The role of the tissue culture in granulomatous mediastinal lymphadenitis: tuberculosis or not

Serpil Sevinc1, Seyda Ors Kaya1, Saban Unsal1, Sevket Dereli2, Timucin Alar3, Kenan Can Ceylan1, Nur Yucel4

1Department of Thoracic Surgery, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital, Izmir, 2Department of Chest Disease, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital, Izmir, 3Department of Thoracic Surgery, Canakkale Onsekiz Mart University Faculty of Medicine, Canakkale, 4Department of Pathology, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital, Izmir; Turkey

ABSTRACT

Aim To evaluate the role of the tissue culture via mediastinoscopic biopsy in granulomatous mediastinal lymphadenitis.

Methods The dossier data of 92 cases with mediastinal lymphadenitis showing granulomatous lymphadenitis features by cervical mediastinoscopy and whose clinical, radiological and bacteriological definitive diagnosis is tuberculosis and sarcoidosis were examined retrospectively. The rate of the positive tissue culture of mediastinoscopic biopsy in the diagnosis of granulomatous lymphadenitis was calculated.

Results There were 65 (71%) females and 27 (29%) males. The mean age of the patients was 42.5 (range 15-75) years. Non necrotizing granulomatous lymphadenitis was detected in 58 (63%) cases while necrotizing granulomatous lymphadenitis was seen in 34 (37%) cases.

There were 29 cases diagnosed with tuberculosis. Acid resistant bacilli culture positive rate was 38% (in 11 cases). There were 21 (62%) cases of necrotizing granulomatous lymphadenitis and eight (14%) cases of non-necrotizing granulomatous lymphadenitis diagnosed with tuberculosis. Culture positivity was identified in two (25%) of eight cases whose differential diagnosis could not be made histopathologically as tuberculosis/sarcoidosis.

Conclusions In addition to clinical, radiological and histopathological diagnosis, the study aims to highlight the importance of tissue culture in definitive diagnosis, especially undetermined incidents.

Key words: Mediastinal lymphadenopathy, granulomatous lymphadenitis, mediastinoscopy, tuberculosis, tissue culture
INTRODUCTION

The causes of mediastinal lymphadenopathy are generally sarcoidosis, tuberculosis (TB), fungal infections and malignancies (1-3). It is difficult to diagnose mediastinal lymphadenopathies which occur without pulmonary parenchymal disease (4). Tuberculosis and sarcoidosis are two different diseases which differ in etiology, clinical features and treatment and are also involved in the causes of granulomatous lymphadenitis (5).

Intrathoracic tuberculous lymphadenopathy occurs most commonly in Asian and black people (6). Invasive diagnostic procedures gain importance due to the high rate of TB prevalence both in Turkey and developing countries because of the low diagnostic yield of routine laboratory methods, such as sputum examination and the tuberculin skin test (7). In addition to its diagnosis with endobronchial sonographically guided transbronchial needle aspiration (EBUS-TBNA), transbronchial needle aspiration (TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), mediastinoscopy is still the golden standard for mediastinal lymphadenopathy diagnosis (8-11). However, the cytologic examination of lymph node sampling by mediastinoscopy may, indeed, be insufficient in granulomatous lymphadenitis differential diagnosis (12). Clinical and radiological correlation by a pathologist is recommended at this stage (12).

Tuberculosis diagnosis can be ensured by tissue culture obtained from lymph node sampling by mediastinoscopy (13). There are various studies concerning the results of EBUS and diagnostic mediastinoscopy in the literature (3,9,11). There is no other study which examines the histopathological and bacteriological results of a homogenous group diagnosed with histopathological granulomatous mediastinal lymphadenitis by mediastinoscopy with the exception of Cameron’s study in 1978 (3). Aim of this study was to assess the contribution of the tissue culture in diagnosis of TB, in addition to the histopathological examination of the granulomatosis lymphadenopathy by mediastinoscopic biopsy.

PATIENTS AND METHODS

Between January 2005 and January 2010, standard cervical mediastinoscopy was applied on 153 cases with diagnostic purposes due to mediastinal lymphadenopathy and 92 cases, which showed granulomatous lymphadenitis histopathology after cervical mediastinoscopy, and whose clinical, radiological, and bacteriological definitive diagnosis was TB or sarcoidosis. The case files were analyzed retrospectively according to pathology interpretations. Tuberculosis or sarcoidosis provisional diagnosis of the pathologist was registered. All the patients had a chest roentgenogram and thorax computed tomography scan (Figure 1) together with fiber optic bronchoscopy examination. Mediastinal TB was defined as isolated mediastinal lymphadenopathy on thorax computed tomography scan without parenchymal or pleural disease. Acid resistant bacilli (ARB) condensation and culture were studied both on phlegm and bronchoscopic lavage samples. Cases were excluded if they had positive result of sputum bacteriology. Standard cervical mediastinoscopy was applied in operation hall under the general anesthesia as described by Carlens (15). Multiple biopsies (at least 3 punch biopsies) were performed during mediastinoscopy to the lymph nodes with a short diameter of 1 cm or bigger which were detected by thorax computerized tomography. The results of lymphatic tissue culture sampled during mediastinoscopy were analyzed. Patient’s samples were cultured in liquid automated BACTEC 960 system (Becton Dickinson, Sparks, MD, USA) and solid Löwenstein-Jensen (LJ) medium (Salubris AS/Istanbul/Turkey). Samples were incubat-
ed until the determination at the BACTEC instrument and/or growth at the LJ medium. Negative samples were incubated at 37 °C for up to 42 days. Conventional bacteriological methods and the BACTEC 460 NAP test (Becton Dickinson, Sparks, MD, USA) were used for Mycobacterium tuberculosis complex identification.

In tissue samples, the detection of growth in LJ culture and BACTEC system medium was considered as positive and the detection of epithelioid histiocytic granulomatous reaction regardless of classification necrosis was accepted as histopathological positivity in terms of TB.

Tuberculosis detected patients were treated with pyrazinamide, isoniazid and rifampicin for two months. After two months, these patients were observed on the regime of rifampicin and isoniazid for another four to six months. In sarcoidosis patients 20-40 mg/day prednisone was used in decreased doses for at least 12 months. Patients were reviewed regularly in the outpatient department every month. The follow up time ranged from six to 20 months after completion of the treatment. Clinical and radiological outcome was recorded.

The study was approved by the Scientific Council of Izmir Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital.

Descriptive statistics were applied.

RESULTS

Cervical mediastinoscopy was applied on 153 patients for diagnosis of mediastinal lymphadenopathy between January 2005 and January 2010. Histopathological diagnosis of mediastinal lymph nodes biopsy was reported as “granulomatous lymphadenitis” in 92 (60%) cases, 65 (71%) of which were females and 27 (29%) of which were males. The average age of the patients was 42.5 ranging from 15-75 years. Tuberculosis was diagnosed in 32% (29/92) of the cases and the rate of ARB culture positivity in tissues was 38% (11/29).

Examining the histopathological results the pathologist reported TB in 39 cases and sarcoidosis in 45 cases. However, histopathological differential diagnosis was not applied in eight patients. Two (25%) of these cases were diagnosed with TB after the detection of culture positivity (Table 1).

An examination of histopathological specimens, necrotizing granulomatous lymphadenitis and non-

Table 1. Contribution of bacteriological results on diagnosis of cases that were histopathologically preliminarily diagnosed as tuberculosis/sarcoidosis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Definitive diagnosis of sarcoidosis*</th>
<th>Definitive diagnosis of tuberculosis*</th>
<th>Culture positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (n=39)</td>
<td>16 (41%)</td>
<td>23 (59%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Sarcoidosis (n=45)</td>
<td>42 (93%)</td>
<td>3 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Lack of differential diagnosis (n=8)</td>
<td>5 (62.5%)</td>
<td>3 (37.5%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Total (n=92)</td>
<td>63 (68%)</td>
<td>29 (32%)</td>
<td>11 (12%)</td>
</tr>
</tbody>
</table>

*final diagnosis of tuberculosis/sarcoidosis made after clinical, radiological, histopathological and bacteriological examination;

necrotizing granulomatous lymphadenitis were observed in 34 (37%) and 58 (63%) cases, respectively. Tuberculosis was diagnosed in 21 (62%) cases of necrotizing granulomatous lymphadenitis and in eight (14%) cases of non-necrotizing granulomatous lymphadenitis. Culture was positive in 11 patients (nine cases were necrotizing granulomatous lymphadenitis, two were non-necrotizing granulomatous lymphadenitis) (Table 2). The patients were hospitalized for two days in average. Pneumothorax emerged in one case and it resorbed without drainage tube. No mortality was registered.

Table 2. Granulomas characteristics of cases whose clinical, radiological and bacteriological definitive diagnosis was tuberculosis or sarcoidosis and tissue culture results

<table>
<thead>
<tr>
<th>Finding</th>
<th>Definitive diagnosis of sarcoidosis*</th>
<th>Definitive diagnosis of tuberculosis*</th>
<th>Culture positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing granulomatous lymphadenitis n=34 (37%)</td>
<td>13 (38%)</td>
<td>21 (62%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Non-necrotizing granulomatous lymphadenitis n=58 (63%)</td>
<td>50 (86%)</td>
<td>8 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Total n=92 (100%)</td>
<td>63 (68%)</td>
<td>29 (32%)</td>
<td>11 (12%)</td>
</tr>
</tbody>
</table>

*final diagnosis as tuberculosis after clinical, radiological, histopathological and bacteriological examination

DISCUSSION

Sarcoidosis, tuberculosis, cat-scratch disease, lymphogranuloma venerum, brucella, paracoccidioidomycosis, histoplasmosis, leishmaniosis, leprosy, foreign body granulomas (talk, silica) and granulomas accompanying malignancies are among the causes of granulomatous lymphadenitis (16). The histopathological appearance of tuberculosis and sarcoidosis may sometimes show similar characteristics and bacteriological examination and clinical correlation gain importance in final diagnosis (17-19).

Bacteriological identification of mycobacterium tuberculosis ensures the definitive diagnosis of tuberculosis (5). Smear-positive pulmonary tuberculosis
cases can easily be diagnosed, whereas it is much more difficult to conclude a diagnosis on smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis cases (5). Tuberculosis can be diagnosed showing ARB in body fluid or tissues by direct inspection or condensation or producing tuberculosis culture in culture media (6). But the diagnostic yield of sputum examination is low in patients without lung lesions (6). In addition to the top priority method, bacteriological method, indication of typical histopathological change in tissue, which is caused by tuberculosis bacilli, can also be used in diagnosis (21). Although many studies concerning the diagnostic value of histopathological examination of tissue samples have been conducted, there are still few studies regarding the diagnostic value of tissue sample cultures (6). The diagnostic value of histopathological examination was rated high in most of the studies, while tissue culture diagnostic value was rated higher in some studies (22). Generally, it is acknowledged that referring to tissue cultures in addition to histopathological examination increases the diagnostic rate (23).

There exist some studies including the transbronchial needle aspiration (TBNA), endobronchial sonographically guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), mediastinoscopic biopsy results for mediastinal lymphadenopathy diagnosis (3,9,10,24,25). The study conducted by Caglayan et al. was an EBUS study in which granulomatous lymphadenitis cases were compiled (9). Sarcoidosis/tuberculosis was diagnosed with the existence of non-caseificated granulomas/caseification detection in addition to the clinic and radiological findings in this study. EBUS-TBNA diagnostic value was numbered 79.5%, 84.2% and 80.9% in sarcoidosis, tuberculosis and granulomatous diseases (9). Jacob et al. stated that only 37 of 160 mediastinal tuberculosis cases were diagnosed by mediastinoscopy. It is recommended in this study that diagnosis can be made by family history and anamnesis and antituberculous treatment can be initiated for trial purposes (26). Characteristic histopathological morphologic finding of sarcoidosis is noncaseating granulomas (27). Granulomas rarely include focal coagulative necrosis. On the contrary, seeing common caseificaton necrosis granulomas is a characteristic feature of tuberculosis (27). However, it would be wrong to name characteristic morphological finding unless clinical, radiological and microbiological examinations show consistency both in sarcoidosis and tuberculosis (27,28). In the presented study, 62% of the cases with necrotizing granulomatous lymphadenitis were diagnosed with TB, 26% of which were culture positive. Additionally 14% of non-necrotizing granulomatous lymphadenitis cases were diagnosed with TB and culture positivity was detected in 3% of the cases with non-necrotizing granulomatous lymphadenitis. In the study of Cameron in 1978 (14), which is the most similar to our study, 14 cases were diagnosed with tuberculosis as a result of lymph node biopsy by mediastinoscopy and tuberculosis culture positivity was identified in 64% patients. Positive culture rate was 38% in TB diagnosed cases in our study.

Tuberculosis is a global problem, with 9.4 million new cases in 2008 and a high mortality rate of 1.8 million deaths a year (26). Definitive diagnosis is very important since there is a difference in treatment modalities between these two diseases; especially as tuberculosis is an infectious disease and may cause mortality if it is left untreated (29). According to the results of this study, tissue culture which is obtained from operation materials, in particular, is of great importance to guide the clinicians in order to differentiate tuberculosis and sarcoidosis, especially in the countries where tuberculosis prevalence is high.

FUNDING

No specific funding was received for this research.

TRANSPARENCY DECLARATION

Competing interest: none declared.

REFERENCES