Multimacronodular pulmonary tuberculosis (bacteriologically negative) confirmed histologically

Tuberculoză pulmonară multi macronodulară (bacteriologic negativă) confirmată histologic

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Abstract

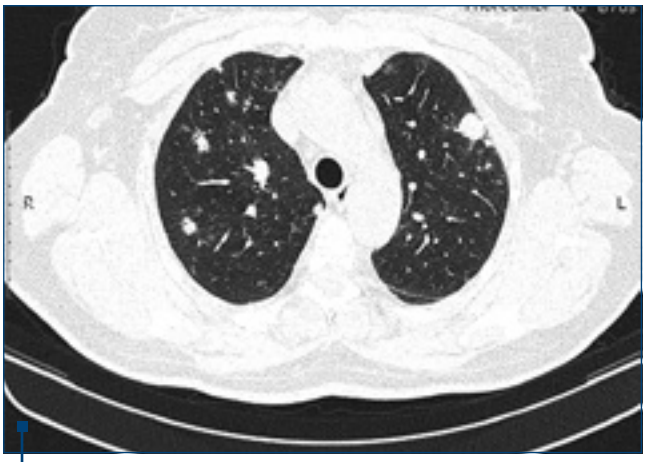
Background: *Pulmonary tuberculosis can be confirmed by positive bacteriology of sputum, bronchial aspirate or by biopsies (microscopy and/or culture) or by histopathological examination highlighting specific tuberculous granulomas. When microscopy is repeatedly negative during noninvasive methods, lung biopsy by thoracoscopy is needed for confirmation and differential diagnosis.*
Case presentation: *A 40-year-old female patient (nonsmoker, diabetic, with previous exposure to chemicals) was admitted to the hospital for weight loss, dry cough, loss of appetite, pallor, and fatigue. Chest-X-ray and thoracic CT revealed multiple irregular macronodules with various shapes, randomly spread across the lungs. Bacteriology for acid fast bacilli (AFB) from six spontaneous sputum was negative. Bronchoscopy showed an acute bronchitis. Bronchial aspirate was negative for tumor cells and AFB. Several biopsies from bronchial wall showed unspecific changes. The molecular biology tests for specific nucleic acids detection (Polymerase Chain Reaction) or positron-emission-tomography (to differentiate benign nodules from malign ones) were not accessible. Multiple biopsies from lung parenchyma and pleura were obtained using thoracoscopy. Histopathology revealed multiple specific tuberculous granulomas. The complex antituberculous treatment (9 months) has led to the total cure of the disease and resorption of the nodules. The patient's last visit (after 2 years) showed no clinical/imagistic or bacteriologic relapse of the disease.*
Conclusion: *Tuberculosis may present in the form of multiple macronodules spread randomly across the lung parenchyma. Thoracoscopy coupled with multiple large lung biopsies are recommended for diagnosis of multinodular lung lesions, especially when common bacteriology/cytology from bronchoscopic aspiration failed to achieve diagnosis. Histological exam from thoracoscopic biopsies allows differential diagnosis between entities that have macronodular features: tuberculosis, primitive lung cancer, lymphomas, metastatic disease or invasive fungal disease.*
Keywords: ***tuberculosis, macronodular lesions, tuberculous caseous granuloma***

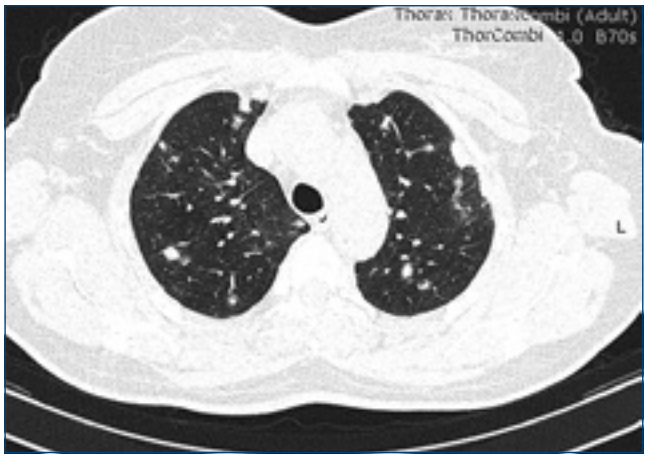
Rezumat

Context: *Tuberculoza pulmonară poate fi confirmată fie prin examenul bacteriologic pozitiv din spută, aspirat bronșic sau prin biopsii (microscopie și /sau cultură), fie prin examinarea histopatologică care evidențiază granuloame tuberculoase specifice. Atunci când microscopia este in mod repetat negativă prin metode non-invazive, este necesară biopsia pulmonară prin toracoscopie pentru confirmare și diagnostic diferențial.*
Prezentare de caz: *O pacientă în vârstă de 40 de ani, de sex feminin (nefumătoare, diabetică, cu expunere în antecedente la substanțe chimice),a fost internată în spital pentru scădere în greutate, tuse uscată, inapetență, paloare, oboseală. Radiografia toracică și CT-ul toracic au evidențiat multipli macronoduli neregulați, cu diferite forme, repartizați în mod aleatoriu în plămâni. Examenul bacteriologic microscopic (BAAR) din șase spute spontane a fost negativ. Bronhoscopia a evidențiat bronșita acută. Aspiratul bronsic a fost negativ pentru celule tumorale și BAAR. Mai multe biopsii din peretele bronșic au prezentat modificări nespecifice. Testele de biologie moleculară pentru detectarea specifică a acizilor nucleici (Polymerase Chain Reaction) sau tomografia cu emisie de pozitroni (pentru a diferenția nodulii benigni de cei maligni) nu au fost accesibile. Biopsii multiple din parenchimul pulmonar și pleură au fost obținute prin toracoscopie. Examenul histopatologic a relevat multiple granuloame tuberculoase specifice. Tratamentul complex antituberculos (9 luni) a dus la vindecarea totală a bolii și resorbția nodulilor. Ultima vizită a pacientei (după 2 ani) nu a arătat recidivă clinică /imagistică sau bacteriologică a bolii.*
Concluzie: *Tuberculoza se poate prezenta sub forma unor multipli macronoduli răspândiți aleator în parenchimul pulmonar. Toracoscopia împreună cu multiple biopsii pulmonare largi este recomandată pentru diagnosticul leziunilor pulmonare multinodulare, mai ales atunci când examenul bacteriologic / citologic din aspiratul bronșic nu a reușit să certifice diagnosticul. Examenul histologic din biopsiile toracoscopice permite diagnosticul diferențial între entitățile cu manifestări macronodulare: tuberculoză, cancer pulmonar primitiv, limfom, metastaze sau boli fungice invazive.*
Cuvinte-cheie: ***tuberculoză, leziuni macronodulare, granulom cazeos tuberculos***

Introduction

Pulmonary tuberculosis (TB) can be confirmed by positive bacteriology of sputum, bronchial aspirate or tissue biopsy (Ziehl Neelson acid fast bacilli stain and/or culture on Löwenstein Jensen) or by histopathological examination highlighting specific TB granulomas. Accurate bacteriological assessment of pulmonary TB consists in 3 probes of sputum collected during a 24 hour period, on different days. The use of "induced sputum" technique in 3 different days, is indicated in patients who do not cough[1,2,3]. When microscopy is repeatedly negative, bronchoscopy with aspirate or bronchoalveolar lavage offer a targeted sampling[3]. In spe-





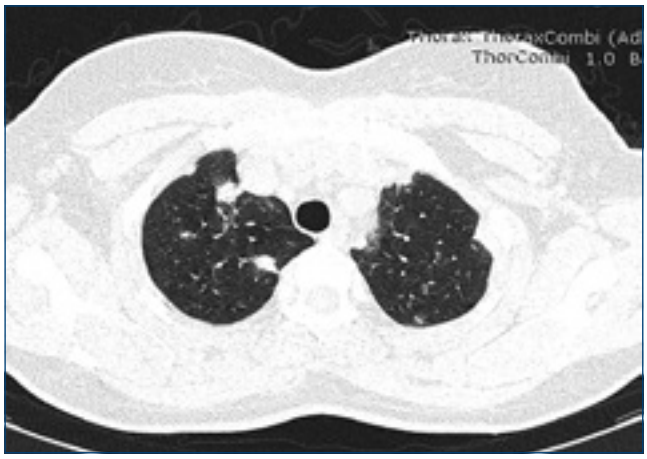


Figure 1,2,3. *CT scan of a 40 year - old women. Irregular macronodules spread randomly in the two lungs*

cific cases, there is a need to perform a differential diagnosis with other lung lesions such as tumors, metastasis, lymphoma, invasive fungal disease or recurrent lung infarction. Video-thoracoscopy or open lung biopsy by thoracotomy with large targeted biopsies offer valuable diagnostic confirmation[3,4]. The sensibility of thoracoscopy in the TB confirmation is 100%[4].

Case report

A 40 year-old woman (nonsmoker, diabetic, with known exposure to chemicals) was admitted in the hospital for a slow onset of general symptoms: significant weight loss (8 kg in 2 months), dry cough, loss of appetite, pallor and fatigue. The patient had a medical history of diabetes and mild hypertension well controlled by treatment. We did not find any recent or previous contact with a source of TB.

The **chest X-ray** and thoracic **computed-tomography (CT)** revealed multiple irregular macronodules with different shape and dimensions (between 1 – 3 cm), randomly spread in the two lungs (Figures no. 1, 2 and 3).

Microbiological examination for acid fast bacilli (AFB) from 3 independent collections of sputum **(**Ziehl Neelsen technique) and 3 induced sputum yielded negative results.

Bronchoscopy showed an acute bronchitis and required collection of bronchial aspirate and bronchoalveolar lavage for cytology and bacteriology (both were negative). Multilevel bronchial biopsy specimens were negative for tumor cells, AFB, fungi or sarcoid granuloma. The molecular biology tests for specific nucleic acids detection (Polymerase Chain Reaction) for a rapid confirmation of TB were not available.

The **bronchoalveolar lavage** examination showed nonspecific bacterial flora (Gram stain) and was negative for fungi and *Pneumocystis jiroveci* (silver methenamine stain).

Further investigation ruled out the suspicion of pulmonary metastasis: gynecological examination that found benign cystic ovaries; mammography who revealed fibrocystic breast disease; abdominal ultrasound – (gallbladder stones), abdominal CT scan (without evidence for tumoral lesions), HIV antibodies – negative and no clinical sign for haematologic diseases. **PET-CT** (positron-emission tomography-CT) was not available for our patient.

Histopathological examinations were performed from tissue specimens obtained by **thoracoscopy.** Larger tissue fragments (5 collections from different sites) were resected in order to have representative biopsies of the lesions, to facilitate differential diagnosis with other disorders: malign lung tumor, metastasis, benign tumors, lymphoma, fungal disease or recurrent lung infarctions. The biopsies from lung and pleura showed chronic inflammatory lesions with granuloma formation, highly suggestive of tuberculous granulomas.

The granulomas showed caseation necrotic center and Langhans-type giant cells (Figure no. 4, 5). Pulmonary parenchyma adjacent to granulomas showed bronchiolitis obliterans organizing pneumonia (BOOP) pattern, mostly limited around a 1-2 mm rim around granulomas (Figure no. 6).

Treatment

The patient followed standard antituberculous treatment for 9 months which led to total cure of the disease and resorption of the nodules (Figure 7-9). The 7 repetitive cultures from sputum and bronchoalveolar lavage specimens were negative at 2 months but the culture isolated from the bioptic tissue was positive (12 colonies) after 2 month of incubation.

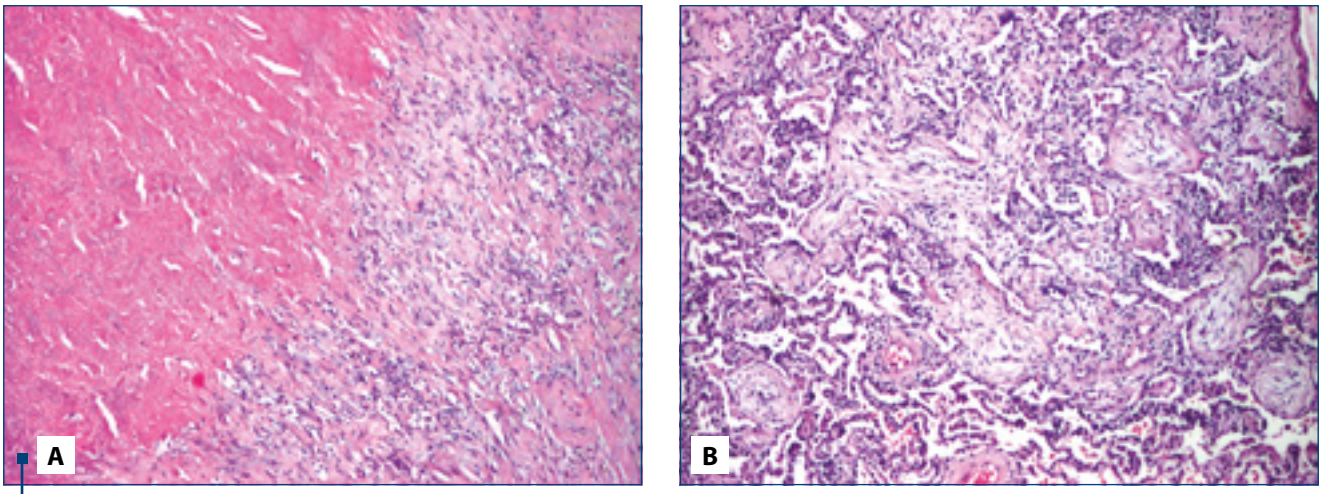


Figure 4,5. *Histopathology of necrotizing granuloma (lung and pleural biopsies)*
(A) Note the characteristic Langhans-type giant cells admixed with epithelioid histiocytes;
(B) Central aspect of the granuloma with eosinophilic necrotic material and epithelioid cell arranged in radial fashion.

Clinical, imagistic and bacteriologic controls made at 9 month, 1 year, 2 years from the treatment-ending did not show any relapse of the disease or complication.

Discussions

The patient had common risk factors for TB reactivation (diabetes, professional exposure) nevertheless no recent or previously known TB exposure was documented. The symptoms were significant weight loss, fatigue, and loss of appetite, which raised the possibility of either TB or neoplastic process.

In the absence of the Koch bacilli the clinical presentation and the chest CT aspect with multiple irregular bilateral macronodules with randomly distribution was strongly suggestive for pulmonary metastases. The existence of the gynecological pathology and breast pathology (even suggestive for benign disorders) needed an accurate differential diagnosis of the multiple pulmonary nodules with possible dissemination from a primary genital/breast tumor.

Macronodular TB (tuberculoma) can yield negative microscopy with Ziehl Neelsen stain, therefore modern tools for rapid confirmation, such as PCR, would be necessary to prove the presence of the organism.

In our case microscopy was constantly negative of AFB from spontaneous sputum, but even the induced sputum or bronchial lavage were negative (it is known that they could increase the yield for confirmation in TB)[5,6]. The mycobacteria cultures from sputum were also negative at 2 months. Fortunately, the confirmation by histology (specific granuloma) was decisive for starting the treatment. In addition, the culture from bioptic tissue was finally also positive but with a great delay - over 2 months).

The PET-CT scan is strongly recommended in the diagnosis and staging of pulmonary nodules (predominantly highlighting primary tumor and lymph node/distant metastasis). PET–CT is able to analyze the tracer FDG – Fluorodeoxyglucose fixation by the nodules (increased capture of the FDG is associated with an increased metabolism and a "malignant character")[7,8]. This noninvasive investigation was not available to our patient.

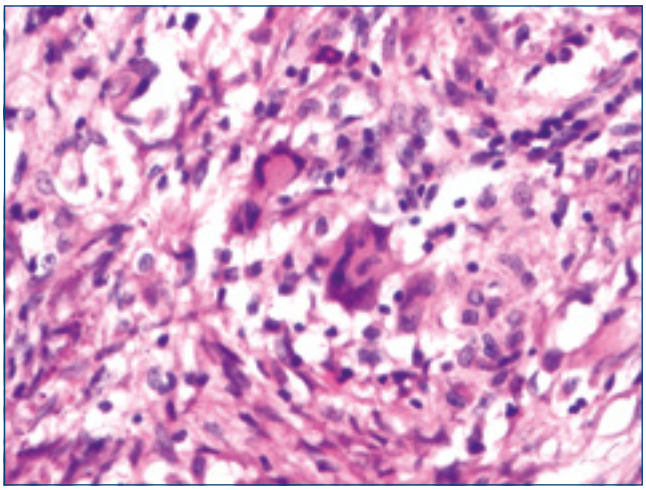
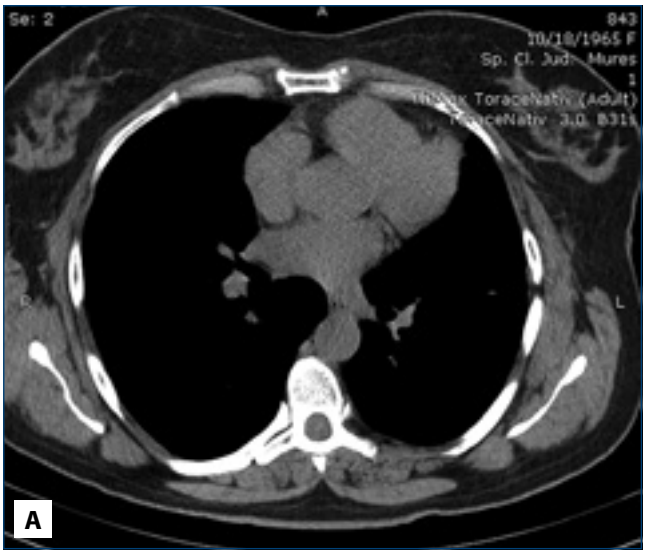


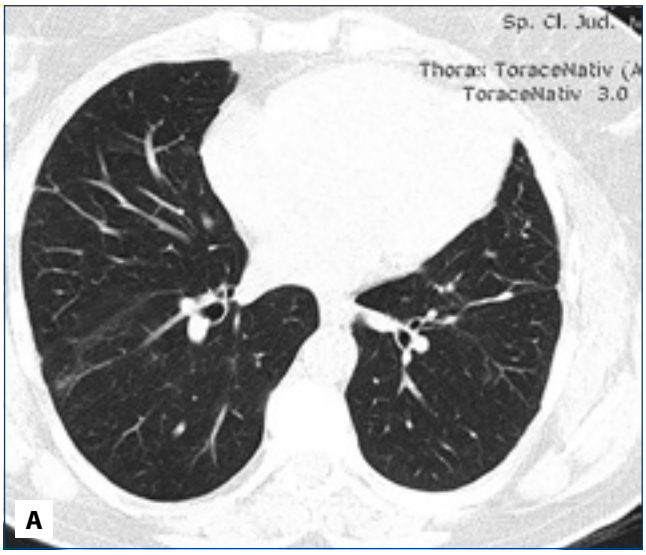
Figure 6. *Pulmonary parenchyma adjacent to necrotizing granulomas showing bronchiolitis obliterans organizing pneumonia pattern*

EBUS (endobronchial ultrasound) coupled with TBNA (transbronchial needle aspiration) using bronchoscopy is a minimally invasive method used to confirm the nature of pulmonary nodules (but it was not available for our patient)[9,10].

Determination of various tumor markers, such as CA 15-3 and CA-125, were both negative. Several studies showed that CA 15-3 is positive in up to 20% in primary breast cancer and in 61-84% in metastatic breast cancer. The marker CA-125 secreted by ovarian epithelial tumors is the standard in the evaluation of pelvic masses and has a sensibility of near 85%[11,12,13].

Thoracoscopy was recommended to confirm the diagnosis of lung nodules when CT scan, sputum bacteriology, bronchoscopy and other general noninvasive investigations failed to provide a conclusive diagnosis[4]. Thoracoscopy permitted histopathological diagnosis from several large biopsies and microbiological investigation for different infections: non-specific germs, Koch bacilli, and fungi[14,15,16].





Conclusions

TB may express macronodular lesion with random lung distribution which raises the need of accurate differentiation with metastasis. Macronodular TB can yield negative microscopy with Ziehl Neelsen stain; therefore, modern tools for rapid non-invasive confirmation, such as PCR, would be necessary to prove the presence of the mycobacterial organism. Considering the lack of rapid molecular biology tests (PCR) and the delay of the diagnosis by Löwenstein Jensen culture (over 2 months) the confirmation by histology (specific granuloma) was decisive for starting the treatment. Thoracoscopy was an accessible diagnostic method to perform large multiples biopsies and confirm the nature of pulmonary nodules.

Specific accurate histology allowed the confidence of the diagnostic in the pulmonary TB suspicion with repeatedly negative bacteriology and made the differential diagnosis with lung cancer, lymphomas, metastasis, invasive fungal disease, lung infarction or other nonspecific infections. In the same time tissue biopsies offered occasion for positive cultures absolutely required for drug susceptibility tests for a targeted treatment. ■

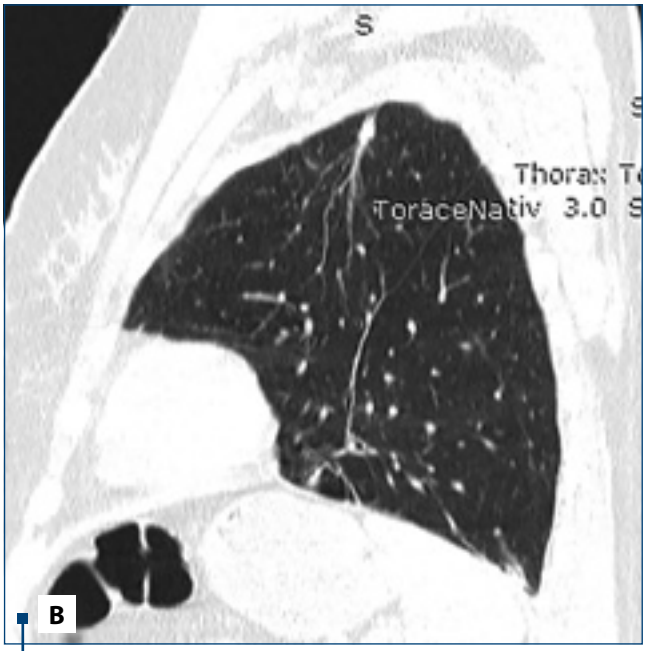


Figure 7,8,9. *CT scan after 6 month of antibiotic treatment for tuberculosis (A. axial plan). B sagittal plans*

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