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Clinico-morphological Correlation and Diagnostic Accuracy of Synovial Biopsy in Synovitis: Experience in Tertiary Care Hospital

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Abstract

Synovium is a specialized mesenchymal tissue in which varied pathological lesions can occur, but most common are non neoplastic lesions. *Aim of the Study:* To determine histopathological spectrum of non-neoplastic lesions of synovium and to correlate the clinical and histopathological diagnosis in our tertiary care hospital. *Materials & Methods:* Prospective study of 65 synovial biopsy samples. Patient's complete clinical data, radiological findings, biochemical and serological parameters were obtained. Synovial fluid analysis was done in available cases. Histopathological examination of synovial biopsy tissue was done with routine and special histochemical stains wherever necessary. Statistical analysis for sensitivity, specificity and diagnostic accuracy was done. *Results:* We observed arthritis was common in 5th decade with Male-Female ratio of 1.7: 1. Most were monoarticular disease with the knee joint commonly affected. The common clinical manifestation was joint pain and swelling. The most common lesion was chronic nonspecific synovitis followed by osteoarthritis, tuberculous arthritis, rheumatoid arthritis and septic arthritis. One case of pigmented villonodular synovitis [PVNS], gouty arthritis and ochronotic arthritis were observed in our study. In our study, the diagnostic accuracy of synovial biopsy in comparison with clinical impression was 85% with 73% sensitivity, 97% specificity, 96% positive predictive value and 78% negative predictive value, 27%false negative rate and 3% false positive rate. *Conclusion:* In our study, we observed that synovial biopsy is cost effective and offers immense help to clinicians in providing appropriate treatment for patients, especially in long standing and subtle inflammatory lesions.

Keywords: Synovial Biopsy; Synovitis; Histopathology; Correlation; Diagnostic Accuracy.

Introduction

Synovium is a soft tissue made up of macrophage and fibroblast like synoviocytes, resting on the loose fibrofatty connective tissue with few capillaries. It lines synovial joints, tendon sheath and bursa providing nutrients to avascular structures such as cartilage. Less than 5 ml of synovial fluid present in these joints forms an interface between the surfaces of the articular cartilage allowing friction free movement of the articular surfaces [1-3].

Neoplastic lesions of synovium are rare as the cells lining the joint spaces are not transient and doesnot undergo frequent mitosis [4]. The non-neoplastic lesions are much more common in the synovim. Inflammatory synovial lesions classified into two types: infectious arthritis of known microbial etiology and inflammatory arthritis of unknown etiology such as rheumatoid arthritis, Still's disease, seronegative spondyloarthopathies, psoriatic arthritis, reiters syndrome and sarcoidosis [5].

Joint pain is the commonest chief complaint of the patient in the orthopaedic practice in all ages without gender predilection due to varied causes. Clinically, etiology of arthritis cannot be accurately diagnosed. The histopathological changes in the synovium are characteristic for specific etiologies like tuberculous

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arthritis, rheumatoid arthritis. Synovial biopsy is foremost research tool at the disposal of facilities equipped with arthroscopic instrumentation for specific diagnosis of disease. Identifying specific etiology of arthritis using clinical and laboratory findings is essential to provide definite treatment and avoid indiscriminate use of analgesics and antibiotics.

The objectives of the study are to determine histopathological spectrum of non-neoplastic lesions of synovium and to correlate the clinico-histopathological diagnosis in our tertiary care hospital, Kattankulathur.

Materials and Methods

The materials for the present study, synovial fluid and biopsy were collected from the orthopaedic department. A prospective study was conducted for a period of two years [June 2014 – August 2016] after getting institutional ethical committee clearance. During this period 65 samples were received. The relevant clinical details such as age, gender, joints involved and duration of illness were obtained. Clinically and radiologically diagnosed non-neoplastic lesions were only included. Neoplastic lesions and samples with inadequate or autolysed samples were excluded from this study.

The synovial fluid was available only in 32 cases, for rest of the cases the either the samples were inadequate or unavailable. The synovial fluid was subjected to physical, biochemical, cytological & microbiological examination, on immediately receiving the sample. If there would be delay in processing the sample was refrigerated at 4°C.

The physical examination includes volume, color, appearance, viscosity, mucin clot test and wet mount. Synovial fluid classified into four groups [I -IV] [15] based on its gross appearance [6]. Synovial fluid cell count of WBC and RBC was done after centrifuging the sample at 2000 to 4000 rpm and air dried smears were prepared followed by Leishman staining according to standardized operating procedure. The biochemical parameters like fasting blood glucose & synovial fluid glucose, protein and lactate dehydrogenises [LDH] were recorded. Those cases where synovial fluid culture was done their results are recorded. Erythrocyte sedimentation rate [ESR], Rheumatoid [RA] factor, C-reactive protein [CRP] values were also recorded

Arthroscopic and open synovial biopsy samples were submitted to Department of Pathology. The samples were subjected to 10% buffered formalin fixation for 24 hours and then gross examination with sampling of tissues. Followed by routine tissue processing in histokinette [Leica TP 1020] as per institute standardized protocol. Sections of 4- 5 µm thickness were taken from paraffin embedded tissue blocks using rotary microtome [Leica RM2125RT] and stained with routine Haematoxylin and Eosin [H&E] stain. Special histochemical stains such as Modified Ziehl Neelson stain, Perl's Prussian blue stain, Gram stain and Methylene blue stain were done wherever required. A detailed histopathological examination with clinical and other laboratory findings correlation was done.

The collected data were statistically analyzed for sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy of synovial biopsy. Those cases for which specific clinical diagnosis was correlating with histopathological diagnosis was considered as true positives and those where histopathological diagnosis given as nonspecific arthritis was considered as false positives. Cases wherein the clinical diagnosis of nonspecific arthritis was confirmed on histopathological diagnosis was considered as true negative and as false negatives when definite diagnosis was made on microscopic examination of synovial biopsy. Statistical data analysis was based on Galen and Gambino method and the obtained results were compared to the existing studies in the literature

Results

In the present study, 65 synovial biopsy samples of patients with arthritis were studied. We observed that the arthritis was most common in 5th decade of life with range of 10 – 88 years. Majority of cases of synovitis was observed in males [63%] with male-female ratio of 1.7: 1. Most were monoarticular disease with common joint affected being knee joint. Average duration of illness is 8 months. The common clinical manifestation was joint pain and swelling. Synovial fluid was available only in 32 cases. Physical, cytological and biochemical characteristics of synovial fluid is depicted in Table 1.

Out of 65 cases, the most common lesion was chronic nonspecific synovitis followed by osteoarthritis, tuberculous arthritis, rheumatoid arthritis and septic arthritis. One case of each pigmented villonodular synovitis [PVNS], gouty arthritis and ochronotic arthritis [Figure 1].

Clinicopathological concordance was observed in

55 cases [85%] and discordance in 10 cases [15%].Of the 65 cases of synovial biopsy, specific clinical diagnosis was available in 24 cases which were confirmed by histopathological examination. It includes osteoarthritis [9/24], tuberculous arthritis [5/24], rheumatoid arthritis [6/24], septic arthritis [2/24], pigmented villonodular synovitis [1/24] and ochronotic arthritis [1/24]. Thirty-one cases were diagnosed as chronic non-specific synovitis clinically as well as histologically.

Ten cases had discordance in clinicopathological correlation. Out of these, nine cases that were clinically diagnosed as nonspecific synovitis turned out to be specific definitive diagnosis on histopathology. This included four cases of tuberculosis, two cases of rheumatoid arthritis, two cases of septic arthritis and one case of gout. One case in which clinical diagnosis was septic arthritis, histologically confirmed to be chronic non-specific synovitis only.

Therefore diagnostic accuracy of synovial biopsy was 85% with Sensitivity of 73%, Specificity of 97%, positive predictive value of 96% and negative predictive value of 78%. False negative rate was 27% and false positive rate was 3%.

Table 1: Physical and laboratory findings of Synovial fluid

Diagnosis	Physical examination	Total WBC count cu/mm	Predominat cell type	Biochemical analysis		
				Protein (gm%)	Synovial fluid glucose (mg %)	LDH (U/L)
Chronic non specific synovitis	Group II	1000 - 13000	Variable	2-4	10 - 20	140-230
Osteoarthritis	Group II	250 - 600	Variable	2-3	10 - 20	100 -150
Tuberculous arthritis	Group II	3000 - 15000	Lymphocytes (50 – 80%)	4-6	20 - 45	220 - 300
Rheumatoid arthritis	Group II	7000 - 15000	Lymphocytes (40 – 70 %)andPolymorph nuclear neutrophils (40-70%)	3-6 5	20 - 30	240-330
Septic arthritis	Group III	15000 - 25000	Polymorph nuclearneutrophils(100%)	5-7	40 - 70	250 -360

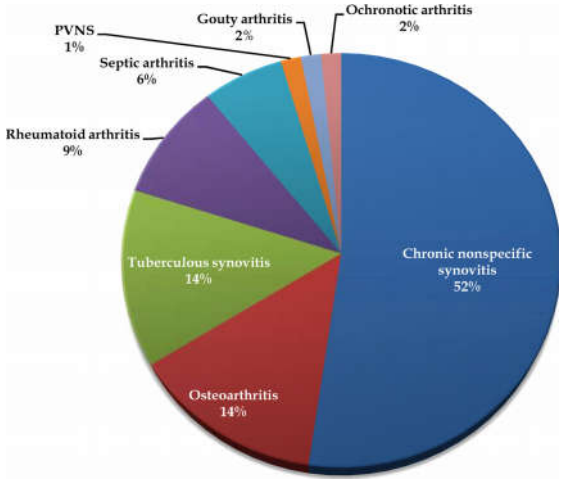

Fig. 1: Distribution (%) of various types of synovitis among study group (n=65)

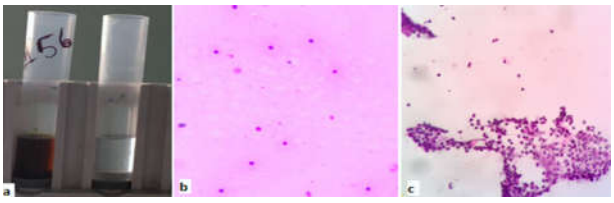

Fig. 2 (a): Group II - synovial fluid is dark colored with turbidity (left test tube) in comparison with distilled water (right test tube. **(b)** Smear showing plenty of mature lymphocytes in Tuberculous arthritis **(c)** Smear of septic arthritis showing numerous neutrophils in clusters and in dispersion.

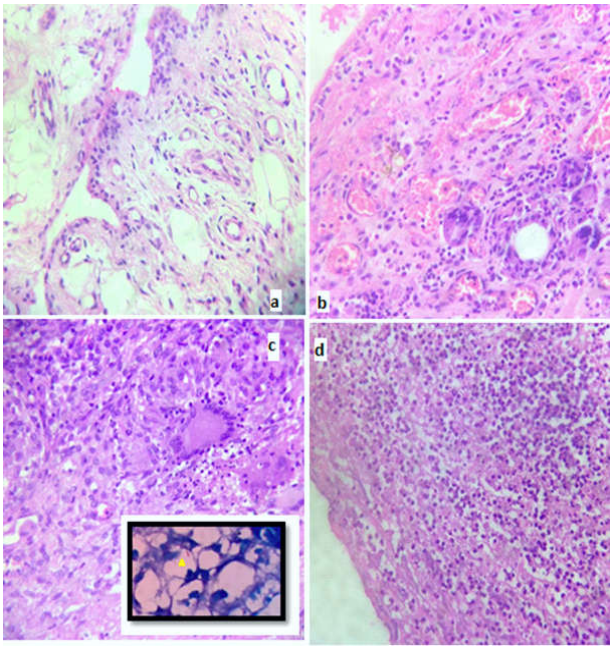

Fig. 3(a): Chronic nonspecific synovitis - mild synovial hyperplasia with diffuse mononuclear cell infiltration **(b)** Chronic nonspecific synovitis – granulation tissue with foreign body giant cell reaction **(c)** Tuberculous arthritis showing epithelioid granuloma with Langhans type giant cell. Inset: Modified Zeihl Neelson stain demonstrating tubercle bacilli (yellow arrow head) **(d)** Septic arthritis: Synovial tissue with dense infiltration of polymorphs. (100X, H&E; Inset 1000 X).

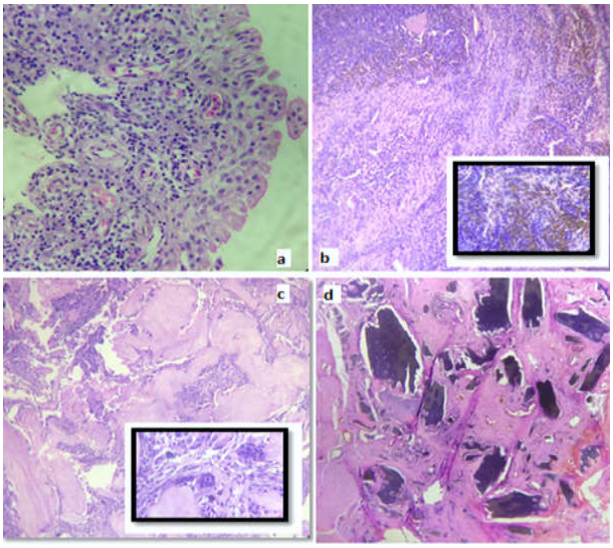

Fig. 4 (a): Rheumatoid arthritis – synovial hyperplasia with villi formation and diffuse infiltration of lymphocytes, plasma cells **(b)** Pigmented villonodular synovitis - stroma shows dense infiltration of mononuclear cells admixed with plenty of hemosiderin laden macrophages (inset). **(c)** Gouty arthritis - pale eosinophilic acellular fluffy deposits surrounded by foreign body granulomatous reaction. Inset - foreign body type of multinucleated giant cells. **(d)** Ochronotic arthritis – Ochre deposits in synovial tissue, (100X, H&E; Inset 400 X).

Discussion

In earlier days of 1932 synovial biopsy was done using dental nerve extractor after about three decades Pearson modified it, to be done under arthroscopic guidance [7]. This gives an advantage of sampling the diseased regions, but still the macroscopic features of inflammation do not predict microscopic features. Histological examination of synovial biopsy is valuable diagnostic tool for confirming and ruling out the definite clinical diagnosis. The laboratory and radiological investigations are equivocal in most of the monoarticular lesions.

In this study, we noted peak incidence of inflammatory synovial lesions between the age 41 – 50 years and it occurred in between 2nd to 8th decade of life. Similarly in studies conducted by Vijay et al [5] and MS Sant et al [8] observed the lesions in the age group of 11 – 50 years and 11 – 30 years respectively. This may suggest, with advancing age, medical attention would be required as the joints bear the brunt of various injuries on the long run.

Males were most commonly affected in our study with M: F ratio of 1.7:1. Similarly male preponderance was reported by Vijay et al [5] and MS Sant et al [8]. This may be due to physical stress laid on the joints and protective hormonal factors in reproductive age group females. Whereas, rheumatoid arthritis was most commonly seen among female population which is comparable with the study done by Edwards et al [9] and other authors. Knee joint was most commonly affected which is in conses with other authors [5,8]

With synovial fluid analysis we observed group II to be the most common group comprising 87% of all. Similar finding was observed by Singhal et al [4], Abhyankar et al [10] and Sheldon et al [11]

Most common cause of inflammatory arthropathy was observed to be chronic nonspecific synovitis in our study, so as by Vijay et al. Whereas, Singhal et al [4] observed that rheumatoid arthritis was the commonest disease followed by tuberculous arthritis and Abhyankar et al [10] observed tuberculous arthritis as the most common cause of synovitis in their study.

Chronic Non-Specific Synovitis

In the current study chronic non-specific synovitis was the most common lesion (52.31%) with the male predominance with the affected age group ranging between 11 – 50 years. Vijay et al [5] attributes higher incidence of chronic nonspecific synovitis to cases in early stage of rheumatoid arthritis or smoldering infection due to non-demonstrable etiological agent or due to inflammatory response either because of local micro trauma or systemic disease.

Most cases presented with complaints of joint swelling associated with pain of knee joint. ESR was elevated ranging from 30 – 60mm/hr. Histologically, synovial hyperplasia with chronic inflammatory cell infiltration was observed (Figure 2a & 2b). Similar results were observed by Vijay et al [4] and MS Sant et al [8].

Tuberculous Synovitis

It accounts about 13.84% of cases in the present study. The lesion was most commonly observed in males [67%], with knee joint [55%] involvement followed by hip [23%], ankle [11%] and elbow joint [11%]. Most commonly, this entity was observed in the adult population between the age group of 23 – 72 years. Most common symptom was pain [100%] followed by swelling [44%] and deformity [11%]. Radiologically, involved joint showed erosion and ESR was elevated in all the cases [40–120 mm/hr]. Synovial fluid was cloudy, pale yellow with predominant of lymphocyte population. These features are comparable with Freemont AJ [14]. Whereas Sakhuja et al observed predominance of neutrophils and high protein content with predominance of mononuclear population in their

study [16].

Clinically four cases were diagnosed as nonspecific synovitis, turned out to be tuberculous lesion only after histopathological examination, this signifies the value of microscopic examination of the synovium, as the classic clinical picture will not be evident in many occasions due to its varied presentation.Both caseating (77.7%) and non caseating granulomas (23. 3%) were observed in the present study. Caseating necrosis (77.7%), epithelioid cell reaction (100%), Langhan type of multinucleated giant cell (100%) were also seen (Figure 2c & 2d). It is comparable with Lal K B & Gupta et al [16] study, the results observed in their study were 46.6%, 100%, 6.7% and 66.6%, 87.5%, 18.7%respectively. The predominant and consistent feature observed in all these studies was epithelioid cell reaction. In our study stain for acid fast bacilli [Zeihl Neelson] was positive in three cases (33.3%) only.

Osteoarthritis

It is multifactorial disease and accounts for about 13.85% of our study. Most commonly observed in the mean age of 50 years with the male predominance, which is comparable with other studies [26]. Knee joint was commonly affected, presenting with complaints of pain and swelling. CRP [0-6mg/dl] and ESR [20-40mm/hr] were mildly elevated. Radiologically, affected joints showed degenerative changes. Histopathologically, mild chronic inflammatory cell infiltrates associated with bone and cartilage destruction was noted [12,13].

Rheumatoid Arthritis

It accounts about 9.27% in the present study. It is an autoimmune disease affecting multiple joints. Age group affected were between 20–63 years.More common among females (66%). Most common symptom was pain and stiffness of multiple small joints of hands and feet along with bilateral knee joints. ESR was elevated (40-80mm/hr). Synovial fluid showed mixed inflammatory cells with predominantly of lymphocytes in four cases and in 2 cases neutrophil predominance was observed. X-ray of the affected joints showed joint space reduction, subchondral cysts and sclerosis.

Serological test for rheumatoid factor was positive only in one case (16%); similar low seropositivity was observed by Garg et al, Grimley & Sokoloff et al [17,19]. However high seropositivity is observed by few authors (Vijay et al [5] & Gracelia et al [18]). It has been observed that rheumatoid factor in synovial fluid would be positive even when serum is negative.

Two cases were clinically diagnosed as non specific but definite diagnosis was made with histopathological examination. At early onset of disease, the clinical and histological features may be subtle enough to diagnose as chronic nonspecific synovitis. Similarly, the histological features of rheumatoid arthritis may also be noted in psoriatic arthritis, SLE etc. It may be helpful when clinical, pathological along with analysis of rheumatoid factor in serum and synovial fluid are taken into account for definitive diagnosis [5]. Histologically all the cases showed lymphoid follicles with diffuse infiltration of lymphocytes, plasma cells, synovial hyperplasia and villous hypertrophy (Figure 4a).

Septic Arthritis

It accounts about 6.15% in our study. Three out of four patients were male. The common symptom was joint pain with swelling and fever. Most were in 10 – 44 years except one in elderly age group [88years]. It is comparable with Sakhuja et al [15] who studied 7 patients of septic arthritis wherein the age group was between 1–55 years. In our study knee joint was commonly involved. It is usually caused by hematogenous spread of infection or less commonly post-surgical or post-traumatic. ESR was elevated (32 – 108mm/hr). CRP was also elevated (12 – 48mg/dl). Synovial fluid was turbid with predominant of polymorphs (Figure 2c) which is comparable with other studies [20-22].

Two cases were clinically considered as nonspecific possibly due to subclinical presentation of severity of illness possibly due to indiscriminate use of antibiotics in general practice. Microscopic examination of biopsy sample showed sheets of neutrophil infiltration in the fibrocollagenous stroma with areas of abscess formation (Figure 3d). Culture showed positive with suppurative organisms-staphylococcus (2 cases) and streptococcus(2 cases). One of the case was clinically diagnosed as septic arthritis but microscopically mononuclear cell infiltrates only were noted.

Pigmented Villonodular Synovitis [PVNS]

It is rare benign proliferative lesion of synovium [27]. We encountered one case of PVNS (1.53%). Patient presented with chronic pain and swelling of knee joint. Synovial fluid was turbid with brownish discoloration. Radiologically masses at juxtacortical region with erosion of bone was noted. Histologically

[27], it showed synovial hyperplasia and nodular architecture [23]. The stroma shows dense infiltration of mononuclear cells with multinucleated giant cells and hemosiderin laden macrophages (Figure 4b) which was positive with Perl's Prussian blue stain.

Gouty Arthritis

It is one of the causes of crystal induced arthropathy [28]. We encountered one case (1.53%) who presented with swelling and severe pain at scaphalo-lunate joint. Clinically, differential diagnosis of inflammatory arthropathy and tuberculosis was made. Radiologically, features were nonspecific with lytic lesion. It was histologically diagnosed, with pale eosinophilic acellular amorphous deposits [28] surrounded by chronic inflammatory cell infiltrates, macrophages, fibroblasts and foreign body type of multinucleated giant cells (Figure 4c). Serum uric acid level was measured retrospectively, it was 8.5mg/dl.

Ochronosis

It occurs due to inborn error of phenylalanine metabolism due to deficiency of homogentesic acid oxygenase. The unmetabolized elevated homogentesic acid in blood is excreted through kidneys thereby causing nephropathy and those which gets deposited in joints cause degenerative changes and deformity [29]. Patient presented with pain at hip joint and limping gait for one year. Deformed acetabulum with altered globular head was noted radiologically. Histopathologically, coffee colored [ochre] deposits surrounded by foreign body reaction was observed. Van Gieson, Perl's Prussian blue and Masson's Fontana stains were done to rule out calcium, hemosiderin and melanin deposits respectively. Methylene blue was positive highlighting the deposits.

The overall clinicopathological correlation in our study was 85 %. It is higher compared to studies conducted by Schumacher et al (65%) [24 - 25] and Singhal et al (68%)[4]. We observed that synovial biopsy plays crucial role in arriving at definite diagnosis. Conclusive diagnosis was given for nine cases with the help of histopathological examination and one case of clinically suspected case of septic arthritis turned out to be only nonspecific arthritis. As the specific treatment would be offered for definitively diagnosed disease averting the unnecessary use of analgesics and thereby improving the quality of life for the patients.

Conclusion

We observed that synovial biopsy is a cost effective procedure, with 85% diagnostic accuracy especially where the clinical diagnosis is nonspecific synovitis. Patients with chronic nonspecific synovitis, requires follow up with synovial biopsy as the histological changes of rheumatoid arthritis and osteoarthritis would be subtle during early onset of disease. On the whole histopathological diagnosis in conjunction with clinical, radiological and laboratory findings would be helpful in diagnosing the specific lesion.

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