CASE REPORT

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Tuberculosis mesenteric adenopathy and polyserositis

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Abstract

A 41-year-old female patient was admitted into Surgery Clinic accusing abdominal pain, diarrhea, fever and chills. Based on clinical, biological and imaging data, it was established a diagnosis of pelviperitonitis and it was initiated an antibiotic and anti-inflammatory treatment. As fever and abdominal pain continued, it was decided to go on with surgery that revealed suppurated and perforated mesenteric adenopathy. Pus was sampled for bacteriological exam and also biopsy was performed for pathological exam. The result of pathological exam was suggestive for a specific granulomatous lesion (TB lesion). It was established diagnosis of TB mesenteric adenopathy and it was initiated specific anti-TB treatment according to *WHO* guidelines. After three, respectively five months of treatment, patient developed a right laterocervical adenopathy that fistulized in both cases, despite the correct treatment administered. No resistant TB strain and no atypical mycobacteria was discovered.

Keywords: extrarespiratory tuberculosis, adenopathy, treatment, evolution, outcome.

Introduction

Tuberculosis (TB) is an infectious endemic disease, which implies the presence of *Mycobacterium tuberculosis* complex bacteria. These germs can develop granulomas with important inflammation or tissue destruction, and the natural outcome is chronic, consumptive and even fatal in approximately five years in the absence of treatment in more than half cases. Nowadays tuberculosis represents a public health problem with approximately eight million new TB cases each year and three million deaths worldwide. In 2011, Romania ranks on 6th place worldwide at TB disease incidence, and Dolj County occupies the first place judging after TB endemic evaluation indicators [1–4].

Extrapulmonary tuberculosis, according to *WHO*, has been recording an ascendant evolution during 2004–2007 with stationary tendency at the end of this period. In Romania, the concern for extrapulmonary localization represented 14% from the overall localizations during 2004–2006 [5–7].

Extrapulmonary tuberculosis includes all TB affects except pleura, lungs, intra-thoracic lymph nodes and larynx, and originates from the hematogenous metastatic affects developed during the prime TB infection period. Peripheral ganglionary TB represents the most detectible localization of extrapulmonary TB. The most affected lymph nodes are the lateral cervical, submandibular, axilar and epitrochlear groups. Diagnosis is sustained by bacteriology and histopathology investigations, and tuberculin intra-dermoreaction is frequently positive [1, 5, 6].

Because of the difficult antituberculosis drugs penetration through caseating ganglionary masses, the treatment regimen I as established within the *National Control Program for Tuberculosis* (*PNCT*) can be prolonged for up to nine months (2HRZE/S-7/7 + 7HR-3/7) [1, 4, 6].

Patient, Methods and Results

A 41-year-old female patient was admitted into Surgery Clinic in June 2011, accusing abdominal pain, diarrhea, fever and chills.

Abdominal ultrasound exam revealed above and posterior of uterus a mass of 9/7/7 cm, with mixed echogenity, needing a differential diagnosis between piosalpinx and degenerated uterine fibroma.

Laboratory findings included a hemoglobin of 8.4 g/dL, hematocrit of 26%, white blood-cells (WBC) count of 12100, serum urea of 16 mg/dL, blood sugar of 74 mg/dL, serum creatinine of 0.43 mg/dL, an elevated aspartate aminotransferase (ASAT) of 114 U/L, and alanine aminotransferase (ALAT) of 57 U/L.

It was established the diagnosis of pelviperitonitis and it was initiated an antibiotic and anti-inflammatory treatment. As fever and abdominal pain continued, it was decided to undergo an exploratory laparoscopy. During laparoscopy, it was discovered pus and false membranes in pelvic cavity, and also turbid effusion with false membranes in both subdiaphragmatic areas. Because it could not be revealed the source of pus by laparoscopy, it was decided to go on with median laparotomy, which revealed suppurated and perforated mesenteric adenopathy.

Pus was sampled for bacteriological exam and biopsy was performed for pathological exam.

Bacteriological exam of the pus revealed a smear negative result for Koch bacillus and Gram-negative non-specific bacillus.

After surgery, patient developed fever 38.5–39^{0}C and an antibiotic treatment with Invanz (Ertapenem) and Avelox (Moxifloxacinum) was initiated.

CT of abdomen, pelvic and thoracic regions revealed: large volume of pleural effusion; pericarditis; large volume of abdominal and pelvic effusion; liver, pancreas and kidneys normally CT; cystic masses inside the spleen with 10–11 mm in diameter; 90 mm uterus transversal diameter; paraaortic microadenopathy.

The result of pathological exam of mesenteric biopsy showed a microscopic structure of fibroconjunctive tissue including large areas of caseation and epithelioid follicles, with multinuclear gigantic cells. The aspects were suggestive for a specific granulomatous lesion (TB lesion).

Based on pathological exam result, it was established the diagnosis of TB mesenteric adenopathy and it was initiated anti-TB treatment including Isoniazide, Rifampin, Pirazinamide and Streptomycin.

During the first three months of the treatment, patient evolution was good, without any medication side effects. After three months of treatment, patient developed a right laterocervical adenopathy, which led to fistulization revealing caseum.

Pleural echography and echocardiography revealed resorption of the pleural and pericardial effusion.

Bacteriological exam from fistular caseum was smear-negative, but the culture was positive for Koch bacillus.

Antibiogram was carried out revealing sensitive strain of Koch bacillus.

Also, enzymatic tests showed there were no atypical mycobacteria involved.

Human immunodeficiency virus (HIV) test was negative.

Patient continued anti-TB treatment according to *WHO* guidelines, but he developed a second right latero-cervical adenopathy after another two months, which also fistulized and expressed a small quantity of caseum (Figure 1).

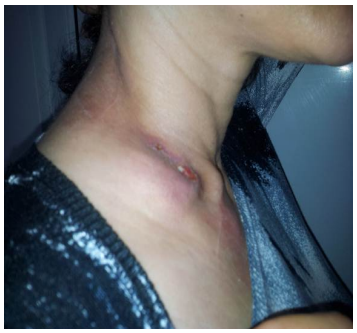

Figure 1 – ***Second right latero-cervical adenopathy developed after five months of anti-TB specific treatment.***

Microscopic examination was smearing negative and culture results are expected.

Presently, patient continues anti-TB treatment, without any complications.

Histopathology findings

Usual Hematoxylin–Eosin staining allowed us to observe the general structure of the lymph node. The tuberculous granuloma is surrounded by a lymphocyte crown (Figure 2A) containing epitheloid cells, as well as several large cells (Langhans cells) with multiple nuclei in their periphery ("horseshoe aspect") and intensely acidophilic cytoplasm (Figure 2B).

Further immunohistochemical studies revealed the predominance of macrophages within the granuloma (Figure 3A), several positive CD68 cells within the outer area of the granuloma, towards the cortical zone as well as an abundance of macrophages in the center (Figure 3B).

After CD34 immunostaining, we could not observe normal blood vessel architecture within the nodule. Arterioles appeared amputated within the inflammatory area (Figure 4, A and B), with significantly lower blood vessel counts at the center of the granuloma. Further analysis showed that the blood vessel network maintained its normal structure at the periphery of the granuloma (Figure 4C).

In contrast, positive CD2–40 staining revealed the normal lymphatic vascularization, within the nodule as well as the rest of the lymph node, with no alteration within the medullar area, due to the inflammatory process (Figure 5, A–C).

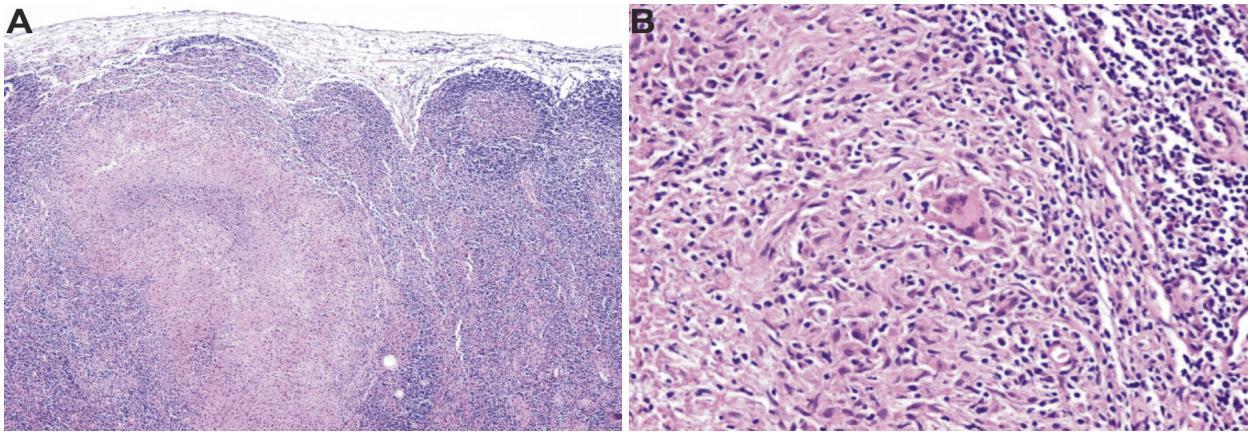

Figure 2 – ***(A) Tuberculous granuloma, overview. HE staining, ×40. (B) Detail of a tuberculous granuloma. We could observe a giant multinucleate cell with multiple peripheral nuclei. HE staining, ×200.***

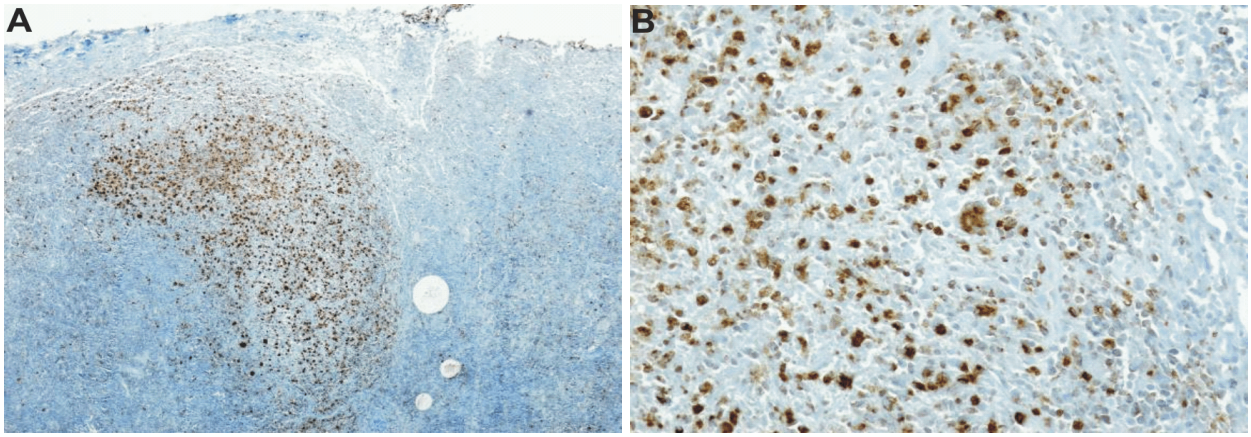

Figure 3 – *(A) Abundant macrophage infiltrate within the tuberculous granuloma. CD68 immunostaining, ×40. (B) Detail of the abundant macrophage infiltrate within the tuberculous granuloma. CD68 immunostaining, ×100.*

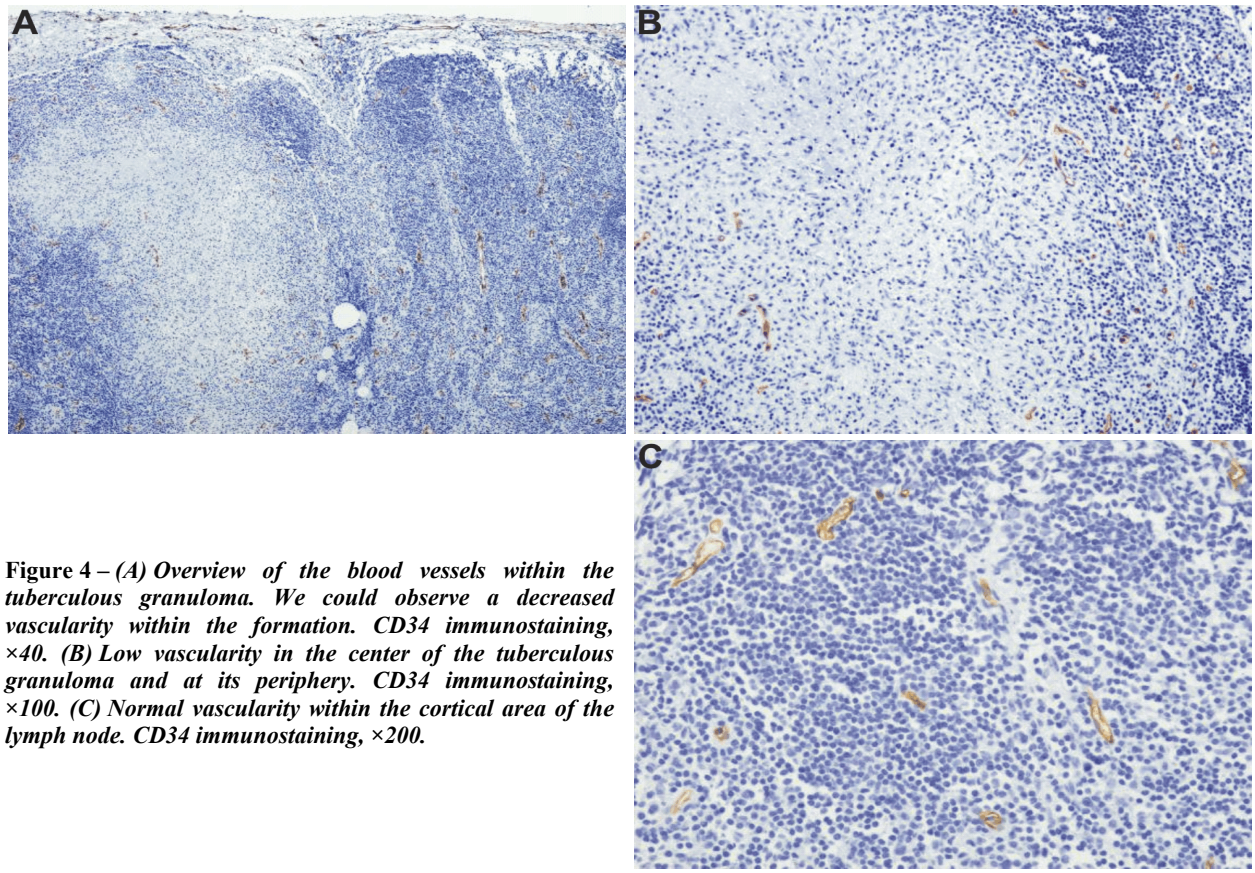

Figure 4 – *(A) Overview of the blood vessels within the tuberculous granuloma. We could observe a decreased vascularity within the formation. CD34 immunostaining, ×40. (B) Low vascularity in the center of the tuberculous granuloma and at its periphery. CD34 immunostaining, ×100. (C) Normal vascularity within the cortical area of the lymph node. CD34 immunostaining, ×200.*

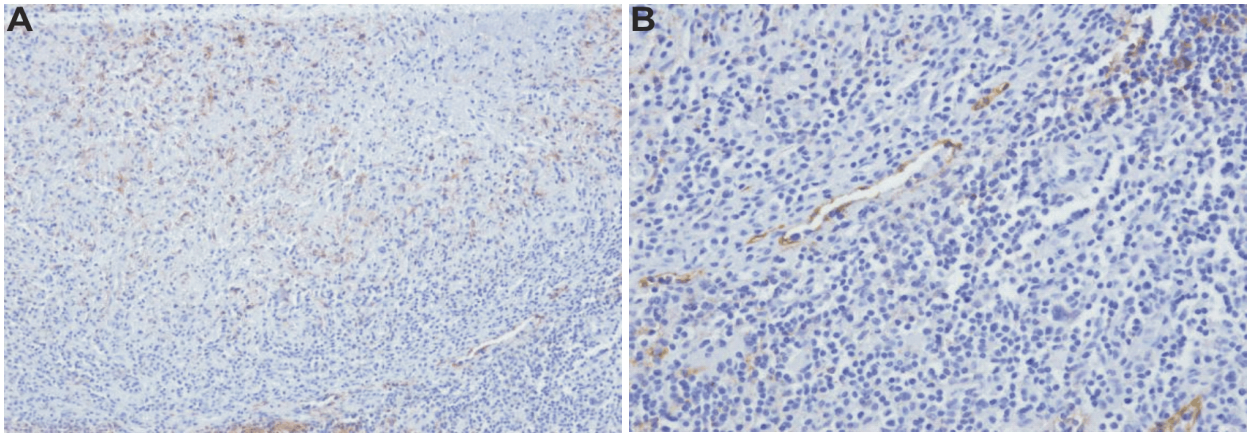

Figure 5 – *(A) Tuberculous granuloma with normal lymph vessels. CD2–40 immunostaining, ×40. (B) Normal lymph vessels at the periphery of the tuberculous granuloma. Normal lymphatic vascularity at the periphery of the tuberculous granuloma (cortical area). CD2–40 immunostaining, ×100.*

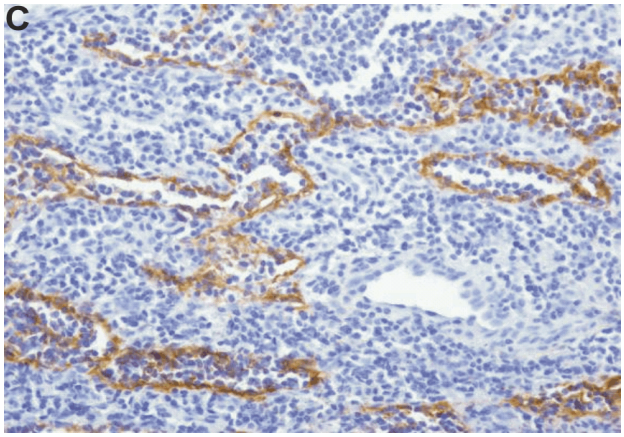

Figure 5 (continued) – ***(C) Normal lymph vessels in the medulla of the lymph node, unaffected by the inflammatory process. CD2–40 immunostaining, ×200.***

Discussion

Extrarespiratory TB refers to all TB localizations that do not involve lungs, pleura, intrathoracic lymph nodes and larynx. Origin of extrarespiratory TB lies in metastatic hematogenous outbreaks developed during TB primary infection [1]. Evolution of the disease can be precocious before healing of the primary infection, or late after primary infection, due to reactivation of initial lesions.

Lymph node infection is the most frequent localization of extrapulmonary tuberculosis. However, there is still no consensus for the length of antimicrobial treatment [8].

Tuberculosis remains a public health concern worldwide, particularly in Third World countries. Lymph node (LN) tuberculosis is the most frequent extra lung localization. Because of modern transport and mass migration from the developing to the developed world, it is important for all clinicians to keep this diagnostic possibility in mind. Jniene A *et al.* evaluated demographic characteristics, diagnosis approaches, therapeutic strategies and evolutionary aspects while treatment in patients with confirmed LN tuberculosis. Data was retrospectively analyzed in 69 patients collected in two health centers in Rabat over a period of four years. There was a female (70%) and a young age predominance of patients (31.4±13.1 years). The median duration between the onset of symptoms and diagnosis was long: 115 days (inter-quartile range 34–150 days) explicated by low socioeconomic conditions ($p<0.05$). The cervical LN were most frequently involved (85.5%). The confirmation was histological in 98.5%, bacterial in the liquid from puncture LN in 1.5% of cases. Around 48% of patients had received treatment according to the national guide of tuberculosis. Half of the patients had received prolonged treatment on average of seven months and a half (7.3±1.3 months) because of the paradoxical response (PR) ($p<0.05$). At the end of treatment, LN had returned to their normal size in 80% of patients, we noted residual nodes in 11.6%, and scrofula in 8.6%. The delay of diagnosis of LN tuberculosis is still important, and the treatment is prolonged because of PR [9].

Simultaneous involvement of extrathoracic and intra-abdominal lymph nodes, associated with polyserositis (pleural, pericardial and peritoneal effusion) required HIV testing, which was negative.

Diagnosis of lymph nodes TB is bacteriological, from fistular secretion and/or pathological, from lymph node biopsy [2–7].

During drug treatment of tuberculous lymphadenitis, paradoxical response (PR) may occasionally occur. Park IS *et al.* defined PR as clinical or radiological worsening of pre-existing TB lesions, or development of new lesions in a patient who had received anti-TB therapy for at least two weeks [10].

Cho OH *et al.* evaluated the clinical characteristics and risk factors for the paradoxical response (PR) in non-HIV-infected patients with peripheral lymph node tuberculosis. Three hundred patients with lymph node TB were included. Of these, 235 patients (78%) had confirmed TB; the remaining 65 (22%) had probable TB and were excluded from the final analysis. Among the 235 study patients, their mean age (± standard deviation) was 37.6 (±13.9) years and 175 (75%) were female. PR occurred in 54 (23%; 95% confidence interval 18–28%) patients, at a median onset time of eight weeks (inter-quartile range, 4–14 weeks) after starting anti-TB medication. In multivariate analysis, younger age (OR 0.96), male gender (OR 2.60), and the presence of local tenderness at the time of diagnosis (OR 2.90) were independently associated with PR. Same authors concluded that PR was relatively common, occurring in one-fifth of non-HIV-infected patients with peripheral lymph node TB, and was associated with younger age, male gender, and the presence of local tenderness [11].

The morphological substrate of the peripheral lymph nodes tuberculosis is caseation with or without Koch's bacillus [12].

Intra-abdominal and mediastinal lymphadenopathy poses a diagnostic and management challenge in highly endemic regions for tuberculosis. Opting for empirical anti-tuberculosis treatment raises the risk of wrong or delayed treatment. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound-guided trans-bronchial needle aspiration are the procedures of choice for tissue acquisition from peri-luminal lymph nodes. Dhir V *et al.* studied the utility of EUS-FNA in evaluating intra-abdominal lymph nodes of unknown etiology, in the setting of highly endemic tuberculosis. Consecutive patients with intra-abdominal lymph nodes of unknown etiology underwent EUS-FNA using a 22-gauge needle. Final diagnosis was based on surgical histology or on six-month follow-up.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic yield were calculated. Sixty-six patients were included. Final diagnoses were tuberculosis, 35 (53%); metastatic adenocarcinoma, 11 (16.7%); lymphoma, three (4.5%); carcinoid, one (1.5%) and reactive nodes, 16 (24.2%). EUS-FNA provided a diagnosis in 61 patients (92.4%). Sensitivity, specificity, PPV and NPV for diagnosing tuberculosis via EUS-FNA were 97.1%, 100%, 100% and 96.9%, respectively. In 10 (15.2%) patients receiving empirical anti-tuberculosis treatment, the final diagnoses were metastatic adenocarcinoma (5), lymphoma (2), carcinoid (1) and reactive adenopathy (2). The authors concluded that despite being in a highly endemic area, almost half of the patients studied had a non-tuberculosis etiology [13].

WHO recommended for lymph node TB regimen I of anti-TB treatment, using the association of Isoniazide, Rifampin, Pirazinamide and Ethambutol (or Streptomycin) in the first two months, continuing with Isoniazide and Rifampin three times a week up to nine months.

Complete but also slow resorption of pleural and pericardial effusion after three months of anti-TB treatment suggests the same TB etiology for polyserositis.

Blaikley JF *et al.* studied the variation behavior of TB lymph nodes during and after treatment and concluded that it causes clinical uncertainty. Six months of chemotherapy is effective for fully susceptible TB in routine clinical practice in England. Investigation of new signs is important in differentiating patients with relapsed TB from normal varied behavior [14].

No reliable published data was found as to the optimal duration of treatment. A high quality clinical trial should be carried out to suggest a consensus [8].

Surgery retains an important place in the diagnosis and treatment of cervical lymph node tuberculosis [15].

Continued treatment or lymph node aspiration improves PR without severe sequelae [10].

In a retrospective analysis, Hawkey CR *et al.* concluded that paradoxical deterioration of lymph node tuberculosis in human immunodeficiency virus-uninfected patients was common, occurring in 25 (23%) of 109 patients after treatment had been given for a median of 46 days (inter-quartile range, 21–139 days) and persisting for a median of 67.5 days (inter-quartile range, 34–111 days). The authors found no association between the use of steroids and the duration of reaction [16].

We considered our case to be an interesting one because of a multitude of simultaneous localizations of the disease (pleural, pericardial, mesenteric and latero-cervical lymph nodes) at a female patient without factors of immunodepression (HIV test negative, no history of chronic diseases or autoimmunity).

Pathological features of lesions in lymph node TB leads to a difficult penetration of TB medication into caseous masses, therefore, fistulization cannot be stopped by TB drugs. That explains why the two consecutive right latero-cervical lymph node masses that occurred during TB treatment evolved to fistulization despite the correct treatment administered to the patient. Our immunohistochemical study revealed a dense macrophage population within the granuloma. Further special staining with CD34 revealed an impaired blood circulation within the inflammatory process, which would probably lead to a decrease in the drug delivery within the granuloma. CD2–40 staining showed normal disposition of the lymphatic circulation within the inflamematory process, as well as throughout the lymph node architecture. This might be the reason why this kind of disease evolution requires a prolonged treatment of up to 9–12 months.

Minakuchi M *et al.* published in 2005 the case of a 27-year-old man who was admitted to their hospital due to a painful mass in the right neck and fever. Cervical and superior mediastinal computed tomography showed an enlargement of right supraclavicular lymph node and multiple swollen mediastinal lymph nodes, including low-density areas and contrast medium-enhanced septa and margins. Smears of the pus obtained from right supraclavicular lymph node showed acid-fast bacilli identified as *M. tuberculosis* by PCR method. He was treated with anti-tuberculous drugs with INH, RFP, EB, and PZA. PZA was given for initial two months. Six months later, productive cough developed and chest X-ray films showed infiltrative shadow in the right upper lung field. One month after the onset of cough, bronchoscopy revealed a polypoid lesion with a white coating in the right main bronchus. Microscopic examination of the specimen obtained by transbronchial biopsy revealed many epithelioid cell granulomas, consistent with tuberculosis. From these findings, pulmonary lesion was suggested to be due to invasion of the mediastinal lymph node into the bronchus. After one year of antituberculous chemotherapy, the swelling of the cervical-mediastinal lymph nodes was reduced and the abnormal chest X-ray shadows disappeared [17].

Centkowski P *et al.* described in 2005 the case of a 47-year-old man admitted to the Department of Hematology because of fever, enlarged cervical and supraclavicular lymph nodes, hepatosplenomegaly and non-specific lung infiltrations. The histopathological examination of the cervical lymph node revealed Hodgkin's lymphoma (HL) NS type I. Clinical evaluation revealed stage IVB according to Ann Arbor classification and the presence of five unfavorable prognostic factors according to the *International Prognostic Index*. Despite *BEACOPP* chemotherapy (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone), the enlarged lymph nodes, lung infiltrations and fever persisted. Microbiological and serological tests did not lead to the identification of any viral or bacterial pathogens. Bronchoscopy showed chronic inflammation and post-tuberculosis (TB) scars in bronchi without acid-fast bacilli in bronchoalveolar lavage (BAL) in culture and polymerase chain reaction (PCR) tests. However, the biopsy of the supraclavicular lymph node revealed multiple, caseating and necrotizing granulomatous lesions with scattered Reed–Sternberg (R–S) cells. The auramin staining presented acid-fast bacilli and allowed the diagnosis of productive and caseating TB coexisting with HL. The four tuberculo-

statics regimen and ABVD chemotherapy (Adriamycin, Bleomycin, Vincristine, Dacarbazine) resulted in a complete clinical response after three months of treatment. The association between HL and TB should be considered, especially in countries where the latter is endemic. Diagnosis may be difficult due to similarities in the clinical course, laboratory tests and imaging procedures [18].

Barinov VS *et al.* examined 102 patients with verified tuberculosis of the peripheral lymph nodes (TPLN), including 40 patients with specific process in the respiratory apparatus. The lymph nodes of the neck were found to be primarily affected in such patients (89%); by the second month, conglomerates develop from such nodes, with the latter evolving into fistulas (44.4%) and into abscesses (40%). A high specificity and sensitivity of the test with the blood serum for adenosine deaminase were proven. Different types of anti-tuberculosis antibodies are isolated with various rates; therefore, it is advisable to study the answers to all serological reactions [19].

Conclusions

Further morphology studies are necessary in order to explain the difficulty of anti-TB drugs intra-ganglionary penetration, as this might be the explanation of the prolonged evolution in these particular TB localization cases. Amputation of the blood vessels may contribute to the lack of efficacy of the anti-TB treatment, while the maintained lymph circulation may favor the dissemination of the disease to other sites.

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