

## Synovial Biopsy: Role in Diagnosis and Management of Unilateral Synovitis Knee

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### What to Learn from this Article?

Minimally invasive method for differentiating between tubercular and early arthritis.

### Abstract

**Background:** Monoarticular synovitis is relatively difficult to diagnose and delay in diagnosis leads to poor outcomes. Long-term occurrence of synovitis can result in degeneration of the joint due to the release of inflammatory cytokines which resulted in increased synthesis of matrix metalloproteinases and decreased expression levels of inhibitors. Tubercular synovitis and early arthritis are difficult to diagnose due to the atypical clinical presentation and lack of specificity in diagnosis.

**Materials and Methods:** This study was conducted from March 2015 to September 2016, where 50 patients underwent synovial biopsy and biopsy reports were evaluated. 44 patients underwent arthroscopic-assisted synovial biopsy and open biopsy was done in 6 patients. Samples obtained were sent for histopathological examination. The paired *t*-test was used to compare serial changes in pain intensity using numeric pain rating scale.

**Results:** Out of 50, 21 (42%) cases were diagnosed as inflammatory synovitis, 9 (18%) cases as tubercular synovitis, 6 (12%) cases of osteoarthritis, and 14 (28%) cases of non-specific chronic synovitis. The mean age of patients was 40.32 years, with 58% of the patients presenting in the range between 36 and 50 years. As a diagnostic aid, the role of synovial biopsy was found to be significant ( $P < 0.05$ ).

**Conclusion:** Monoarticular arthritis should be thoroughly investigated rule out infectious or metabolic diseases for their destructive potential to destroy cartilage rapidly. Arthroscopic-assisted synovial biopsy has added advantage as it permits macroscopic evaluation of the synovium, and cartilage inadequacy could also be noted along with serving as therapeutic purposes in some cases.

**Keywords:** Monoarticular, synovitis, synovial biopsy, numeric pain rating scale.

### Introduction

Synovitis is the medical term for inflammation of the synovial membrane. The main purpose of this synovium is to provide smooth motion by preventing the bones of the leg from grinding together when the knee is moved. Knee synovitis occurs when the synovial membrane which lines and lubricates the knee joint, becomes inflamed. This condition is usually painful, particularly when the joint is moved.

Common causes of synovitis include infection (septic arthritis), direct joint trauma, allergic reaction, gout, overuse syndromes, systemic autoimmune inflammatory diseases (rheumatoid arthritis [RA]), osteoarthritis, pigmented villonodular synovitis, and idiopathic. Synovitis may occur in association with other systemic diseases such as lupus, psoriasis, and other conditions. Early diagnosis and timely institution of antitubercular treatment (ATT) is crucial as delay leads to irreparable damage to the



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joint and restriction of joint mobility. Establishing the diagnosis of tuberculosis (TB) beyond doubt is very important when considering the cost and duration of treatment and the effects of delayed treatment including psychosocial implications [1]. Even in disease-endemic countries, only suspicion and imaging results are not accurate enough to diagnose and treat joint TB. Sensitivity of most tests is very low in joint TB, as there is dilution of tubercle bacilli in synovial fluid [1, 2]. Conventional microbiological methods such as smear and culture have low sensitivity and specificity, especially in synovial TB due to the paucibacillary nature of disease [1, 3]. In addition, the culture of *Mycobacterium tuberculosis* is time-consuming, taking 6-8 weeks for the growth to appear and much longer time for positive growth, especially in paucibacillary cases such as joint TB [4, 5, 6].

Common conditions, such as RA, rarely cause diagnostic problems as they cause symmetrical joints involvement. Monoarticular synovitis is, however, difficult to diagnose and often times, routine X-ray and pathological investigations including synovial fluid analysis are unable to give conclusive result. Synovial biopsy is then helpful in distinguishing between various etiologies such as infective, traumatic, or crystal induced [7, 8]. Synovitis is usually a secondary condition, which may also be caused by an injury to the knee joint or cancer (synovial sarcoma). For this reason, it is important that suspected cases of synovitis are investigated thoroughly.

### Materials and Methods

This prospective study was conducted on patients attending the Orthopedic Outpatient Department and Emergency Department of S.N. Medical College, Agra, from March 2015 to September 2016 presenting with pain and swelling of the single knee, not responding to nonsteroidal anti-inflammatory drugs (NSAIDs). All participants were recruited after taking written informed voluntary consent. A detailed history and examination (general systemic and local examination) along with investigation was carried out before doing procedure.

Patients were selected on the basis of strict inclusion and exclusion criteria's.

#### Inclusion criteria

- Patients with chief complaint of knee pain and swelling with synovitis not responding to NSAIDs for at least 4-6 weeks
- Patient from both sex aged 18-60 years
- Cases where sufficient conservative trial has failed to give the result.

#### Exclusion criteria

- Age <18 years and >60 years
- Pregnant and lactating women
- Patient with multiple joint involvements
- Patient with low platelet count (<70,000/cumm)
- Advanced radiological osteoarthritic changes.

All good clinical practice guidelines were followed and ethical clearance taken from hospital medical research committee, who

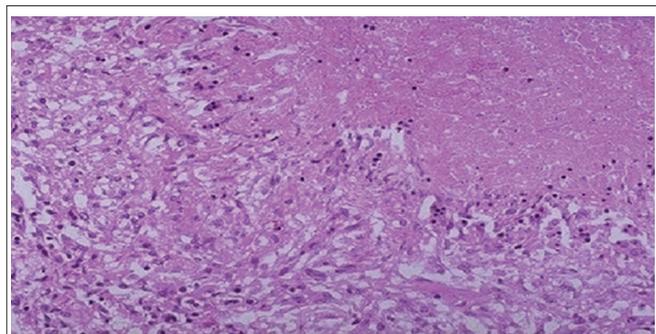
approved the study. The initial aim of the evaluation of a patient with joint pain was to localize the source of the joint symptoms (bone or soft tissue) and to determine the type of pathophysiologic process responsible for their presence. Knee aspiration was done and fluid analysis sent for examination, which was found to be equivocal. Patient examined carefully to rule out the involvement of any other joint and thorough history taken. Pain graded on scale of 0-10 (numeric pain rating scale) and if restriction of movement present, then measured.

Synovial biopsy results were studied and by interpreting histopathological findings diseases were diagnosed. On average, it took 15-18 days for histopathology reports to come. Treatment is started as per the standard measures against any causative condition diagnosed. Patients were kept in follow-up and closely monitored. For first 2 months, patients came on every 15 days after which they were followed every month. Pain grading was done in follow-up to see improvement of patient and pain intensity compared at follow-up of up of 3 months to before treatment.

Out of 50 patients, 44 underwent arthroscopic synovial biopsy and remaining 6 underwent open synovial biopsy.

#### Arthroscopic synovial biopsy procedure

After general investigations, procedure is planned and all surgeries were done under spinal anesthesia. Arthroscopic evaluation was performed by a senior arthroscopic consultant of our institution. Patient was laid supine on OT table, after giving spinal anesthesia and tourniquet applied over respective thigh. Part painted and draped as such, so knee can be flexed and extended during procedure. Standard anteromedial and anterolateral portals were used. Anterolateral portal made during the flexion of the knee at 90° and 8 mm skin incision made over the lateral joint line and another skin incision of 8 mm made over medial joint line for the anteromedial port. Arthroscope camera and arthroscope probe inserted through above-made ports. Irrigation fluid switched on before switching on the light source to avoid thermal damage. On arthroscopic evaluation, joint was thoroughly inspected through standard portals. Sample for synovial biopsy was taken concentrating on suspected focal areas of pathology in synovium. Biopsy is obtained from different places such as suprapatellar pouch, medial and lateral gutter, and from patellar margins. After



**Figure 1:** Necrotizing granulomatous inflammation, comprising of caseous necrosis, surrounded by epithelioid cells, histiocytes, and lymphocytes.

**Table 1: Age wise distribution**

Age in years	Number of cases (%)
18-35	14 (28)
36-50	29 (58)
51-65	6 (12)
>65	1 (2)
Total	50 (100)

**Table 2: Incidence of different diseases as assessed by synovial biopsy**

Diseases	Number of cases (%)
Rheumatoid arthritis	21 (42)
Tubercular arthritis	9 (18)
Osteoarthritis	6 (12)
Non-specific chronic synovitis	14 (28)
Total	50 (100)

the final biopsy sample is taken, the skin is stitched if needed and covered with sterile wound dressing. Arthroscopic partial or subtotal synovectomy was done if needed. Synovial biopsy material is sent for histopathological examination, after packing it in formalin glass bottle.

Patients were regularly followed up clinically, radiologically, and with help of laboratory investigations such as C-reactive protein (CRP) and erythrocyte sedimentation rate. At the end of 3 months, CRP levels were found to be nearly normal. Pain intensity was graded at 3-month follow-up using numeric pain rating scale. Pain intensity scores at 3-month follow-up were compared with pain intensity scores of pre-treatment.

### Results

Out of the 50 cases, we studied monoarticular joint involvement of knee joint were subjected to synovial biopsy investigations, and diagnosis was made on basis of histopathological picture. Figure 1 showing typical tubercular histopathological picture: Necrotising granulomatous inflammation, comprising of caseous necrosis, surrounded by epithelioid cells, histiocytes and lymphocytes. Both rheumatoid ( $n = 21$ , 42%) and tubercular ( $n = 9$ , 18%) were found to be more common compared to other etiologies. Next common etiology observed in our study was chronic non-specific synovitis ( $n = 14$ , 28%). There were 6 cases of osteoarthritis ( $n = 6$ , 12%).

- Rheumatoid was found to be most common etiology, with 21 patients (42%) out of 50 patients
- 6 patients (12%) were found to be suffering from osteoarthritis
- 9 patients (18%) were of tubercular arthritis
- The mean age of patient with synovitis knee, who underwent synovial biopsy was 40.32 years
- Maximum numbers of patients were from age group 36-50 years ( $n = 29$ , 58%)
- The period of hospitalization required ranged from 2 to 3 days and post-operatively, weight bearing and knee movement were allowed as tolerated by patient. No significant complications occurred in all 50 patients post-synovial biopsy

- Pain intensity improved during follow-up with time as graded according to numeric pain rating scale compared to pre-treatment
- Paired *t*-test was applied for comparing pain intensity at pre-treatment and at 3-month follow-up was found  $<0.05$  which is significant
- Diagnosed cases were managed accordingly and responded well to treatment and were monitored during follow-up.

### Age-wise distribution

The youngest patient age was 19 years and oldest patient age was 66 years. 29 patients were in the age group of 36-50 years (Table 1). The average age of patient was 40.32 years.

### Incidence of different diseases as assessed by synovial biopsy

Among the 50 patients, 21 patients were diagnosed with RA, 9 patients with tubercular arthritis, 6 patients of osteoarthritis, and 14 patients of non-specific chronic synovitis (Table 2).

### Discussion

Inflammatory synovitis of the knee is one of the most common clinical presentations in day-to-day orthopedic clinical practice. The etiology remains unclear in many cases. Routine laboratory and radiological investigations in monoarticular joint lesion are often equivocal. Diagnosis of arthritis is often made clinically and treatment is given empirically, due to which results are sometimes disappointing for both patients and doctors.

In our study, synovial biopsy was performed in 50 patients to obtain a sample of the tissue directly under vision from the suspected site of pathology. Synovial tissue was obtained arthroscopic assisted in 44 patients and by open biopsy in 6 patients.

In our study, male-to-female ( $29 + 21 = 50$ ) ratios were 1.38:1. According to etiology, it was 3.2:1 in rheumatoid synovitis, 7:1 in tuberculous synovitis, and 4:7 in chronic non-specific synovitis. The average age of patients was 40.32 years. Youngest patient in this study was 19 years of age and oldest was 66. Maximum cases of unilateral synovitis were found in 4<sup>th</sup> and 5<sup>th</sup> decades. The maximum number of synovitis occurred in the age group of 36-50 years, 30 patients (60%). In Raghunandan *et al.* [9] study, there were 25 males and 15 females with male: female ratio of 5:3.

Histological examination by synovial biopsy was found to be of significant diagnostic value. It was helpful in confirming the diagnosis of the underlying pathology after clinical evaluation in 36 cases (72%) including RA, tubercular arthritis, and osteoarthritis. In remaining 14 cases, no specific pathology was found on histopathology and they were declared as chronic non-specific synovitis. In cases where the clinical diagnosis was non-specific, histological examination of synovial biopsy helped in reaching the final diagnosis.

In our study, most common etiology was found to be rheumatoid followed by cases of non-specific chronic synovitis. RA was found in 21 patients (42%) out of 50 patients. In Singhal *et al.* [10] study, RA was found in 11 patients (22%) out of 50 patients. In

Chen *et al.* [11] study, 39 (52.9%) cases of RA were found out of total 71 patients. In Raghunandan *et al.* [9] study, 5 (12.5%) cases were diagnosed with RA. In Sundararajan *et al.* [12] study, 7 (20.58%) cases were diagnosed with RA out of total 34 patients. In Vijay and Doddikoppad [13] study, RA was found in 4 patients (4.8%). Early diagnosis of RA with help of histopathology helps in improving prognosis of disease. There is evidence that the very early introduction of disease modifying therapy inhibits progressive structural damage maximally. Clinician exploiting this “window of opportunity” therefore requires very early indicators of the diagnosis and outcome in patients who present with an undifferentiated inflammatory arthritis [14]. Serial synovial biopsies in open therapeutic studies and in randomized clinical trials showed that the immunohistological features of RA and other arthropathies changes after treatment with disease modifying antirheumatic drugs (DMARDs). It has been established that DMARDs therapy reduces the rate of progressive joint damage more effectively when introduced within 6 months of the onset of symptoms. It is now standard practice to introduce conventional DMARDs such as methotrexate, and even targeted biological therapies, as the first-line treatment in patient with RA. Although there is no diagnostic role in early RA, synovial biopsy and tissue analysis may provide important prognostic information.

In our study, 9 (18%) cases were diagnosed as tubercular arthritis. These were more commonly found in younger population. In our study, males were more commonly affected than females with ratio of 7:1. In Singhal *et al.* study, tubercular arthritis was found in 13 patients ( $n = 26\%$ ) out of 50 patients. In Raghunandan *et al.* study, 6 cases (15%) were of tubercular arthritis out of 40 patients. In Chen *et al.* study, 5 (6.5%) cases of TB arthritis were found out of total 71 patients [15]. In Sundararajan *et al.* study, 7 (20.58%) cases were diagnosed with tubercular arthritis out of total 34 patients. In Vijay and Doddikoppad study, 15 patients (18.07%) were found of tubercular arthritis. Another study was conducted on 70 cases of tuberculous synovitis by Sant and Bajaj [16] and was published in 1992. In this study, maximum number of cases were found in the age group of 11-30 years (58.58%) with a male preponderance. The knee joint was found to be most commonly (57.12%) affected. Diagnosis of tuberculous synovitis was possible clinically in 75.72% and radiologically in 67.14% of cases only.

Such high percentage of tubercular arthritis patients were found, as our country is endemic for TB. As definitive treatment with antitubercular medication is available, diagnosis of early tubercular synovitis is very essential to prevent cartilage damage. Definitive tissue diagnosis and timely treatment help in achieving excellent results in 3-4 months period [17].

In our study, 14 cases were diagnosed as chronic non-specific synovitis, out of 50 patients. In Singhal *et al.* study, chronic non-specific synovitis was found in 10 patients out of 50 patients (20%). In Raghunandan *et al.* study, 25 cases (62.5%) were of chronic non-specific synovitis out of 40 patients. In Chen *et al.* study, 3 (4.054%) cases of unknown causes were found out of total 71 patients. In Vijay and Doddikoppad study, 59 patients (83.099%) were found of chronic non-specific synovitis. In

Sundararajan *et al.* study, 9 (26.47%) cases were diagnosed with chronic non-specific synovitis out of total 34 patients. Chronic non-specific synovitis is also known as monoarthritis of unknown origin. 80% of these can go into complete remission over 2 years with just conservative treatment. This high occurrence of cases of chronic non-specific synovitis in our study may represent an early stage of RA, in which the disease is still in the stage of evolution without a fully developed picture of RA, some patients may be due to early osteoarthritis not fulfilling histopathological and radiological features for its diagnosis. If these patients are closely followed up and repeat biopsies are carried out in due course, they may help with specific diagnostic features or patients may have self-limited disease or may undergo complete therapeutic remission.

In our study, 6 cases (12%) were diagnosed as osteoarthritis, out of 50 patients. Apart from these four diseases diagnosed in our study, synovial biopsy also helps in diagnosis of other diseases such as pigmented villonodular synovitis, septic arthritis, gouty arthritis, sarcoidosis, osteochondromatosis, hemochromatosis, amyloidosis, seronegative spondyloarthropathy, and any synovial carcinoma.

Arthroscopy is an excellent tool for visualizing and evaluating the condition of the synovium macroscopically, and the suspected areas of increased activity were chosen for biopsy. In a study by Latosiewicz *et al.*, 82 patients underwent arthroscopic synovial biopsy in the course of treatment for chronic knee synovitis. It concluded that arthroscopic synovial biopsy increases diagnostic potential in the synovitis of unclear etiology. In arthroscopic synovial biopsy, gross examination gives added advantage in making a diagnosis, such as visualizing subchondral bone defect. It has added advantage of performing therapeutic procedures along with biopsy at same time and knee joint lavage could be done during biopsy. Arthroscopic partial or subtotal synovectomy may be done if needed. Arthroscopic synovial biopsy was also better in terms of post-biopsy recovery as incision was only made for port entry compared to open biopsy.

Results of histopathology arrived in 15-18 days. Arthroscopic findings can alter or add to the treatment plan which includes surgical tissue resection or medical treatment such as DMARDs to the current treatment. In our study, despite thorough arthroscopic and microscopic evaluation, we were not able to accurately diagnose in 28% of patients, which were finally diagnosed as chronic non-specific synovitis.

### Conclusion

The present case series demonstrates that synovial biopsy can be cost-effective diagnostic tools with therapeutic consequences. This is especially so when the differential diagnosis consists of a disease with characteristic histological hallmarks. Synovial biopsy is useful and cost-effective in monoarticular synovitis cases, especially where advanced radiological facilities such as MRI are not available to general population. In terms of diagnostic accuracy, histopathology was found to be the most economical, accurate, and time-saving method.

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