Original Article

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Histopathological Analysis of Synovial Lesions

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ABSTRACT

Introduction: Histopathological evaluation of synovial tissue is not routinely done for diagnosis in patients of arthritis, however it is of diagnostic value in patients, particularly if the joint involvement is monoarticular.A final diagnosis may be arrived at after considering the clinical and serological findings.

Materials and Methods: We have analyzed a series of 46 cases which included 24 diagnostic biopsies and 22 cases of synovium sampled during joint replacement surgeries. Tissue was processed routinely, stained with Haematoxylin and Eosin and special stains whennecessary. Histopathological findings were correlated with clinical, radiological, serological findings, TB culture and TB- PCR results wherever available.

Results: We observed that knee joint was most commonly affected (73.91). Chronic non-specific inflammation was the most common histological finding seen in 15 cases (32.60%), 5 cases of which was further diagnosed as tuberculous synovitis based on, clinical and laboratory findings. This was followed by 11 cases (23.91%) of chronic degenerative osteoarthritis, nine (19.56%) cases of rheumatoid arthritis, and 5 cases (10.86%) of granulomatous inflammation. Other specific diagnosis included synovial lipomatosis, non-hemophilichemosiderotic synovitis, synovial chondromatosis, gouty arthritis and pseudogout. In this study, we have discussed the importance of histopathological evaluation and clinical correlation in diagnosing synovial lesions.

Conclusion: Histopathological findings in synovial lesions has its own limitations and may also be modified by treatment or chronicity of disease. However when correlated with clinical, serological and other investigations, it is of diagnostic importance in synovial lesions.

Keywords: *Synovitis, Osteoarthritis, Tuberculous, TB-PCR, Calcium Pyrophosphate, Gout.*

Introduction

Synovial tissue is a specialized mesenchymal tissue which is associated with a series of pathologic processes that are characteristic to this tissue [1]. Surgical corrective procedures in chronic degenerative arthritis has made an easy access to synovium for histopathological studies. Though synovial biopsy is not normally required for routine diagnosis in patients with arthritis, histopathological study of synovial tissue may be useful, particularly if the joint involvement is monoarticular [2].

However, histopathological study of synovial biopsy has its own limitations and in many conditions clinical, radiological, and serological findings are necessary to come to a conclusive diagnosis [2]. In the present study we have analysed a series of cases for histopathological findings in synovial tissue.

Materials and Methods

The present study comprises a series of 46 cases where histopathological evaluation of synovial tissue was done over a period of 4 years. These included 24 diagnostic biopsies in patients presenting with inflammatory joint lesions and 22 cases in which synovium was sampled during total knee replacement surgeries in known cases of degenerative arthritis. Tissue was processed routinely, stained with Haematoxylin and Eosin stains and special stains were carried out wherever necessary.

Histological findings were correlated with clinical and radiological finding, synovial fluid analysis, RA factor, Anti-CCP antibodies (Anti-cyclic citrullinated peptide antibodies), and TB-PCR findings wherever available. Data was recorded in data sheet prepared for this purpose using Microsoft office 2007. After data collection, data was analyzed using Excel sheet with the help of SPSS Software version 21. All quantitative data is presented with the help of mean and median.

Result

In our study, cases ranged from 18 years to 80 years. There were 31 females and 15 males with a M: F ratio of 1:1.7. Common symptoms observed were pain and swelling and the most common joint affected was the knee joint comprising 34 cases(74%).These inflammatory lesions were categorised based on histomorphology, as chronic non-specific synovitis, rheumatoid arthritis ,osteoarthritis, granulomatous arthritis, two cases of synovial lipomatosis, and one case each was diagnosed based on histomorphology as non-hemophilic hemosiderotic synovitis, synovial chondromatosis , gouty arthritis and pseudogout (Table- 1).

Out of 46 cases, 15 cases had non-specific chronic inflammation on histology. We received synovial tissue as multiple fibro-fatty and pearly white bits measuring between 1.5 cm to 4.5 cm. All cases showed patchy lymphocytic infiltrate, variable villous hypertrophy, hyperplasia of synoviocytes and blood vessel proliferation. Rheumatoid Arthritis (RA) factor test was negative in all these cases. ESR was raised in 12 cases and ranged from 30-80 mm/hr. Of these 15 cases, 5 cases were suspicious for tuberculous inflammation based on clinical and radiological evidence of tuberculosis (TB) like joint destruction with osteopenia. ESR was raised in all patients. Joint involvement was monoarticular. Three cases were positive for MTB (Mycobacterium *tuberculosis*) complex by TB PCR, done on synovial tissue. Synovial fluid examination was available in two cases having joint effusion which was suggestive of inflammatory pathology characterized by raised total leucocyte counts, high protein levels and raised LDH levels. Grams and Ziehl –Neelsen stains were negative in all cases. Routine cultures failed to show any growth. Remaining 2 out of 5 clinically suspected cases, were treated empirically for TB arthritis and both these patients responded well to treatment.

11 out of 46 cases, were cases of degenerative osteoarthritis diagnosed clinically and radiologically. These belonged to 40 to 80 years age group. RA test was negative in all cases. Two cases had history of trauma to knee joint with meniscal tear. All these cases showed hyperplastic synovial tissue with congested blood vessels and synovial proliferation with chronic non-specific inflammation. Reparative fibrohyaline cartilage and calcification were seen in two cases.

Out of 46 cases, 9 cases showed histological features of rheumatoid arthritis. These included 5 cases in which synovial tissue was obtained at the time of total knee replacement surgery, 3 cases in which synovial tissue was obtained at corrective synovectomy procedure, and one case of diagnostic synovial biopsy . On microscopy, there was moderate to marked villous hypertrophy and hyperplasia of synoviocytes, dense infiltration by lymphocytes and plasma cells, lymphocytic aggregates, lymphoid follicles and focal fibrinous exudates (Figure 1). ESR was raised in all cases .RA test was positive in two cases and negative in 7 cases .Anti-CCP (ant-cyclic citrullinated peptide) antibody test was available in 4 cases and was positive in all 4 cases.This also included one case of juvenile rheumatoid arthritis, an 18 years male patient with multiple joint pain, lymphadenopathy, fever and early morning stiffness. RA test and anti-CCP antibody test was negative.HLAB-27 was positive, ANA was negative, C-reactive protein was negative .X-ray knee did not reveal any abnormality. Synovial biopsy from knee joint revealed histological features of rheumatoid arthritis.

Five out of the ten cases suspected of TB arthritis showed granulomatous inflammation with caseation necrosis (Figure2). None of these cases had pulmonary TB at the time of presentation.

0ne case was diagnosed as Non-haemophilic hemosiderotic synovitis on histology. This was a 75 years old female with long standing osteoarthritis of bilateral knee joints ,presenting with increasing pain in left knee along with swelling in the suprapatellar region .A total knee replacement was done of the left knee jointand synovium obtained from the supra-patellar pouch grossly revealed fibrofatty yellowish tissue piece with areas of haemorrhage .Microscopically there was marked proliferation of synovium with fine villous architecture and deep brown granular pigment deposition in the synovial lining cells (Figure 3), positive for Prussian blue stain. There was no proliferation of mononuclear synovial cells, lipid laden cells, or multinucleated giant cells, ruling out PVNS. History and investigations excluded bleeding disorders and collagen vascular diseases. There was no drug history or history of trauma. Platelet counts were within normal limits. Sickling test was negative with normal haemoglobin electrophoresis.

One case of tenosynovitis of flexor tendon of right little finger on exploration and histopathological evaluation was diagnosed as synovial chondromatosis. Grossly there was firm nodular synovial bits which on microscopy revealed lobular areas of chondroid metaplasia with focal clustering of chondrocytes and scattered mononuclear cells (Figure 4). Two cases of osteoarthritis of the knee joint revealed features of synovial lipomatosis in addition to features of osteoarthritis. There was stromal replacement by adipose tissue up to the synovial lining epithelium and moderate lymphoplasmacytic infiltrate (Figure 5).

One case of hyperurecemia, presented with pain and swelling in right knee, right great toe and right olecranon. Biopsy from olecranon revealed multiple tophi surrounded by infiltration of lymphocytes, histiocytes and many foreign body type giant cells (Figure 6). One case of chronic degenerative osteoarthritis with chronic kidney disease presented with right knee pain. Synovial tissue revealed hyperplasia and calcified deposits of crystalline material along with granulation tissue (Figure 7). RA test was negative. Serum uric acid levels were normal .Serum calcium pyrophosphate levels were normal. C-reactive protein was raised.

Table 1: Histopathological findings in synovium.

Synovial lesions	No. of cases	PERCENTAGE (%)
Inflammatory- a)chronic non-specific Synovitis. b) Rheumatoid arthritis c)Granulomatous Inflammation d)Crystal induced changes	 15 9 5 2	 32.60 19.56 10.86 4.34
Degenerative osteoarthritis	11	23.91
Synovial-proliferative lesions. Synovial lipomatosis Synovial chrondromatosis Non-hemophilic hemosiderotic synovitis	 2 1 1	 4.34 2.17 2.17
Total	**46**	**100%**

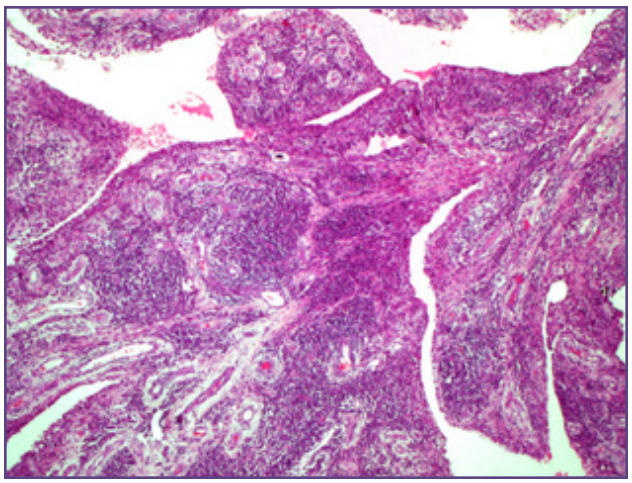

Fig. 1: Rheumatoid Arthritis: villous hyperplasia, hyperplasia of synoviocytes, dense infiltration of lymphocytes, plasma cells and lymphoid follicles, (H & E, x40).

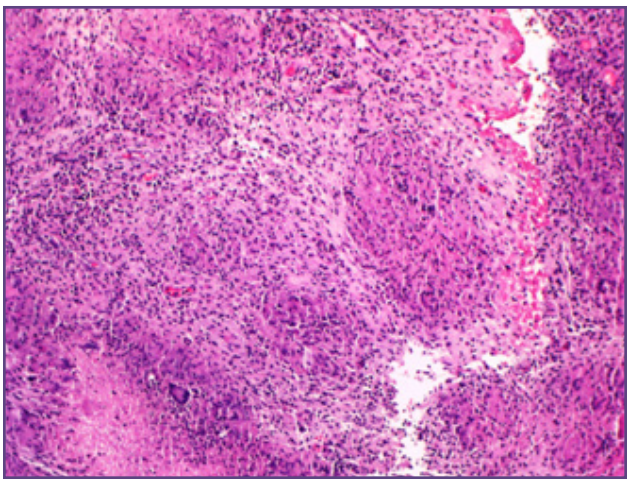

Fig. 2: Tuberculous synovitis:granulomatous inflammation, caseating epithelioid cellgranulomas with Langhan's giant cells, (H & E, x100).

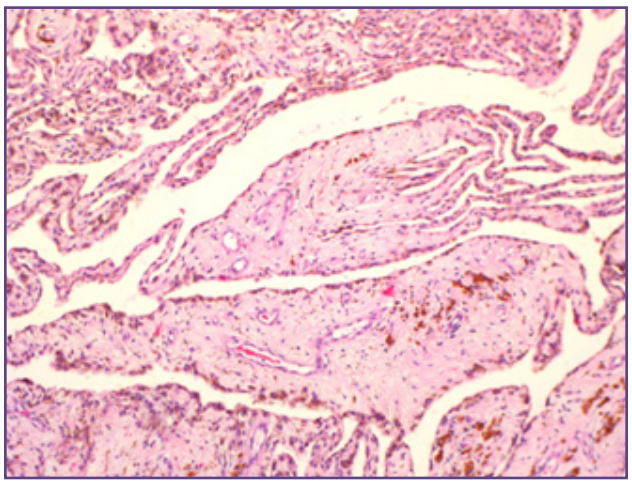

Fig. 3: Non-hemophilichemosiderotic Synovitis: marked villous proliferation with deep brown hemosiderin pigment deposition in the synovial lining epithelium and subsynovialmacrophages,(H & E, x100).

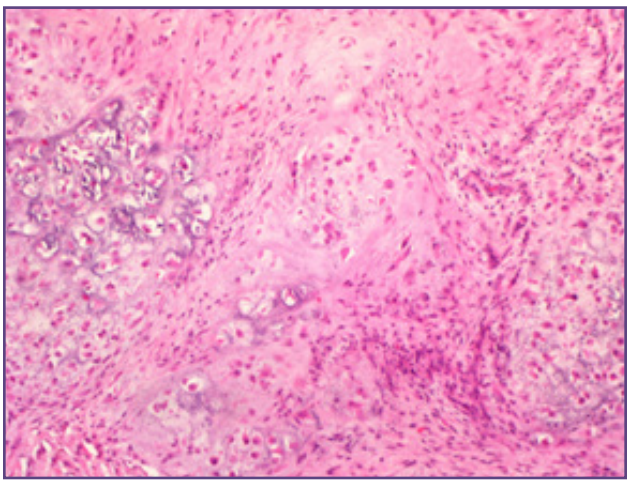

Fig. 4: Synovial Chondromatosis: lobular areas of chondroid metaplasia, focal clustering of chondrocytes and scattered mononuclear cells, (H & E, x100).

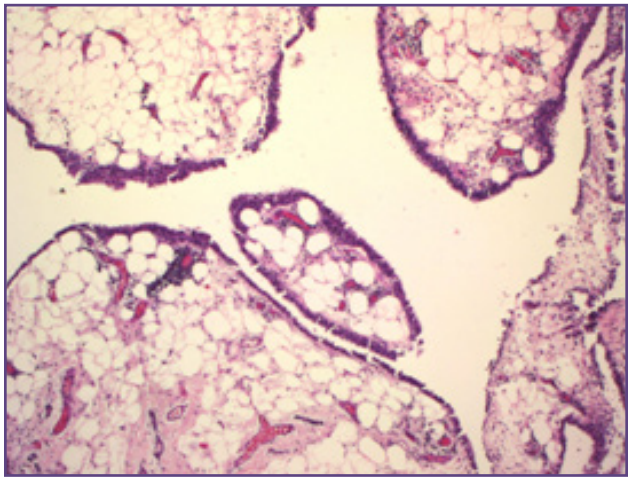

Fig. 5: Synovial Lipomatosis: stroma replaced by adipose tissue up to the synovial lining epithelium with lymphoplasmacytic infiltrate, (H & E, x40).

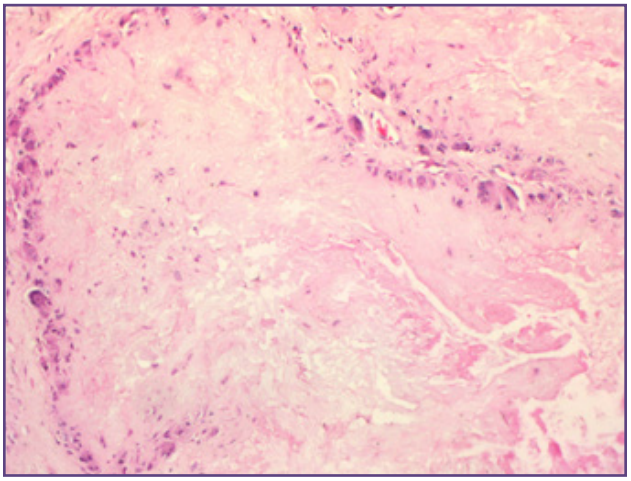

Fig. 6: Gout:tophaceous masses surrounded by foreign body giant cells with chronic inflammatory cells, (H & E, x100).

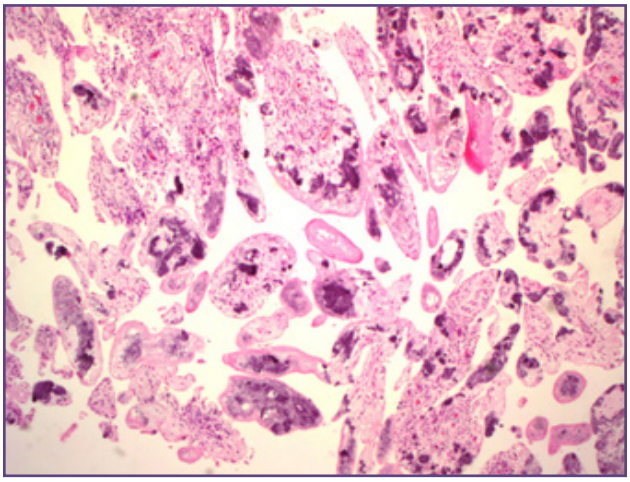

Fig. 7: Pseudogout: synovial hyperplasia, calcified deposits of crystalline material and granulation tissue, (H & E, x40).

Discussion

In the present study out of 46 samples, knee joint was the most commonly affected site, comprising 34 (74%) cases. Chronic degenerative osteoarthritis was the most common diagnosis based on histogical evaluation, clinical findings and investigations, comprising 11 patients [23.9%] of the total 46synovial lesions. There were 15 (32.60%) cases of chronic nonspecific inflammation, 5 of which was later on diagnosed as Tuberculosis based on clinical and radiological findings as well as TB PCR. Five (5) cases showed granulomatous inflammation with caseation necrosis. There were 9 cases of rheumatoid arthritis. The affected age group ranged from 18 to 80 years. This wide age range is due to the single case of juvenile rheumatoid arthritis and cases of chronic osteoarthritis undergoing total knee replacement surgeries.

A similar series of synovial lesion by Abhyankar et al [3] reported tuberculosis of joint as the most common observation. The study however, included all cases in which diagnostic synovial biopsy was done. Another study by P.M. Vijay et al [2] reported chronic non-specific synovitis as the most common inflammatory synovial lesion (71%). In the study by M.S.Sant in 1994, the author reported chronic nonspecific synovitis in 65 patients (47.10%) as the common lesion affecting the knee joint followed by tuberculous synovitis in 40 patients (28.98%).[4]

In our study, 13 clinically diagnosed cases of degenerative chronic osteoarthritis underwent total knee replacement and there was an additional 2 cases of secondary osteoarthritis following trauma and meniscal tear. The patients affected were between 40-80 years of age and

all presented with knee joint involvement with pain. Of these, 11 cases showed features consistent with clinical diagnosis of osteoarthritis, and the remaining 4 cases on histology showed other specific diagnosis including Non-haemophilic hemosiderotic synovitis (NHHS), pseudogout or calcium pyrophosphate deposition disease (CPDD), and 2 cases of synovial lipomatosis thus emphasizing the importance of histopathological evaulation.

Osteoarthritis is generally considered to be a non-inflammatory condition and is frequently referred to as degenerative joint disease. The older publications suggest that the synovial membrane is normal in appearance in osteoarthritis **,** showing no intimal cell hyperplasia or significant cellular infiltrate ,though there may be fibrosis, increased vascularity and fragments of cartilage present [5]. Recently ,the presence of a low grade synovitis has been noted in osteoarthritis and some cases have been described in which the histological appearance were similar to those seen in rheumatoid arthritis and other chronic synovitides. [5]Our cases of osteoarthritis revealed hyperplastic synovial tissue with congested blood vessels and mild synovial proliferation with chronic perivascular inflammation and reparative fibrohyaline cartilage in few cases. Granulation tissue and subepithelial plasma cell infiltrate was seen in one case. These findings are consistent with recent reports in literature [5], regarding presence of low grade synovitis in cases of osteoarthritis.

Two cases of synovial lipomatosis were reported based on histopathology in the present study in patients clinically diagnosed as osteoarthritis. These patients were 64 years and 68 years old respectively. Review of literature reveals that synovial lipomatosis commonly affects adults [6].In the series studied by Hallel et al, the age group ranged from 39-66 years [7].Synovial lipomatosis may mimic tumorous lesion like lipoma or hemangioma and its distinct histomorphology helps in distinguishing it from these lesions. It possibly represents a secondary phenomenon following the degenerative process of the joint. For conclusive diagnosis of synovial lipomatosis, histopathology is necessary [8].

In present study, we reported a rare case of non-hemophilic hemosiderotic synovitis (NHHS) of the right knee joint, in which the patient lacks history of any bleeding diathesis. It develops as a result of chronic intra-articular hemorrhage. A subset of hemosiderotic synovitis is caused by intrasynovial hemangiomas. Fewer than 200 cases have been reported of intra-synovial hemangioma. Knee joint is the most frequently affected joint and hemorrhage is rarely as progressive as in bleeding diathesis and accelerated osteoarthritis is usually not a feature [11]. Its definitive diagnosis is possible only by histopathological examination [9]. Prompt recognition and awareness of underlying causes should lead to earlier diagnosis, appropriate therapy, less joint destruction, and better outcome. [9, 10, 11].

Our study had one case of synovial chondromatosis, presenting as right little finger tenosynovitis. Synovial chondromatosis refers to the development of cartilage from synovial connective tissue in which secondary calcification and ossification commonly occur [12 ,13 14 15]. Cases affecting the hand and wrist are rare, with one retrospective case series reporting a prevalence of 7.5% among 53 synovial chondromatosis cases compared with 74% in the knee [15]. It presents with nonspecific clinical symptoms and surgical excision and histological examination are thus required for diagnosis.

In our study, one case each was diagnosed as calcium pyrophosphate deposition disease (CPDD) and Gout respectively. Diagnosis of CPDD can be confirmed by the demonstration of rhomboid or rod shaped , weakly positive birefringent CPDD crystals in synovial fluid or articular tissue and the presence of characteristic intra-articular calcified deposits in synovium, articular cartilage or menisci.[16]The knee joint is the most commonly affected site [16]. CPDD arthropathy is often associated with other medical conditions, including hyperparathyroidism, hemochromatosis chronic gout, renal failure and hypophosphatemia [17 ,18].Chronic tophaceous arthritis occurs as a result of repetitive acute attacks of gout with deposition of urate crystals. The deposits can occur in peri-articular cartilage, synovium, and soft tissue. A chronic inflammatory cell infiltrate composed of histiocytes and multinucleate giant cells are seen. The characteristic appearance is that of a scalloped palisade of histiocytes containing an amorphous-appearing pale to pink deposits in the centre [19].

The term chronic non-specific synovitis included those cases in which there was absence of specific inflammatory etiology and absence of diagnostic features related to rheumatoid arthritis. Early stages of rheumatoid arthritis and osteoarthritis can also show histological features of chronic nonspecific synovitis [2]. Hence it is necessary to follow up cases showing chronic non-specific inflammation on histology and correlate with clinical, serological and radiologic findings to rule out specific inflammatory conditions involving the joint.Abhyankar et al[3],in his study of 200 synovial biopsies, classified 80 patients diagnosed as chronic nonspecific synovitis in to various disease entities, following which only 6 patients (3%) could not be classified in to any specific condition

indicating the necessity of follow up and correlation with clinical and serological findings.[2, 3]

Out of 46 cases in the present study, there were 9 cases of rheumatoid arthritis in which polyarticular involvement was seen in 5 (55%) cases and in 4 (45%) cases, joint involvement was monoarticular. Other studies reveal similar findings [3, 20]. The 9 cases also included a case of an 18 year old male with left knee and left ankle joint involvement. Synovial biopsy obtained revealed histological features of rheumatoid arthritis. RA factor test and anti-CCP antibody test was negative. HLAB-27 was positive in this case. The case was diagnosed as Juvenile rheumatoid arthritis (JRA) and started on disease modifying ant- RA drugs. However on follow up, there was no response to treatment and hence the patient was started on cytotoxic drugs as well as steroids.

Of the 9 patients diagnosed as RA , serological test for rheumatoid factor was positive in 2 cases (22.2%) only and remaining 7 patients (77.8 %) were sero-negative. In the study by P M Vijay et al [2] 3 out of 4 cases of rheumatoid arthritis showed RA factor positivity. Many authors have observed seronegativity in 10-30 % of rheumatoid arthritis patients [21, 22, 23]. In the present study of the total 9 cases, anti CCP antibody was available only in 4 cases and was positive in all 4 cases. Antibodies to CCP is the latest serological marker available for the diagnosis of RA. It also predicts the eventual development into RA when found in undifferentiated arthritis. With 2nd generation anti-CCP assay the specificity for diagnosing RA has increased to 96-98 % [24].Histopathological changes of rheumatoid arthritis when present are highly characteristic however in the absence of these features clinical and serological correlation is important.

Of the ten (10) suspected cases of TB arthritis, 5 had histopathological features of tuberculosis like caseating granulomas and 3 cases were diagnosed as TB based on results of TB PCR, of which two cases were TB culture positive. The remaining two cases were treated empirically on the basis of clinical presentation and radiological findings as tuberculous synovitis. Joint involvement was monoarticular in all cases.Diagnosis of extra-pulmonary paucibacillary tuberculosis can be challenging. Multiple biopsies are recommended [25]. The detection of bacterial DNA by TB-PCR in synovial biopsy or synovial fluid samples can be of diagnostic help in these cases. Negi et al, in their study compared the utility of PCR test, ZN stained AFB smear examination and BACTEC culture for diagnosing osteoarticular TB and found that TB PCR showed a much higher sensitivity when compared with other two tests [26].

TB PCR is an extremely sensitive and specific technique to detect extremely small quantities of mycobacteria in clinical samples and has been suggested as a useful tool for diagnosis of extra-pulmonary tuberculosis [27-30]. In the present study synovial fluid analysis was done in 2 clinically suspected patients of TB synovitis with joint effusion which showed neutrophil predominance in one case and lymphocytes in other case. In the study by P M Vijay et al [2], in which synovial fluid analysis was done in two suspected cases of TB, neutrophil predominance was noted in both cases. Hence it may be difficult to differentiate between acute inflammatory and tuberculous arthritis based on synovial fluid analysis, however TB PCR assay of synovial fluid can be used for detecting MTB Complex.

Conclusion:

Histopathological study of the synovial tissue is useful for diagnosing various inflammatory and non-inflammatory synovial conditions. It is of particular importance in diagnosing specific conditions like non-hemophilic siderotic synovitis, synovial chondromatosis and pseudogout, where a clinical diagnosis of chronic degenerative arthritis is made. Diagnosis of other specific synovial lesion also require serological correlation and other ancillary testing like TB culture and TB- PCR assay for tuberculosis along with histopathological evaluation.

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