Evaluation of the Role of Pathology in the Diagnosis and Differential Diagnosis of Pulmonary and Extrapulmonary Sarcoidosis

Jelena Stojišić¹, Violeta Vučinić-Mihailović², Dragana Jovanović², Mira Stojković³, Jelica Videnović-Đivanov², Snežana Filipović²

¹Department of Thoracopulmonary Pathology, Service of Pathology, Clinical Centre of Serbia, Belgrade, Serbia; ²Clinic of Pulmonology, Clinical Centre of Serbia, Belgrade, Serbia; ³Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade, Serbia

INTRODUCTION

Sarcoidosis is a multisystem, granulomatous disease of unknown aetiology. Morphology of some granuloma types is characteristic of specific diseases so that this is basis for reaching the final diagnosis. Therefore, this type of inflammation has been defined as specific [1, 2, 3]. Sarcoidosis belongs to the entities of specific inflammations, because of being characterized by inflammatory lesions, i.e. granulomas. The term “sarcoidosis” originates from the Greek word “sarkodes” meaning “fleshy” and suffix “-osis” meaning “condition” [1].

Sarcoidosis was described for the first time as a skin disease in 1877, in patients with multiple purplish patches on the face and hands. Identical appearance of sarcoid granuloma can be seen regardless of the involved organ [1, 2, 3]. Sarcoidosis mostly develops in younger and middle aged persons, predominantly women, in all geographic areas. It quite frequently occurs presenting severe clinical features in Afro-Americans [1-5].

OBJECTIVE

The important aim of this study was to estimate the role of pathology in the diagnosis and differential diagnosis of sarcoidosis and to point out the importance of establishing the diagnosis of sarcoidosis only in association of clinical with pathological studies. The purpose was to establish other conditions presenting with sarcoid granulomas and to estimate other conditions where hilar and mediastinal lymphadenopathy could be the major symptom of the disease different from sarcoidosis.

METHODS

Out of the total number of 751 patients, 663 biopsy positive sarcoidosis patients were analyzed in five-year period (1995–1999). Biopsy samples were obtained from different tissues and organs. All obtained tissue samples were routinely fixed and paraffin embedded and hematoxylin-eosin (H&E) stained [6]. The majority of the tissue samples were obtained by transbronchial and bronchial biopsy during bronchoscopy. Open lung biopsy was performed in patients when repeated bronchoscopy did not resolve the etiology of the disease. Buffered formalin instillation with dispersion into the pulmonary parenchyma was made to distend alveolar spaces in their natural size and shape [6, 7]. Sarcoidosis was diagnosed by liver biopsy, splenectomy and skin biopsy.
Acid-fast staining was performed to exclude or to detect the presence of acid-fast bacilli in granuloma in differential diagnosis to tuberculosis. Phospholipids within the capsule of bacilli were stained red and visible for microscopy.

Periodic Acid Schiff (PAS) staining was performed for distinction of fibrinous necrosis in sarcoidosis from other types of necrosis. Fibrinous necrosis was stained as a clear and lightly red tiny granular mass [7, 8].

Peripheral fibrosis and hyalinization around granulomas was stained by silver impregnation of fibrous fibres.

RESULTS

Sarcoidosis was confirmed in 431 female and 232 male patients, in total ratio 1.9:1. The predominant number of patients (78.4%) was aged below 50 years, with a peak between 41-50 years (Table 1). The youngest patient was a 16-year-old girl. The oldest one was a 67-year-old man.

Sarcoidosis was most frequently diagnosed in stage I of lung disease by transbronchial biopsy and rarely in II or III stage of lung disease by transbronchial and bronchial biopsy (Table 2).

By liver biopsy and splenectomy the diagnosis of sarcoidosis was confirmed in six patients, also by skin biopsy in six patients. In nine patients the diagnosis of sarcoidosis was established by open lung biopsy.

Sarcoidosis was the leading cause of hilar and mediastinal lymphadenopathy in 72.2% of our patients (Table 3). The diagnosis was made by transbronchial biopsy. Metastatic deposits in lymph node tissue of malignant tumours of other organs were diagnosed also by transbronchial biopsy. The origin of metastasis was accurate as confirmed by immunophenotipization. Mediastinal lymphomas, mostly of Hodgkin type, in 13 patients (1.8%) were the cause of lymphadenopathy.

Tuberculosis was diagnosed in four patients in whom acid-fast bacilli in caseating granulomas was detected.

DISCUSSION

Sarcoidosis is a specific granulomatous disease. It is still a question weather sarcoidosis is a syndrome or an entity [9].

Sarcoidosis can be diagnosed in all ages, but predominantly in young and middle aged persons of both genders, but frequently in women, in all parts of the world and in all races. The incidence is quite high in the Scandinavians. Sarcoidosis is almost unknown disease in South-East Asia and China [4].

Due to the clinical course of sarcoidosis, spontaneous remission is possible. Most often sarcoidosis patients develop symptoms like dry cough, short breath and arthralgia. There are indications that the disease is hereditary [1, 4].

According to the chest radiological findings sarcoidosis is classified in 4 stages: stage 0 – regular chest X-ray; stage I – hilar and mediastinal lymphadenopathy; stage II – hilar and mediastinal lymphadenopathy accompanied with infiltrates in pulmonary parenchyma; stage III – pulmonary infiltrates without hilar and mediastinal lymphadenopathy, with frequent formation of the so-called ground glass effect; stage IV – pulmonary fibrosis [10, 11].

A typical morphological pattern of sarcoidosis is noncaseating granuloma appearing after accumulation of mononuclear inflammatory cells in involved tissue. Accumulation of macrophages transformed to epitheloid cells are surrounded mostly by T cell population of lymphocytes. It is presumed that prolonged antigen stimulation leads to transformation of macrophages to epitheloid cells and appearance of giant, multinuclear cells, specifically of Langhans type [6].

By electron microscopy two types of epitheloid cells are estimated, the first one with the developed endoplasmatic reticulum with a few vacuoles and granules and the second one with a lot of fine granular material. Cytoplasm of epitheloid cells contains enormous amount of dipeptile carboxydase enzyme (angiotensin-converting enzyme), so that these cells are responsible for the increasing level of this enzyme in blood serum. The epitheloid cells are specialized for extra cellular secretion, not for phagocytosis [7].

Giant, multinuclear cells arise in fusion of two or more macrophages. Numerous nuclei are pressed to cell membrane, looking as sickle-like or half-moon shaped nuclei (Langhans type cell) or chaotically “thrown” all the way through cell cytoplasm. Sometimes the nuclei are “pushed away” by the Schaumann body. Characteristic cytoplasmatic inclusions are sometimes present, but are not typical only for giant multinuclear cells in sarcoid granuloma. They are asteroid and Schaumann bodies. Asteroid bodies are lipoprotein and acidophilic star shaped inclu-

Table 1. Age of patients with sarcoidosis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>148 (22.4%)</td>
</tr>
<tr>
<td>31–40</td>
<td>162 (24.5%)</td>
</tr>
<tr>
<td>41–50</td>
<td>210 (31.5%)</td>
</tr>
<tr>
<td>51–60</td>
<td>117 (17.7%)</td>
</tr>
<tr>
<td>≥61</td>
<td>26 (3.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>663 (100%)</td>
</tr>
</tbody>
</table>

Table 2. Histological diagnosis of pulmonary sarcoidosis classified by stages

<table>
<thead>
<tr>
<th>Stage of pulmonary sarcoidosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>542 (81.7%)</td>
</tr>
<tr>
<td>II</td>
<td>100 (15.1%)</td>
</tr>
<tr>
<td>III</td>
<td>21 (3.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>663 (100%)</td>
</tr>
</tbody>
</table>

Table 3. Differential diagnosis: causes of hilar and mediastinal lymphadenopathy

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary sarcoidosis – stage I</td>
<td>542 (72.2%)</td>
</tr>
<tr>
<td>Reactive lymphadenopathy</td>
<td>160 (21.3%)</td>
</tr>
<tr>
<td>Metastasis of other malignant tumours</td>
<td>32 (4.2%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13 (1.8%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>751 (100%)</td>
</tr>
</tbody>
</table>
sions. They present amorphic material arising from microfilaments, microtubules, mature and immature centrioles. The Schaumann bodies contain protein matrix impregnated with iron and calcium salts in concentric lamellas and crystals capable for light polarization. This inclusion is formed in epitheloid giant cells or extracellularly, near the peripheral sinus. The granular endoplasmatic reticulum is weakly developed in giant cells. Mitochondria and lysosomes show degenerative changes and cytoplasm contains numerous vesicles and different particles [7].

Among epitheloid cell CD4+ lymphocytes and CD8+ lymphocytes are found peripherally. In bronchoalveolar lavage the number of CD4+ lymphocytes is increased compared to CD8+ lymphocytes. A fibrous rim develops around the granuloma spreading to its centre. It is a sign of progression of sarcoidosis and the beginning of the scar arising in the parenchyma probably causing organ’s dysfunction and insufficiency. Sometimes granulomas are similar to those in hypersensitive pneumonitis [7, 10, 11].

Necrotizing sarcoid granulomas are described in the literature. They involve pulmonary parenchyma exclusively and are characterized by fibrinous and coagulate necrosis in the central zone of granuloma, without the presence of acid-fast bacilli. Necrosis is clearly red stained by PAS. Necrotizing sarcoid granulomas are the result of vasculitis. Giant cells are more numerous around the necrosis than in sarcoid granulomas. Epitheloid cells are also increased in this type of granuloma. There is no fibrosis and hyalinization around necrotizing sarcoid granulomas. These granulomas resolve after cytostatic and steroid therapy [10].

Differential diagnosis from other granulomas due to their morphology pattern is relatively easy, particularly by open lung biopsy. Pulmonary parenchyma changes are mostly bilateral reticular and reticuloendothelial infiltrates less than 1cm in size, accompanied with emphysema and “honey comb” lungs. Pleural effusion appears in sarcoidosis very rarely [11, 12]. Sarcoid granulomas are grouped within the parenchyma of the lungs. They can be confluent or non-confluent, separated by fibrous or hyaline thickened septa, and distributed peribronchiolarly, perivascularly, interlobularly or under the pleura. Emphysema or even the “honey comb” pattern can be present in the surrounding pulmonary parenchyma [11, 13, 14].

Stage I of pulmonary sarcoidosis is lymphadenopathy, manifested in hilar and mediastinal lymph nodes enlargement. This stage of the lung disease is diagnosed most frequently, in about 90% of patients. The lymph nodes enlarged size increase from 20mm to 30mm causing dry cough and sensation of the tightness in the chest, but the patient may also be without any of the symptoms. In the lymph node parenchyma numerous, mostly confluent and no confluent granulomas, with or without giant cells are present. Uninvolved lymph node parenchyma is without active follicles [7, 8].

Some conditions (berylliosis), different substances (talc) and lymphomas provoke a lymph node reaction, remaining on sarcoid granulomas [15]. So, they are called sarcoid-like reaction, sarcoid-type reaction or sarcoid-related granulomas. Mostly, they arise in lymph nodes draining organs involved by tumour, called lymph node draining carcinomas. Most frequently they appear in draining lymph nodes in carcinoid tumours, lung and breast cancer and testicular tumours [16, 17].

Vasculitis and systemic fibrous tissue disease, even HIV infection of lymph nodes may provoke a sarcoid reaction. This condition also arises in pulmonary tissues as a sign of rejection after lung transplantation. The sarcoid-related reaction arises as a morphological pattern of post-irradiation pneumonitis with the presence of numerous non-caseating granulomas, surrounded by fibrous tissue. In the sarcoid-like reaction lymph nodes may be increased in measure and in morphology similar to sarcoidosis, so the proper diagnosis is difficult to obtain [6, 8].

Cervical lymph nodes are enlarged in sarcoidosis, as well as in lymphoma. Hodgkin’s lymphoma and sarcoidosis arise in younger persons. Almost always Hodgkin’s lymphoma is manifested as neck, hilar and mediastinal lymphadenopathy, as well as sarcoidosis [8, 16, 17].

In cases of hilar and mediastinal lymphadenopathy pathological diagnosis of accidentally detected metastasis may not be a surprise. Tumour origin may be from close (lung and breast carcinoma) or distant (intestinal carcinoma) organs [11, 12].

Sarcoidosis often involves skin, eye, liver, spleen, heart, bone marrow, salivary glands, muscles and nervous system [1, 13, 15].

Skin sarcoidosis arises in about 75% of patients with the diagnosis of pulmonary sarcoidosis. Granulomas are often commonly called Boeck sarcoïds, arising in the derm and rarely in the hypoderm. They are manifested as soft multiple purplish patches or nodules. Numerous confluent or non-confluent granulomas without necrosis form a skin lesion. Older granulomas contain a high number of giant multinuclear cells and intra-cytoplasmatic inclusions. Around the edges of the granuloma there is only a small number of lymphocytes and a rim of dense fibres [3, 13, 14].

Skin changes often occur associated with sarcoidosis, most frequently erythema nodosum. It is localized in the hypoderm manifested as painful red or livid nodules. A non-specific inflammation is histological presentation [1, 13, 14].

Ocular involvement can occur in patients with sarcoidosis, but the most frequent site is the uvea and iris, cusing regional inflammation, glaucoma or blindness. Lachrymal and parotid glands may be involved by sarcoidosis at the same time [3, 13, 14].

The spleen is involved in approximately 75% of patients with pulmonary sarcoidosis, although real splenomegaly is present in about 20%. Sarcoid granulomas are only visible when granulomas are confluent. Numerous tiny granulomas, cellular or hyaline, are diffusely distributed mostly in the white pulp [15, 18, 19].

The liver is also involved but rarely enlarged. Sarcoid granulomas are mostly localized in the portal space, less frequently in the liver acinus. The sarcoid granulomas can be diagnosed by needle biopsy of liver parenchyma [18, 19].
Numerous granulomas are seen in the bone marrow with resorption of bone cortex. Hands and feet are most frequently involved [3, 13, 20, 21].

CONCLUSION

Sarcoidosis is a multisystem disease, with predominance in young persons. Radiological finding of mediastinal and hilar lymphadenopathy is the most frequent sign of pulmonary sarcoidosis. In this stage of the lung disease transbronchial biopsy is most suitable to confirm sarcoidosis, but the unexpected diagnosis as lymphoma, metastatic tumour, tuberculosis and reactive lesions could be possible.

By routine microscopic examination, diagnosis of epitheloid granulomas, containing varies numbers of giant, multinuclear cells with or without fibrosis and hyalinization, the diagnosis of sarcoidosis is confirmed. Morphological appearance of sarcoïd granuloma is the same despite of the involved organ.

In patients, even when typically clinical, radiological, biochemical and immunological results clearly point to sarcoidosis, biopsy is necessary to confirm the diagnosis.

REFERENCES

КРАТАК САДРЖАЈ

Увод Саркоидоза је мултисистемско, грануломатозно обољење непознате етиологије. Саркоидни грануломи настају као имунски одговор на одређени, али још непознати, агенс у организму.

Циљ рада Циљ истраживања био је да се укаже на важну чинjenicu да се дијагноза саркоидозе поставља једино у клиничко-патолошкој корелацији, сарадњом клиничара и патолога.

Методе рада Од укупно 751 болесника за којег се сумњало да болује од саркоидозе, анализирана су 663 (431 жене и 232 мушкараца) код којих је током петогодишњег периода постављена дијагноза сва три стадијума овог обољења. Дијагноза болести постављена је на основу биопатологичког материјала добијеног током бронхоскопије, налаза хируршке биопсије плућа, биопсије коже и биопсије јетре, као и на основу спленомегалне непознатог порекла.

Резултати Однос болелих жена и мушкараца био је 1,9:1. Болесници су имали између 16 и 67 година. Већина болесника (78,4%) била је стара до педесет година. Код највећег броја испитаника установљен је први стадијум плућне саркоидозе (81,7%). Саркоидоза је била најечених узрок хиларне и медиастиналне лимфаденопатије (72,2%).

Закључак Пацијенте код којих клинички, биохемијски и имунолошки тестови јасно покажу да болују од саркоидозе по требно је обавезно подвргнути биопсiji и патохистолошкој дијагностично узорка узетог ткива пре започињања лечења.

Кључне речи: грануломатозно обољење; медиастинална лимфаденопатија; дијагностика