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Clinical Science

Clinic - Morphologic and Morphometric Criteria for Differential Diagnosis of Sarcoidosis and Pulmonary Tuberculosis

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Keywords: Sarcoidosis; Tuberculosis; Granulomatous; Differential diagnosis; Morphometry

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Abstract

BACKGROUND: Currently incidence and prevalence of sarcoidosis are increasing. Sarcoidosis is a systemic granulomatous lung disease of unknown aetiology, which is characterised by the involvement of different organ systems, variable disease course affecting young people and possessing an important issue in the modern world. The disease is extremely heterogeneous with an unpredictable clinical course. Interesting clinical cases are described in which, with a sufficient illustration of the stages of the course and diagnosis of sarcoidosis of the lungs and peripheral lymph nodes, the diagnosis was difficult. Late diagnosis and lack of correct therapy make prognosis in patients with lung sarcoidosis unfavourable.

AIM: To conduct a morphometric study with the determination of the cellular composition of granulomas for the differential diagnosis of morphogenesis of granulomas in sarcoidosis and pulmonary tuberculosis.

MATERIAL AND METHODS: An analysis of transthoracic biopsy of 89 patients with a verified diagnosis of sarcoidosis of the lungs and disseminated form of pulmonary tuberculosis was carried out. The resulting lung tissue material was carried out according to the standard histological method; conducted morphometric analysis.

RESULTS: Sarcoid granulomas are characterised by an increase in lymphocytes, indicating the immune character of the lesion, an increase in fibroblasts, fibrocytes, and signs of activation of angiogenesis. While for TB granuloma an increase in the number of granulocytes and epithelioid cells is characteristic. These morphological criteria for the diagnosis of sarcoidosis of the lungs and lymph nodes are necessary for use in the practice of pathologists to verify the clinical diagnosis.

CONCLUSION: Developed morphological and morphometric criteria for the differential diagnosis of sarcoidosis and pulmonary tuberculosis must be used in the practice of a pathologist to verify the clinical diagnosis, which will determine the adequate tactics of examination, administration, correction of the disease, and evaluation of the prognosis of the disease, taking into account identified clinical and laboratory data, results of instrumental research methods.

Introduction

Morphological differential diagnosis of sarcoidosis and other types of disseminated granulomatous lung diseases remains a significant issue for TB specialists and pulmonologists. Currently, the incidence and prevalence of sarcoidosis are increasing, and the frequency of the disease remains high among young and middle-aged people [1], [2]. Sarcoidosis possesses a diagnostic problem being very similar in clinical presentation and morphological picture with other types of granulomatous lung diseases. This is why often patients present to the hospitals at the late stage of the disease, leading to late diagnostic workup, which results in worsening of the disease prognosis and decline in the quality of life [3], [4]. Taking this into consideration, diagnostic errors account for 75-80%. For diagnostic purposes, not only presence or absence of the symptoms play a role, but also their intensity, variability, as well as associated symptoms, including extrapulmonary ones [5], [6].

Sarcoidosis leads to the formation of non-caseating granulomas; the disease is characterised by multisystem involvement of various organs and activation of T-cells in the area of granulomatous inflammation with release of different chemokines and cytokines, including tumour necrosis factor [7], [8]. In clinical practice differential diagnosis of lung sarcoidosis often has to be done with the granulomatous process of pulmonary tuberculosis

(TB), rarely with other types of disseminated processes like granuloma with Langhans giant cells, allergic alveolitis, leiomyomatosis, sometimes with the tumours [9].

We aimed to conduct a morphometric study with the determination of the cellular composition of granulomas for the differential diagnosis of morphogenesis of granulomas in sarcoidosis and pulmonary tuberculosis.

Materials and Methods

Retrospective analysis of medical records of in-patients, transthoracic biopsies of the patients examined at the Medical center "Office of the President of the Republic of Kazakhstan" (Astana city), "Oblast city hospital" (OCH) (Karaganda city) and "Oblast TB dispensary" (OTBD) (Karaganda city) during the period of 2011 to 2016 was performed.

Eighty-nine patients were examined. Sixty-two of them aged from 26 to 63 years old, mean age 42.9 ± 1.6 years, males and females, had disseminated lung TB; 27 patients aged from 24 to 67 years old, mean age 47.3 ± 1.4 years, males and females with lung sarcoidosis.

Results

Review of medical history records showed similar clinical presentation, but different degree of clinical symptoms for patients diagnosed with sarcoidosis versus disseminated lung TB. Table 1 represents a summary of clinical presentations. It is evident that clinical symptoms are significantly heterogeneous: some symptoms are common for both groups of the diseases; however, their frequency varies.

Table 1: Characteristic of the clinical symptoms for sarcoidosis and disseminated lung TB

Clinical symptom	Sarcoidosis (n = 27)	Disseminated lung TB (n = 62)
The course of the disease	Chronic	Acute, subacute or chronic
Age, years	47,3±1,4	42,9 ± 1,6
Generalized weakness	21 (78%)	60 (97%)
Dyspnea, %	22 (82%)*	21 (34%)*
Cough, %	22 (80%)	53 (85%)
Hemoptysis, %	-	4 (6%)
Sub febrile temperature	15 (56%)*	57 (92%)*
Chest pain	7 (26%)	18 (30%)
Loss of appetite	17 (64%)	57 (92%)
Weight loss	18 (67%)	54 (90%)
Muscle, joint pain	4 (15%)	15 (24%)
Cyanosis	3 (11%)	22 (35%)
Sweating	21 (79%)	53 (85%)

*statistical significance at p < 0.05.

As seen from the table patients with sarcoidosis had a significantly higher rate of dyspnea (82% against 34% with p < 0.05) compared to the lung TB group. Sub febrile temperature was more often seen in patients with disseminated lung TB (92% against 56%, with p < 0.05). Analysis of other clinical symptoms did not reveal any significant difference between the groups. Some symptoms like hemoptysis are nonspecific and can be seen in a variety of other diseases.

Two hundred ten cases of comorbid conditions were identified among the examined group of patients. Forty-seven (52.8%) of those patients had psychological and behavioural disorders due to alcohol consumption and some types of psychoactive substances, 23 (26%) had chronic bronchitis, 21 (23.5%) – chronic obstructive pulmonary disease (COPD), 17 (19.1%) had arterial hypertension. Detailed analysis of comorbid conditions showed that the rate of bad habits was higher among lung TB group (64.5%), while patients with sarcoidosis more often had COPD – 48.1% and 44.4% arterial hypertension (Figure 1).

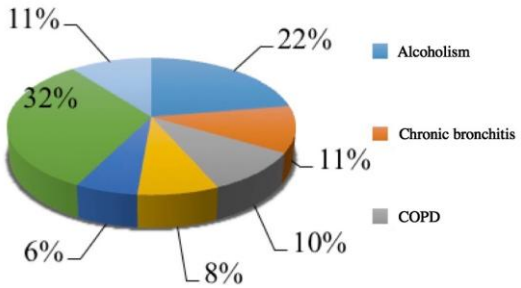

Figure 1: Comorbid conditions in patients with sarcoidosis and disseminated lung TB (n = 89)

All patients were examined for lung dissemination syndrome. This radiological syndrome, however, can be present in other types of diseases. Radiological examination results are summarised in Table 2.

Table 2: Comparison of radiological changes in groups

Patient's group	Lung tissue consolidations and intrathoracic lymph node enlargement, n, %								
	Quantitatively		Based on size				Homogeneity		Lymph node size
	Single	Multiple	Unilateral	Bilateral	Patchy	Infiltration-like	Homogeneous	Heterogeneous	Enlarged
Sarcoidosis (n = 27)	932.7	18 67.3	311.2	2488.8	2696.9	13.1	27100	- 0	2696.9*
Lung TB (n = 62)	2337.1	3962.9	69.7	5690.3	6096.7	23.3	5690.2	69.8	3048.3*

*statistical significance at p < 0.05.

No statistically significant difference was noted when radiological films were examined for the presence of lung consolidations in sarcoidosis and disseminated lung TB. Statistically significant difference, however, was found for the rate of lymphadenopathy 96.9% against 48.3% with p < 0.05.

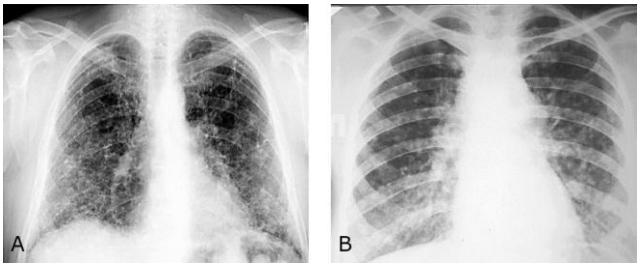

Figure 2: CT picture of disseminated lung TB and lung sarcoidosis; A) Lung sarcoid; B) Disseminated lung TB

CT investigation showed symmetrical lymph node enlargement of all lymph nodes of central mediastinum and lung roots. It is important to note that characteristic feature of sarcoidosis was multiple lymph nodes enlargement in every anatomical group with formation of big aggregation especially in a bifurcating group, while in case of disseminated lung TB enlargement of tracheobronchial, broncho-pulmonic lymph nodes were noted, sometimes with regions of calcification. In both cases, dissemination has spread approximately to the same extent (95.5% for sarcoidosis and 96.7% for disseminated lung TB) in lung parenchyma of each lobe. Measurement of the lung-thoracic index has shown that pulmonary hypertension was not significant. But is somewhere at the edge of the upper limit of the norm; in 4 cases (14.8%) of sarcoidosis and 2 cases (3.1%) of disseminated lung TB mild pulmonary hypertension was noted 8.3 ± 1.1. “Ground glass” sign was an important CT finding of sarcoidosis. In some patients, limited zones of consolidation of lung parenchyma of ground glass type of irregular shape, with indistinct boundaries were formed by multiple small focuses, while these findings are atypical for disseminated lung TB (Figure 2 A, and B).

To objectify morphological changes due to sarcoidosis and TB, quantitative evaluation of cellular infiltration of histological specimens of the lung tissues using the dot method with the help of square of Avtandilov was performed. Using eyepiece micrometre granuloma size (in mcm^2) was determined: diameter of granuloma as well as an oval, square area using the formula $S = 7i (Rj/2 + R_2/2)^2$.

Size of granuloma in sarcoidosis patients was 198576 ± 2119 mcm^2, for lung TB-302074 ± 62800 mcm^2, which shows that the size of granuloma is bigger in the case of TB.

Table 3: Cellular content of granuloma, stromal component and angiogenesis in disseminated lung TB and lung sarcoidosis

Cellular content of granuloma	Disseminated lung TB	Lung sarcoidosis	p
	Median (quartiles)		
Granulocytes	102 (98; 106.5)	30 (26.5; 40)	P = 0.011*
Lymphocytes	126 (120.5; 138)	161 (154; 174.5)	P = 0.057
Plasma cells	12 (9.5; 13.5)	44 (37; 50)	P = 0.003*
Macrophages	66 (57; 76.5)	54 (44.5; 58)	P = 0.171
Epithelial cells	89 (82; 95)	52 (40.5; 58)	P = 0.012*
Giant multinucleated cells	9 (8; 10)	3 (1; 3.5)	P = 0.000*
Structural elements of the stroma (fibroblasts, fibrocytes)	92 (86; 96)	165 (155; 178.5)	P = 0.016*
Angiogenesis	7 (5.5; 8)	21 (17;23)	P = 0.00*

Table 3 shows that the main components of the cellular composition of granuloma in case of TB are granulocytes, epithelial cells and giant multinucleated cells, which is a sign of productive phase of the inflammatory process in the lung tissue. In the case of sarcoidosis number of plasma cells and lymphocytes is increased, which is indicative of the immune type of reaction, while the number of granulocytes and epithelial cells is declining. In the case of sarcoidosis number of structural elements of the stroma (fibroblasts, fibrocytes) and vessels is also increased. Obtained data regarding the cellular composition of granuloma could serve as morphometrical criteria for differential diagnosis of sarcoidosis and disseminated lung TB.

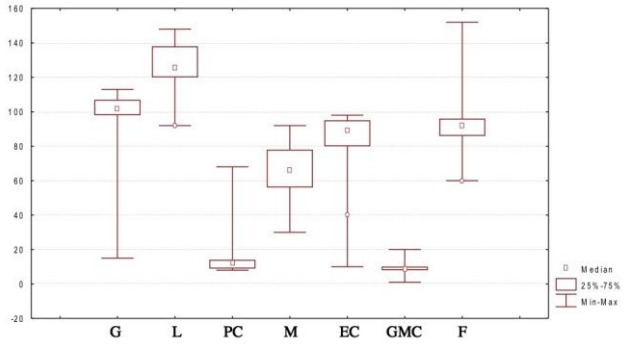

*Figure 3: Cellular composition of granuloma in disseminated lung TB; *G – granulocytes; L – lymphocytes; PC – plasma cells; M – macrophages; EC – epithelial cells; GMC - giant multinucleated cells; F – fibroblasts*

Obtained results’ analysis shows that patients with lungs sarcoidosis have increased the number of structural elements of the stroma, which could be a sign of deep destructive changes in parenchyma of the lungs, leading to the formation of “honey-comb” lung. Active angiogenesis is aiding lung tissue remodelling, which leads to subsequent changes and destruction of interstitial tissue.

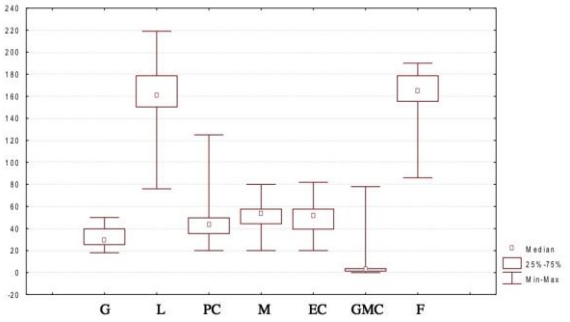

Figure 4: Cellular composition of granuloma in lung sarcoidosis; G – granulocytes; L – lymphocytes; PC – plasma cells; M – macrophages; EC – epithelial cells; GMC - giant multinucleated cells; F – fibroblasts

Distribution of cellular composition was checked using the graphical method with histograms and quantum diagrams as well as quantitative method

assessing Kolmogorov-Smirnov criteria.

The average tendency was described using medians and quartiles. Statistical significance between two groups was assessed using chi-square, between several groups using Kruskal-Wallis criteria.

Figure 3, 4, and 5 show indicators of the cellular composition of granuloma, stromal components and angiogenesis in disseminated lung TB and lung sarcoidosis.

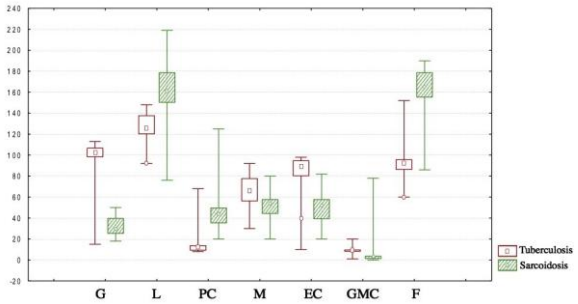

Figure 5: Cellular composition of granuloma, stromal cells and angiogenesis in disseminated lung TB and lung sarcoidosis; G – granulocytes; L – lymphocytes; PC – plasma cells; M – macrophages; EC – epithelial cells; GMC - giant multinucleated cells; F – fibroblasts

The following morphological features of granuloma composition in sarcoidosis were identified as a result of the investigation: increased severity of destructive and fibrotic changes due to proliferation of fibroblasts, more distinctive angiogenesis with a reduced number of giant multinucleated cells, granulocytes and plasma cells. Morphological features of lung tissue changes for sarcoidosis are granuloma formation, development of lymphocytic alveolitis, sclerotic changes and neoangiogenesis.

In the case of disseminated lung TB, a statistically significant increase in the number of epithelial cells was noted. Very often epithelial-cellular granulomas were so big that were visualised along with the whole biopsy specimen cut; their contours were visible in micro specimens as consolidation. Some epithelial cells had an oval or spindle-like shape; nuclei were big occupying two third of cytoplasm volume. Other epithelial cells had an irregular polygonal shape with rounded or reniform nuclei and vacuolation cytoplasm. Statistically significant increase in several giant multinucleated cells, which were significantly polymorphic was noted. Macrophages granuloma in case of lung TB was composed of cells of various size and number of nuclei, were located mostly peripherally, under the cytoplasmic membrane of “Langhans cells” or in the centre similar to foreign bodies. In some cases, giant cellular granuloma of multinucleated cells with individual epithelial cells were predominant.

Morphological criteria for differential diagnosis of sarcoidosis and disseminated lung TB were based on the structural organisation of the granuloma. Granulomatous inflammation due to tuberculosis is characterized depending on the phase of granuloma formation process, in the initial phase – pronounced cellular infiltration with central zone of caseating necrosis, with granulocytes and epithelial cells around, individual multinucleated cells, while new vessels formation is not observed, in productive phase formation of giant cells granuloma with giant multinucleated cells of Langhans is typical.

In the case of sarcoidosis, granuloma composition is also determined by the stage of granuloma process formation. In the initial stage, the granuloma is composed of lymphocytes and plasma cells without the central zone of caseous necrosis. Usually, granuloma has a perivascular location; angiogenesis is typical. In giant cells granuloma formation phase development of concentric structures around granuloma with pronounced fibrosis are characteristical, while giant multinucleated cells have nuclei of various sizes and forms, usually located centrally or in the form of a placer of coins.

Further, you can find examples from clinical practice, when lung granuloma was mistakenly interpreted.

Case Report 1

Patient 62 years old. Was consulted by the therapist with a chief complaint of permanent weakness, dyspnea on mild physical exertion, dry cough, and diaphoresis in 2011. The patient denied the previous history of tuberculosis and contact with TB patients. Chest X-ray is done annually. A course of non-specific antibacterial treatment for 7 days (cephalosporin, ambro) was admitted with no positive dynamic. She was referred for further investigation; chest X-ray showed disseminated lung disease of unknown aetiology. Triple sputum analysis for *M. tuberculosis* showed negative result from 12.06.2011. She was referred to TB specialist: sputum for *M. tuberculosis* registration number #2526 from 16-18.06.2011 was negative in 6 portions. Lung-CT results from 08.07.2011 – signs of disseminated disease, the differential diagnosis between lung sarcoidosis and disseminated lung TB is needed. Lung roots and mediastinum lymphadenopathy. Following an investigation, the diagnosis of disseminated lung disease of unknown aetiology was made. She was referred to the oblast TB dispensary. The patient was admitted there for the subsequent diagnostic evaluation. From medical history: the patient did not have a history of Hepatitis A, skin or sexually transmitted diseases. The patient denied any bad habits and illicit drug use. Family history is insignificant. Objective status: the patient is discharged in satisfactory conditions. Body temperature – 37.3°C. Skin and mucosal lining had physiological colour. No peripheral lymphadenopathy. The patient had hypersthenic form of the chest. On lung auscultation – diminished vesicular lung sounds,

no wheezing or additional lung sounds. Breathing rate equal to 19 per minute. Heart sounds are diminished correct rhythm. Pulse – 80 per minute, blood pressure – 120/70 millimetres of mercury. No other significant findings on physical examination. Bronchoscopy was performed (18.07.2011) with the following result: chronic endobronchitis, operation: diagnostic video-assisted thoracoscopy, right lung biopsy with the following result #2814-15 from 30.07.2011 – granulomatous lung tissue inflammation with granuloma of sarcoidosis type. The final diagnosis was made on 05.08.2011 – lung sarcoidosis. Respiratory insufficiency stage 0. She was transferred to the pulmonology unit. After receiving pathogen-oriented, restorative therapies was discharged with improvement. Was followed by regional pulmonologist once a year, in case of decomposition was receiving treatment in in-patient clinic. Instrumental findings for the following 5 years are given further.

Lung CT results from 11.07.11: Axial CT-scan and reconstructive images show normal chest shape. Multiple small monomorphic focuses located chaotically are found in all lung fields from apexes to diaphragm, big focus up to 2.0 cm in diameter some with cavitation are located peripherally. Lung roots are moderately dilated due to bronchopulmonary lymph nodes enlargement. Trachea and bronchi are patents. Mediastinum located centrally. In anterior, central and posterior parts pathological changes are not found. Lymph nodes of the mediastinum are moderately enlarged. The heart is dilated to the left due to the left ventricle. A musculoskeletal system without pathological changes. Soft tissues normal.

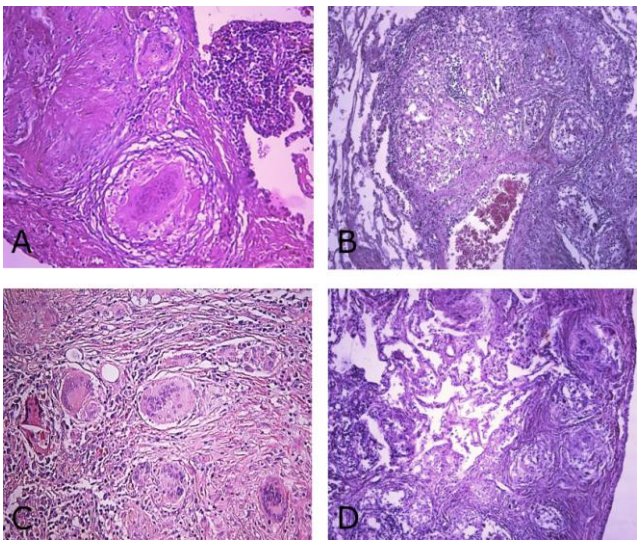

Figure 6: Granulomatosis in case of sarcoidosis with epithelioid macrophage granuloma formation: a – granuloma in the subpleural zone; b – granuloma around blood vessels; c – epithelioid cell granuloma, multinucleated giant cells; d – granuloma fibrosis, dystelectasis, desquamated alveolates in alveolar space. Staining: hematoxylin and eosin. Magnification: H and E: a - x 400; b - x 200; c - x 400; d - x 200

Microscopic investigation of left lung tissue specimen revealed granuloma formation with epithelial cells and individual giant multinucleated cells. Granuloma is located mainly in sub pleuritic zone and perivascularly, limited by circularly located connective fibres, in some places fibrosis, hyalinosis, dystelectasis and compensative emphysema are found, interalveolar septa are thickened in some places, some alveoli have desquamated alveolates, regions of exudate and haemorrhages. In some granuloma and perivascular zones, there are pigmented macrophages. Pleura is thickened, fibrosis (Figure 6 A, B, C, and D). The described pathological picture gives represents lung sarcoidosis with epithelial-macrophage granuloma formation.

Case Report 2

Patient 45 years old, lives in Karaganda region. Was admitted to the pulmonology unit of oblast clinic with a diagnosis of severe bilateral pneumonia. Was delivered by ambulance due to the severity of the condition. Chief complaint on admission: high-grade fever up to 39-40°C, diaphoresis, weakness, fatigue, cough with mucopurulent discharge, dyspnea. From the patient's history: symptoms were developing over 2-3 weeks with gradual deterioration; however, the patient did not go to the clinic. Self-treated with no improvement. Denied a history of tuberculosis, did not have contact with TB patients. Had hepatitis A in childhood, denied skin problems or the presence of sexually transmitted diseases. The patient is a smoker. Family history is significant for hypertension in both parents, bronchial asthma in sister. Has a history of hypertension since 2010, takes Enalapril 10 mg inconstantly; peptic ulcer over the last year, last exacerbation 1 month ago – takes Omeprazole 20 mg once a day, Almagel 170 ml three times a day from time to time. Objective status: in moderate distress due to respiratory distress. The skin has a physiological colour with local hyperemia of the face, normal turgor, clean. Lymphadenopathy of submandibular and supraclavicular lymph nodes. Breathing rate equal to 28 per minute. The chest has a cylindrical shape, breathing is symmetrical, dull sound on percussion with resonant regions, on auscultation bronchial sounds with rales. Heart sounds are diminished, heart rhythm is regular, short systolic murmur on the apex. Blood pressure 170/100 millimetres of mercury. Pulse 94, heart rate 94 per minute. No other significant findings on physical examination.

Laboratory findings: sputum analysis insignificant. Triple sputum analysis for *M. tuberculosis* showed a negative result. Chest X-ray – disseminated syndrome.

In in-patient ward, IV fluids and symptomatic treatment were delivered. No improvement noted. Disseminated lung TB was suspected, and the patient was sent for further investigation (PPD test was positive). Diagnostic thoracoscopy with biopsy sampling was performed. The suspected diagnosis

was confirmed histologically. In microscopic specimen, there is specific granuloma formation with the central zone of caseous necrosis, elongated epithelial cells, lymphocytes, macrophages and giant multinucleated cells of Langhans that are located around. Novel vessels are absent inside the granuloma (Figure 7 A and B). Complex treatment was begun; currently, the patient is on supportive treatment.

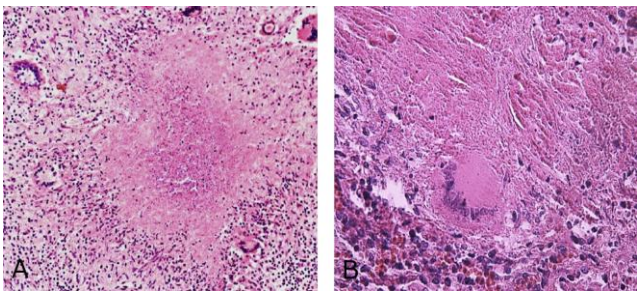

Figure 7: Granuloma in case of lung TB. A – caseous necrosis in the centre of granuloma, epithelial cells located peripherally, lymphocytes, giant multinucleated cells of Langhans; b-giant multinucleated cell of Langhans; Staining: hematoxylin and eosin. Magnification. H and E: a - x 200; b - x 400

Described clinical cases are telling about the need for a thorough examination of histological material to differentiate the granuloma process taking into account characteristic features for sarcoidosis and disseminated lung TB. To make the final diagnosis complex interpretation of clinical, laboratory, CT investigation should be carefully examined with the help of pathological findings using diagnostic thoracoscopy with biopsy is needed. It helps for the early differential diagnosis of granuloma formations in the lungs and following treatment choice.

Discussion

Diagnosis of disseminated lung diseases is considered to be one of the most challenging in the differential diagnosis of lung pathologies. One of the most difficult is the differential diagnosis of sarcoidosis and lung TB, which is attributed to the absence of pathognomonic clinical or radiological features. This is why the morphological investigation is the gold standard in the diagnosis of disseminated lung tissue diseases. Morphological features and granuloma composition are the main component of the final diagnosis, which help to start a prompt and specific therapy.

Morphological results analysis showed that standard methods have low efficacy in the differentiation of sarcoidosis and lung TB. Our study has shown that the most diagnostically valuable investigation in difficult cases is modern morphometric methodology based on quantitative assessment of granuloma composition.

Developed morphological and morphometrical criteria of differential diagnosis of sarcoidosis and lung TB are needed to be implemented in the every-day practice of pathologists to confirm a clinical diagnosis. It will help to determine the cause of the disease, investigation plan and treatment correction and disease prognosis taking into account clinical, laboratory and instrumental findings.

References

1. Vizel IYu, Vizel AA, Shaimuratov RI. X-ray, laboratory, and functional parallels in intrathoracic sarcoidosis. Terapev arkh. 2015; 3:48-2. https://doi.org/10.17116/terarkh201587348-52 PMid:26027240

2. Terpigoev SA, El-Zein BA, Vereshchagina VM, Paleev NR. Sarcoidosis: problems in classification. Annals of the Russian academy of medical sciences. 2012; 67(5):30-7.

3. Tussupbekova MM, Stabayeva LM, Bakenova RA, Nygyzbayeva RZh, Imanbayeva GN. Morphological verification of sarcoidosis with other granulomatous lesions of the lungs. Medical News. 2016; 9:60-2.

4. Piotrowski WJ, Górski P, Duda-Szymańska J, Kwiatkowska S. Mycobacterium tuberculosis as a sarcoid factor? A case report of family sarcoidosis. Am J of Case Rep. 2014; 15:216-20. https://doi.org/10.12659/AJCR.890014 PMid:24847413 PMCid:PMC4026149

5. Vizel AA. A review of data on sarcoidosis presented in the European Respiratory Society Congress 2014. Russian Pulmonology. 2014; 5:123-28. https://doi.org/10.18093/0869-0189-2014-0-5-123-128

6. Tussupbekova MM, Bakenova RA, Stabayeva LM. Features of the clinical and morphological picture of pulmonary sarcoidosis. J Clin Med Kaz. 2017; 4:33-6. https://doi.org/10.23950/1812-2892-JCMK-00523

7. Zinserling VA. the importance of morphological investigations in diagnostics and study of infections tissue microbiology. J Infectology. 2018; 10(3):124-32. https://doi.org/10.22625/2072-6732-2018-10-3-124-132

8. Karpina NL. Features of the differential diagnosis of pulmonary diseases with infiltration syndrome. Vestnik. 2018; 1:26-2.

9. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Resp Journal. 2005; 25:783-88. https://doi.org/10.1183/09031936.05.00083404 PMid:15863633