





Multiple pulmonary cavitating nodules in female with endometrium adenocarcinoma history – difficulties in differentiation between metastases, sarcoidosis and sarcoid-like reaction. Case report

Liczne guzki kawitujące w płucach
u kobiety z historią raka gruczołowego endometrium
– trudności w różnicowaniu pomiędzy przerzutami,
sarkoidozą a reakcją sarkoidalną. Studium przypadku

Alicja Gałeczka-Turkiewicz¹ , Dagmara Galle¹ , Agnieszka Goryczka¹ , Maja Zarzecka², Dariusz Jastrzębski² ,
Dariusz Ziara² 

¹Student Society of the Department of Lung Diseases and Tuberculosis, Faculty of Medical Sciences in Zabrze,
Medical University of Silesia, Katowice, Poland

²Department of Lung Diseases and Tuberculosis, Faculty of Medical Sciences in Zabrze,
Medical University of Silesia, Katowice, Poland

ABSTRACT

Pulmonary cavitary lesions visible on a chest radiograph can be a diagnostic challenge. It is necessary to take into consideration a wide differential diagnosis and to conduct a wide range of examinations to confirm their exact cause.

A 44-year-old woman with a history of endometrial adenocarcinoma was admitted to the pulmonology department to diagnose mediastinal lymphadenopathy with coexisting nodules in the lung parenchyma. The X-ray and positron emission tomography (PET) showed cavitating lesions in the lungs, which could correspond to metastases, but the laboratory and histopathological tests did not confirm any neoplastic features. In specimens obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and video-assisted thoracoscopic surgery (VATs) non-caseating granulomas were found, which suggested sarcoidosis or a sarcoid-like reaction. At an advanced stage of pulmonary changes, the presence of neoplastic cells was revealed in the sputum. Despite chemotherapy the patient died. Multiple pulmonary metastases were confirmed in the post-mortem examination.

This case is an example of a rare sarcoid-like reaction in the mediastinum and lung parenchyma due to cancer located below the diaphragm. Differentiating between sarcoidosis, a sarcoid-like reaction and lung metastases in similar cases may be difficult. For this reason, it should be advisable to repeat diagnostic procedures in patients with malignancies in the past, including EBUS-TBNA and VATs.

KEY WORDS

pulmonary cavitary nodules, sarcoidosis, sarcoid-like reaction, sarcoid granuloma, multiple pulmonary metastases, endometrial adenocarcinoma

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Address for correspondence: Alicja Gałeczka-Turkiewicz, Student Society of the Department of Lung Diseases and Tuberculosis, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, ul. Ks. Koziółka 1, 41-803 Zabrze, tel. +48 696 835 001, e-mail: alicjagaleczka@gmail.com



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STRESZCZENIE

Zmiany kawitujące w płucach obrazowane na zdjęciu rentgenowskim klatki piersiowej mogą być diagnostycznym wyzwaniem. W celu dokładnego ustalenia ich przyczyny konieczne jest wzięcie pod uwagę szerokiej diagnostyki różnicowej i przeprowadzenie licznych badań.

Kobieta, 44-letnia, z gruczolakiem endometrium w wywiadzie została przyjęta na oddział pulmonologiczny w celu diagnostyki powiększonych węzłów chłonnych śródpiersia i współwystępujących w mięszu płuc guzków. Zdjęcie rentgenowskie i pozytonowa tomografia emisyjna (*positron emission tomography* – PET) uwidocznily zmiany kawitujące w płucach, które mogły stanowić przerzuty płucne; jednakże badania laboratoryjne i histopatologiczne nie potwierdziły obecności zmian nowotworowych. W materiale pobranym w trakcie przezoskrzelowej biopsji węzłów chłonnych pod kontrolą ultrasonografii wewnątrzoskrzelowej w czasie rzeczywistym (*endobronchial ultrasound-guided transbronchial needle aspiration* – EBUS-TBNA) oraz wideotorakoskopii (*video-assisted thoracoscopic surgery* – VATs) zostały znalezione niesierowaciejące ziarniniaki, które sugerowały rozpoznanie sarkoidozy lub reakcji sarkoidalnej. Dopiero w zaawansowanym stadium zmian płucnych komórki nowotworowe zostały ujawnione w płwocinie. Pomimo wdrożenia chemioterapii pacjentka zmarła. Liczne przerzuty płucne zostały potwierdzone w badaniu post-mortem.

Opisany przypadek jest przykładem rzadkiego zjawiska reakcji sarkoidalnej w śródpiersiu i mięszu płuc w wyniku nowotworu zlokalizowanego poniżej przepony. Różnicowanie pomiędzy sarkoidozą, reakcją sarkoidalną i przerzutami do płuc w podobnych przypadkach może stanowić trudność diagnostyczną. Dlatego powinno się powtarzać procedury diagnostyczne takie jak EBUS-TBNA lub VATs u pacjentów z wywiadem onkologicznym.

SŁOWA KLUCZOWE

płucne guzki kawitujące, sarkoidoza, reakcja sarkoidalna, ziarniniak sarkoidalny, liczne przerzuty płucne, gruczolakorak endometrium

INTRODUCTION

Pulmonary cavities are pathological structures filled with gas. In a radiograph they are depicted as an area of low-attenuation that surrounds a mass or a surface of consolidation [1]. Many different pathological processes may manifest themselves as a cavity, e.g. necrosis, cysts, cystic dilation, and the desquamation of a tumour with accompanying liquefaction [2,3]. Its origins may be various: from rheumatic disorders to infectious causes; however, the most common causes of cavitory lesions are primary malignancies and septic emboli [1,4]. Malignant cavitating nodules in the lungs may develop due to necrosis of the tumour or due to a specific check-valve mechanism in which the tumour infiltrates into the bronchial tree [4]. Approximately 4% of pulmonary metastases evolve from solid to cavitory lesions [5]. This transformation may be self-generated, mostly in primary cancers, or induced by both radiotherapy and chemotherapy [6,7]. In two-thirds of metastatic cavitory nodules, squamous cell carcinomas are primary lesions; mainly the head and neck, oesophageal, and uterine carcinomas [4,5,8]. We would like to present the case of a 44-year-old woman with non-characteristic pulmonary lesions, which turned out to be cavitating metastases of endometrial adenocarcinoma. During the differential diagnosis, sarcoidosis or a sarcoid-like reaction was considered due to the histopathologic findings.

CASE REPORT

A 44-year-old female patient was admitted to the Pulmonology Department, Prof. Stanisław Szyszko Independent Public Clinical Hospital No 1 in Zabrze in December, 2017 to diagnose mediastinal lymphadenopathy with several coexisting nodules in the lung parenchyma. In 2015 the patient was treated in the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology (Gliwice Branch) due to endometrial adenocarcinoma in stage G2 with metastases to the parametrium and regional lymph nodes, and therefore underwent a total hysterectomy. After the surgery she received chemotherapy (6 cycles of carboplatin and paclitaxel), then radiotherapy and brachytherapy. In September, 2016 she finished her oncological treatment. Positron emission tomography (PET) conducted in November, 2016 did not reveal any abnormalities – neither evidence of biomarker hyper-accumulation, nor elevated glucose metabolism characteristic of the spread of endometrial adenocarcinoma. In June, 2017 a second PET was conducted; nevertheless, its results were questionable and did not rule out the presence of lung metastases. The chest computed tomography (CT) scan showed a few isolated focal lesions – most of them were cavitory (Figure 1), and minimal hilar node enlargement. In October, 2017 in the Thoracic Surgery Department, Prof. Stanisław Szyszko Independent Public Clinical



Hospital No 1 in Zabrze the patient underwent a real-time endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). No neoplastic cells were found; however, sarcoidosis was suspected. The patient remained without any complaints, hence no specific treatment was ordered. Nonetheless, in November, 2017 radiological progression was observed, and therefore the patient was admitted to our pulmonary department.



Fig. 1. Chest CT scan (June 2017).

Ryc. 1. TK klatki piersiowej (czerwiec 2017).

During the hospitalization, routine laboratory analyses were within the normal ranges. Neither anti-neutrophil cytoplasmic antibodies (ANCA), nor cytoplasmic type of atypical anti-neutrophil cytoplasmic antibodies (cANCA) were positive. Fiberoptic bronchoscopy (FB) revealed no pathology in the bronchial tree. In bronchial washing no suspicious cells were found: samples taken from the bronchial wall revealed no pathology. Bacteriological and mycological smears and culture (including *Mycobacterium tuberculosis*) were negative. The patient was discharged home with the suspicion of sarcoidosis, and prednisone (30 mg daily) was administered. In further follow-up, the patient refused to take medication and to undergo a surgical lung biopsy during video-assisted thoracoscopy (VATS). In January, 2018 the patient was re-hospitalised in our department and appeared to be asymptomatic. The laboratory test results were within the normal range; nevertheless, the chest X-ray showed the

progression of lesions in number and diameter. In a repeated EBUS-TBNA no suspicious cells were found, and once again sarcoid granulomas typical for a sarcoid or sarcoid-like reaction were found. Eight weeks of continued prednisone treatment with tuberculosis prophylaxis (pyrazinamide, ethambutol, rifampicin and isoniazid) showed no success, and in February, 2018 the patient was admitted again to our department with dyspnoea during exercise and further radiological progression. The CT scan revealed numerous cavitating nodules within both lungs, rimmed by the limbus of ground glass (Figure 2, 3). In addition, numerous enlarged lymph nodes within the mediastinum were present. The laboratory tests were yet again within the normal range. The sputum cytology examination was negative. The patient eventually agreed to VATs and lung sampling, which confirmed the suspicion of a sarcoid-like reaction. The pathologist appended the following comment: "Granulomatous diseases and – because of the clinical picture and the chemotherapy the patient underwent – a sarcoid reaction or hypersensitivity pneumonitis should be taken into account in the differential diagnosis. No suspicious cells or lung foci were found". These results were also confirmed in the Pathology Department of the Tuberculosis and Lung Diseases Institute in Warsaw.

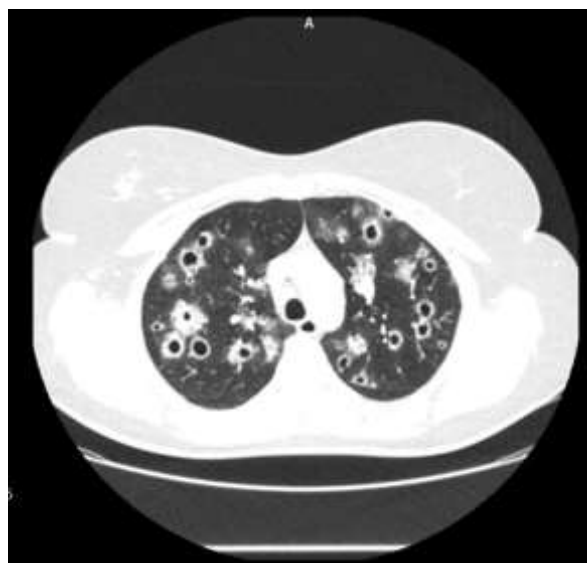


Fig. 2. Chest CT scan (February 2018).

Ryc. 2. TK klatki piersiowej (luty 2018).



Fig. 3. Chest CT scan (February 2018). Bilateral numerous cavitating nodules surrounded by limbus of ground glass opacity. In mediastinum enlarged subcarinal lymph nodes (up to 17 mm in short axis) and numerous lymph nodes measuring maximum 10 mm in short axis. Enlarged pulmonary hilar lymph nodes: right one up to 18 mm, and left one up to 11 mm in short axis.

Ryc. 3. TK klatki piersiowej (luty 2018). Obustronne, liczne kawitujące zmiany otoczone rąbkim mlecznej szyby. W śródpiersiu: powiększone węzły chłonne podoługowe (do 17 mm w osi krótkiej) oraz liczne węzły chłonne do 10 mm w osi krótkiej. Powiększone węzły chłonne wewnątrz płuc: prawy do 18 mm, lewy do 11 mm w osi krótkiej.



Fig. 4. Chest X-ray (April 2018).

Ryc. 4. Zdjęcie rentgenowskie klatki piersiowej (kwiecień 2018).

DISCUSSION AND CONCLUSIONS

Despite continued anti-mycobacterial and steroid therapy throughout April, 2018 the patient was readmitted to our department due to dyspnoea at rest. Her general condition was moderately severe, with a blood pressure of 140/70 mm Hg and a heart rate of 98 bpm. Laboratory tests showed increased concentrations of lactate dehydrogenase (273 IU/L) and D-dimers (1.39 µg/ml). The sputum examination revealed only the presence of *Candida albicans*. The tuberculosis panel was negative, nor was *Pneumocystis jirovecii* found. During the gynaecological consultation, there was no evidence of a recurrence of the cancer. After oxygen treatment, intravenous methylprednisolone (3 pulses × 0.5 g), cyclophosphamide (1.5 g intravenous, then 3 × 0.5 g per os), broad-spectrum antibiotics, and itraconazole (2 × 200 mg per os), slight improvement in the patient's general condition, including respiratory function was achieved, despite massive chest X-ray opacities (Figure 4). The fourth cytological examination of induced sputum finally revealed adenocarcinomatous cells in May, 2018. After an oncological consultation, the decision was made to undergo carboplatin treatment in monotherapy. This treatment was not effective and the patient died in June, 2018. The post-mortem examination revealed numerous metastases of adenocarcinoma in the lungs.

This case is an example of a very rare sarcoid-like reaction in the mediastinum and lung parenchyma due to cancer located below the diaphragm. Our case also exemplifies the difficulties in differential diagnosis between a sarcoid-like reaction, a cavitating form of sarcoidosis, and multiple pulmonary metastases due to endometrial adenocarcinoma.

The differential diagnosis of pulmonary cavities is very broad and should include infections (bacterial, mycobacterial, fungal, parasitic), as well as systemic diseases such as malignancies and rheumatic disorders (sarcoidosis – especially the nodular type, Wegner's granulomatosis, granulomatosis with polyangiitis, nodular amyloidosis) [4,9,10]. Septic emboli and subsequent pulmonary vessel thrombosis may result in pulmonary cavities as well. Cavitory lesions in bacterial infections can be a result of multiple abscesses or necrotising pneumonia. Although this kind of process is most characteristic of *Staphylococcus aureus* and *Klebsiella pneumoniae* infections, it can also be seen in *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Actinomyces*, *Nocardia* and *Rhodococcus* contagions. Pulmonary tuberculosis (caused by *Mycobacterium tuberculosis*) and pulmonary mycobacteriosis caused by non-tuberculous mycobacteria may also be the reason why cavitating pulmonary nodules mimic metastases, especially among patients that already



suffer from pulmonary diseases in countries like Poland with a relatively high annual incidence of tuberculosis [10,11,12]. Among certain patients percutaneous transthoracic needle aspiration may be diagnostically helpful [12]. In our patient, an infection was excluded. Additionally, pulmonary sarcoidosis may manifest as nodular cavitory lesions. The incidence of cavitory nodules in sarcoidosis is yet to be determined. Some authors have estimated its frequency from 1 to 2% and others even at 11.8%, with the highest share in chronic pulmonary sarcoidosis [9,13,14]. The mechanism of cavity formation in sarcoidosis is still unknown. The theories include: bullae formation, comorbid infections and the development of cystic bronchiectasis, whereas the reason for true cavities are: the expulsion of hyaloid material from the fibrous tissue and necrosis within aggregation areas of sarcoid granulomas [14,15]. In most cases, patients with pulmonary cavitory sarcoidosis have symptoms of dyspnoea and chronic coughing and they have a good response to glucocorticoid treatment [14].

We did not observe any positive effect of prednisone in this case, hence we suspected a sarcoid-like reaction, which is an immunologic abnormality that also results in the formation of epithelioid-cell granulomas. It is associated with an ongoing or past malignancy and usually develops in local lymph nodes and contributes to their draining. A sarcoid-like reaction is diagnosed by the exclusion of other disorders in patients with a history of oncological diseases, who have not met the criteria for sarcoidosis [16]. A sarcoid-like reaction usually occurs in about 13% of cases of Hodgkin disease, 7% of non-Hodgkin lymphoma, and only in 4.4% of carcinomas, while its incidence in lung cancer varies from 4.3% to 7% [16,17]. A sarcoid-like reaction and sarcoidosis are indistinguishable in radiologic imaging, including PET scanning [18]. A sarcoid-like reaction can be distinguished from sarcoidosis by the presence of B cells in granuloma lesions in the former [19]. It seems that EBUS-TBNA, with an evident sensitivity of 89–94% should be performed to provide the pathologic material from mediastinal nodes, and it is believed to be a gold standard in diagnosing sarcoidosis or a sarcoid-like reaction [18,20,21]. Tyan et al. [22] confirmed metastases from extra thoracic malignancies in only 25 out of 350 patients with isolated mediastinal and hilar lymphadenopathy using EBUS-TBNA (7%).

Pulmonary metastases usually mould into solid changes and manifest themselves as numerous nodose lesions, hydrothorax and lymphatic vessel proliferation [6,23]. In addition, cavernous, singular lesions in primary lung

tumours are described as quite frequent [24]. They are also related to a worse prognosis [25]. Seo et al. [26] also noticed that the incidence of cavitory nodules in primary lung cancers is more common (9%), while the frequency of their occurrence as metastatic lesions is only 4%.

Endometrial adenocarcinoma metastases to a pulmonary location are very rare and mainly solid [27]. In the D'Orsi et al. [25] study the incidence of pulmonary metastases varied from 3.2% to 4.7%. Among 24 patients with metastases in the lungs due to carcinoma of the endometrium, none of the patients had cavitory lesions. The mean time from the demonstration of pulmonary metastases to their detection amounted to 12 months, whereas the mean time from detection to death was 5 months. Pulmonary metastases are difficult to diagnose properly, mainly due to the lack of symptoms and surreptitious extension [4]. Only 5% of patients with lung metastases have such symptoms as dyspnoea, pain in the chest, a cough or haemoptysis [23]. Our patient remained asymptomatic for 2 years. Therefore, pulmonary metastases should be suspected in all patients with cavitory lesions and a history of a primary tumor.

Because of the inconsistent examination findings in our case, diagnostic procedures were repeated several times. Neoplastic cells appear in the sputum only when there is any communication between the tumour and the bronchial tree, thus in unadvanced pulmonary lesions both bronchial washing and sputum can be negative [6]. EBUS-TBNA seemed to be the best procedure to make a proper diagnosis, but each time its results led to the sarcoid-like reaction diagnosis, hence the chemotherapy regimen was delayed in our patient.

To the best of our knowledge, our report of the distant sarcoid reaction accompanying endometrial adenocarcinoma metastases is extremely rare in the literature. In 2008, Kennedy et al. [28] reported a sarcoid-like reaction in a patient with endometrial cancer. In 2018, Lashari et al. [29] described two cases of a distant sarcoid reaction in patients with adenocarcinoma of the uterus, but it appeared during an active neoplastic disease directly after the confirmation of a malignancy, unlike in our patient.

To summarise, the differentiation between sarcoidosis and a sarcoid-like reaction of lung metastases is extremely difficult, especially when the primary tumour is located outside the chest cavity. For this reason, it is important to repeat diagnostic procedures in patients with malignancies in the past, including EBUS-TBNA and VATs.



Author's contribution

Study design – D. Ziora, M. Zarzecka, A. Galeczka-Turkiewicz

Manuscript preparation – A. Galeczka-Turkiewicz, D. Galle, A. Goryczka

Literature research – D. Ziora, A. Galeczka-Turkiewicz, D. Galle, A. Goryczka

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