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# Hemoptysis in a patient with multifocal primary pulmonary angiosarcoma

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## Abstract

Primary pulmonary angiosarcoma (PPA) is a rare tumour arising from arterial or venous pulmonary vessels of various size. It is characterized by aggressive course and poor prognosis. The early diagnosis is difficult due to diverse clinical and radiological manifestations. We present a case report of 70 year-old man, active cigarette-smoker, with a 2-month history of non-massive hemoptysis. The thorax CT revealed several solid pulmonary nodules surrounded by areas of ground glass opacity. As bronchoscopy failed to deliver adequate tissue samples, video assisted thoracic surgery (VATS) with pleura and lung biopsy was necessary. Histopathological findings were consistent with pulmonary angiosarcoma. Since no extrapulmonary lesions were demonstrated, the final diagnosis of primary pulmonary angiosarcoma was made. The patient died three months after the onset of symptoms. Our case report highlights that differential diagnosis in patients with hemoptysis and pulmonary nodules should include primary pulmonary sarcoma.

**Key words:** angiosarcoma, primary pulmonary angiosarcoma, hemoptysis, spontaneous hemothorax, lung tumor

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## Case presentation

A 70-year-old man was referred to our department from one of municipal hospitals in January 2016 with a 2-month history of non-massive hemoptysis (daily volume of expectorated blood was approximately 15 ml). The patient also reported weight loss of 3 kg during the last month, general weakness and mild recurrent epistaxis. His past medical history included arterial hypertension and chronic sinusitis, both diagnosed approximately 10 years ago. He had also undergone endovascular stent grafting of abdominal aorta aneurysm as well as transurethral resection of the prostate due to benign prostatic hyperplasia. He was an active cigarette-smoker with a history of 52 pack-years of tobacco smoking. During the hospitalisation in the municipal hospital two

pulmonary nodules in the left lower lobe were found in chest radiograph. These findings were confirmed in thorax CT scan which also showed ground glass areas surrounding the nodules (halo sign).

On admission the patient's general condition was satisfactory. His vital signs were within normal range: arterial blood pressure was 120/80 mm Hg, heart rate 80 beats per minute, transcutaneous arterial oxygen saturation 93% while breathing room air. Dullness to percussion and diminished breath sounds over the left lower lung field was noted on physical examination. Except these findings the physical examination did not reveal any relevant abnormalities.

The results of laboratory studies showed normocytic anaemia (hemoglobin level 90.5 g/L), an elevated peripheral white blood cell count (WBC)

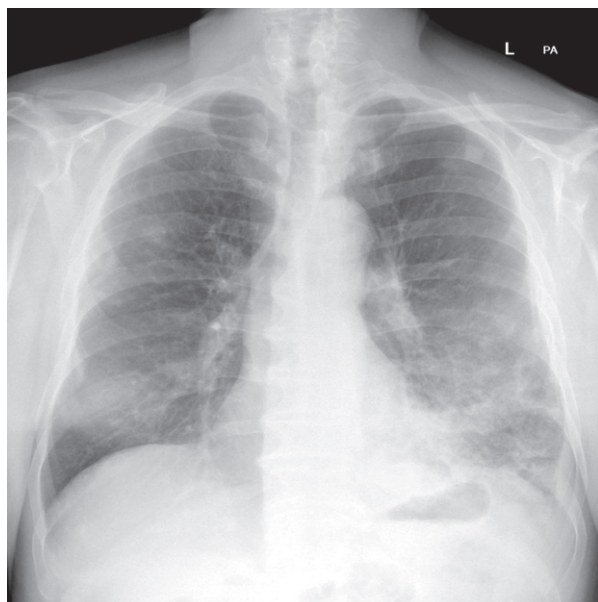
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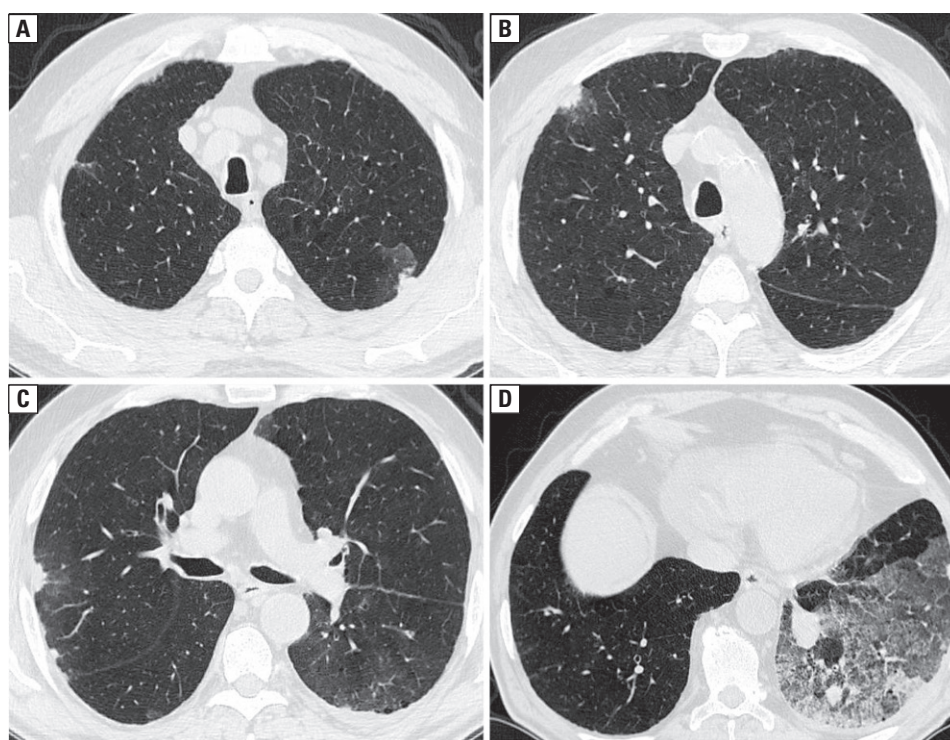


**Figure 1.** Posteroanterior chest radiograph taken on admission showing a large parenchymal opacity in the left lower lung field and several ill-defined nodules in both peripheral lung fields

( $13.7 \times 10^9/L$ ) and increased serum concentration of C-reactive protein (116.8 mg/L). The chest X-ray demonstrated extensive parenchymal opacities in the left lower lung field. Some different sized, ill-defined pulmonary nodules were also seen in

both peripheral lung fields (Fig. 1). The chest CT scan confirmed several nodules in subpleural regions of both lungs surrounded by irregular ground-glass areas (halo sign). There was a large area of ground-glass opacity with thickening of interlobular septa in the left lower lobe and at least two nodules located within the area of increased attenuation. There were no features of pulmonary emboli or mediastinal lymph nodes enlargement (Fig. 2). Computed tomography of paranasal sinuses demonstrated mild thickening of the sinus lining with small polyps in maxillary and ethmoid sinuses. An abdominal ultrasound did not show any abnormalities. Also, an echocardiography and lower limbs venous ultrasonography did not reveal any abnormal endovascular findings. The endoscopy of nasal cavity and sinuses did not show any significant mucosal lesions or local bleeding.

Since granulomatosis with polyangitis was one of the differential diagnoses, the serum level of antineutrophil cytoplasmic antibodies (ANCA) was assessed. However, serum ANCA, as well as anti-nuclear antibodies (ANA) were within the normal limits. Fiberoptic bronchoscopy was performed as the next diagnostic step. This revealed fresh blood in the central and peripheral airways. However, after blood removal



**Figure 2.** The chest CT at four different scan levels demonstrating several nodules in subpleural regions of both lungs and adjacent areas of irregular ground-glass opacities (halo sign). There is a large area of ground-glass attenuation with thickening of interlobular septa in the left lower lobe corresponding to alveolar hemorrhage

and bronchial washing there was no evidence of endobronchial tumour or other endobronchial sources of bleeding. Intensified bloody appearance of the consecutive bronchoalveolar lavage (BAL) samples was consistent with alveolar hemorrhage. Transbronchial lung biopsy of the left lower lobe was also performed and histological examination of the biopsy specimen showed non-specific chronic inflammation with some minor interstitial lung fibrosis. No malignant cells were found. All microbiological examinations of BALF, including bacterial and fungal cultures, *Aspergillus* galactomannan as well as direct microscopy and PCR for *Mycobacteria* gave negative results.

During 14 days of hospital stay several episodes of fever (max. 38,5°C) were observed. However, the serum concentration of procalcitonin was within the normal range and the blood cultures were negative. Except increasing volume of left sided pleural effusion the chest radiograph did not show any new parenchymal opacities. As transthoracic ultrasound showed highly echogenic effusion with multiple loculations the patient was not regarded a good candidate for diagnostic thoracentesis. Due to further decrease in blood hemoglobin concentration to 80.1 g/L the patients received transfusion of 5 units of red blood cells.

Since an extensive workup did not reveal the nature of pulmonary lesions and a true cause of pulmonary bleeding remained unknown, the patient was scheduled for video assisted thoracic surgery (VATS) with pleura and lung biopsy. During the procedure 800 ml of bloody effusion was removed from left pleural cavity. Intra-operative visual inspection of the left pleural cavity revealed markedly thickened and hypervascularized parietal and visceral pleura with some clots in the pleural cavity, atelectatic lung and necrotic lung specimen. The samples of parietal pleura and the lower lobe of the left lung were obtained for histopathological analysis.

Microscopic examination of pleural samples showed a big amount of necrotic masses intermingled with clots and necrotizing neoplastic cells. Lung samples revealed neoplastic infiltration involving visceral pleura and subpleural lung parenchyma. The cells were large, epithelioid with atypical, polygonal nuclei and conspicuous eosinophilic nucleoli. A high number of mitotic figures was observed, some figures were atypical. Neoplastic cells did not form any organoid structures. In the lung parenchyma the neoplastic cells infiltrated not only interalveolar septa but also filled the lumen of alveoli along with erythrocytes, fibrinous exudate and numerous

hemosiderin-laden macrophages. The immuno-histochemical analysis of the neoplasm revealed weak and focal reactivity with anti-CD31 (JC70, Cell Marque, CM) and Factor VIII (polyclonal, CM) antibody and strong and diffuse expression of vimentin (V9, Ventana Medical Systems Inc, VMS), WT-1 (6F-H2, CM) and FLI-1 (MRQ1, CM) (Fig. 3). The reactions with anti-pankeratin (AE-1AE3/PCK26, VMS), EMA (E29, VMC), TTF-1 (SP141, VMS), p63 (HA4, VMS), CEA (CEA31, CM), Ep-CAM (Ber-Ep4, CM), podoplanin (D2-40, CM) and S-100 (polyclonal, VMS) were all negative. Single cells demonstrated weak reactivity with anti-calretinin (SP65, VMS), anti-MART1/Melan A (A103, VMS) and anti-melanosome (HMB-45, VMS) antibodies but these reactions were considered as false positive. Histochemical staining for mucicarmine was also negative. The final diagnosis of epithelioid angiosarcoma was established. Differential diagnosis included epithelioid malignant melanoma, epithelioid malignant mesothelioma and non-small cell lung carcinoma.

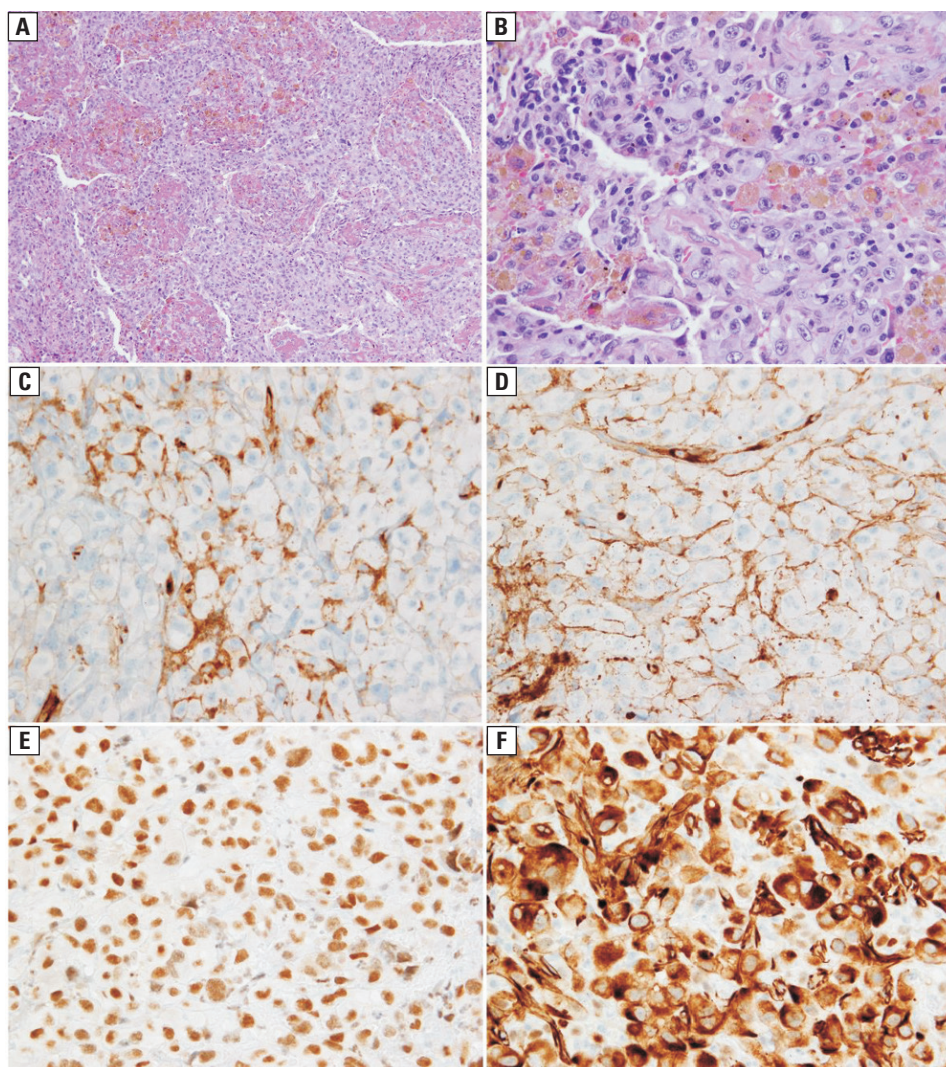
The postoperative period was complicated by prolonged drainage of the pleural effusion and impaired healing of the chest tube wound. Due to decreased blood hemoglobin concentration the next transfusion of 4 red blood cell units was necessary. Although, the patient's general condition has deteriorated, his hemoptysis was categorized as mild and he remained relatively stable. Follow-up chest X-ray showed the progression of parenchymal lesions in the left lung and increased volume of pleural effusion in the left pleural space (Fig. 4). The results of laboratory tests revealed significantly elevated number of WBC ( $30 \times 10^9/L$ ) and serum concentration of C-reactive protein (233.9 mg/L).

On the basis of histopathology findings, a final diagnosis of pulmonary angiosarcoma was made. As previous imaging studies of abdomen, heart and lower limbs veins had not demonstrated any extrapulmonary vascular lesions primary pulmonary angiosarcoma (PPA) was diagnosed. The patient was discharged and referred to oncology centre to consider any further therapeutic options. However, five days after leaving our department, the patient died at home, probably due to the progression of the disease. Post-mortem examination has not been performed.

## Discussion

Angiosarcoma is an uncommon soft tissue tumour that represents about 1–2% of all sarco-





**Figure 3.** Epithelioid angiosarcoma of the lung — histopathological examination. **A, B** — low and high magnification of the neoplastic infiltration composed of huge, highly atypical epithelioid cells mixed with erythrocytes, yellowish haemosiderin-laden macrophages and pink, homogenous masses of fibrin (HE staining, magn.  $\times 100$  and  $\times 400$ ); **C, D** — anti-CD31 positive membranous reaction (**C**) and Factor VIII (**D**) in a group of neoplastic cells (CD31, magn.  $\times 400$ ; FVIII, magn.  $\times 400$ ); **E** — diffuse nuclear anti-FLI-1 reaction (FLI-1, magn.  $\times 400$ ); **F** — prominent cytoplasmic anti-WT-1 reaction in majority of cells (WT-1, magn.  $\times 400$ )

mas. It primarily develops in skin, liver, breast, trunk, heart, chest, bones and extremities. The known risk factors are exposure to therapeutic radiation, chemicals (vinyl chloride, radium, anabolic steroids) and chronic lymphoedema caused by different conditions [1, 2]. To the best of our knowledge the reported patients had no history of exposure to known causative factors. This is consistent with other reports on primary pulmonary angiosarcomas [3–5].

In the majority of patients with pulmonary angiosarcoma lung involvement represents metastases from primary extrapulmonary sites of the diseases. Primary pulmonary angiosarcoma (PPA) is a very rare tumour arising from arterial or venous pulmonary vessels of various size.

According to one recent paper only 32 case reports had been published to 2015 [6]. However, the above number is certainly too low, as at least several reports have not been identified by the authors of this paper [7, 8]. The mean age of patients affected by PPA was 55.9 years (range, 23–82 years), with significant men predominance [6]. The early diagnosis is very difficult due to non-specific signs and symptoms presented by the patients. The majority of reports emphasize the following symptoms: (1) hemoptysis (the most common sign related to the vessel injury [7, 9], (2) cough, dyspnea (related to local growth) [7], (3) chest pain [1], (4) non-specific symptoms: weight loss, malaise, fatigue, fever [5, 7, 10]. Nevertheless, some patients may present the



**Figure 4.** Post-surgery posteroanterior chest radiograph showing significant progression of parenchymal opacities in both lungs and increased volume of left-sided pleural effusion

asymptomatic course of the disease [11]. Physical examination plays limited role in establishing the diagnosis of PPA. In patients with alveolar or bronchial filling local (or even diffuse) crackles can be found on auscultation. Decreased vocal fremitus, dullness to percussion and diminished breath sounds may suggest pleural involvement with pleural effusion. However, these signs are not specific and can be found in all patients with pleural effusion, regardless of its causes. Blood laboratory tests, including the most common but nonspecific finding of decreased hemoglobin concentration, are not particularly useful in making the diagnosis. In our patient, granulomatosis with polyangitis was one of the leading differential diagnoses. This could have been supported by typical symptoms (hemoptysis, history of chronic sinusitis and nose bleeding), but was not confirmed by the result of ANCA testing. Also, the endoscopy of nasal cavity and paranasal sinuses did not revealed the typical lesions.

Primary pulmonary angiosarcoma may have various radiologic manifestations. Although chest radiograph is usually the first imaging study that shows pulmonary and/or pleural lesions, it is often insufficient to demonstrate some details that can be useful in differentiating between the underlying causes. In thorax CT scan PPA can present as a solitary or multiple lung nodule, tumor or mass (with or without a halo sign), diffuse consolidation, solitary or interstitial infil-

tration [6, 11, 12]. Pulmonary angiosarcomas are often associated with ground-glass opacity (halo sign) and mediastinal lymphadenopathy [12]. Presence of pleural effusion strongly suggest pleural invasion [7].

A thorough analysis of the literature reveals two major patterns of radiologic presentations of PPA: a single tumor or mass and multiple nodules of different shape and size [7]. A slight predominance of solitary tumors has been reported [7]. The differential diagnosis of these radiological patterns covers numerous pulmonary pathologies including lung carcinoma, infectious pneumonia (e.g. invasive pulmonary mycoses, tuberculosis), interstitial pneumonia associated with autoimmune disease (e.g. granulomatosis with polyangitis) and metastatic malignancies [7, 13]. There have been two reports demonstrating that PET/CT scan was a helpful tool in imaging pulmonary and pleural lesions which were later identified as PPA [11, 14].

The role of bronchoscopy in establishing the diagnosis is equivocal. In majority of patients with PPA different amount of blood in bronchi, with or without other nonspecific changes were reported. Although direct visualization of the airways with bronchoscopy may help to localize the source of bleeding, bronchoscopy rarely provide the adequate tissue samples enabling the pathologic diagnosis. This is because specific endobronchial lesions are uncommon. In three patients a tumor or mass occluding bronchus and slowly growing hemorrhagic tumor were reported [10, 15, 16]. Also, tissue samples obtained by transbronchial biopsy are rarely sufficient to diagnose the nature of the tumor. Thus, VATS or even thoracotomy with lung biopsy is often necessary to provide an adequate material for histopathological examination [7, 8]. This was also the case in our patient.

Microscopic examination revealed the neoplastic infiltration by large, epithelioid cells with prominent atypia and concurrent morphological evidence of haemorrhage, i.e. a great number of haemosiderin-laden macrophages, extravasated erythrocytes and fibrinous intraalveolar exudate. Such epithelioid neoplasm in the lung always requires differentiation with non-small cell carcinoma, primary or metastatic and epithelioid malignant mesothelioma, but both epithelial and mesothelial immunohistochemical markers were negative. Immunohistochemical profile was ambiguous: weak and focal reaction with anti-CD31 and Factor VIII, diffuse reaction with WT-1 (cytoplasmic) and FLI-1 (nuclear) and weak



immunoreactivity with Melan A and HMB-45 in single cells. Due to immunohistochemical findings, two main neoplasms were taken into consideration: epithelioid angiosarcoma and melanoma [17–20]. Considering accompanying prominent intraalveolar haemorrhage and clinical symptoms such as haemoptysis, final diagnosis of epithelioid angiosarcoma was established.

There are no strong recommendations on the most effective treatment of PPA [10]. Currently, the surgical resection of PPA lesions seems to be the first line therapy. However, it might be proposed only for patients with early stages of the disease presenting with solitary nodule or tumor [21]. Due to multifocal lesions and/or poor clinical status the majority of patients are not good candidates for surgery. The literature brings evidence of using some chemotherapeutic regimens [11, 13, 22, 23], radiotherapy [5, 16], immunotherapy [16], or combination of methods [5, 16, 17, 19]. The chemotherapy regimens include gemcitabine, docetaxel [23], ifosfamide and adriamycin [12]. Stacher et al. suggested that taxanes and trofosfamide may be particularly beneficial in epithelioid angiosarcoma [24]. Due to the presence of the vascular endothelial growth factor (VEGF) signalling pathway in angiosarcoma cells, there may be a possibility of developing the “targeted therapy” [24].

The general prognosis in patients with PPA is very poor. The data coming from the analysis of 24 PPA cases suggests the median survival time of 3 months (range 0.5 — 39 months) [7]. Similarly, almost one third of patients reviewed by Shimabukuro et al. died within the first two months after establishing the diagnosis [6]. There have been only few reports of survival time longer than 12 months [5, 11, 23].

Comparing our patient to other patients with PPA, we have to admit that the clinical presentation and the course of the disease was very similar to those reported in earlier published papers. Hemoptysis, as the major sign, progressive fatigue and disseminated pulmonary nodules with halo sign demonstrated in thorax CT scan resembled some cases presented by other authors. As imaging studies have not demonstrated any extrapulmonary foci of the tumor, we believe our patient had multifocal primary pulmonary angiosarcoma. The course of the disease was quite aggressive and the patient died three months after the appearance of first symptoms.

In summary, the PPA is a rare tumour but probably not as uncommon as reported previously. In our single centre experience we had two

patients with PPA treated in the last 10 years. Primary pulmonary angiosarcoma should be considered as a differential diagnosis in patients with hemoptysis and single or multiple lung nodules/tumors with surrounding ground glass opacity. The course of the disease is aggressive, with poor prognosis. The only curative treatment seems surgical resection, but the majority of patients with PPA are not suitable candidates for major surgery.

### Conflict of interest

The authors declare no conflict of interest.

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