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Pulmonary epithelioid haemangioendothelioma — interferon 2-alpha treatment — case report

Płucny *haemangioendothelioma epithelioides* — leczenie interferonem 2-alfa — opis przypadku

Streszczenie

W pracy przedstawiono przypadek 62-letniej chorej, otyłej palaczki tytoniu (10 paczko/lat), przyjętej do Instytutu Gruźlicy i Chorób Płuc w Warszawie w celu diagnostyki stwierdzanych w badaniu radiologicznym klatki piersiowej dobrze wysyconych cieni okrągłych. Zmiany te były widoczne w badaniach radiologicznych od 5 lat, jednak w ostatnim okresie uległy zdecydowanemu powiększeniu. Chora leczyła się z powodu nadciśnienia tętniczego, cukrzycy insulinoniezależnej oraz łuszczycy z zajęciem skóry. W chwili przyjęcia uskarżała się na kaszel z niewielkim odkrztuszaniem śluzowej wydzieliny i okresowe bóle kostno-stawowe. W badaniu przedmiotowym stwierdzono zmiany skórne o charakterze łuszczycowym, niewielkie obrzęki na kończynach dolnych oraz palce pałeczkowate. Odczyn tuberkulinowy był dodatni. W badaniu tomograficznym klatki piersiowej wykazano obecność częściowo uwapnionych guzków o średnicy około 1 cm zlokalizowanych głównie w dolnych i środkowych polach płucnych bez powiększenia węzłów chłonnych wnęk i śródpiersia. Badaniem histologicznym wycinków uzyskanych drogą biopsji otwartej płuca stwierdzono obecność w obrębie pęcherzyków i naczyń płucnych nacieku nowotworu pochodzenia naczyniowego. Komórki tego guza wykazywały obecność antygenów: czynnika VIII, CD31 i CD34, co pozwoliło postawić rozpoznanie *haemangioendothelioma epithelioides* płuc. Po 6 miesiącach od biopsji otwartej płuca doszło do istotnej progresji choroby, co było powodem podjęcia próby leczenia interferonem 2-alfa. W trakcie leczenia zaobserwowano nieznaczną regresję zmian, a przez następne 6 miesięcy stabilizację choroby.

Słowa kluczowe: płucny *haemangioendothelioma epithelioides*, płuco, interferon 2-alfa

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Abstract

A 62-year-old, obese woman, smoking 10 pack/year was admitted to the National Tuberculosis and Lung Diseases Research Institute to diagnose small, round opacities revealed by routine chest X-ray examination. These lesions had been observed for 5 years. The patient had been treated for psoriasis, hypertension, and insulin-independent diabetes. On admission she was in good condition, complaining of a slight productive cough as well as intermittent osteoarticular pain. Physical examination revealed cutaneous psoriatic lesions, slight edema of the lower limbs, and clubbed fingers. Tuberculin test was positive.

Chest Computer Tomography scanning showed partially calcified nodules (up to 1cm in diameter) located in the middle and base areas of both lungs. No evidence of hilar nor mediastinal lymph node enlargement was seen. Lung specimens displayed intraalveolar and intravascular growth of neoplastic cells. Immunohistochemical expression of Factor VIII, CD31 and CD34 antigens was present. Pulmonary epithelioid haemangioendothelioma was diagnosed.

After 6 months of observation, progression of the disease was shown. Interferon alpha treatment was introduced. During the therapy, a slight regression of pulmonary changes was noticed and since then stabilization of the disease was observed.

Key words: pulmonary epithelioid haemangioendothelioma, lung, interferon 2-alpha

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Introduction

Epithelioid haemangioendothelioma (EH) is a rare tumour of mesenchymal origin [1]. It is more commonly seen in other organs such as the skin, liver, soft tissues, and bones; occasionally involvement of the lung, mediastinum, and pleura is noticed [2–5]. Approximately 80 cases of pulmonary involvement have been reported worldwide [3]. Dail et al. (20 cases) and Kitaichi et al. (21 cases) presented a large series of EHs [4, 5]. Pulmonary epithelioid haemangioendothelioma (PEH) is usually manifested radiographically as well-circumscribed, multi-centric nodules localized in the middle and lower parts of the lungs.

It was shown that some antiangiogenic agents, such as interferon alpha-2a, inhibited proliferation and migration of endothelial cells [6–9]. Interferon alpha-2a is a potent angiogenesis inhibitor that acts by blocking the action of basic fibroblast growth factor. There has been considerable experience with the use of interferon alpha-2a in the treatment of haemangiomas in children and some adults with haemangioendothelioma [7, 8].

This paper presents a patient with PEH, with typical localization, who was treated with interferon alpha-2a. Slight regression of lung lesions was noticed after a course of interferon alpha-2a treatment and stabilization of the disease was observed afterwards.

Case report

In May 2003 a 62-year-old, obese woman, smoking 10 pack/year was admitted to the National Tuberculosis and Lung Diseases Research Institute to diagnose small, round opacities revealed by a routine chest X-ray examination. These lesions had been observed for 5 years. The patient had worked in an office, but in her youth she was employed in a halogen factory. Her father died of tuberculosis 30 years ago, her mother died of a liver cancer, and her sister of a tongue cancer. The patient was operated on for left nephrolithiasis at the age of 28. For many years she has been treated for psoriasis with cutaneous involvement, and for 3 years for arterial hypertension and insulin-independent diabetes.

On admission, the patient had good performance status (1-in ECOG scale), complaining of a slight productive cough as well as intermittent osteoarticular pain. Physical examination revealed psoriatic cutaneous lesions on her palms, elbows, and head, slightly swollen lower limbs, and clubbed fingers.

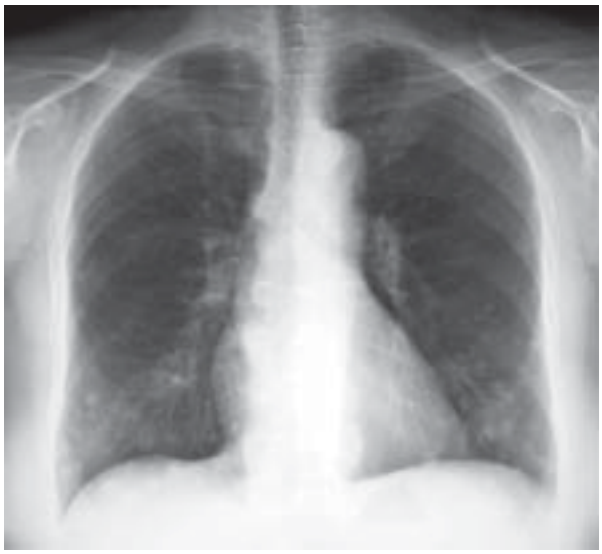

Figure 1. Chest X-ray — numerous pulmonary nodules, up to 1 cm in diameter, located predominantly in the lower lobes of the lungs. The hilar and mediastinal lymph nodes are not enlarged

Rycina 1. Badanie RTG klatki piersiowej — liczne guzki o średnicy powyżej 1 cm zlokalizowane w środkowych i dolnych polach płucnych, bez powiększenia węzłów chłonnych wnęk i śródpiersia

The accessory investigations disclosed accelerated ESR (20 mm/hr), elevated blood glucose level (7.48 mmol/l), and Mantoux test of 24 mm with a blister.

The chest X-ray showed numerous pulmonary nodules of up to 1 cm in diameter predominantly located in the lower lung lobes. No evidence of hilar nor mediastinal lymph node enlargement was seen (Fig. 1). High Resolution Computer Tomography (HRCT) scanning confirmed the presence of partially calcified lesions in the middle and base areas of both lungs (Fig. 2). Fiberoptic bronchoscopy showed inflamed mucosa covering a normal tracheobronchial tree. Transbronchial lung biopsy was performed and the specimen disclosed inflammatory infiltrates within the bronchial wall. Multiple cultures of sputum and bronchial secretion were negative for bacteria, acid-fast bacilli, and fungi. The PCR examination did not reveal the genetic material of the Mycobacterium tuberculosis. Cytological evaluation of these samples was negative. Samples of her stool were examined for eggs of parasites and also produced negative results. No antibodies against Toxaocara sp. and Toxoplasma sp. were found, spirometry did not demonstrate any ventilatory disorder, blood gases were normal, exertion test did not reveal any de-saturation, ultrasound of the abdomen was normal, there was no pathology on routine gynaecological examination, and the mammography results were within normal limits.

Open lung biopsy was performed in order to establish a final diagnosis. The lung specimen dis-

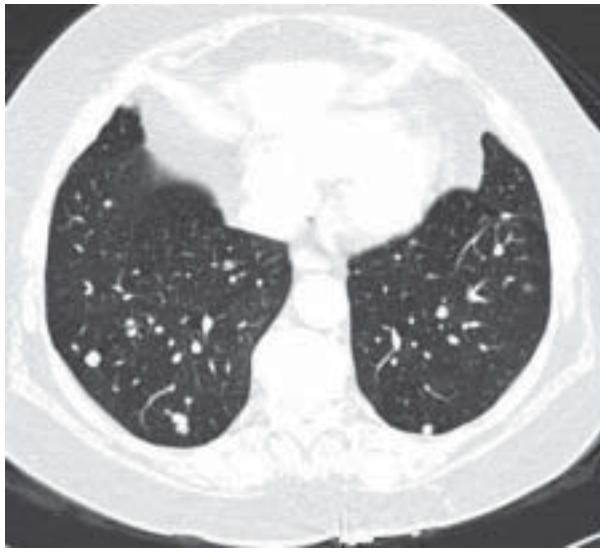

Figure 2. HRCT scanning — presence of partially calcified lesions in the middle and base areas of the lungs

Rycina 2. Tomografia komputerowa wysokiej rozdzielczości — liczne, częściowo uwapnione guzki w środkowych i dolnych polach płucnych

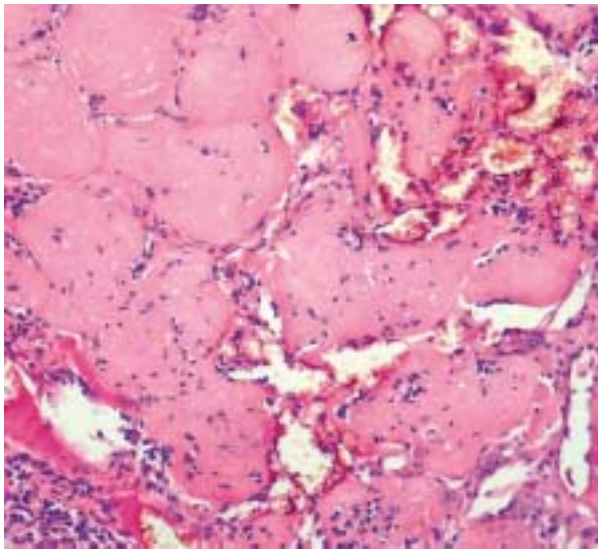

Figure 3. Histological examination. Pulmonary epithelioid haemangioendothelioma. The central part of the nodule shows hyaline sclerosis; at the periphery polypoid extension into adjacent airspaces is seen (HE, 100 ×).

Rycina 3. Badanie histologiczne — *hemangioendothelioma epithelioides* płuc. W centrum guzka pole szkliwienia, a na obwodzie polipowate rozrosty do otaczającego miąższu płuc (HE, 100 ×)

played circumscribed, pale eosinophilic nodules with central hyalinization, coagulative necrosis and calcification. The peripheries of the nodules were more cellular. The balls of tumour tissue extended to alveolar spaces, bronchioles, blood, and lymphatic vessels. The neoplastic cells were cytologically bland with round nuclei and uniform small-sized nucleoli, without any mitotic activity. Occasionally, the cells contained sharp single cytoplasmic vacuoles thought to represent vascular lumen differentiations. Expression of FVIII (+), CD31 (+), and CD34 (+)antigens within neoplastic cells were shown in immunohistochemical examination. Pulmonary epithelioid haemangioendothelioma was diagnosed (Fig. 3, 4).

Six months after open-lung biopsy, progression of the disease was observed. The interferon alpha-2a treatment was introduced in a dose of 3 mil U/d, 3 days per week s.c. After 3 months of the therapy a slight regression of the pulmonary lesions was observed (Fig. 5). However, the patient discontinued the interferon therapy because of adverse reactions such as: prostration, chills, elevated temperature, and musculo-articular pains. During the next 6 months the pulmonary lesions did not deteriorate; however, after that she was lost from observation.

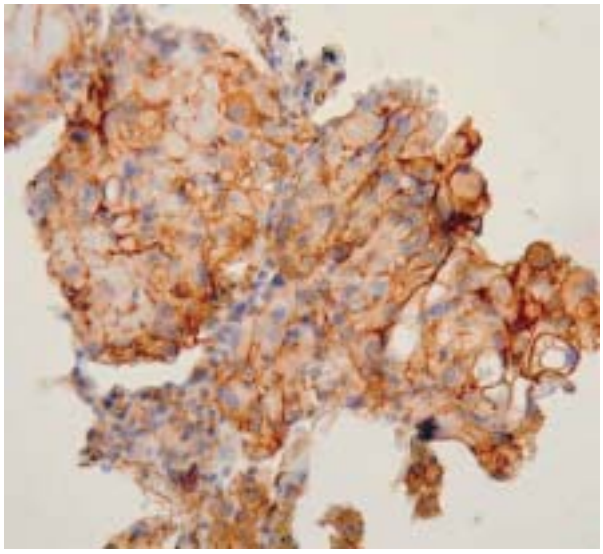

Figure 4. Pulmonary epithelioid haemangioendothelioma — immunohistochemical staining. Positive expression of CD 31 antigen in the tumour cells (CD31, 200 ×)

Rycina 4. Płucny *epithelioid haemangioendothelioma* — barwienie immunohistochemiczne. Komórki guza z dodatnią reakcję na obecność antygenu CD31(CD31, 200 ×)

Discussion

Pulmonary epithelioid haemangioendothelioma (PEH) is a tumour, derived from the endothelium of pulmonary vessels.

The aetiology of this tumour is unknown. However, different angiogenic stimulators may act as promoters of the proliferation of endothelial cells [10]. Recently it was presented that monocy-

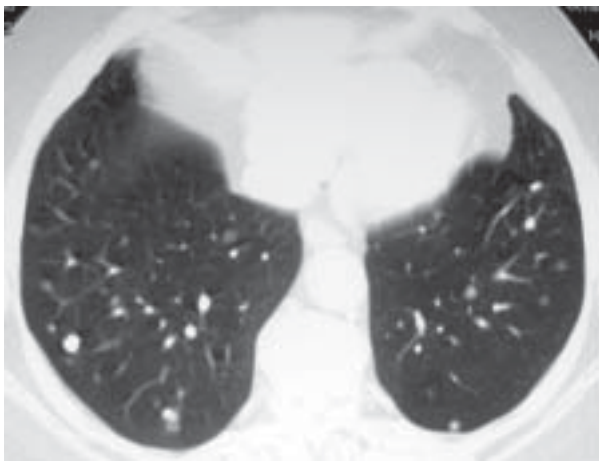

Figure 5. HRCT after treatments light regression of pulmonary changes was seen

Rycina 5. Tomografia komputerowa wysokiej rozdzielczości, badanie po leczeniu — widoczna niewielka regresja zmian guzkowych w płucach

te chemo attractant protein-1 (MCP-1) was required for EH proliferation and might promote the growth of these lesions by stimulating the angiogenic behaviour of endothelial cells [9]. Several clonal abnormalities such as complex unbalanced translocation between chromosome 7 and 22, translocation of chromosome 14, and loss of chromosome Y, were also revealed in tumour cells [10].

PEH occurs in more often women, representing nearly 62–80% of cases presented in the literature [2–5]. The patients' ages for the initial examination ranged between 2 and 76 years, and the median age for diagnosis ranged from 36 to 42.7 years [2, 3]. There are no characteristic symptoms of this disease. Over 50–76% of patients are asymptomatic at the time of diagnosis [2, 3]. The most common symptoms are: chest pain, cough with and without sputum expectoration, mild dyspnoea, and occasionally haemoptysis.

The characteristic radiological appearance consists of multiple, well-defined small nodules up to 2 cm in diameter localized predominantly in the lower parts of the lungs. About 60% of cases displayed these types of changes. Unilateral opacities, single and multiple nodular, and "grand glass" attenuations, linear changes, and intralobular septal thickenings can be also seen. Usually, hilar and mediastinal lymph nodes are not enlarged. Pleural effusion is not common, but if it does present, it is indicative of worse prognosis [2–5]. The lesions show a slow growth rate and cause progressive respiratory insufficiency. Our patient was a little older than the median age of previously observed female patients [4, 5]. She had mild respiratory symptoms and clubbed fingers. Dail et al. and Ledson et al. also observed cases of PAH with this type of fingers [2, 12]. In our patient, radiological changes were revealed incidentally 5 years before diagnosis in the form of multiple pulmonary nodules.

The diagnosis of PEH was made on the basis of the histological features, confirmed by immunohistochemistry results. In this case, histological examination of the specimen obtained by open-lung biopsy was typical for the PEH. Neoplasmatic cell proliferation with typical immunohistochemical presentation, which is characteristic for endothelial cells, involved alveolar spaces, bronchioles, blood, and lymphatic vessels. Cytological atypia and mitotic figures were absent. However, other authors described some cases of PEH with cytological atypia and numerous mitotic figures, which are symptoms of a worse prognosis [1–5, 12]. Positive immunohistochemistry staining for endothelial cell markers such as Factor VIII, CD31, and CD34 confirmed the diagnosis.

During 5-year observation progression of the disease was rather slow but accelerated after the open lung biopsy. This was the stimulus for the introduction of the treatment. Due to the rarity of the tumour, there is no standard treatment. The slow progressive course is typical for PEH, and patients die 2–24 years after diagnosis [2–5, 11–13]. For each individual case it is difficult to predict a natural history of the disease. In some cases, partial spontaneous regression was observed [2]. Existing literature recommends different types of treatment: for a solitary nodule, surgical resection seems to be the treatment of choice, whereas chemotherapy and radiotherapy proved to be ineffective. Regimens containing mitomycin C, cyclophosphamide, vincristine, cisplatin, 5-fluorouracil, gemcitabine, docetaxel, and etoposide have been tested without showing any benefit [2, 3]. However, Pinet et al. observed a complete regression of pleural epithelioid haemangioendothelioma after six courses of carboplatin and etoposide chemotherapy [14].

In the last few years, antiangiogenic activity of interferon 2-alphas has been tested in several clinical situations. There are incidental reports about the effectiveness of this type of treatment in PEH patients. Roudier-Pujol et al. described a woman with multifocal epithelioid haemangioendothelioma with pulmonary involvement, in whom partial remission was achieved after one year of interferon alpha-2a treatment [7]. In addition, Kayler et al. presented a woman with disseminated haemangioendothelioma, who was successfully treated with interferon alpha 2b. In spite of good

results of interferon therapy, she died of graft rejection [8]. Kumar et al. reported significant effects from interferon alpha-2a (3 million units 3 times per week for 6 months) treatment in a patient with a mediastinal haemangioendothelioma. This therapy was of benefit and allowed a complete resection of the tumour [9]. Cronin et al. treated a 35-year-old woman with PEH, with interferon alpha-2b, at a dose of 1.5 million units three times a week. The disease remained stable for a certain period but afterwards progression was noticed. Chemotherapy was introduced, but it was ineffective. The patient died of disease progression [6].

Our patient was treated using interferon alpha-2a over a 3-month period. This treatment resulted in a slight regression of pulmonary lesions and subsequently, stabilization of the disease. Due to adverse reactions, the interferon treatment was discontinued. Prognosis of this patient is unpredictable. Unfortunately, the patient was lost from observation.

Conclusion

We presented a rare case of PHE treated with interferon 2-alpha in which stabilisation of the disease was observed.

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