53 gene and protein over expression in the epithelial as well as the stromal component were observed[8,30]. CD117 was found to be expressed in both components[27]. Beta-catenin gene mutations were observed in CBPB and WDFA (frequently) with aberrant nuclear/cytoplasmic localisation of beta-catenin. The beta-catenin mutation is associated with a common histological feature, namely morule formation.

The presence of this genetic alteration found in both WDFA and CBPB implies a histogenetic linkage between these tumours. By contrast, most conventional lung carcinomas show membranous localisation of beta-catenin with no mutations in the gene[24,31].

PB is an aggressive tumour associated with a poor prognosis[29]. The poor prognosis is owing to rapid growth of the tumour, lymph node metastasis, and late discovery. However, surgical treatment of N0 cases showed favourable prognosis when combined with postoperative chemotherapy[8,32,33], especially in CBPB. The recurrence rate is high and requires close follow-up, especially the first year following surgery[4]. In our case, the patient has no lymph node metastasis (N0) and is doing well on chemotherapy until the time of writing this manuscript.

Up to our knowledge, this report is the first case of CBPB in Saudi Arabia, not only to add to literature, but to increase the experience from different institutions to improve diagnostic approaches, therapeutic intervention and disease outcome. Molecular characterisation of this tumour is required to identify efficient prognostic factors. However, the rarity of tumour may render large scale studies difficult, but inter-institutional cooperation may achieve this goal.

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الوَرَمُ الأَرومِيّ الرئوي ثنائي الطور الكلاسيكي: تقرير عن حالة ومراجعة ما كُتب عن الورم

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جـدة – المملكة العربية السعودية

المستخلص. الوَرَمُ الأَرومِيّ الرئوي هو ورم خبيث عنيف المسلك ونادر الحدوث عامة ويحدث في البالغين ولكن في سن أصغر من باقي الأورام السرطانية الرئوية. ينقسم هذا الورم إلى الورم الرئوي الجنيني الغدي المتمايز – الورم الأرومي الرئوي ثنائي الطور – الورم الأرومي الرئوي الجنبي الرئوي. الورم الأرومي الرئوي ثنائي الطور يتكون من نسيج ظهاري ولحمي غير ناضج يشبه الرئة الجنينية. يتم تشخيص هذا الورم من خلال الأعراض والتي تظهر في ٦٠٪ فقط من المرضى وأيضًا بالأشعة والفحص الباثولوجي. تم تشخيص الحالة التي بصددها هذا التقرير لفتاة تبلغ من العمر ١٦ عامًا بمستشفى جامعة الملك عبدالعزيز. وهي تحت العلاج الكيميائي حتى كتابة التقرير. وتعتبر هذه الحالة الأولى التي تسجل بالمملكة العربية السعودية، وفي هذا التقرير تم عرض الصفات الباثولوجية المختلفة للورم وطريقة تشخيصه ومراجعة ما تم نشره عن هذا الورم.