

R E V I E W

Diagnostic and interventional radiology fundamentals of synovial pathology

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Summary. The synovial membrane is a specialized mesenchymal tissue that lines the diarthrodial joints surfaces, bursae, and tendon sheaths of the body. This article aims to provide an overview of the fundamentals of synovial tissue, with particular regard to the imaging findings of the main pathologic processes that can affect the synovia and the role of image-guided interventions. (www.actabiomedica.it)

Keywords: synovia, knee, MRI, ultrasound, CEUS, joint injection

Synovial anatomy, physiology, and pathophysiology

Normal synovium is made up of two layers, the synovial intima, and subsynovial tissue. The synovial intima is formed by a layer of loosely connected synovial cells, while the subsynovial tissue widely varies in the structure based on its location, and it may be mainly fibrous, areolar, or adipose. The subsynovium is characterized by the presence of a vascular and lymphatic network; through this capillary network, fluid enters into the joint cavity as an ultrafiltrate of blood plasma. Synovial membrane roles are the production of synovial fluid, the removal of articular debris, and the facilitation of the sliding between the articular surfaces (1).

Synovial tissue reacts to the numerous kinds of stresses it may be subjected in a fast but stereotypical manner, and the pathogenesis of the majority of the synovial disorders routes into a final and common anatomopathological pathway. The initial fast response is characterized by the increase of blood flow that causes edema, alteration of the synovial matrix, and

intra-articular effusion. The process proceeds inducing synovial proliferation accompanied by mononuclear infiltration; this leads to synovial hyperplasia that encroaches upon the articular surface. In the chronic phases, fibrotic changes may also occur (2, 3).

As in most anatomical districts, although the first step of the approach to synovial pathology is clinical evaluation, this can often have low sensitivity and specificity. Diagnostic imaging modalities, uniquely if integrated, are reliable support to diagnosis by demonstrating the type of anatomic alteration, approaching - in most cases - the final pathologic diagnosis, and being a noninvasive follow-up tool (4-20).

Synovial effusion

Synovial effusion is defined as the increase of the normal quantity of fluid on the articular cavity: its distribution is specific for each joint and follows the capsule anatomy. The normal synovium is barely percepti-

ble at MR imaging. Visualization of the synovium, in fact, suggests the presence of underlying pathologic changes. However, this is a nonspecific finding as it can be associated with traumatic, degenerative, overload, inflammatory and neoplastic pathology (21). So, effusion can be considered a sensitive indicator of joint pathology, but it may occur in either the presence or absence of proliferative synovitis. Due to the release of pluripotent cells (mainly fibroblasts), the synovial membrane undergoes to hyperplasia and/or hypertrophy that can be less or more fibrous, depending on the kind and the time lasting of the stress. Synovial thickening or proliferation can be challenging to detect in the presence of a joint effusion since both reveal themselves as an increased signal intensity on fluid-sensitive (T2-weighted) images. During the subacute stage of the pathology, in case of repeated stress, synovial thickening becomes more prominent and so more detectable from the synovial fluid. Additional morphologic findings may help in the differential diagnosis between synovial effusion and synovial thickening, such as the presence of scalloping or

truncation of the prefemoral fat pad, defects of Hoffa's fat pad and the non-visualization or irregular margins of the quadriceps fat pad, that have been described as signs of synovial proliferation. The administration of intravenous gadolinium can be considered highly accurate in differentiating proliferative synovium from joint effusion (**fig. 1**). Besides being highly sensitive in the detection of the presence of joint effusions and synovitis, MR imaging is a reliable tool in quantifying synovial and effusion volumes. Its ability to quantify these synovial processes has important clinical implications: assessment of disease severity and response to therapy. Several studies have shown how MR imaging with the use of advanced quantitative evaluation of synovial hypertrophy and synovial fluid is an essential tool in the diagnostic and follow-up stages of many degenerative and inflammatory conditions (22, 23). Even if MR imaging remains the gold standard in the evaluation of synovial disorders of the knee, ultrasounds technique has been considered to find correlative accuracy in measurement of synovial thickness, vascularization, and effusion, most of all for its simple,

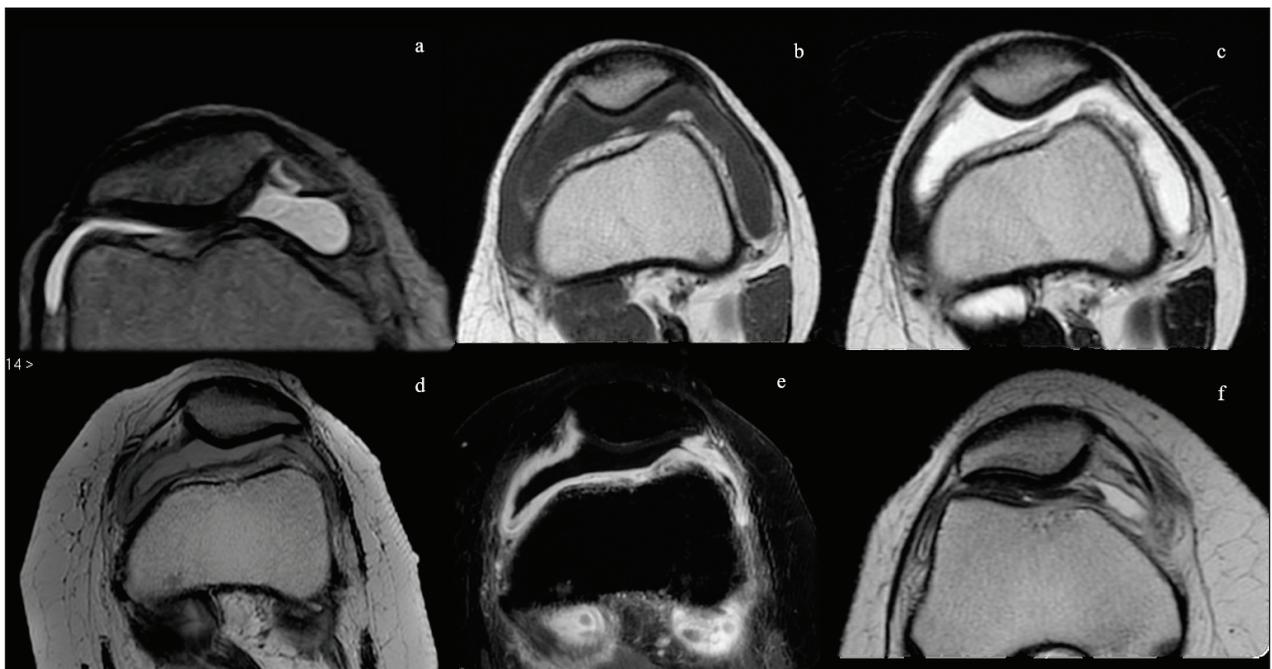


Figure 1. Imaging features of synovial effusion. In the acute phases (a), there is an increase of joint fluid, with the typical T2-hyperintensity and T1-hypointensity. In the subacute stages (b), the thickened synovial lining can be appreciated. Progressively, synovial hyperplasia and hypertrophy can be differentiated by the synovial effusion as it is clearly thickened, with villous appearance (c, d). The distinction is even more evident with the administration of gadolinium, where only the active synovial thickening enhances (e). In the chronic stages (f), the joint fluid can be less prominent and fibrotic aspects may occur

inexpensive, and beneficial properties. At US, synovial hyperplasia and hypertrophy are evident as a thickening of the synovial lining hyperechoic compared to the intra-articular effusion. Depending on the degree and chronicity of inflammation, it can have a smooth, irregular, villous/villonodular profile. Power-doppler and Color-doppler sampling are useful for documenting the degree of proliferation of neovessels within the hypertrophic synovial tissue (24). In several studies, the evaluation with contrast-enhanced ultrasound (CEUS) showed higher sensitivity (95%) for synovitis detection than CE-MRI (82%), power Doppler US (64%), or grayscale US (58%) (24, 25).

Inflammatory arthritis

The synovia is typically involved, as a prime pathophysiological process, in a wide range of inflammatory arthritis. Among them, the most frequent are represented by rheumatoid arthritis (RA) and psoriatic arthritis (PsA) (26-36). Though bone involvement has typical different pathologic and imaging patterns, all inflammatory arthritis are progressive inflammatory disorders, primarily affecting the synovium (37-40). Articular tumefaction reflects the synovial inflammation that is the primary target of the pathological process. The earliest anatomopathological alteration is the exudative synovitis characterized by increased vascularization and permeability, synovial effusion, and inflammatory infiltration (41, 42). Synovitis is an early phase of the process, and together with the bone edema is an important predictive factor of bone lesions. Synovitis can be exudative or proliferative, and MR imaging is crucial for its differentiation. MR imaging has become a central tool in the evaluation of inflammatory arthritis because of its superior soft-tissue contrast, its ability to detect and quantify synovial thickening/volume, and the fact that these measurements correlate highly with synovial inflammatory activity. Fat-suppressed T1-weighted 3D gradient-echo images offer an excellent differentiation of cartilage and joint fluid in patients with RA (43, 44). However, it is recognized that gadolinium-enhanced MR images offer superior differentiation of enlarged or hyperplastic synovium from the adjacent joint fluid. Synovitis

is described as an area in the synovial compartment that shows an increased contrast enhancement after intravenous administration of gadolinium (45). For this reason, the administration of gadolinium turns out to be essential to obtain information about vascularization and – consequently- the activity stage of the disease; this, furthermore, allows both qualitative and quantitative evaluations (45, 46). For quantitative evaluation, dynamic imaging is used in order to appreciate the synovial enhancement and to obtain values of signal intensity according to acquisition time (47). The rate of early enhancement (30 to 60 seconds following injection) correlates highly with microscopic evidence of active inflammation (vessel proliferation and mononuclear leukocyte infiltration). The distinction between synovium and joint fluid is most reliable in the first 10 minutes following injection of gadolinium contrast, because the gadolinium diffuses into the joint, thereby obscuring the border between synovium and effusion. Synovitis can be evaluated by US as well and, as MR imaging, can be considered highly reliable and accurate when used to follow disease progression and monitor response to therapy (48). The thickened intra-articular synovial pannus can show Doppler signal, according to its increased vascularization. The Doppler signal intensity relates to the quantity of neo-formed vessels and thus with the severity of the inflammation (49, 50).

Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis and a major cause of joint pain and disability (51, 52). Traditionally, OA has been considered primarily a disease of hyaline cartilage with associated bone involvement, caused by overload or overuse; however, the pathophysiology of OA development is now appreciated to be more complex. The newest evidence suggests that synovitis and the resultant pro-inflammatory mediators have a major and early role in the pathogenesis of OA, with secondary effects on articular cartilage. In light of this, MRI imaging and US have been used to assess the presence of “macroscopic” inflammation and have supported the role of synovitis as an active component of the OA process, associated with both pain and structural progression

(53-55). The histological pattern of synovium involvement in OA patients is characterized by synovial lining hyperplasia, sublining fibrosis, and stromal vascularization. Synoviocytes react by producing pro-inflammatory mediators, which in turn attract immune cells, increase angiogenesis, and induce a phenotypic shift in chondrocytes. A vicious cycle follows as chondrocytes produce additional cytokines and proteolytic enzymes that eventually increase cartilage degradation and induce further synovial inflammation (55). At the “macroscopic” level, MRI provides valuable insights into synovitis and can visualize synovial hypertrophy, synovial fluid volume, and level of synovial enhancement after intravenous injection of contrast agent. Several studies also demonstrated how MRI inflammation measures correlate well with histological inflammation and clinical symptoms.

Interventional radiology

Interventional radiology can propose a wide range of therapeutic procedures also in musculoskeletal pathology through ultrasound, CT, and MRI guidance (56-64). Based on the evidence reported above, the synovia – and namely synovial inflammation – has become one of the main therapeutic targets not only for inflammatory arthropathies but also in degenerative osteoarthritis. Corticosteroids are undoubtedly the most used anti-inflammatory drugs. The possibility, through image guidance, of direct intraarticular drug injection, is the key to maximize the therapeutic effects while minimizing the known systemic side effects (65). In addition to intra-articular administration, ultrasound imaging guidance is beneficial for intrabursal and peritendinous administration, where corticosteroids can have anti-inflammatory action on synovial tissue. The imaging guide also allows minimizing other risks of unguided infiltration of corticosteroids, such as tendon rupture. Hyaluronic acid (HA) injection is another interventional radiology procedure aimed at degenerative joint pathology (namely osteoarthritis) but primarily aimed at the synovium. Hyaluronic acid is a glycosaminoglycan consisting of highly hydrophilic chains of D-glucuronic acid and N-acetylglucosamine. There are numerous types of hyaluronic acid on the

market, which mainly distinguish themselves by their molecular weight. Those with low molecular weight, able to bind to binding proteins (hyaladerine) and CD44 receptor, act mainly with a biological effect of viscoinduction (i.e., stimulating the endogenous production of HA) (66-68). Those with high molecular weight, on the other hand, have a lower biological effect, while performing a powerful viscosupplementation action, thanks to their rheological properties. Even if metanalysis highlight the heterogeneity of the available studies, intraarticular HA injections appear effective in the treatment of arthritic pain (mild-moderate OA) both at the level of the knee and the hip. The size of the effect on pain varies according to the studies, with a peak at 8 weeks (higher than corticosteroids). Cross-linked products (high molecular weight) have greater pain efficacy than linear HA, and there are evidences to support HA efficacy also concerning functional improvement (level 1B). In all guidelines, the use is recommended for the management of osteoarthritis as a second-line treatment in symptomatic patients after conservative therapy (NSAID) (69). Platelet-rich plasma injection is another therapeutic tool we can consider. This product, consisting of a platelet ultrafiltrate, performs its action through the release of several growth factors (PDGF, TGF-B, EGF, CTGF) with anti-inflammatory activity and trophic action on different joint tissues. There are several in vitro and clinical evidences that intraarticular PRP injection may exert a positive influence in patients affected by knee cartilage degeneration and OA and that it may have higher and longer efficacy than HA in improving pain and articular function (70, 71).

Synovial tumors and pseudotumors

Synovial cysts and ganglia

Synovial cysts are fluid-filled masses lined with synovium located within or about joints. They can be intraneural, extraneural, or between or within muscles. The distinction between a synovial cyst and ganglion cyst is made primarily based on the histological nature of the lining of the cyst, the contents of the cyst, and the presence/absence of communication with the joint

(72, 73). Ganglion cysts are lined by spindle-shaped cells and are characterized by myxoid contents. Because true synovial cysts are, by definition, lined by synovial cells, they manifest disease and are affected by the same disease processes as other synovial structures. They are most commonly encountered about the knee and occur with synovial inflammatory disorders, rheumatologic and otherwise, as a result of trauma, and in conjunction with osteoarthritis. Synovial cysts can arise from different causes (degenerative articular processes, chronic microtrauma soft tissue/bursae, or reflect anatomical remnants), and knowledge of the most relevant localizations, pathological and radiological picture is helpful for a correct diagnosis (74).

Pigmented villonodular synovitis (PVNS)

Pigmented villonodular synovitis (PVNS) is a rare, benign synovial proliferative process whose distribution is usually monoarticular. The disorder is idiopathic with two primary forms, localized and diffuse, either intra-articular or extra-articular (75-77). Although any synovial joint may be involved, the knee is the most frequently affected. Patients usually present with nonspecific symptoms such as monoarticular pain and decreased range of motion. The disease is characterized by the presence of abundant hemosiderin-laden macrophage deposition into a bulky, mass-like synovium. MR imaging is the imaging method of choice for the diagnosis, surgical planning, and evaluation of recurrence (75). Clumps of

hemosiderin-laden macrophage deposits demonstrate low signal intensity on T1- and T2-weighted images due to the paramagnetic effects of the iron in the ferric state, and this is the most reliable diagnostic feature (**fig. 2**). A large amount of joint effusion is usually present, but not specific. The pathological equivalent at the level of the tendon sheaths is the giant cell tumor of the tendon sheaths (GCTTS) (77).

Lipoma arborescens

Lipoma arborescens, or villous lipomatous proliferation of the synovial membrane, is a rare intra-articular lesion that usually involves the knee. It is characterized by villous proliferation of the synovium and extensive replacement of the subsynovial tissue by mature adipose cells. It is usually a monoarticular condition. MR imaging shows a frond-like morphology with high signal intensity (isointense to subcutaneous fat) on T1-weighted images (78, 79). Lack of enhancement after injection of intravenous contrast material excludes the diagnosis of other synovial inflammatory or neoplastic processes (**fig. 3**).

Synovial chondromatosis

Idiopathic synovial osteochondromatosis is a non-neoplastic, proliferative, and metaplastic disorder of the synovium characterized by the presence of multiple cartilaginous or osteocartilaginous bodies

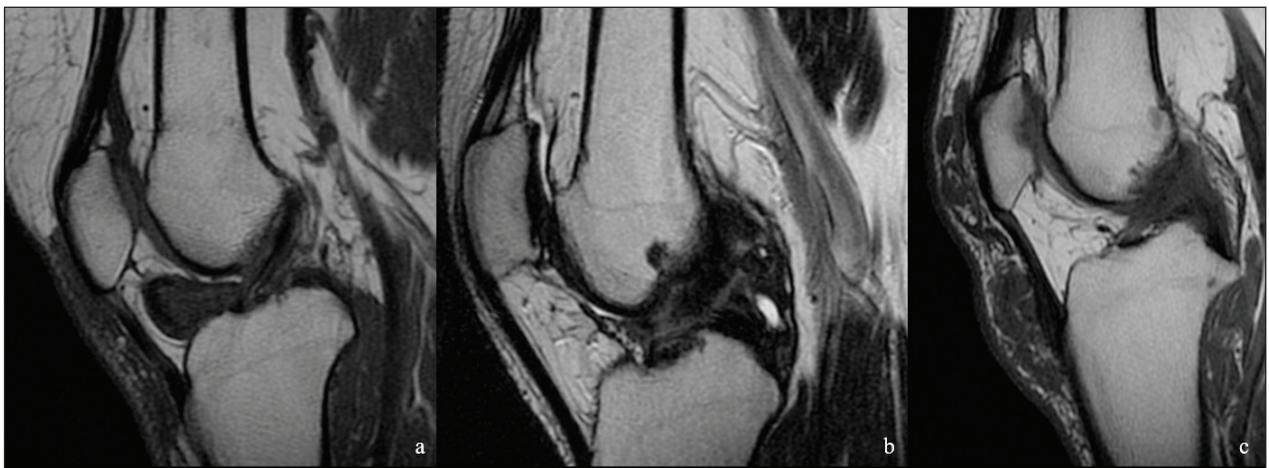


Figure 2. Imaging features of pigmented villonodular synovitis (PVNS) in solitary (a), diffuse (b), and extraarticular form. Note the low signal intensity on both T1- and T2-weighted sequences



Figure 3. Imaging features of synovial chondromatosis. In a and b, note the right hip joint effusion with intraarticular osteocartilaginous bodies with signs of ossification. In c, a plain film of the knee with secondary synovial chondromatosis showing osteocartilaginous bodies distributed in the joint recesses

within an articulation or adjacent synovial lined structure (80). Two forms of the condition occur, primary and secondary osteochondromatosis. The secondary one is more common and characterized by the presence of intraarticular osteocartilaginous bodies against a backdrop of degenerative joint disease. The second type, primary synovial osteochondromatosis, is relatively uncommon. The condition is usually progressive, leading to early osteoarthritis. The MR imaging characteristics depend on the presence and extent of calcification and or ossification in the bodies. In the case of intra-articular bodies composed primarily of cartilage, the bodies are lobulated in appearance with intermediate to low signal intensity on T1-weighted sequences with high signal intensity on fluid-sensitive sequences. In the case of calcified intraarticular bodies, the signal characteristics are described as foci of low signal intensity on both T1-weighted and fluid-sensitive sequences (81). Marrow-containing bodies will show the high signal intensity of the marrow within the bodies on T1-weighted images (**fig. 4**). Heterogeneous enhancement of cartilaginous bodies can be seen after the administration of intravenous contrast material.

Conclusions

Imaging is a central piece of the complex puzzle of synovial diseases; the role of multimodal imaging is crucial in many aspects regarding the management of

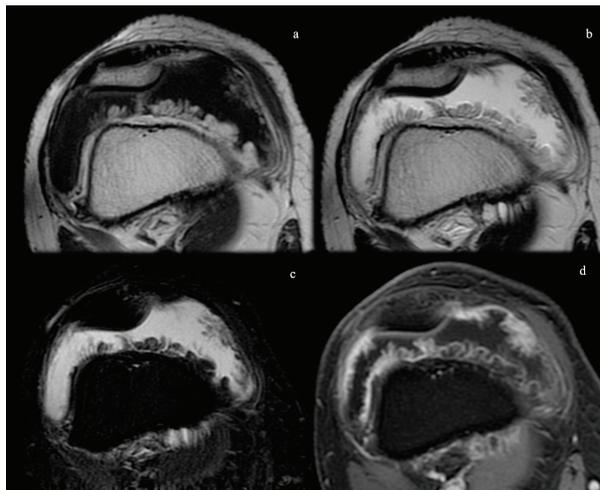


Figure 4. MRI imaging features of a lipoma arborescens of the knee. Note the typical frond-like thickening of the synovium in the supra-patellar recess showing signal intensity of fat (T1- and T2-hyperintense in a-b and hypointense in the fs-T2 sequence in c). After gadolinium administration (d) there is enhancement only of the superficial synovial lining

these disorders from the very beginning of the diagnosis, going through the follow-up and the treatment as well.

Conflict of interest: Authors declare that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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