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Diagnostic efficacy of ultrasound-guided core-needle biopsy of peripheral lymph nodes in sarcoidosis

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Abstract. *Background:* Core-needle biopsy guided by ultrasound can be performed for investigating peripheral lymph node (PLN). The aim of this study was to determine the efficacy of this technique in sarcoidosis. *Methods:* Retrospective review of files of all patients in the database of the radiology department of Avicenne university hospital who underwent PLN biopsies guided by ultrasound from January 2008 to June 2011 (n=292). Cases with either granulomas at histology with the procedure or with a final diagnosis of sarcoidosis were included in the study. *Results:* The histological specimens were adequate in 282 out of 292 cases (96%) showing non-caseating granulomas in 22 cases (n=20 patients with a final diagnosis of sarcoidosis and n=2 patients with tuberculosis). After reviewing clinical files of the 282 patient, 22 were confirmed to have sarcoidosis, at initial presentation (n=19) or later during flare-up or relapse (n=3) with only 2 patients having no granuloma on PLN biopsy. PLN were palpable in 18 cases and only detected by ^{18F}FDG-PET/CT showing increased PLN uptake in 4 cases. The sensitivity and specificity of adequate biopsy were 91 and 99% and the positive and negative predictive values were 91 and 99%, respectively. *Conclusion:* Core-needle biopsy guided by ultrasound has a high efficacy for evidencing granulomas in sarcoidosis patients with PLN involvement either clinically palpable or in the presence of ^{18F}FDG-PET/CT uptake. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 31: 188-193)*

Key words: PET/CT, sarcoidosis, peripheral lymph node, niopsy, granuloma

Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown cause that most frequently involves the lung and the lymphatic system. The diagnosis is established when suggestive clinical and radiological findings are supported by histological evidence of its hallmark, i.e. non-caseating epithelioid cell granulomas, and when other diseases with a similar histological or clinical presentation can be excluded (1, 2). The site for biopsy depends on accessibility, safety, and potential yield of the procedure according to presentation (3). In keeping with these criteria, superficial lesions, including skin lesions other than erythema nodosum, palpable peripheral lymph node (PLN), or visible conjunctival nodules should be considered as the first targets (2).

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PLN are clinically detected in about one third of sarcoid patients (4) either at presentation or during follow-up, in relation to flare-up/relapse or comorbid conditions. PLN may represent an accurate site for biopsy, for both the demonstration of granulomatous lesions (5) and the exclusion of differential diagnoses. PLN can be investigated by ultrasound (US) guided core-needle biopsy, which is a minimally invasive and high cost/efficiency technique. Lymph nodes core-needle biopsy has become the method of choice for the diagnosis of lymphoma in many institutions (6, 7) as it provides larger samples than fine-needle aspiration cytology. Surprisingly, the role of PLN core-needle biopsy has not yet been comprehensively assessed for the diagnosis of sarcoidosis, whereas it could be a safe alternative to surgical biopsy and a more informative procedure than fine-needle aspiration cytology (8, 9).

PLN core-needle biopsy could be proposed if PLN are detected during physical examination (palpable PLN) or following imaging investigation, including F18- Fluorodeoxyglucose -Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT) in patients with suspected sarcoidosis or in sarcoid patients for which the occurrence of a comorbid condition is raised (1, 10). Therefore, the purpose of this study was to evaluate the yield and safety of PLN US guided core-needle biopsy for the diagnosis of sarcoidosis.

Materials and Methods

This retrospective study was approved by the institutional review board of our institution and patients received written information. We reviewed all histological and clinical reports of patients who underwent PLN US guided biopsies in the Radiology Department (Avicenne Hospital, Bobigny, France) from January 2008 to June 2011 (n=292 biopsies in 282 patients). Patients with sarcoidosis were all recruited in the same hospital suffering from various pulmonary diseases with PLN involvement. From this database, we focused our attention on the one hand on patients with histological findings of non-caseating granulomas and on the other hand on those who had a final diagnosis of sarcoidosis based on other investigations and clinical follow-up according to the statement on sarcoidosis (11).

PLN US guided Biopsy technique

The biopsies were performed under ultrasound guidance (Aplio 50, Toshiba Medical Systems, Puteaux, France) by a senior radiologist (PYB, OT, AM). A high frequency linear ultrasound probe (> 7.5 MHz) was used to guide the biopsy. Only PLN with a diameter over 10 mm were considered for biopsy. Lidocaine hydrochloride (10 mg/ml Aguettant®, France) was used for local anaesthesia. Tissue samples were thereafter obtained by means of a 14 to 20 Gauge needle (Temno; CareFusion, San Diego, California, USA), enabling up to a 20 mm long core of tissue to be obtained. For every patient, 1 to 6 samples were taken. Specimens were immediately fixed in formalin and then paraffin-embedded and conventionally processed. A sample was sent for bacteriological analysis and mycobacterial culture in patients at risk for tuberculosis,.

Analysis of clinical, radiological, biopsy processing, and pathological data

The following clinical data were noted: gender, age, history of sarcoidosis (presentation, suspicion of flare-up/relapse or comorbid condition), the presence of palpable PLN, sarcoidosis visceral localizations, and serum angiotensin-converting enzyme level. Imaging data, including ^{18F}FDG-PET/CT were reviewed. Roentgenographic staging of intrathoracic changes was determined according to the sarcoidosis statement (11). Information regarding PLN core-needle biopsies was also reviewed, including the site, number, and size, as well as the occurrence of any adverse event.

The adequacy of the material obtained was also considered. Inadequate results referred to cases with insufficient material for a proper histological diagnosis or non-caseating necrotic tissues (7). When the material was adequate, the different pathological diagnoses were collected.

Statistical analysis

Only patients with adequate samples were included for further statistical analysis. Clinical, radio-

logical, biopsy processing and pathological data were assessed by descriptive statistics. Regarding the diagnosis yield of the core-needle biopsy, sensitivity, specificity, and negative/positive predictive value were calculated. A biopsy result was considered to be true-positive when the tissue sample was adequate and the histologic diagnosis indicated "granulomas without caseating necrosis" with a final diagnosis of sarcoidosis. A false-positive result referred to tissue samples considered adequate with a histological diagnosis indicating "non-caseating granulomas" while the final diagnosis was not sarcoidosis. A false-negative result referred to tissue samples considered adequate where histologic diagnosis indicated "no granuloma" while the final diagnosis was sarcoidosis. A true-negative result referred to other cases of adequate tissue sampling.

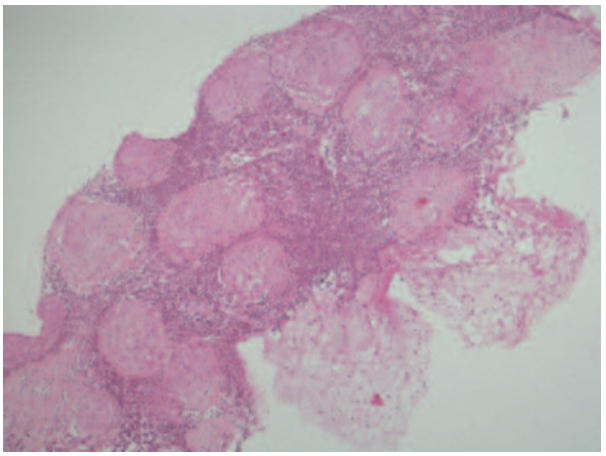

Fig. 2. Histological view (Hematoxylin and eosin stain, x100) of a core-needle lymph node biopsy (patient 1, 16 Gauge). Multiple small epitheloid granulomas with few giant cells are disseminated into the lymphoid tissu, some surrounded by discrete fibrosis. Necrosis is absent

Results

Specimens were adequate for histological analysis in 282/292 biopsies (96.5%). No adverse event was observed following the procedure.

The pathological diagnoses are shown in Figure 1. Twenty-two patients had non-caseating granulomas (8%, Figure 2), including 20 patients with a final diagnosis of sarcoidosis and 2 patients with tuberculosis (false positive). After reviewing the clinical files of the 282 patients, 22 were confirmed to have sarcoidosis. For 20 of these 22 patients (91%, true positive), non-caseating granulomas were observed while the exam was negative showing no granuloma for the remaining 2 cases (false negative). Therefore, the sensitivity and specificity of the core-needle biopsy were 91% and 99%, respectively, while the positive and negative predictive values were 91% and 99%, respectively.

The clinical characteristics of the sarcoid patients are shown in Table 1. The population consist-

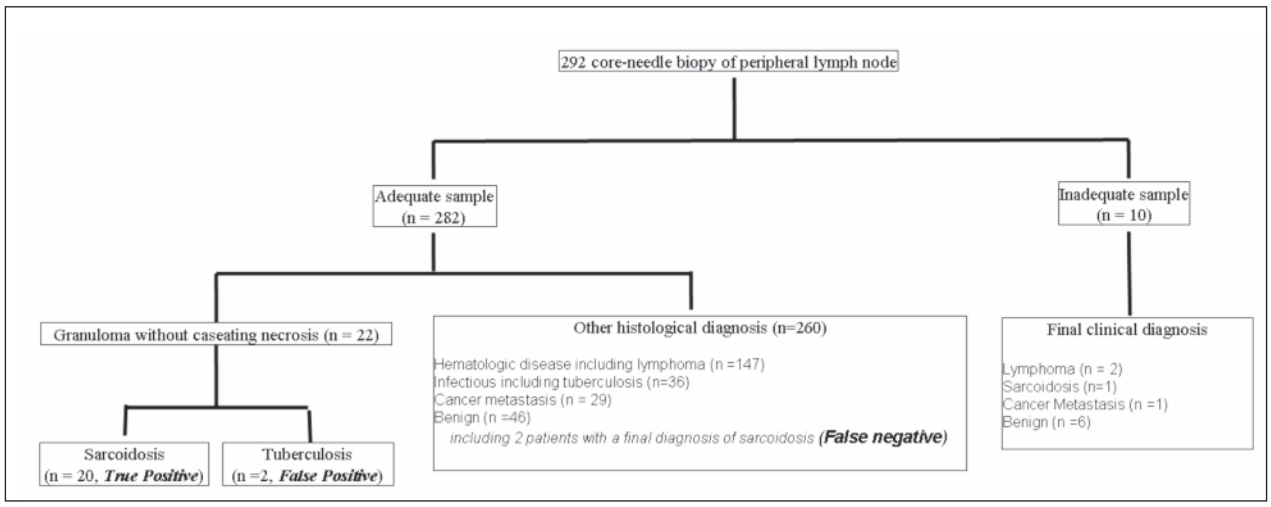

Fig. 1. Study flowchart. Among the 282 patients who underwent 292 Peripheral Lymph Node (PLN) ultrasound-guided core-needle biopsies, 22 had a final diagnosis of sarcoidosis

Table 1. Characteristics of patients with a final diagnostic of sarcoidosis. Abbreviations: peripheral lymph nodes (PLN), not available (NA), Serum Angiotensin-Converting Enzyme (SACE), 18F-FDG-PET/CT was considered positive in cases of increased PLN uptake, endobronchial biopsies (EBB), minor salivary gland (MSG). Mediastinoscopy*, EBB*: * refers to previous history of sarcoidosis with PLN biopsy performed to confirm sarcoidosis relapse

	Clinical data						Imaging		Peripheral lymph node biopsy technique			Histological data	
Patient	Sarcoidosis Histological Diagnosis	Sex (Male/ Female)	Age (Years)	Palpable PLN (Yes=1, No=0)	SACE (xN)	Organ involvement (extra-nodal and extra-pulmonary)	RX stage	PLN uptake on PET/CT (n=13)	Site	Samples (n= 71)	Needle size (Gauge)	Other biopsy sites	Diagnosis of granuloma (Positive)
1	True positive	M	55	0	1.5	Spleen, parotid, eye	2	Positive	Cervical	2	16	No	PLN
2	True positive	F	19	1	N	Eye	1		Cervical	2	16	EBB	PLN
3 *	True positive	F	47	1	N	0	1	Positive	Cervical	1	16	EBB Mediastinoscopy*	PLN Mediastinoscopy*
4	True positive	M	37	1	4	Liver, spleen	2	Positive	Cervical	4	14	EBB	PLN EBB
5	True positive	M	24	1	4	Skin, sinus	2		Cervical	3	18	EBB	PLN EBB
6	True positive	F	36	1	NA	0	1		Supra-clavicular	3	16	MSG	PLN
7	True positive	M	49	1	2	Eye, parotid	4	Positive	Epitrochlea	3	18	EBB	PLN
8	True positive	F	52	1	N	0	1		Inguinal	4	16	No	PLN
9	True positive	F	71	0	2	0	2	Positive	Inguinal	4	18	EBB MSG	PLN
10 *	True positive	F	50	1		0	4		Supra-clavicular	4	16	EBB*	PLN EBB*
11	True positive	F	71	1	N	Eye, joint	0	Positive	Supra-clavicular	3	18	EBB MSG	PLN
12	True positive	F	52	1	1.5	Liver	3	Positive	Axillary	3	18	EBB	PLN
13	True positive	F	58	1	5.6	Liver, spleen	1		Supra-clavicular	4	16	EBB	PLN EBB
14	True positive	F	57	1	N	0	2		Cervical	4	16	No	PLN
15	True positive	F	28	1	2.5	Eye, skin, liver	2	Positive	Cervical	2	20	EBB MSG	PLN MSG
16 *	True positive	M	72	0	1.5	Skin, Liver	4	Positive	Supra-clavicular	2	NA	EBB Mediastinoscopy*	PLN EBB Mediastinoscopy*
17	True positive	F	53	1	N	0	0		Cervical	6	14	MSG	PLN
18	True positive	F	53	1	5	0	NA	Positive	Inguinal	NA	NA	EBB MSG	PLN
19	True positive	M	34	1	NA	Sinus	2	Positive	Cervical	6	16	EBB Skin	PLN EBB Skin
20	True positive	F	26	1	4	Liver, joint, Skin	2	Positive	Cervical	4	16	No	PLN
21	False negative	F	49	0	1.2	Skin	0	Positive	Inguinal	3	16	Skin	Skin
22	False negative	F	28	1	NA	Skin	NA		Cervical	4	20	Skin	Skin

ed of 16 females and 6 males with a mean age of 46.4 (range, 19-72). Patients most often exhibited multi-organ involvement and serum angiotensin-converting enzyme dosage was ≥2N in 36% of cases. PLN biopsy was performed at presentation of sarcoidosis in 19 cases and to differentiate between flare-up/relapse or comorbid condition in 3 cases (Table 1). Eighteen patients had palpable PLN and 4 had clinically unapparent PLN that were detected by increased ^{18F}FDG-PET/CT uptake. A 16 Gauge needle was used in most cases (n=11). Biopsy was mainly performed on cervical (50%, n=11/22) and supraclavicular (23%, n=5/22) areas.

As shown in Table 1, it must be underscored that in 17 patients with PLN biopsies other tissue sampling was concurrently performed for the diagnosis. Among the 11 patients who underwent endobronchial biopsies and in the 5 cases who underwent minor salivary gland biopsy, PLN was the only site showing granulomas in 7/11 and 5/5 respectively.

Discussion

This study demonstrates that the low-invasive US guided core-needle biopsy is a safe and highly efficient procedure, which may represent the most appropriate investigation to obtain granulomas face to suspected sarcoidosis with PLN. The sensitivity and positive predictive value for the diagnosis of sarcoidosis were found to be 91% and 99%, respectively. In addition, our study underscores that infra-clinical PLN detection through ^{18F}FDG-PET/CT also allows obtaining granulomas with this technique.

PLN biopsy has a long history in sarcoidosis. In the late 1950s, the surgical scalene lymph node biopsy was described by Daniels et al. (12) and proved to be an excellent method to obtain histological evidence of granulomas in sarcoidosis with a yield greater than 80% (13). Such surgical biopsies were performed even in the absence of palpable PLN but have been withdrawn in clinical practice with the generalization of mediastinoscopy. More recently, Lohela et al. proposed a new approach for supraclavicular lymph nodes through fine-needle aspiration cytology guided by US (9). Nowadays, fine-needle aspiration tends to be replaced by core-needle biopsy in most radiology departments, especially those dealing with hematologic patients, as it provides larger samples with possible analysis of lymph node architecture and immunostaining (6). Our results highlight the need to look carefully for PLN before more invasive investigations are proposed. Indeed, PLN biopsy performance seems as high as that reported for endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) (14-16).

In our study, we observed two patients classified as false positive. These patients had a histological diagnosis of granulomas without caseating necrosis, but tuberculosis was the final diagnosis (mycobacterial culture from the PLN biopsy was positive in both cases). Such observation confirms the importance of always combining mycobacterial culture with histological results in patients at risk for tuberculosis transmission. Moreover, a special attention should be paid during ultrasound examination which could alert for tuberculosis. Features suggestive of tuberculosis have been well described during EBUS, including coagulation necrosis and heterogeneous echotexture (17, 18). Finally, the risk of false positive results highlights the need to exclude all other causes of granulomas before a diagnosis of sarcoidosis can be ascertained (19, 20). Indeed, since the presence of sarcoid-like granulomas in a PLN may also result from a reaction to a nearby malignant tumour (including lymphoma) or inflammatory disease, the quality of biopsy samples is critical, especially when PLN develops late after the diagnosis of sarcoidosis.

The main limitations of our study are due to its mono-centric and retrospective design. Because Avicenne Hospital is a third care centre for sarcoidosis, this disease is overrepresented in our population of PLN biopsies (8%), with a higher proportion than expected according to the literature (7).

Conclusions

Our results confirm that core-needle biopsy guided by US in patients with PLNs should be considered as a first intention technique for the diagnosis of sarcoidosis (either at initial diagnosis or relapse), besides skin lesions or visible conjunctival nodules biopsy. This technique could be proposed before more invasive investigations in patients with palpable PLN or increased PLN uptake on ^{18F}FDG-PET/CT.

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