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Conjunctival biopsy as a first choice to confirm a diagnosis of sarcoidosis

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Abstract. *Background*: Sarcoidosis is a granulomatous systemic disease of unknown aetiology. The diagnosis needs histological confirmation of the presence of non-caseating granulomata. One option is a conjunctival biopsy. The aims of this study were to evaluate conjunctival biopsy for the diagnosis of sarcoidosis with respect to its sensitivity and to assess its cost effectiveness by comparison with other histopathological diagnostic procedures. *Methods*: Patients were identified from the database of the Interstitial Lung Disease Clinic (ILDC) of the Chest Department of Ege University Hospital from May 2008 to June 2014. The patients who had biopsy procedures performed for the definitive diagnosis of sarcoidosis were assessed. Their diagnostic procedures and the cost of procedures were recorded. The cost per positive result for each procedure was calculated. *Results*: In total, 280 patients were followed up with a diagnosis of sarcoidosis, of whom 174 had histological confirmation; these constitute the study population. There were 127 females and 47 males with a median age of 46 years (range 14-78 years). Forty three patients had conjunctival biopsy and we could establish a diagnosis in 54% of these by means of conjunctival biopsy. Moreover, we showed that this biopsy can provide positive result for sarcoidosis patients who lack abnormal eye findings. Additionally, it is cost effective approach and without complications. *Conclusion*: This study re-asserts the value of conjunctival biopsy, which was described in the past but is not commonly used nowadays. In the presence of suggestive clinic and radiologic findings, we recommend conjunctival biopsy as the first choice for the histopathological confirmation of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 196-200)*

Key words: sarcoidosis, conjunctiva, biopsy, diagnosis, cost effectiveness

Introduction

Sarcoidosis is a granulomatous systemic disease of unknown aetiology that most commonly affects the lungs and mediastinal lymph nodes. The diagnosis needs histological confirmation of the presence of non-caseating granulomata in a patient with compatible clinical and radiological findings, as itemised in the ATS/ERS/WASOG Statement, and the exclusion of other granulomatous diseases (1). The granulomata are usually widely distributed, the choice of biopsy being determined by consideration of the likelihood of a positive result, and the availability and risks of the procedure. One option is a conjunctival biopsy, as was first described in the 1950s but it is not a commonly used diagnostic approach nowadays. This is despite its relative simplicity and availability (2-5). We aimed to evaluate conjunctival

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biopsy for the diagnosis of sarcoidosis with respect to its sensitivity and to assess its cost effectiveness by comparison with other histopathological diagnostic procedures.

Methods

Patients were identified from the database of the Interstitial Lung Disease Clinic (ILDC) of the Chest Department of Ege University Hospital from May 2008 to June 2014. The biopsy procedures performed for the definitive diagnosis of sarcoidosis in newly presenting patients, along with the patient characteristics and radiological findings were ascertained.

Patients for conjunctival biopsy were sent to a team of named ophthalmologists. They underwent examination of the eyes for signs of sarcoidosis. Following application of an eyelid speculum, 1% lidocaine was injected into the subconjunctival space, ballooning up the area for biopsy. The lower eyelid was then retracted and the inferior fornix was grasped with toothed forceps. An area of approximately 5x15 mm from the inferior fornix conjunctiva was excised using Westcott scissors. Haemostasis was achieved by applying pressure for 2-3 minutes and prophylactic antibiotic drops were instilled into the lower fornix (6). This procedure, performed on both eyes in each patient, was undertaken on an outpatient basis.

For all of diagnostic procedures, the cost was gleaned from the Hospital Information System of the Medical School of Ege University. The cost per positive result for each procedure was calculated.

Statistical analyses

The data management and analysis of all data was conducted using SPSS for Windows 16.0 software. Descriptive statistics were used for demographic data. The Shapiro-Wilk test was applied to identify the distribution of numeric data. The Mann Whitney U test and Student's t-test were used for non-parametric and parametric tests respectively. The Chi-square test was utilized for the comparison of demographic and clinical factors that may have an effect on positive conjunctival biopsy result; $p<0.05$ was considered statistically significant.

Results

In our ILDC, in total 280 patients were followed up with a diagnosis of sarcoidosis, of whom 174 had histological confirmation; these constitute the study population. There were 127 females and 47 males with median age of 46 years (range 14-78 years). Further demographic characteristics are shown in Table 1. Disease stage information was available in 152 patients, with most patients having stage I disease (53%), followed by stage II (36%). Five percent had only extra-pulmonary sarcoidosis. The average follow up was 20 months (range 1 to 160 months).

Bronchoscopic sampling or conjunctival biopsy were the preferred initial approaches to histological confirmation, according to which could be scheduled first, taking into consideration the patient's fitness. Lymph node sampling was performed in 147 patients, comprising bronchoscopic fine needle biopsy of mediastinal lymph nodes, conventionally in 37 and by endobronchial ultrasound (EBUS) in 35, scalene lymph node biopsy in 36, peripheral lymph node biopsy in 20, and mediastinal nodal sampling by mediastinoscopy or mediastinotomy in 19. Transbronchial parenchymal lung biopsy was performed in 39, bronchial mucosal biopsy in 37 and surgical lung biopsy in 19. Forty three patients had conjunctival biopsy, of whom 61% were stage I and 35% stage II. In addition, this cohort of patients underwent 11 skin, 7 nasopharyngeal, 6 liver, 5 lip minor salivary gland, 2 parotid gland, 2 abdominal lymph node, one upper gastrointestinal tract, one myocardial and one transthoracic core needle biopsies, and one splenectomy. Diagnostic approaches and diagnostic rates were shown in Figure 1. 95 patients required more than one biopsy to achieve histological confirmation.

The most sensitive modalities were surgical biopsy, be it of the lung (100%), mediastinal lymph

Table 1. Demographic characteristics of patients (n=174)

Number of cases, n (F/M)	174 (127/47)
Age (years)*	46 (14-78)
Smoking history, n (%)	38 (21.8)
Pack-years*	7.5 (1-150)
Comorbidities, n (%)	66 (37.9)
Cardiovascular disease	32 (18.4)
Diabetes mellitus	18 (10.3)
Others	16 (9.2)
Family history, n (%)	5 (2.8)
History of pulmonary tuberculosis, n (%)	6 (3.4)

*: median value (range)

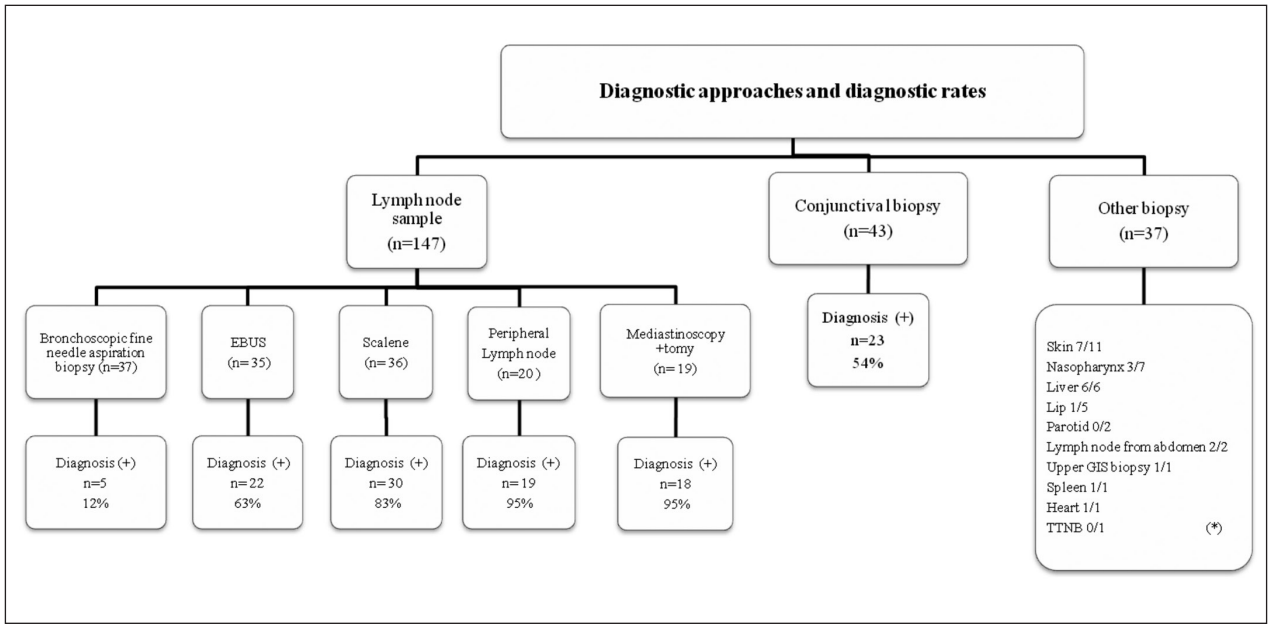

Fig. 1. Diagnostic approaches and application results
*: positive diagnostic result number/totally biopsy number

nodes (95%), peripheral lymph node (95%) or scalene lymph node (83%). Bronchoscopic biopsy had a sensitivity of 59% for transbronchial parenchymal and 35% for bronchial mucosal samples. Bronchoscopic fine needle aspiration of mediastinal lymph nodes had a sensitivity of 63% when performed by EBUS but only 12% when performed blindly. Conjunctival biopsy had a sensitivity of 54%.

Only three patients had eye findings or symptoms, which were uveitis in two and dry eye in the other patient; positive conjunctival biopsy was shown in two of them. There was no significant correlation of the patient's age, gender, symptoms, signs, stage or radiological findings with the conjunctival biopsy result. The only correlation was with serum angiotensin converting enzyme level, which was significantly higher in the group that had a positive result via conjunctival biopsy [83 U/L (range 10-177 U/L) vs 55 U/L (range 39-170 U/L), reference range 8-52 U/L, p= 0.011]. After conjunctival biopsy, the only complications were redness of the eyes and all patients left the hospital on same day.

We assessed the cost for all diagnostic approaches. Based on the cost of the procedure and the cost per positive result, conjunctival biopsy was the cheapest approach (Table 2).

Table 2. Diagnostic methods, sensitivity and cost of the procedure

Methods of sampling	Diagnostic Sensitivity	Cost of Procedure TL ($)	Cost per positive result TL ($)
Surgical lung biopsy	100% (19/19)	973 (453)	973 (453)
Mediastinoscopy	95% (18/19)	368 (171)	387 (180)
Peripheral/scalene lymph node biopsy	88% (49/56)	212 (99)	241 (112)
EBUS	63% (22/35)	501 (233)	795 (370)
Transbronchial biopsy	59% (23/39)	320 (149)	542 (252)
Conjunctival biopsy	54% (23/43)	121 (56)	224 (104)
Bronchial mucosal biopsy	35% (13/37)	318 (148)	909 (423)
Fine needle aspiration biopsy (via bronchoscopy)	12% (5/37)	250 (116)	2083 (970)

Abbreviations: TL; Turkish Lira, $; American dollar

Discussion

Histological demonstration of non-caseating granulomata is essential for the confirmation of sarcoidosis in a patient with compatible clinical and radiological findings. This study has shown that we could establish a diagnosis in 54% of sarcoidosis patients by means of conjunctival biopsy. Although this biopsy technique was described in the 1950s, it is generally not used as the primary diagnostic procedure in sarcoidosis patients who do not have eye findings. However, we have shown that this biopsy can provide positive result for sarcoidosis patients who lack abnormal eye findings. Additionally, it is cost effective approach and without complications.

The rate of positivity in conjunctival biopsy in the literature varies widely, ranging from 27% to 55%, with a mean of 37% (3, 5, 7-11). The specificity of a diagnostic method is as important as its sensitivity, the granulomas of sarcoidosis needing to be distinguished from other granulomatous diseases. The conjunctiva has the advantage of usually being spared by other systemic granulomatous conditions. Khan et al (7), reported 100 conjunctival biopsies on patients with pulmonary tuberculosis (25 biopsies), non-specific inflammatory diseases of the lung and eye (15 biopsies), and histologically definitive sarcoidosis diagnose (60 biopsies). Although the positive biopsy rate in sarcoidosis was only 33%, none of patients with other disease showed conjunctival granulomata. Another study by Bornstein et al (3) included 11 patients with tuberculosis or histoplasmosis; none showed conjunctival granulomata.

The most common findings in conjunctival involvement of sarcoidosis are multiple or solitary yellow nodules (12) but our patients who underwent conjunctival biopsy had no finding to indicate eye involvement, despite which over half were diagnosed with sarcoidosis by such a biopsy. In the study by Leavitt et al (8), 57% of the patients who had no visible conjunctival lesion had a positive conjunctival biopsy. Ocular examination does not predict which patient will have a positive conjunctival biopsy (7).

In a recent meta-analysis, which analysed 21 studies with stage I and II disease, the diagnostic rate of conventional transbronchial needle aspiration was reported as 62% with a wide range from 6% to 90%, achieved without major complications in more than 900 patients (13). Our diagnostic rate of 12% is at the low end of this range but even with a higher rate, it would be more expensive per positive result than conjunctival biopsy. Our higher diagnostic rates of 59% by transbronchial parenchymal biopsy and 63% by EBUS are comparable to those in the published literature (14, 15). However, EBUS requires equipment and skills which are not universally available, may necessitate deeper sedation and these procedures are associated with occasional complications.

Other surgical procedures such as mediastinoscopy, mediastinotomy, open and video associated thoracic surgery are much more invasive and expensive, requiring the use of an operating room and full anaesthesia with post-procedural hospitalisation. By contrast, ophthalmologists perform conjunctival biopsy with local anaesthesia and patients do not need to be hospitalised. It can be performed in patients with a poor functional status. After biopsy, none of our patients had significant complications. Additionally, conjunctival biopsy is cheaper than other diagnostic procedures.

The higher ACE level in those with positive conjunctival biopsies is an interesting observation as it may be a reflection of granuloma load. In order to ascertain whether it should guide the mode of biopsy, we would need to examine its correlation with the rate of positivity of all diagnostic modalities.

This study has re-asserted that conjunctival biopsy, which was described in the past but is not commonly used nowadays, being displaced by novel methodologies, remains a valuable tool for the histological confirmation of sarcoidosis. This procedure can obviate the need for other, invasive, approaches in nearly half of patients, is without complications and is cost-effective. In the presence of suggestive clinic and radiologic findings, we recommend conjunctival biopsy as the first choice for the histopathological confirmation of sarcoidosis

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