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Benign pulmonary metastasizing leiomyoma uteri. Case report and review of literature

Łagodne przerzutowe mięśniaki w płucach. Opis przypadku i przegląd piśmiennictwa

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Abstract

Benign metastasizing leiomyoma (BML) is a rare condition in middle-aged women with a history of uterine leiomyomata. It is characterized by the proliferation of, usually multiple, smooth muscle nodules. Approximately 100 cases have been reported in the literature, and the lungs were the most common site of metastases.

We report a case of 52-year-old obese woman (BMI 31), hospital worker, smoker, admitted to the hospital with exertional dyspnoea, night sweats, loss of weight, and productive cough.

Hysterectomy for a uterine leiomyoma was performed 9 years earlier. In addition, a history of two episodes of superficial vein thrombosis 3 and 2 years before admission was noted. Chest X-ray and subsequently CT chest examinations revealed multiple, non-calcified nodules within the middle and lower parts of both lungs. Specimens obtained by transbronchial biopsy (TBLB) and from open lung biopsy displayed benign muscle cell proliferation compatible with BML. The levels of sex hormones were characteristic for the menopause; therefore, observation was advised. Additionally, Streptococcus pneumoniae was cultured from bronchial washing, and bronchitis was diagnosed. Antibiotics, bronchodilators, and mucolytics were administered, and dyspnoea and cough with expectoration were diminished. Two years later pulmonary lesions have been stable; however, she has put on weight. Subsequently the patient has developed deep vein thrombosis with pulmonary embolism. Anticoagulant treatment was introduced, with some improvement.

Key words: benign metastasizing leiomyoma, BML, pulmonary nodules, round nodules, pulmonary metastases, leiomyoma

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Streszczenie

Łagodne przerzutowe mięśniaki (BML) są rzadką chorobą występującą u kobiet w średnim wieku (które chorowały lub chorują na mięśniaki macicy) charakteryzującą się proliferacją mnogich guzków zbudowanych z komórek mięśni gładkich. Opisano około 100 chorych, a płuca należą do najczęstszych lokalizacji zmian przerzutowych.

Pięćdziesięciodwuletnia chora, pracownica szpitala, palaczka tytoniu (30 paczkolat), otyła (BMI 31) przyjęta do szpitala z powodu duszności wysiłkowej, produktywnego kaszlu, nocnych potów i utraty masy ciała. Dziewięć lat wcześniej z powodu mięśniaków macicy wykonano u chorej resekcję macicy bez przydatków. Na 3 i 2 lata przed hospitalizacją była leczona przeciwkrzepliwie z powodu zakrzepicy żył powierzchownych kończyn dolnych. W badaniu radiologicznym klatki piersiowej oraz tomografii komputerowej klatki piersiowej uwidoczniono mnogie dobrze odgraniczone guzki w obu polach płucnych, z przewagą w dolnych i środkowych polach płucnych ulegające wzmocnieniu po podaniu kontrastu. W badaniu histologicznym specimenów pobranych z biopsji transbronchialnej płuca, a następnie potwierdzonych w biopsji otwartej płuca stwierdzono proliferujące, łagodne, komórki mięśni gładkich. Dodatkowo z wydzieliny oskrzelowej wyhodowano *Streptococcus pneumoniae*. Podano antybiotyk, broncho- i mukolityki, uzyskując ustąpienie duszności i odkrztuszania. Z uwagi na brak dynamiki choroby w okresie wstępnej obserwacji oraz wejście chorej w stan menopauzy nie wdrażano leczenia

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przyczynowego. W trakcie dwuletniej obserwacji stwierdzono stabilizację radiologiczną zmian płucnych. Jednakże chora przytyła oraz doszło do zakrzepicy żył głębokich w kończynie dolnej prawej powikłanej zatorowością płucną. Wdrożono leczenie przeciwkrzepliwe, uzyskując poprawę.

Słowa kluczowe: łagodne przerzutowe mięśniaki, BML, guzki płucne, cienie okrągłe, przerzuty do płuc, mięśniaki
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Introduction

Benign metastasizing leiomyoma (BML) is a rare condition in middle-aged women with a history of uterine leiomyomata, characterized by the proliferation of, usually multiple, smooth muscle nodules. Over 100 cases were presented in the literature, and the lungs were the most common site of metastases [1–8]. The first case was presented as fibroleiomyomatous hamartoma by Steiner in 1939 [1]. It is a usually disease of women in late childbearing age, and sex hormone levels are closely connected with its clinical course[1–8].

The lesions mainly occur in the lungs, trachea, skin, urinary bladder, liver, intra-abdominal lymph nodes, oesophagus, skeletal muscles, breasts, soft tissues, bones, central nervous system, and heart [1–13].

Mostly the diagnosis is incidental and pulmonary lesions are discovered during routine chest radiological examinations. Some patients have symptoms such as cough, pain, or dyspnoea but they are frequently connected with underlying conditions such as pneumonia or bronchitis. Pulmonary changes can be seen from 3 months to 26 years after hysterectomy [1–13].

Open lung biopsy is the standard diagnostic procedure in this disease.

Therefore, we presented a woman with a history of hysterectomy in the course of leiomyoma and BML in the lungs, who was diagnosed on examinations of specimens obtained by TBLB. However, because of the rarity of the tumour, diagnosis was proved subsequently by open lung biopsy.

Case report

A 52-year-old obese (BMI 31) woman, smoker (30 pack/year), was admitted to the hospital because of exertional dyspnoea, productive cough, with expectoration of a slight amount of mucopurulent sputum, night sweats, loss of weight of about 10% during the previous 6 months.

In 2001, because of leiomyoma uteri, she was treated by hysterectomy. Two years later a fibroma of the perianal area was removed surgically. In 2006 the patient developed superficial vein thrombosis, and a relapse was noted one year later — anticoagulants were administered two times for six months each. Arterial hypertension was diagnosed 6 years ago and was treated with ACE inhibitors.

The patient was pregnant two times and delivered healthy children. First menstruation was at 12 years of age, and they were regular, every 27––28 days, lasting 4–5 days. However, in the last 2––3 years before hysterectomy she sometimes had metrorrhagia. Positive family history of cancer was noted, her mother died of pancreatic cancer.

On admission, the patient was in very good general condition. Slight enlargement of the thyroid gland and varices of both legs were noticed. Wheezing in the base parts of both lungs could be heard. Laboratory examinations revealed elevated concentrations of D-dimer (832 μg/ml, pred 500μg/ml), blood sedimentation rate 50 mm/h, but C-reactive protein was within the normal range. Tuberculin test RT23 was positive (20 mm with vesicles), but Qantiferon–Gold test was negative. Serum concentrations of cancer markers such as Ca125.5, Ca19.9, Ca 15.3, and carcinoembryonic antigen (CEA) were all within normal ranges. Pulmonary function tests and diffusion lung capacity for carbon monoxide were within normal limits.

Ultrasound examination of the thyroid gland revealed multiple nodules without lymph node enlargement, a biopsy of which did not detect cancer cells. In addition, ultrasound examination of the abdomen did not show any pathological lesions.

There were no thromboses in ultrasound examination of the deep veins of both legs.

Chest X-ray and CT scan showed multiple small, well-circumscribed, noncalcified, contrast enhancing nodules, which were prominent in the middle and lower parts of both lungs without lymph node enlargement (Fig. 1, 2A, B). Slight inflammation of the bronchial tree was revealed in bronchoscopy. Bronchial washing was negative for acid-fast bacilli and cancer cells. Streptococcus pneumoniae, penicillin sensitive, was cultured from bronchial washing, and patients received antibiotics, mucolytics, and bronchodilators, with improvement. Transbronchial biopsy revealed the proliferation of spindle-shaped smooth muscle cells with regular oval nuclei, without mitosis figures (Fig. 3). The cells were positive for smooth

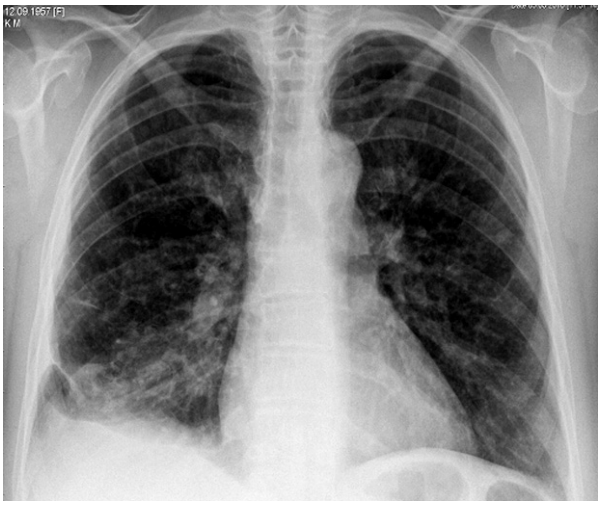

Figure 1. Multiple small nodules predominated in the middle and lower parts of both lungs.

Rycina 1. Liczne drobne guzki w obu płucach z przewagą w dolnych i środkowych polach płucnych

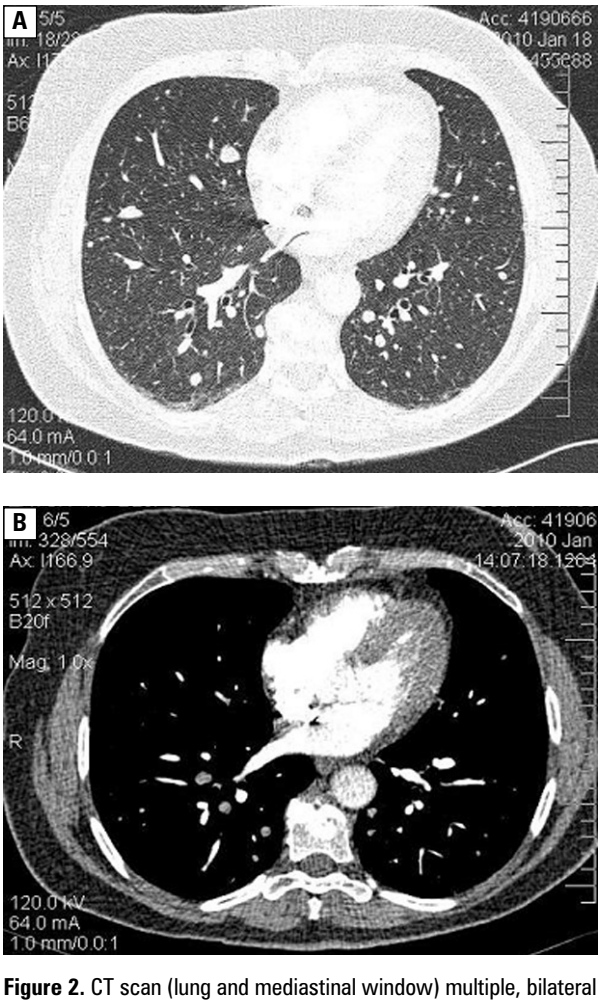

Figure 2. CT scan (lung and mediastinal window) multiple, bilateral well contrast-enhanced nodules

Rycna 2. CT (okna płucne i śródpiersiowe). Liczne dobrze odgraniczone guzki w obu płucach ulegające wzmocnieniu kontrastowemu

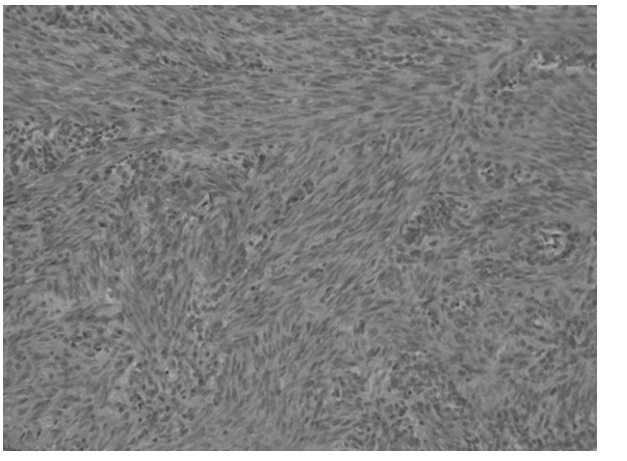

Figure 3. Proliferation of smooth muscle cells, without nuclear atypia

Rycina 3. Proliferacja komórek mięśni gładkich bez cech atypii

muscle actin, and proliferation index was low (less than 2% Ki-67 positive cells). Also, expression of oestrogen alpha and progesterone receptors, smooth muscle actin (SMA), and desmin were shown (Fig. 4). On the basis of these findings benign metastasizing leiomyoma was diagnosed.

Because of the rarity of the tumour, open lung biopsy was performed, and histological examination of specimens confirmed the diagnosis of BML. A comparison of the pulmonary findings with the pathology of previous leiomyoma was performed. Two uterine leiomyomas, well circumscribed, with high cellularity, without nuclear polymorphism, without necrosis, and with 1 mitotic figure per 50 large areas, were revealed. The cells were identical to those observed in pulmonary specimens. Serum concentrations of sex hormones were characteristic for menopause.

During two years of observation the patient put on weight. Stabilization of pulmonary lesions was noticed in CT chest examinations and pulmonary function parameters were within normal limits. Subsequently, in the observation period she developed deep vein thrombosis with pulmonary embolism. Anticoagulant therapy was introduced with improvement.

Discussion

The clinical characteristics of patients with BML described in the literature vary widely [1–13]. All patients were reported to have a history of uterine leiomyoma, and the period between hysterectomy or myomectomy ranged from 3 months to 26 years. Jautzke et al. [5] reviewed 74 cases of BML and found the lungs to be the common site of involvement, similarly to Rivera et al., who found pulmonary lesions in 20 out of 33 cases [4].

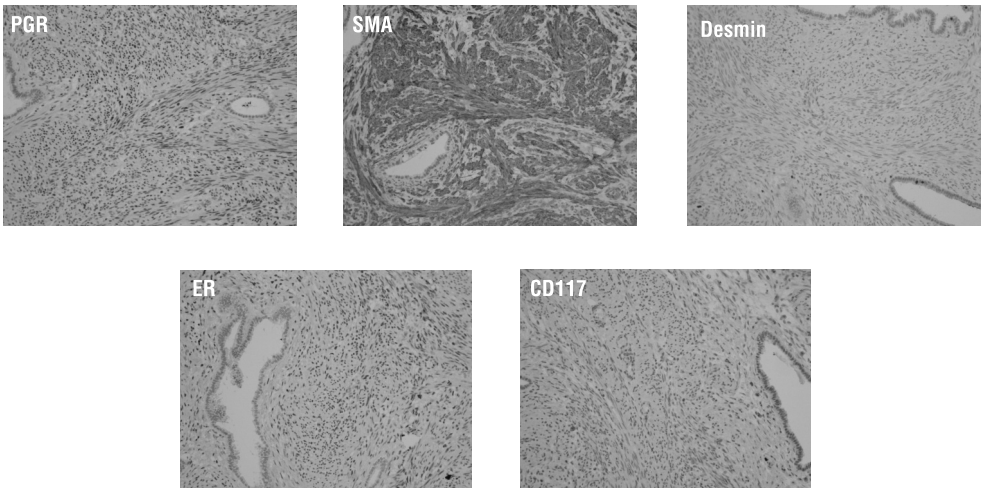

Figure 4. Positive immunostaining for oestrogen alpha, progesterone receptors, smooth muscle actin, and negative for CD 117

Rycina 4. Badanie immunohistochemiczne: dodatnia ekspresja receptorów estrogenowych progesteronowych , aktyny i desminy w komórkach mięsni gładkich , negatywna ekspresja CD117

The mean age of 28 recently collected cases was 43 years [1–13]. Our patient belongs to the group of somewhat older patients in menopause; however, in the period between hysterectomy and diagnosis she had no X-ray chest examination.

Usually the disease is diagnosed incidentally, but also severe courses with mortality related to BML have been reported [3, 7]. The extent of pulmonary lesions only slightly correlated with severity of respiratory symptoms. In the presented case, the symptoms were mainly connected with bronchitis and obesity and they were the stimulus to initiate the diagnostic procedure.

The characteristic radiological findings are circumscribed solitary or multiple noncalcified, contrast enhancing nodules, with sizes ranging from a few millimetres to several centimetres. Miliary dissemination of BML and cavitary lesions was also seen. Occasionally endobronchial and pleural sparing is also observed. In our case the most common pattern of BML, disseminated spread in the lungs, was shown [10]. Recently it has been suggested that total body CT-PET scan can be useful in differentiation of BML with leiomyosarcoma. BML shows little metabolic uptake of 18-fluorodeoxyglucose in comparison with high uptake of malignant, sarcomatoid changes. However it should be taken into account that other lung lesions without FDG uptake also have malignant behaviour, for instance cancer with a mucinous component (lung, breast, renal, gastrointestinal), neuroendocrine tumours including carcinoid tumours [14]

The pathogenesis of this disease is still obscure. Uterine leiomyoma is the most common gynaecological neoplasm, with a prevalence of more than 50% of women above the age of 30 years [15]. The majority of uterine leiomyomas are benign, and malignant behaviour was presented only in 0.13 to 6% of them [15]. Recently it has been suggested that BML is a result of monoclonal, haematogenous spread of benign-appearing uterine leiomyoma. The morphology, molecular, and immunohistochemical futures are characteristic for benign neoplasms in spite of the metastatic potential. As was shown in the presented case, as in others presented in the literature, BMLs have a low mitotic rate and MIB-1 index supporting the low proliferate activity of these tumours [16–20].

Patton et al., in spite of proving the clonality of uterine leiomyoma and BML, showed that telomere shortening was not responsible for metastatic spread [20]. Approximately 25% of the uterine leiomyomas may have a balanced translocation, trisomy 12, and rearrangement of 6p [17, 18]. However, in most of the cases the chromosomal abnormalities associated with BML have been difficult to characterize[19–21].

BML usually express oestrogen and progesterone receptors, and the specimens from our patient were positive for sex hormone receptors [10, 17––19]. This observation led to treatment based on hormonal manipulation such as pharmacological oophorectomy (LH-RH inhibitors), antioestrogen therapy by the use of oestrogen receptor blockers (tamoxifen, raloxifen), or aromatase inhibitors [4, 21–26]. The growth of lesions is hormone dependent, and spontaneous regression of them during pregnancy and during menopause were reported [4, 10, 23].

Long-acting gonadotropin releasing hormone (GnRH) analogues suppress pituitary gonadotrophin synthesis by decreasing the number and sensitivity of GnRH receptors and significant lowering oestrogen levels. This oestrogen reduction is further enhanced by inhibition of their peripheral conversion by aromatase inhibitors [24]. It seems that one of the best therapeutic options is long-acting GnRH analogue with aromatase inhibitors [4].

Surgical excision of solitary tumours is also performed [4, 25].

Another new therapeutic option is tyrosine kinase inhibition. An overexpression of c-kit was shown in low-grade leiomyosarcoma and gastrointestinal stromal tumours, and suppression by imatinib was beneficial. It was suggested that this type of treatment might also be useful in BML patients [1].

The presented woman was in menopause. Thromboembolic disease and obesity were, in this case, contraindications to antioestrogen therapy. Fortunately, stabilization of pulmonary lesions has been observed, and until this time the patient has not required treatment.

Open lung biopsy is the necessary and standard diagnostic procedure in BML. Other procedures, such transthoracic needle lung biopsy, were not effective as was shown by Abramson et al. [10]. However, in our case, with many small nodules on CT scans, it was possible to obtain the diagnosis by assessment of specimens from TBLB.

The conclusion is that in a middle-aged women with a history of uterine leiomyoma with characteristic radiological findings of well-circumscribed, multiple, noncalcified, non contrast enhancing nodules, ranging in size from a few millimetres to several centimetres, TBLB is helpful in establishing the diagnosis of BML.

Conflict of interest

The authors declare no conflict of interest.

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