Success Rate and Utility of Ultrasound-guided Synovial Biopsies in Clinical Practice

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ABSTRACT. ***Objective.*** The utility of synovial biopsy in increasing our understanding of the pathogenesis of inflammatory arthropathies, as well as in evaluating treatments, is well established. Ultrasound (US) allows synovial assessment and therefore assists in biopsying synovial tissue in a safe and well-tolerated manner. This study's objectives were to (1) determine the rate of success in retrieving synovial tissue using US guidance, (2) describe the indications for US-guided synovial biopsies in the clinical setting, (3) determine how frequently the synovial biopsy can lead to a clear diagnosis, and (4) assess the quality of the synovial tissue obtained using this technique.

Methods. Synovial biopsies of small and large joints were performed under US guidance between February 2007 and December 2014 using a semiautomatic core biopsy needle. The biopsy procedure was considered successful if synovial tissue was found at histological examination.

Results. Seventy-four patients with undifferentiated arthritis underwent 76 synovial biopsies. The success rate in retrieving synovial tissue was 81.6% (62/76). One patient taking acetyl salicylic acid at 75 mg at the time of the biopsy presented with hemarthrosis 48 h after the procedure, which resolved following simple arthrocentesis. A definitive diagnosis was achieved in 16% of the patients where synovial tissue was sampled successfully.

Conclusion. US-guided synovial biopsies in clinical practice can be performed safely on patients with undifferentiated arthritis and with heterogeneous presentations. The rate of success in acquiring synovial tissue is high. The procedure usually retrieves quality tissue and leads to a definite diagnosis in a significant minority of patients. (First Release October 15 2016; J Rheumatol 2016;43:2113–19; doi:10.3899/jrheum.151441)

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Synovial tissue is the principal target and end organ involved in the pathogenesis of multiple articular disease processes[1,2]. Synovial tissue analysis has been widely used for basic science and translational and clinical research. Moreover, synovial assessment allows for the study of many aspects of disease processes including pathogenesis[3], the identification of the relevant target's clinical features[4], diagnosis, and prognosis[5], as well as assisting in assessments of response to treatment[6,7,8].

Histological and immunohistological synovial assessment is also used as a diagnostic tool[9]. Indeed, it is especially useful for identifying arthritis of an infectious etiology when synovial fluid (SF) or blood analysis (Gram, Ziehl) and cultures are negative or in cases where empiric antimicrobial therapy has been commenced before it has been possible to examine the SF[10]. The bacterial broad range 16S ribosomal RNA can also be tracked down by PCR on synovial tissue[11]. The same methods allow identification of fungal, mycobacterial, spirochetes, and *Tropheryma whipplei* in the joint. False negatives for monosodium urate crystals and calcium pyrophosphate occur frequently at microscopic examination of the SF[12], and synovial tissue assessment can be helpful with typical histological features. Finally, synovial benign tumors such as primary or secondary osteochondromatosis or villonodular synovitis can be diagnosed as well, showing specific macroscopic and histological pattern.

There are several techniques to obtain synovial tissue from the joints. Synovial biopsy was performed by Forestier using a needle blindly introduced into the knee joint[13]. Polley and Bickel[14] and Parker and Pearson[15] described new smaller-diameter needles that have been widely used over the years for knee synovial biopsies. Beaulé, *et al*[16] and Parlier-Cuau, *et al*[17] then described a technique of synovial biopsy under

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direct visualization under fluoroscopy with a semiautomatic Tru-Cut needle. This technique allows the performance of multisite biopsies such as in the hips, shoulders, elbows, ankles, and wrists. Synovial biopsies were later performed under direct vision using 2 portals through an arthroscope[18]. Although this technique is usually well tolerated[9], it remains invasive, expensive, and not yet widely available. Moreover, it has been shown that microscopic measurements of synovial inflammation do not differ between biopsies taken blindly or under guided vision[19].

More recently, ultrasound (US)-guided synovial biopsies have been developed. Musculoskeletal US is very commonly used today, especially for guiding interventional procedures[20,21]. This technique has the benefit of being low-cost, rapidly and easily performed without the need for exposing the patient to ionizing radiation, and widely available[22]. It is more practical than arthroscopy for biopsying small joints and allows guidance to the thickest synovial zones. Moreover, Kelly, *et al*[23] reported that increasing synovial thickness on US correlated with increasing grades of synovitis on histological examination. However, few studies have reported on synovial biopsies performed in routine clinical practice[24,25]. It is unknown whether the success and the quality of the biopsy are the same as the one performed in a research setting. Finally, their clinical utility is still a matter of debate.

The aims of our study were to (1) determine the rate of success in retrieving synovial tissue using US guidance, (2) describe the indications for US-guided synovial biopsies in the clinical setting, (3) determine how frequently the synovial biopsy can lead to a clear diagnosis, and (4) assess the quality of the synovial tissue obtained using this technique.

MATERIALS AND METHODS

Patients and histological diagnosis. We included all patients who underwent a US-guided synovial biopsy between February 2007 and December 2014 in Nantes University Hospital for arthritis without a definite diagnosis based on the history, clinical examination, or imaging. Ethics approval was not required in accordance with the policy of our institution. During this service evaluation study, we collected epidemiological (age, sex) and clinical data (clinical presentation, indication, biopsied joint, complications) using a standardized form. Final histological diagnosis was reported by 3 pathologists who had an expertise in assessing synovial tissue in a formal report based on H&E staining. Patients were followed to determine the clinical course of their symptoms.

US-guided synovial biopsies. Synovial biopsies were performed under US guidance using a Philips HD11 XE US machine and a 7–13 MHz transducer from Philips Healthcare. They were performed in an outpatient and inpatient setting depending on the patient's presentation. All patients underwent a thorough assessment of the joint to be biopsied. Vascular and nervous structures nearby were identified and synovial thickness was assessed.

All the biopsy procedures were performed by 1 operator (BLG) who had an expertise in US examination under sterile technique (wearing gown, sterile gloves, mask, and a surgical cap). Skin disinfection was processed with a 5-step protocol using iodine polyvidone or antibacterial cleanser if the patient had a history of iodine allergy. The joint was draped and a sterile field was generated. The transducer was covered with sterile gel and sterile sheath. Anesthesia was performed, injecting 5 to 10 ml of lidocaine 2% in the subcutaneous tissue and up to the joint capsule. If an effusion were present, SF was withdrawn and sent to the laboratory for cell count, crystal microscopy, bacteriological, mycobacteriological, and/or fungal analysis depending on the patient's clinical history and features. A semiautomatic guillotine biopsy Tru-Cut needle from Temnos was used for all the biopsies. The caliber used was 16-gauge for small and intermediate joints or 14-gauge for large joints such as the hips, shoulders, and knees. Coaxial needle was inserted under US guidance through the skin until it reached the articular cavity. The coaxial needle was positioned in intimate contact with the synovium. The semiautomatic guillotine biopsy Tru-Cut needle was then inserted through the cannula of the coaxial needle, still under US guidance. Once positioned within the zone of interest of the synovial tissue, the Tru-Cut needle was triggered, collecting a piece of synovial tissue according to the size of the joint. This Tru-Cut needle was repeatedly inserted through the coaxial needle and triggered to obtain the appropriate number of samples. Then, these 2 needles were removed and a bandage was applied. Patients were recommended to have 48 h of rest after the procedure.

Depending on the indication of the biopsy and the size of the joint, 3 to 8 biopsies were performed per procedure and sent for bacteriological, mycobacteriological, and/or fungal examination in appropriate laboratories. At least 1 sample was fixed in formalin 4%, embedded in paraffin, and sent to the pathology laboratory. When the clinical history was relevant, extra samples were sent for universal bacterial PCR (ARN 16S), universal fungal PCR (ARN 18S), and *T. whipplei* or Lyme PCR.

Analysis of the quality and quantity of the synovial tissue retrieved during synovial biopsies. All the synovial biopsies were blindly read by 1 rheumatologist (AN). These characteristics were assessed in a standardized manner with NDP viewer software: the number of samples per patient; the presence or absence of synovial tissue; the presence or absence of a synovial lining layer; the length, width, and total area of the biopsy (mm^2); and the area of proper synovial tissue (mm^2). These findings were compared with the histological findings described in the pathology reports, which were the gold standard. In case of disagreement between rheumatologist and pathologist, an expert reader (DV) was responsible for the final decision. We considered the biopsy successful when synovial tissue was seen at the histological examination. Good quality was defined as the following: sufficiently sized (> 0.5 mm^2)[26] preserved tissue allowing assessment by pathologists and presence of lining layer.

Statistical analysis. Mean and median were used to describe quantitative data according to their Gaussian distribution. Number and percentage were used to report qualitative data. Fisher's exact test had been used to compare percentage. K coefficient calculation was used to assess the interobserver reliability for histological analysis. A p value < 0.05 was considered as statistically significant. All statistics were made through GraphPad Prism 6.0 software.

RESULTS

Patient characteristics. Seventy-four patients underwent 76 US-guided synovial biopsy procedures. Demographic and clinical features of patients included in our study are shown in Table 1. Mean age was 57 years (range 13–86 yrs) and there were 39 men (52.7%). Most of the patients presented with an undifferentiated chronic monoarthritis (54.1, n = 40). The number of joints and their percentages among the patients were as follows: 46 knees (60.5%), 6 ankles (8%), 6 wrists (8%), 5 shoulders (7%), 4 hips (5%), 2 elbows, 2 sternoclavicular joints, 2 metatarsophalangeal joints, 1 pubic symphysis, 1 acromioclavicular joint, and 1 peroneal tenosynovitis. Patients were mainly referred to rule out the diagnosis of septic arthritis (82.4%, n = 61).

Table 1. Demographic and clinical features of the patients. Values are n (%) unless otherwise specified.

Variables	Values
Female	35 (47.3)
Male	39 (52.7)
Age, yrs, mean (range)	57 (13–86)
Indications	
Undifferentiated chronic monoarthritis	40 (54.1)
Acute monoarthritis	18 (24.0)
Chronic undifferentiated oligoarthritis	7 (9.3)
Chronic polyarthritis	6 (8.0)
Chronic bursitis	1 (1.3)
Chronic tenosynovitis	1 (1.3)
Acute polyarthritis	1 (1.3)

US-guided biopsy procedure was safe and successful. Overall, 62 of the 76 biopsies (81.6%) yielded synovial tissue according to the pathologists' analysis. Within these 62 biopsies, the main histological finding was a nonspecific inflammatory mononuclear cell infiltrate (lymphocyte, monocytes, and plasma cells; 81%, n = 50). A mild neutrophil infiltrate was seen in 24 (50%) of these biopsies. Eight (13%) biopsies showed specific histological lesions (Figure 1). A major neutrophil cell infiltrate consistent with a septic arthritis was found in 2 cases. Two biopsies showed a synovial infiltration of positive Perl's siderophages (villonodular synovitis). One biopsy showed vascular and interstitial deposits of Sirius red staining protein consistent with amyloid light-chain amyloidosis. One biopsy contained tophi surrounded by lymphocytes and giant cells. One biopsy found dystrophic cartilage inside the synovial tissue, consistent with synovial osteochondromatosis. One biopsy showed an articular localization of lymphoma. Four biopsies retrieved normal synovial tissue without any inflammatory cell infiltrate (Table 2).

The 14 failed biopsies occurred in both small and large joints. Percentages of failed biopsies per joint were as follows: glenohumeral joints (n = 3/5, 60%), ankle (n = 3/6, 50%), hip (n = 2/4, 50%), wrist (n = 2/6, 33.3%), elbow (n = 1/2, 50%), sternoclavicular joint (n = 1/2, 50%), and knees (n = 2/46, 4.3%). In case of failure, histological analysis showed mainly connective and adipose tissue in 10 cases, fibrin and leukocytes in 3 cases, and tendon in 1 case. Tolerance per procedure was excellent. One patient taking acetyl salicylic acid at the time of the biopsy presented with a hemarthrosis 48 h after the procedure, which resolved following arthrocentesis within 1 week.

Overall, 10 (16.2%) definitive diagnoses were made based only on histological or PCR analysis of synovial tissue.

Longterm followup (mean 34.9 mos, range < 1 mo to 96 mos) and final diagnosis were available for 67 of the 74 patients, and 7 were lost to followup (Table 3). No patient has since been diagnosed with an infectious arthritis or villonodular synovitis or developed any complication of the biopsy procedure. In 3 of the cases where the diagnosis remained unclear despite the US-guided biopsy and in 2 cases of failed biopsy, patients underwent secondary procedures. One of them had an arthroscopic examination after the US-guided biopsy and 4 of them had an open synovectomy. One synovectomy allowed a diagnosis of chondrocalcinosis on pathological examination.

Quality and quantity of the synovial tissue retrieved after US-guided synovial biopsies. Finally, the synovial tissue retrieved was assessed for quality and quantity. For this purpose, we analyzed the histological characteristics per sample retrieved during the procedure (Figure 2). The median number of samples taken per patient was 1 (interquartile range 1–3), leading to a total of 125 samples available for analysis. Mean length and width of the biopsy samples were 6.34 mm (± 3.60) and 1.70 mm (± 0.77), respectively. The mean total area of the samples was 8.77 mm^2.

Biopsies showed synovial tissue at the histological examination in 102 samples (80.1%). The average area of synovial tissue in these samples was 6.36 mm^2, corresponding to 72.5% of the total area of biopsied tissue. The other types of tissue present on these biopsies were connective tissue in 101 cases (80.8%), adipose tissue in 42 cases (33.6%), tendon in 14 cases (11.2%), and fibrin in 24 cases (19.2%). The 23 samples retrieving no synovial tissue were composed of fibrin in 15 cases (12%), conjunctive and adipose tissue in 17 cases (13.6%), tendinous tissue in 3 cases (3.15%), cartilage in 3 cases (3.15%), and muscle in 1 case (0.8%).

Synovial lining layer was found in 92.6% of the successful biopsies.

We compared our histological final findings regarding presence or absence of synovial tissue with those of the pathologist and found 97.1% of agreement. Interobserver reliability for presence/absence of synovial tissue was high, with a κ coefficient of 0.90 (95% CI 0.763–1.000).

DISCUSSION

Because synovial tissue analysis has been mostly used for research purposes, our study highlights the potential diagnostic involvement of synovial biopsy in routine clinical practice. To develop this technique in clinical practice, the patient needs to be offered a well-tolerated technique with an acceptable rate of success.

To date, 2 different techniques of US-guided synovial biopsies have been described. Both have been shown to be safe and well tolerated by the patients[22]. The first method requires a single portal with a flexible or rigid biopsy forceps. The portal is directly introduced inside the joint to perform biopsies[27]. The second technique, as outlined above, requires an empty coaxial needle that is inserted inside the joint and a semiautomatic guillotine-type needle that is inserted through the coaxial. The procedure is not painful after local anesthesia and once the coaxial needle is settled, and this technique

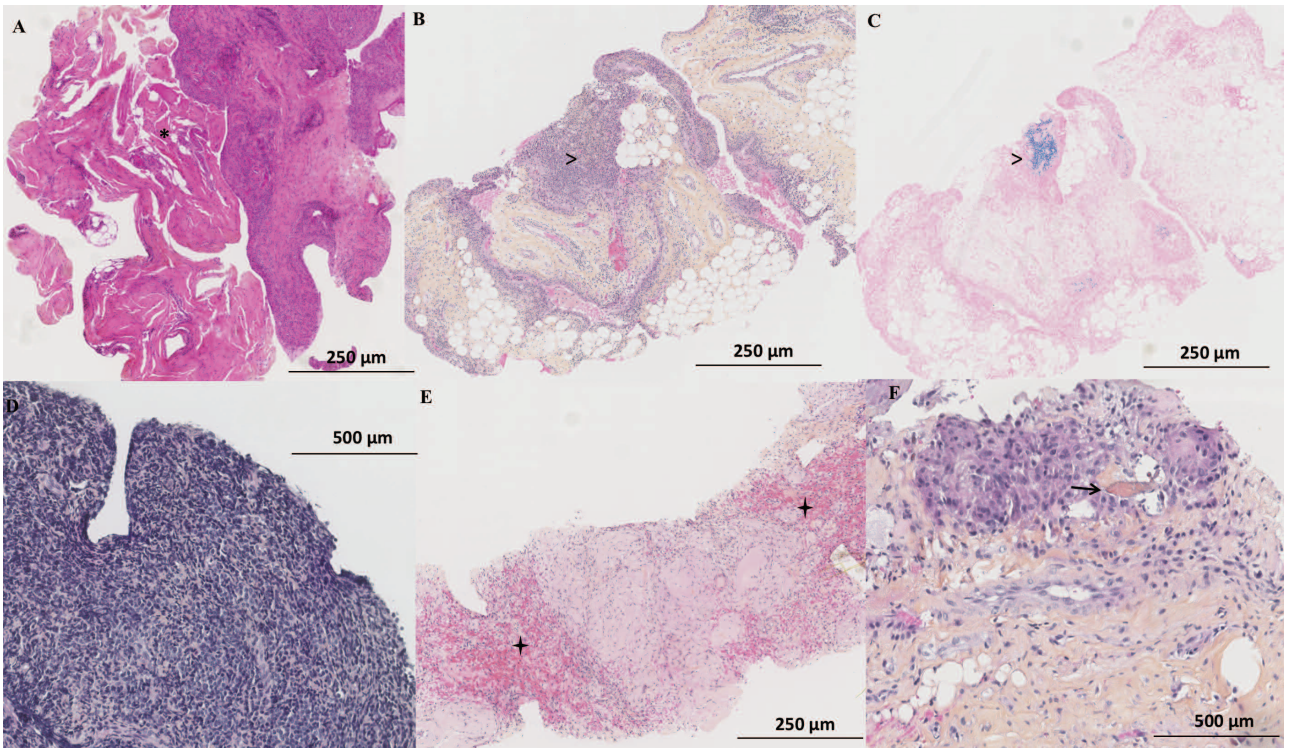

Figure 1. Synovial biopsies of 5 specific histological lesions. (A) Fibrin deposits with neutrophils infiltrate (asterisk). Septic arthritis. (B) Villonodular synovitis. H&E staining showing siderophages (arrowhead). (C) Villonodular synovitis with Perl's staining showing siderophages (arrowhead). (D) Cell infiltrate within synovial tissue in an articular lymphoma. (E) Amyloids (crosses) revealed by Sirius red staining. Amyloid light-chain amyloidosis. (F) Micro tophi surrounded by giant cells and lymphocytes (arrow) leading to gout diagnosis.

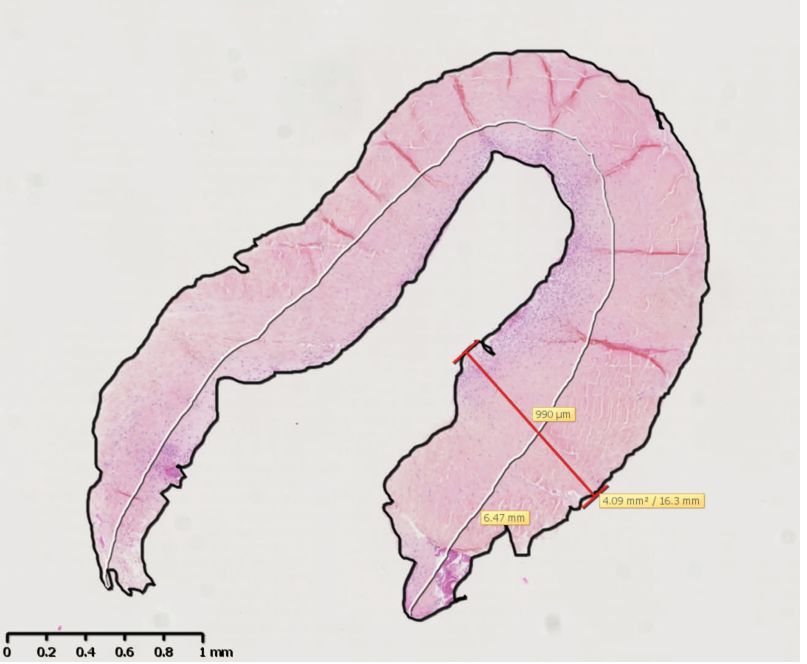

Figure 2. Example of the sample histological analysis. Black line is the global area measurement, red line is the width measurement, and white line in the length measurement.

Table 2. Histopathological analysis.

Histopathological Findings	No. Biopsies
Normal synovium	4
Inflamed synovium	50
Cell infiltrate:	
Lymphocytes	50
Plasma cells	22
Neutrophils	24
Specific lesions	8
Villonodular synovitis, shoulder and knee	2
Infectious arthritis*	2
Amyloid arthritis, knee	1
Articular localization of mantle B cell lymphoma, ankle	1
Gout, first MTP	1
Osteochondromatosis, knee	1
Failure	14

* Two infectious arthritis sites (hip, ankle) treated on typical histological aspect with no relapse after 6 weeks of empiric antibiotics. MTP: metatarsophalangeal.

Table 3. Overall final diagnosis after followup. Values are n (%).

Final Diagnosis	Values
Rheumatoid arthritis	7 (9.5)
Ankylosing spondylitis	2 (2.7)
Psoriatic arthritis	5 (6.8)
Degenerative arthropathy	12 (16.2)
Crystal arthropathy	4 (5.4)
Chondrocalcinosis	2 (2.7)
Gout	3 (4.1)
Villonodular synovitis	2 (2.7)
Osteochondromatosis	1 (1.4)
Giant cell arthritis	1 (1.4)
Behçet disease	1 (1.4)
Latent infectious arthritis	4 (5.4)
Others	2 (2.7)
Undifferentiated arthritis	21 (28.4)
Lost to followup	7 (9.5)
Total	74 (100)

allows retrieving several biopsies during the same procedure without moving the coaxial needle. To our knowledge, 5 other studies reporting their experience of US-guided synovial biopsies have been published to date. Two reported their experience using the first technique[27,28], 1 a technique using semiautomatic guillotine-type needle without coaxial needle[23], and 2 using the second technique outlined above[24,25].

The success rates in retrieving synovial tissue described by other authors vary from 89% to 100%[23,25,27,28,29]. The rate of success in our cohort was slightly lower, for several possible reasons. Our patients comprised a heterogeneous group regarding clinical features and the joints that were biopsied. There were also minor differences in techniques in 2 of the studies referended above. Moreover, no biopsies were done prior to 2007 in our center and 43% of the failures occurred within the first 18 months (6 of the 14 total failed biopsies), especially in more challenging joints such as the ankles, wrists, hips, or shoulders. This might correspond to the operator learning curve. However, our success rate remains equivalent to the highest rates described for synovial biopsies with blind needle (48%–85%)[30].

In our study, patients were referred mostly by their general practitioner or their rheumatologist with no clear diagnosis despite multiple punctures for SF analysis and computed tomography (CT) scans or magnetic resonance imaging (MRI). Because low-grade infection often evolves in chronic arthritis with joint destruction, it is very important to pursue atypical germs such as tuberculosis, fungi, *T. whipplei*, and *Borrelia burgdorferi*. Moreover, some of the more common bacteria can be responsible of low-grade infection in some rheumatic patients because of immunosuppression. In all these situations, the biopsy allows a quick bacteriological examination with Gram staining, then later culture and PCR analysis for atypical organism. Indeed, 2 patients were diagnosed with Lyme and articular Whipple disease by PCR analysis. Interestingly, the Whipple PCR that was performed on the SF collected during procedure was negative. There is 1 previously reported similar case in which SF PCR failed to demonstrate the presence of *T. whipplei*, but the synovial tissue PCR was positive[31].

Bacterial culture in both SF and synovial membrane is a key method for septic arthritis diagnosis. However, using those methods, infectious agents were isolated in only 41.2% of the patients (38.7% of SF and 23.5% of synovial membrane positive cultures)[32]. Therefore, histological synovial cell infiltrate analysis is also relevant for septic arthritis assessment. A neutrophilic cellular infiltrate has been shown to be highly associated with septic arthritis[33]. That presence inside the synovial tissue is considered sufficient for the diagnosis of septic arthritis. Regarding our data, the diagnosis of septic arthritis was established following the histological examination of 2 patients. Interestingly, after empiric antimicrobial therapy began in these 2 patients, no relapse occurred within at least 6 years of followup for both. Our analysis can also be useful in fibrocartilaginous joints (acromioclavicular, pubic symphysis), in which fluid is rarely found even in cases of inflammation. Further, we can conclude from our data that no patient of our cohort has been further diagnosed with infectious arthritis. This technique can, therefore, be considered reliable to rule out septic arthritis assessment, thus permitting local treatments such as steroid injections.

More rarely, synovial biopsy can be performed for synovial tumor assessment, especially villonodular synovitis or osteochondromatosis. The 2 patients in our cohort diagnosed with villonodular synovitis underwent surgical synovectomy. The histological examination of the tissue confirmed those findings.

For the biopsy to be useful in clinical practice, the quality

of the biopsies retrieved has to be good. Quality of a synovial biopsy has been defined for research recently[23]; however, no definition has yet been given for the clinical setting. In our study, we defined good quality as the following: sufficient size defined by synovial tissue area > 0.5 mm^2, preserved tissue allowing assessment by pathologists, and presence of lining layer. In our cohort, the quality was good enough to allow a histological examination in all biopsies retrieving synovial tissue. Lining layer was found in 92.2% of the cases. In some instances, the lining layer could be identified but was not connected to the main biopsy. This separation may have occurred during tissue processing or may represent separation due to fibrin deposition in case of ulcerative synovitis.

No study has thus far demonstrated a predictive clinical value for histological findings in identifying those with early arthritis or those who will go on to have an aggressive disease course[6,9,10]. Indeed, multiple studies tried to match histological cell infiltrate patterns with different rheumatologic conditions. There are undeniable differences between rheumatoid arthritis (RA) and psoriatic arthritis (PsA)[34,35], RA and ankylosing spondylitis (AS)[36], and RA and osteoarthritis (OA)[37,38]. OA synovial membrane is known to show less inflammatory infiltrate and less vascularity than its inflammatory counterparts in RA, PsA, and AS. RA synovium has shown a higher number of B cells and more rarely ectopic follicles, helping in the diagnosis. The high-grade synovitis features are more consistent with RA[39]. However, despite those differences, no algorithm is able to predict the evolution in early arthritis[33].

Given this, the histopathologist was rarely able to determine the type of inflammatory arthritis. However, by ruling out or confirming infectious arthritis or synovial tumor, it is clear that US-guided synovial biopsy is helpful for patients with remaining unknown diagnosis despite SF analysis, radiograph, CT scan, and/or MRI examinations. In our setting, synovial biopsies allowed the treatment of some patients by providing a definite diagnosis. They also indicated the use of systemic immunosuppressive or local therapies such as intraarticular steroid injections.

We acknowledge that our work has limitations, such as the monocentric design of our study. The biopsies were performed by a trained investigator, and the pathologists in our center had expertise in biopsy assessment. This could be a limit for the generalization of those results. Although all patients had 3 to 8 biopsies taken, 55% of them had a single fragment sent to the pathology department. This might be another limitation.

Finally, one of the main concerns about any procedure is its tolerance. In our cohort, 1 patient treated with salicylic acid presented with knee hemarthrosis 48 h after the procedure. Overall, in our cohort, the adverse effects rate was 1.35% (95% CI –1.3 to 4.0, 1/74) and no severe adverse event occurred (life-threatening, leading to patient admission to hospital, or with a risk of sequelae). The arthroscopic biopsies have the advantage to be retrieved under direct vision and therefore allow a histological analysis of the inflamed areas within the joint. However, this procedure is more invasive and has multiple adverse effects (joint infection, wound infection, hemarthrosis, deep venous thrombosis, neurological damage, thrombophlebitis)[40].

Our study highlights the potential diagnostic involvement of synovial biopsy. To our knowledge, ours is the first study describing indications, tolerability, rate of success, diagnosis involvement, and quality of US-guided synovial biopsy in a clinical setting. US-guided synovial biopsy was performed in clinical practice in a heterogeneous population with variant clinical features. The success rate of the procedure remains high, with only rare and minor complications; 13.3% achieved a definitive diagnosis leading to a specific treatment. In other patients, we could rule out the diagnosis of septic arthritis. Therefore, this procedure should be used not only for research purposes but also routinely in undifferentiated arthritis.

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