CASE REPORT

Nagoya J. Med. Sci. **78**. 507 ~ 516, 2016
doi:10.18999/nagjms.78.4.507

What do we know about pulmonary blastoma?: review of literature and clinical case report

Dorota Brodowska-Kania[1], Ewa Kotwica[1], Aleksandra Paturej[1], Witold Sośnicki[2], Janusz Patera[3], Agnieszka Giżewska[4] and Stanisław Niemczyk[1]

[1]*Department of Internal Medicine, Nephrology and Dialysis, Military Institute of Medicine, Warsaw, Poland*
[2]*Department of General Surgery, Oncology, Metabolic and Thoracic Surgery, Military Institute of Medicine, Warsaw, Poland*
[3]*Department of Pathology, Military Institute of Medicine, Warsaw, Poland*
[4]*Department of Nuclear Medicine, Military Institute of Medicine, Warsaw, Poland*

ABSTRACT

Pulmonary blastoma (PB) is a rare form of lung tumour and is accountable for 0.25–0.5% of primary pulmonary malignancies. Initially pulmonary blastoma was divided into three subtypes: biphasic pulmonary blastoma (BPB) consisting of an epithelial and mesenchymal component, well differentiated fetal adenocarcinoma (WDFA) built of well differentiated epithelium and a mesenchymal component and malignant pleuropulmonary blastoma (PPB). Prognosis in this type of cancer is really poor. We present a current review of literature and a clinical case report. Treatment of PB is very difficult. Data and recommendations about the treatment of pulmonary blastoma are still available therefore we should use only observations and clinical case reports.

Key Words: blastoma pulmonary, lung cancer, chronic kidney disease

INTRODUCTION

Pulmonary blastoma (PB), a rare lung tumour, is accountable for 0.25–0.5% of primary pulmonary malignancies.[1)] Since the first description by Barnett and Barnard in 1945 only about 300 cases have been described worldwide.[2,3,8)] The cancer was named in 1961 by Spencer for the similarity of its microscopic image to the fetal lung at the 10–16 week stage of development (paraadenomal stage of lung development).[4,5)] Initially pulmonary blastoma was divided into three subtypes: biphasic pulmonary blastoma (BPB) consisting of an epithelial and mesenchymal component, well differentiated fetal adenocarcinoma (WDFA) built of well differentiated epithelium and a mesenchymal component as well as malignant pleuropulmonary blastoma (PPB).[1)] The World Health Organization (WHO) classification from 1999 and 2004 qualifies BPB as a variant of pulmonary blastoma.[5)] Four collective studies on PB were published: Koss published a description of 53 cases from the archives of the Armed Forces Institute of Pathology from

Received: July 12, 2016; accepted: October 6, 2016

Corresponding author: Dorota Brodowska-Kania, MD
Department of Internal Medicine, Nephrology and Dialysis, Military Institute of Medicine,
Szaserów 128, 01-141 Warsaw, Poland
Tel/fax: +48261816811, Email: dbrodowska-kania@wim.mil.pl

1948 to 1988.[6] Larsen and Sorensen reviewed 202 Medline cases from 1962 to 1995, Van Loo analysed Medline cases from 1995–2011 and Yun-Xi Wang *et al.* collected 18 cases from General Hospital of PLA, Beijing (China) between 1989–2013.[7-9]

HISTOLOGICAL STRUCTURE AND AETIOLOGY

The tumour is built of an epithelial and mesenchymal stroma, where foci of osteosarcoma, chondrosarcoma, rabdomiosarcoma and yolk sac may be found.[10] Tumour specimens typically contain areas of necrosis and haemorrhage.[10-12] Tall, tubular glandular cells, translucent cytoplasm and hyponuclear vacuoles may be present.[4] Histogenesis of the disease is yet unknown, the mature mesenchymal tissue is composed of undifferentiated cells, which may return to their embrionic state and express into mesenchymal or epithelial tissue.[13] Risk factors of PB are not clearly defined. Smoking was reported in 67–82% of cases.[8,9] Additionally, benzopyrenes (by product of cigarette smoke) were found in the tumour mass.[14] A p53 gene mutation in PB similar to ones found in other pulmonary cancers may suggest a common aetiology.[14] A correlation between presence of cystic pulmonary disease among children and later development of pulmonary blastoma was observed.[7] A single case of a probable Epstein Barr Virus infection related pulmonary blastoma was reported.[15] A description of a 34-year-old man with von Recklinghausen's disease and pulmonary blastoma was found.[16] Another case concerns a patient with immunosuppressive therapy for graft-versus-host disease c-GVHD after allogeneic haematopoietic cell transplantation.[17] A single study analysed the role of mutation in beta-catenin genes in distinguishing PB from other types of lung cancer. Unfortunately, the authors analysed only five cases.[18] Nakatani suggests that nuclear β-catenin accumulation should be used as an additional criterion for the diagnosis of pulmonary blastoma.[19] Different immunohistochemic staining in PB was researched by Larsen and Sorensen. 35 different dyes were tried out on 156 different specimens and 9 stains were examined in more than 10 samples. The highest stain sensitivity was found with vimentin (90%), muscle actin (92%), neuron specific enolase (NSE – 83%), α-fetoprotein (AFP – 82%), cytokeratin (81%), epithelial membrane antigen (EMA – 71%) and carcinoembryonic antigen (CEA – 77%).[7]

EPIDEMIOLOGY

The average patients age at tumour diagnosis was between 39–53 years old.[6-9] Peaks of cancer incidence were noted in the 4th and 7th life decade.[7] Male predominance was noted by most reviewers, yet similar male female ratio is reported by Koss.[6-8,18] The disease is diagnosed among women at the age of 29 versus 48.2 years old among men.[20]

DIAGNOSTIC AND CLINICAL SIGNS

Asymptomatic tumours, accounting for 40% of cases, are detected during incidental chest x-rays.[6,8] The most common symptoms that occur are: cough, haemoptysis, shortness of breath, recurrent pneumonia, fever and weight loss.[6,8] Occasionally spontaneous pneumothorax or neurological symptoms were present.[8] A single case of a 4 year old boy with pulmonary blastoma preceded by pneumothorax was reported.[21] Chinese research shows 83% of patients to have nonspecific symptoms like: cough, haemoptysis, chest pain, and chest tightness.[9] In 98% of cases the tumour is restricted to one lung, with higher incidence in superior lobes and no

side preference.[6,8] The mean tumour size was 7–10 cm.[6,8,9] On radiographs the mass is well circumferenced, limited and may displace the mediastinum.[8] In CT scans PB is composed of dense and vesical elements with varying contrast uptake and central necrosis.[8] Invasion of pleura is possible and endobronchial growth is present in 25% of cases.[22] Preoperative undisputable histopathological diagnosis is difficult due to the presence of both an epithelial and mesenchymal component. Acquiring a diagnostic biopsy specimen may be challenging as the tumour does not originate from the bronchi wall and pressure exerted by the mass may close the bronchi lumen. It is important to emphasize that PB is a lung neoplasia not originating from bronchial epithelium. A PET CT scans reveals abnormal increased FDG uptake.[9] No characteristic PB markers were found. A single report described elevated serum levels of AFP and CEA, in another case specific enolase was elevated in serum.[14,23]

PROGNOSIS AND RISK FACTORS

Prognosis is poor, 60% of patients die within 2 years of diagnosis, only 16% and 8% survive 5 and 10 years post diagnosis, respectively. Singular cases of long-term survival are reported.[6] Metastasis is present in ~43% of cases and is typically found in the brain, mediastinum, pleura, diaphragm, liver and soft limb tissue submandibular glands, scrotum and ovaries.[24,25] Interestingly relapses occur mostly within the first 12 months of the tumours' surgical removal.[7] Relapses observed shortly after the time of excision may suggest regrowth of an incompletely removed tumour. Relapse, presence of metastasis and tumour size exceeding 5 cm are reported to be unfavourable prognostic factors.[6]

TREATMENT

Because of well-localised mass, surgery is the preferred method of PB treatment. The range of operations should be determined individually and depends on the tumour size, lymph node metastasis, pleural invasion and comorbidities. The average survival rate among operated patients is 33 months, as compared to 2 months' survival in non-operated patients.[6] The survival rate after partial lobectomy was found to be higher than compared to total lung resection.[7] Retrospective analysis from a single center reports the longest PB survival to be 9 years. Two year and five year survival rates were 85.7% and 71.4% respectively. Additionally, registered deaths were not a result of disease recurrence or therapy.[26] Non-metastatic tumours, not exceeding 5 cm may be treated with radiotherapy.[22] Radiotherapy is used in unresectable tumours resistant to other forms of treatment and as an adjuvant therapy in brain metastasis.[8,27] Use of chemotherapy was reported only in sporadic cases, randomized trials on the effectiveness of chemotherapy are lacking. Due to complex histological tumour structure, chemotherapy must be effective against both components. Response to treatment was observed by Larsen and Sorensen among 26% of patients who received chemotherapy as the first line of treatment. No response was noted in patients who received chemotherapy as the secondary line of treatment. Reaction was only achieved with multidrug treatment including alkylating agents, antibiotics and mitotic inhibitors.[7] One of the first therapies suggested in 1984 included cyclophosphamide, vincristine, doxorubicin and dactinomycin, therapy effective in histologically similar neoplasia to pulmonary blastoma: nephroblastoma and rabdomyosarcoma.[28] Recent publications report effectiveness of chemotherapy in singular cases. Partial response in a postsurgical PB relapse was achieved using ifosfamide combined with doxorubicin and radiotherapy.[29] The combination of cisplatin with etoposide

allowed a reoperation in another case of PB relapse. Response to sorafenib was also reported.[30] The literature describes a complete 3 month remission (on-going follow-up) after treatment with an adjuvant platinum-based chemotherapy comprising of ifosfamide, carboplatin, and etoposide (ICE protocol).[31] Chemotheraphy – etoposide and cisplatinum were used in inducing a remission in a 16 year old boy suffering from PB stage 4. He survived one year.[32] In another case carboplatin, paclitaxel and bevacizumab proved to be temporarily effective.[23] After two courses of the chemotherapy, serum levels of AFP decreased from 1120.0 to 441,2 ng/mL, those of NSE decreased from 15,2 to 9,6 ng/mL, and those of CEA decreased from 4,7 to 3,1 ng/mL). Bevacizumab, an IgG monoclonal antibody against vascular endothelial growth factors (VEGF), prevents the binding of VEGF with its receptor on vascular endothelial cells, thus showing antitumor effect.[33] A single case reports sorafenib's use in PB with kidney metastasis, which allowed for a radical nephrectomy to be performed.[30] There is no conclusive data on the effectiveness of chemotherapy or radiotherapy in PB. Most data from literature refers to case reports.[14,16,34] Randomized clinical trials are needed to determine recommendations for the treatment regimen in pulmonary blastoma.

CLINICAL CASE REPORT

We present a case report of a 73 year old patient (height 178 cm, weight 81 kg, BMI 25.56), who has remained under monthly supervision of the Nephrology Clinic for 4 years. Four years

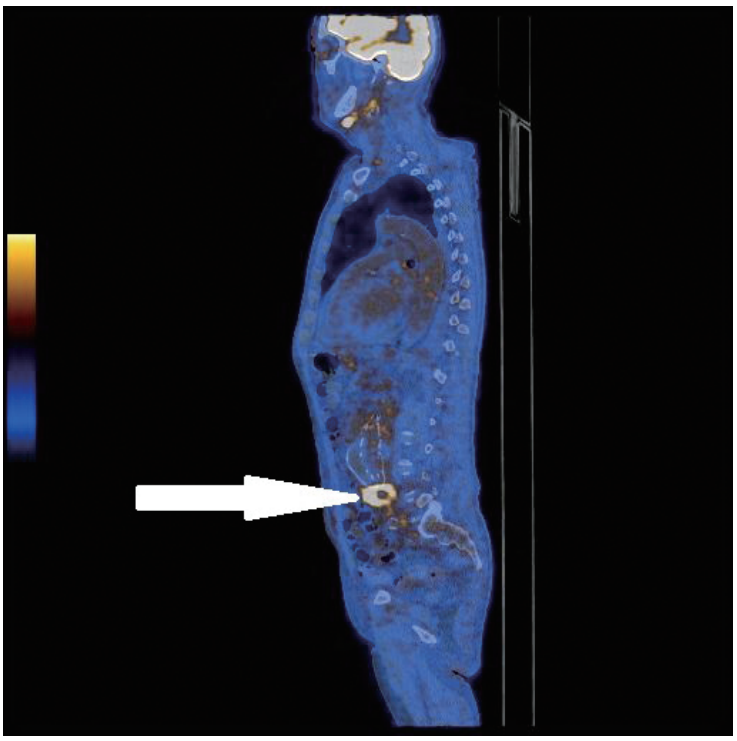

Fig. 1 PET-CT, sagittal plane, patient after implantation of the aortic graft. Arrow marks the focus of intensively increased glucose uptake in the retroperitoneal space, on the border of the abdominal aorta and the left iliac artery – limited inflammatory infiltration of the graft.

prior to tumour diagnosis, the patient underwent a stent graft implantation due to an abdominal aorta aneurysm. The procedure was complicated by a contrast induced nephropathy requiring temporary haemodialysis. After two months of supportive care, haemodialysis was started in an urgent manner (left subclavian vein). After 2 months the patient developed a systemic Methycilin Resistant Staphylococcus Aureus (MRSA) catheter-related bloodstream infection. The patient was treated for 8 weeks with vancomycin (with the drug's concentration monitored). A PET CT scan during hospitalization revealed increased fluorodeoxyglucose uptake in the extraperitoneal space – an abscess (5 cm in diameter) (Fig. 1). Conservative treatment of the catheter related sepsis and modification of the hypertension's treatment resulted in an improvement of the kidney function (chronic kidney disease (CKD) stage IV), dialyses were no longer compulsory. The patient remained in stage IV CKD and thus participated in an erythropoietin programme run by the Nephrology Clinic for 17 months (until the tumour's detection). The patient was treated with a long-acting erythropoietin receptor activator (60 μg of *Mircera* (Roche)) for 17 months. Furthermore, medical history included hyperuricemia with gout attacks, hypertension and diet controlled type II diabetes.

After two years' the patient was admitted in an urgent manner to the Nephrology Clinic due to treatment-resistant pneumonia (on 5th day of cefuroxime therapy). Presenting symptoms included progressive asthenia, resting dyspnoea, productive cough with purulent, sanguineous sputum lasting 7 days, no fever. During physical examination the patient was in strenuous condition and central cyanosis was present. Additionally, rhonci and a quiet vesicular sound on the left side were noted. Laboratory tests showed signs of inflammation (CRP 7.3 mg/dl (0–0.8); procalcitonin 0.26 ng/ml, fibrinogen 731 mg/dl (200–400), significant iron deficiency (Fe 50 ug/dl (70–180), but no anaemia (RBC 4.15/10^9 (3.5–5.5), HGB 12.7 g/dl (11.0–18.0), kidney dysfunction (creatinine 3.1 mg/dl (0.7–1.2) urea 123 mg/dl (18–55) and an elevated D-dimer value 20.3 μg/ml (0.00–0.50). In the lateral view of the chest x-ray an oval nodule in the area of the posterior mediastinum at Th4/5 was observed. In the anterior-posterior AP view persistent peribronchial thickening in the lower lobes was noted (Fig. 2A–B). One and a half

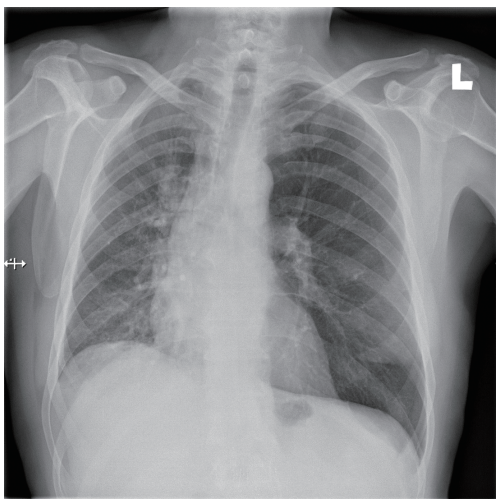

Fig. 2A Chest X-ray, posterior-anterior view – persistent peribronchial thickening in the lower lobes.

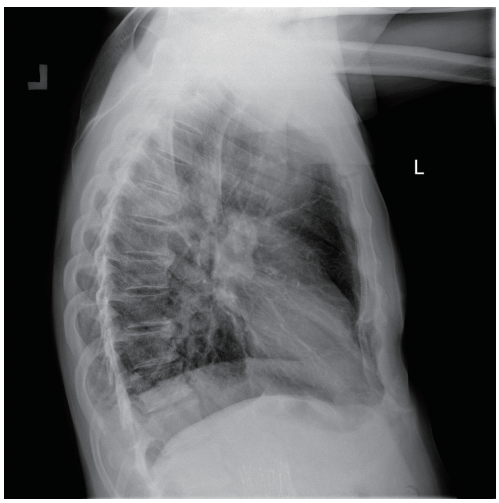

Fig. 2B Chest X-ray, latero-lateral view. Oval lesions in area Th4/Th5

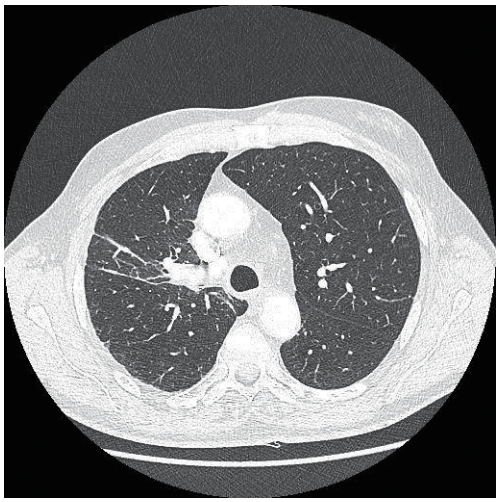

Fig. 3 CT scan shows tumour in the right lung measuring 52×30 mm. No enlarged mediastinal lymph nodes.

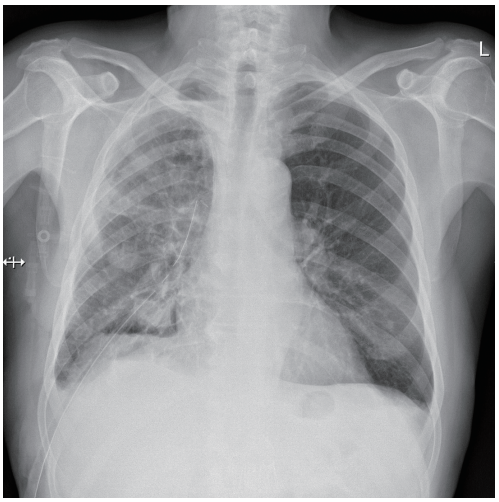

Fig. 4 Chest X-ray, posterior-anterior view after the surgical removal of the intermediate lobe of the right lung. Drain in the right pleural cavity. The postoperative chest radiograph revealed no pneumothorax.

years earlier no abnormalities were present in a routine chest X-ray. Furthermore, four weeks prior to hospitalization during a routine out-patient visit, no symptoms of respiratory infection were present. A homogenous, solid mass measuring 52×30 mm at the base of right lung's segment 2 was revealed in a CT scan without contrast due to CKD (Fig. 3). Furthermore, the right bronchus was obstructed by a mass communicating with the tumour. Intrabronchial nodules, thickening of the bronchial walls leading to the 2nd and 3rd segment, a ground glass pattern at the border of 2nd and 3rd segment as well as slight peripheral consolidation of the lung tissue was described in the CT scan, with no enlarged mediastinal lymph nodes. Two enlarged submandibular lymph nodes (5,2×13 mm and 4,7×11,3 mm) without hilus abnormalities were observed in neck ultrasonography. No aberrations were found in a neck CT scan. A flexible bronchoscopy revealed an exophytic mass closing the right bronchus, from which a pinch biopsy was taken. The biopsy was undiagnostic. As second bronchoscopy was once again undiagnostic, a rigid bronchoscopy was performed. The microscopic image was suggestive of a complex neuroendocrine macrocelullar cancer with a fusiform component and focal squamous differentiation. The patient was qualified for tumor resection. The patients level of chromogranin A was significantly elevated: 1529 ng/ml (19.4–98.1). In order not to delay the operation, further neuroendocrine diagnosis was postponed until after the resection. Prior to operation the following hormone levels were measured: adrenocorticotropic hormone (ACTH), morning cortisol level, thyroid stimulating hormone (TSH). There were no abnormalities.

Three months after pneumonia a wedge resection of the right lungs upper lobe was performed. The operation included right anterolateral thoracotomy, right upper lobe resection, mediastinal lymphadenectomy and right intercostal drain. Somatostatin was administered preventively during the operation as the tumour's hormone production was unknown. The postoperative chest radiograph revealed no pneumothorax (Fig. 4). Post-surgical histopathology affirmed the presence of pulmonary blastoma: a multifocal tumor, infiltrating the parenchyma, lobar and segmental bronchi with areas of necrosis and a clear resection margin (Fig. 5A–D). Cancer staging was

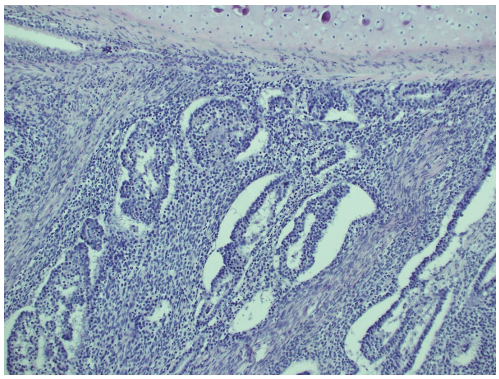

Fig. 5A Pulmonary Blastoma. Hematoxylin and eosin stain (H&E). Biphasic tumor composed of bronchioling epithelial tubules or cords set in an undifferentiated stroma. On top of the image stroma with chondroid differentitation. (magnification 100×)

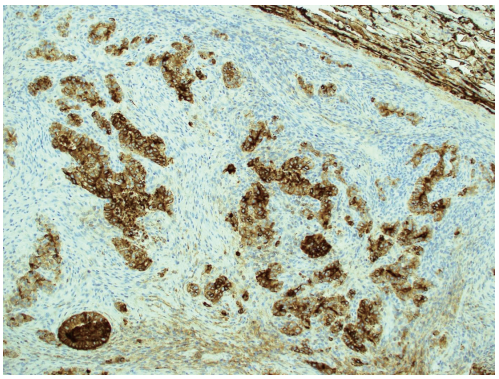

Fig. 5B Pulmonary Blastoma. Cytokeratin AE 1/3 stain. (magnification 100×)

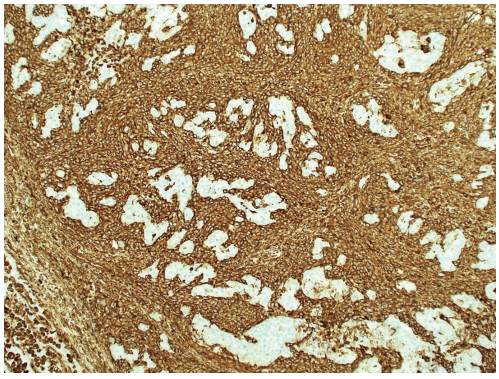

Fig. 5C Pulmonary Blastoma. Vimentin stain. The mesenhymal components and pseudocapsula. (magnification 100×)

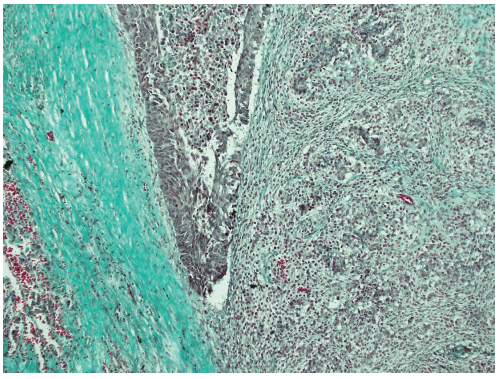

Fig. 5D Pulmonary Blastoma. Trichrom Masson stain. (magnification 100×)

Fig. 5 (A–D) Histopathological results. The microscopic picture of pulmonary blastoma – staining with hematoxylin and eosin (H&E), cytokeratin, Vimentin and Trichrom Masson. (magnification 100×)

pT2aN0M0. The patient did not receive adjuvant therapy. During two months the patient's body mass reduced by 10 kg. Further clinical course was complicated by recurrent pneumonia that was treated effectively with piperacillin and tazobactam.

A control CT chest scan 3 months after surgery visualized free fluid in the area of right lung's upper lobe, partially penetrating a horizontal fissure. Furthermore, the horizontal fissure was thickened with gas alveoli in the central part and post-surgical clipses in the vicinity. In addition, the lung hili were enlarged, (most likely due to lymph node enlargement). Chromogranin A concentration elevated to 760.9 ng/ml (19.4–98.1).

Due to chronic kidney disease the possibilities of diagnostic imaging were limited. To diagnose the elevated level of chromogranin A, a PET CT scan was ordered, which showed a spot of

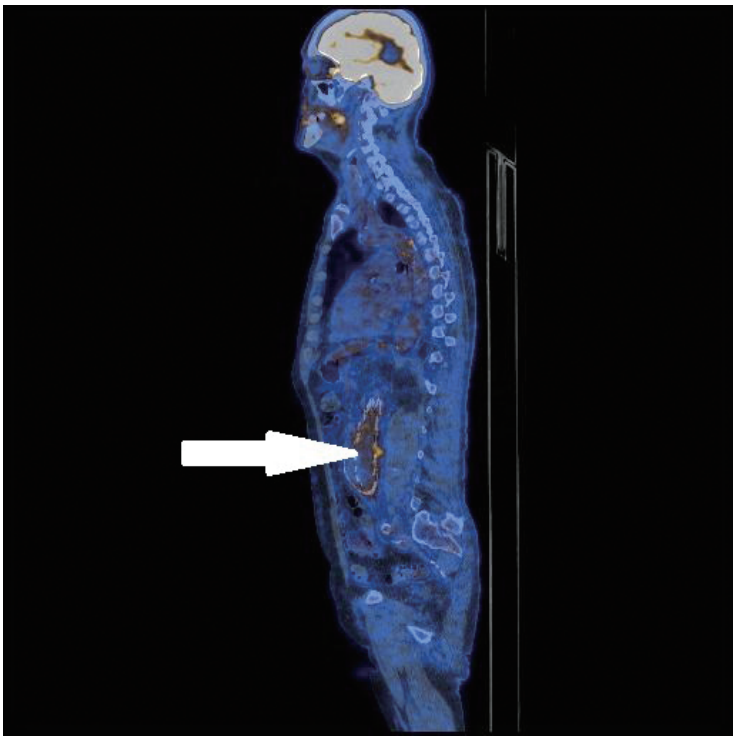

Fig. 6 Image of PET-CT in the sagittal plane on the same patient after surgery. Arrow, marked focus moderately increased metabolism 18F-FDG in the retroperitoneal space – residual reactive changes. (Changes with a history catheter sepsis). No outbreaks of increased metabolic fluorodeoxyglucose. No evidence of cancer of increased FDG metabolism.

increased fluorodeoxyglucose uptake in the vicinity of the resected lobe remnants (Fig. 6). A bronchoscopy showed a nodule in the scar tissue, yet no cancerous cells in the histopathology were found. Chromogranin A levels remained too high.

In a control CT scan 24 months after diagnosis, no pathological lesions in the lungs and lymph nodes were observed. The patient is currently in good clinical condition, no symptoms from the respiratory system or anaemia are present. The patient was once again entered in to the erythropoietin programme. After 48 months the patient remains in full remission with no indications of relapse or metastases. A control CT scan is performed every 3 months.

DISCUSSION

Pulmonary blastoma is a rare tumour among the elderly. The presented case report shows typical symptoms and rapid tumour growth, however late onset is uncharacteristic. The diagnosis was difficult as the use of iodinated contrast was limited due to CKD. Furthermore, 2 biopsies were inconclusive due to tumour growth in the lung parenchyma constricting the primary bronchus. The tumour did not infiltrate the primary bronchus wall. High chromogranin A concentration (over 20 times the upper limit at the time of diagnosis) could have suggested neuroendocrine tumours (NET) or be a result of comorbidities: CKD or the use of proton-pump inhibitors. Furthermore,

surgical biopsy suggested diagnosis of NET. Despite comorbidities the patient was qualified for marginal resection, which is rarely performed nowadays. Due to comorbidities and expected complications, the patient was disqualified from adjuvant therapy. The patient has remained in good clinical condition for the past 36 months, and the favourable outcome is rare for this tumour type. Furthermore, patient achieved remission despite lack of adjuvant therapy, the marginal lung resection was sufficient. Relapses are usually associated with incomplete tumour resection. There is a correlation between time and use of erythropoietin stimulating agent (ESA) and the tumour development. Yet, the oncogenic potential of ESA is not supported by any literature. Further trials and observations are needed to determine the correlation between ESA and the tumour growth. As the patient is in remission, he has been returned to the erythropoietin programme and is monitored for relapse.

SUMMARY

Pulmonary blastoma is a really rare and malignant neoplasm with poor prognosis. It grows rapidly, and diagnosis is problematic due to its two-phase construction and localization. The patients' outcome is negatively affected by the delay in diagnosis. Lack of specific treatment remains a major problem. The selection of appropriate drugs is difficult due to the complex structure of the cancer and a need to connect two lines of therapy directed against different components. The rarity of the cancer also causes difficulties in developing an effective treatment regimen. Therefore, it should be noted that the treatment regimen must be developed individually for each patient.

ACKNOWLEDGMENTS

All authors of the manuscript declare no conflict of interest. All authors agree with the content of the manuscript. The paper has not been published or submitted for publication elsewhere.

REFERENCES

1) Smyth R, Fabre A, Dodd J, Bartosik W, Gallagher C, McKone E. Pulmonary blastoma: a case report and review of the literature. *BMC Res Notes*, 2014; 13: 294.
2) Barnett N, Barnard W. Some unusual thoracic tumors. *Br J Surg,* 1945; 32: 441–457.
3) Jethava A, Dasanu C. Adult biphasic pulmonary blastoma. *Conn Med,* 2013; 71: 19–22.
4) Spencer H. Pulmonary blastomas. *J Pathol Bacteriol,* 1961; 82: 161–165.
5) Travis W, Brambilla E, Muller-Hermelink H, Harris C. World Health Organization classification of tumors: pathology and genetics of tumors of the lung, pleura, thymus and heart. *IARC Press: Lyon;* 2004.
6) Koss M, Hochholzer L, O'Leary T. Pulmonary blastomas. *Cancer,* 1991; 67: 2368–2381.
7) Larsen H, Sorensen J. Pulmonary Blastoma: a review with special emphasis on prognosis and treatment. *Cancer Treat Rev,* 1996; 822: 145–160.
8) Van Loo S, Boeykens E, Stappaerts I, Rutsaert R. Classic biphasic pulmonary blastoma: A case report and review of the literature. *Lung Cancer*, 2011; 73: 127–132.
9) Wang Y, Zhang J, Chu X, Liu Y, Li F, Wang ZB, *et al.* Diagnosis and multi-modality treatment of adult pulmonary blastoma: Analysis of 18 cases and review of literature. *Asian Pac J of Trop M,* 2014; 7: 164–16.
10) Desai H, Amonkar GP, Kavishwar VS, Deshpande J. Pulmonary blastoma with yolk sac elements. *Indian J Pathol Microbiol*, 2010; 53: 875–876.
11) Yu L, Li X, Yang W. Pulmonary Blastoma Metastatic to the Ovary. *Int J Gynecol Pathol*, 2009; 28: 59–62.
12) Corrin B, Nicholson A. Pathology of the Lungs, 3rd Edition. 564–591, 2011. Elsevier, Churchill Livingstone.
13) Maeda R, Isowa N, Onuma H, Miura H, Kawasaki Y, Yamamoto K. Biphasic pulmonary blastoma with

rapid progression. *Gen Thorac Cardiovasc Surg,* 2009; 57: 104–107.
14) Surmont V, van Klaveren R, Nowak P, Zondervan P, Hoogsteden H, van Meerbeeck J. Unexpected response of a pulmonary blastoma on radiotherapy: a case report and review of the literature. *Lung Cancer*, 2002; 36: 207–211.
15) Wyatt D, Coyle P. Persistent polyclonal B lymphocytosis with Epstein-Barr virus antibodies and subsequent malignant pulmonary blastoma. *J Clin Pathol*, 1991; 44: 966.
16) Robert J, Pache J, Seium Y, de Perrot M, Spiliopoulos A. Pulmonary blastoma: report of five cases and identification of clinical features suggestive of the disease. *Eur J Cardiothorac Surg*, 2002; 22: 708–711.
17) Cluzeau T, Sirvent A, Lassalle S, Mouroux J, Mounier N. Pneumoblastoma: a rare lung tumour occurring as a long-term complication after allogeneic haematopoietic cell transplantation. *Bone Marrow Transplant*, 2010; 45: 197–198.
18) Macher-Goeppinger S, Penzel R, Roth W, Dienemann H, Thomas M, Schnabel PA, *et al.* Expression and mutation analysis of EGFR, C-KIT and β-catenin in pulmonary blastoma. *J Clin Pathol,* 2011; 64: 349–353.
19) Nakatani Y, Miyagi Y, Takemura T, Oka T, Yokoi T, Takagi M, *et al.* Aberrant nuclear/cytoplasmic localization and gene mutation of beta-catenin in classic pulmonary blastoma: beta-catenin immunostaining is useful for distinguishing between classic pulmonary blastoma and a blastomatoid variant of carcinosarcoma. *Am J Surg Pathol,* 2004; 28: 921–927.
20) Francis D, Jacobsen M. Pulmonary Blastoma. *Curr Top Pathol*, 1983; 73: 265–294.
21) Mammas I, Koutsaftiki C, Tapaki-Papadopoulou G, Myriokefalitakis N. Pneumothorax in a child with pulmonary blastoma. *J Pediatr*, 2011; 159: 162.
22) Liman S, Altinok T, Topcu S, Tastepe AI, Uzar A, Demircan S, *et al.* Survival of biphasic pulmonary blastoma. *Respir Med*, 2006; 100: 1174–1179.
23) Sakata S, Saeki S, Hirooka S, Hirosako S, Ichiyasu H, Kohrogi H. A Case of Biphasic Pulmonary Blastoma Treated with Carboplatin and Paclitaxel plus Bevacizumab. *Case Rep Oncol Me,* 2015; 2015: 842621.
24) Syrigos K, Katirtzoglou N, Ntomi V, Pierrakou A, Chorti M, Stratakos G, *et al.* Pulmonary Blastoma with Submandibular, Scrotum and Adrenal Metastases: Case Report. *Respiration,* 2012; 83: 83–86.
25) Kawasaki K, Yamamoto K, Suzuki Y, Saito H. Surgery and radiation therapy for brain metastases from classic biphasic pulmonary blastoma. *BMJ Case Rep,* 2014; 3: 2014.
26) Adluri R, Boddu S, Martin-Ucar A, Duffy J, Beggs FD, Morgan WE. Pulmonary blastoma – a rare tumor with variable presentation. *Eur J Cardiothorac Surg,* 2006; 29: 236–239.
27) Zaidi A, Zamvar V, Macbeth F Gibbs AR, Kulatilake N, Butchart EG. Pulmonary blastoma: medium-term results from a regional center. *Ann Thorac Surg,* 2002; 73: 1572–1575.
28) Medbery CA, Bibro MC, Phares JC, Veach SR, Martin JE, Pasquale DN. Pulmonary blastoma. Case report and literature review of chemioterapy experience. *Cancer*, 1984; 53: 2413–2416.
29) Lindet C, Vanhuyse M, Thebaud E, Robin YM, Penel N. Pulmonary blastoma in adult: dramatic but transient response to doxorubicin plus ifosfamide. *Acta Oncol,* 2011; 50: 156–157.
30) Mulamalla K, Truskinovsky A, Dudek A. Pulmonary Blastoma with Renal Metastasis Responds to Sorafenib. *J Thorac Oncol,* 2007; 2: 344–347.
31) Alahwal MS, Maniyar IH, Saleem F, Alshiekh M. Pulmonary blastoma: a rare primary lung malignancy. *Case Rep Med,* 2012; 471613.
32) Cutler CS, Michel RP, Yassa M, Langleben A. Pulmonary blastoma. Case report of a patient with a 7-year remission and review of chemotherapy experience in the world literature. *Cancer,* 1998; 82: 462–467.
33) Gerber H, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Research*, 2005; 65: 671–680.
34) He W, Jiang G, Xie B, Liu M. Radical resection of a pulmonary blastoma involving the pulmonary artery. *Eur J Cardiothorac Surg,* 2008; 34: 695–696.