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CASE REPORT

Diffused Pigmented Vilonodular Synovitis / Diffuse Type Tenosynovial Giant Cell Tumour of the knee treated with arthroscopic synovectomy and adjuvant Yttrium local infiltration. A case report, a "safe treatment algorithm" and the peer literature

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ABSTRACT

Pigmented villonodular synovitis (PVNS) is a unique mesenchymal lesion that arises from the synovial tissue of the joints. It is divided into a localized type (LPVNS) and a diffuse type (LPVNS) also known as Tenosynovial Giant Cell Tumor. The latter, is a predominantly intra-articular, aggressive, infiltrative process, characterized by both inflammatory or neoplastic properties and local destructive progression. A high recurrence rate is observed after surgical synovectomy alone. The positivity of colony-stimulated factor 1 (CSF1), its receptor (CSF1R), and receptor activator of nuclear factor kappa-B ligand (RANKL) with the clinical outcomes and the recurrence rates is a field of interest in therapeutic targeting with the use of biological factors/agents such as anti-TNFa. Adjuvant intra-articular injection of Yttrium-90 in the immediate post-operative period effectively reduces the rates of local recurrence. We present the case of a 59-year-old female patient with diffuse PVNS of the left knee treated with arthroscopic synovectomy and adjuvant Yttrium-90 local infiltration following a "safe treatment algorithm".

KEY WORDS: Pigmented Villonodular Synovitis, Arthroscopic Synovectomy, Biological factors, Yttrium-90 infiltration

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A 59-year-old female patient presented to our clinic reporting gradual onset of debilitating left knee pain over the course of the last 12 months. Pain was accompanied by joint effusion and stiffness during the last 9 months. The patient had been already treated conservatively by means of non-steroid anti-inflammatory medication (NSAIDs) and paracetamol per os intake, platelet rich plasma (PRP) intra–articular injections and physiotherapy without any significant improvement. The patient denied any history of trauma. Her medical history included hypertension and thyroidectomy for which she was currently being treated with Perindopril, Ramipril\hydrochlorothiazide and Levothyroxine respectively.

On clinical examination, cardinal manifestations included a large left knee joint effusion accompanied by diminished range of motion ranging between 0 to 110 degrees. Plain radiography failed to identify any specific pathology. However, the Magnetic Resonance Imaging (MRI) set the diagnosis of Diffused Pigmented Villonodular Synovitis (PVNS) (**Fig. 1**) and the "safe treatment algorithm" was implemented. (**Table 1**) This treatment algorithm is applied in our department as a standard procedure according to evidence-based medicine.

The patient underwent arthroscopic synovectomy through two main (antero-lateral and antero-medial) and one accessory (postero-medial) portals. Hypertrophic synovitis of characteristic brownish appearance, along with hemorrhagic fusion were the main arthroscopic findings. (**Fig.2**). Synovial tissue biopsies were obtained for histopathologic examination and synovial fluid samples were sent for cytology. Meticulous removal of the inflammatory synovium was then performed. The hazardous removal of the synovial membrane off the posterior wall was accomplished through the postero-medial portal as well as through the intercondylar approach between the anterior and posterior cruciate ligaments. The patient remained hospitalized for 24 hours and discharged with instructions including cryotherapy, mild kinesiotherapy and load bearing as tolerated with the use of crutches.

Histological examination revealed the papillary configuration of the membrane, the local presence of multinucleated osteoclastic type giant cells and monocytoid cells and the deposition of haemosiderin confirming the preoperative diagnosis of PVNS. (**Fig.3**)

Six weeks post-surgery, a Tc-99m bone scan was performed to assess the presence of any residual synovial tissue. (**Fig.4**) A week later, under radiological guidance and aseptic conditions, arthrography of the affected knee was initially performed with the use of a 2 ml contrast agent (lobitridol 350mg/ml, XENETIX, Guerbet Inc., France) in order to confirm the integrity of the synovial capsule. (**Fig. 5**) Aspiration of almost 10ml joint fluid was performed in order to reduce the intra-articular volume and 1.5 ml of Yttrium (^{90}Y) 5 mCi was subsequently injected into the joint. Finally, a flush of 2 ml of hydrocortisone was administered to reduce any local reaction as the needle was withdrawn. The joint was then passively mobilized throughout its range of motion for one minute to facilitate the distribution of the radiological agent to the synovial capsule. A Robert-Jones bandage was applied to the knee. A Geiger counter close to the affected joint, ensured that no systemic environmental leakage of ^{90}Y took place. At the end of the procedure, almost one hour later, a bone scan was conducted to rule out any systematic leakage of ^{90}Y in the extra-articular space. (**Fig. 6**) The patient was discharged with instructions to rest and keep the involved extremity in full extension for two days.

At the first follow up, 2 days later, the patient had no side effects of leakage, joint swelling, febrile reactions or skin irritation. Range of movement was almost normal and the patient was allowed to return to her daily activities. At 6-month and 1-year follow up, the patient remained asymptomatic with a fully functional joint. The patient was discharged from clinic; however, she was advised to report back any symptoms related to the affected left knee in the future.

Discussion

Pigmented Villonodular Synovitis (PVNS) represents a benign, hyperplastic and proliferative synovial disease. It does not metastasize but can potentially be aggressive to the surrounding soft or

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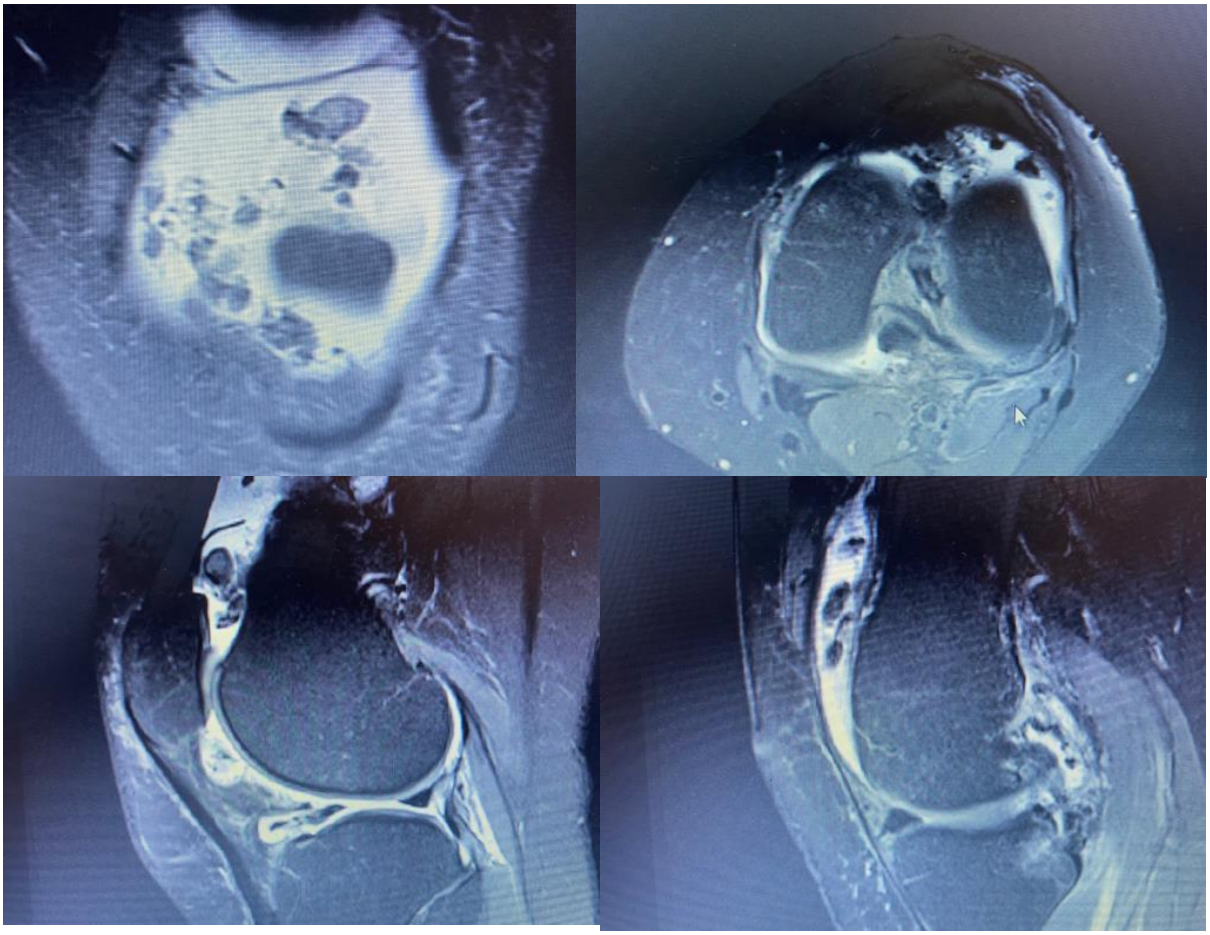

Figure 1. *MRI scan typically showed diffuse mass-like synovial proliferation with lobulated margins with low signal intensity due to hemosiderin deposition.*

TABLE 1.

The "safe treatment algorithm" followed for the management of knee diffuse PVNS in our hospital	
1. Clinical examination	• Symptomatology • Clinical signs • Synovial fluid aspiration
2. Imaging	• X-rays, MRI
3. Arthroscopy	• Synovectomy • Synovium biopsy for histological examination • Synovial fluid aspiration for cytological examination
4. Scintigraphy	• Tc^{99} three-phase bone scan
5. Radiohymenolysis	• Knee arthrogram for joint capsule integrity • $Yttrium^{90}$ administration for radiohymenolysis • Tc^{99} three-phase bone scan for Yttrium lekage
6. Rest	• 48 hours rest with Robert-Jones bandage
7. Follow up	• At 2 days for side effects • At 6 weeks, 6 months and 1 year for clinical manifestations of the involved joint

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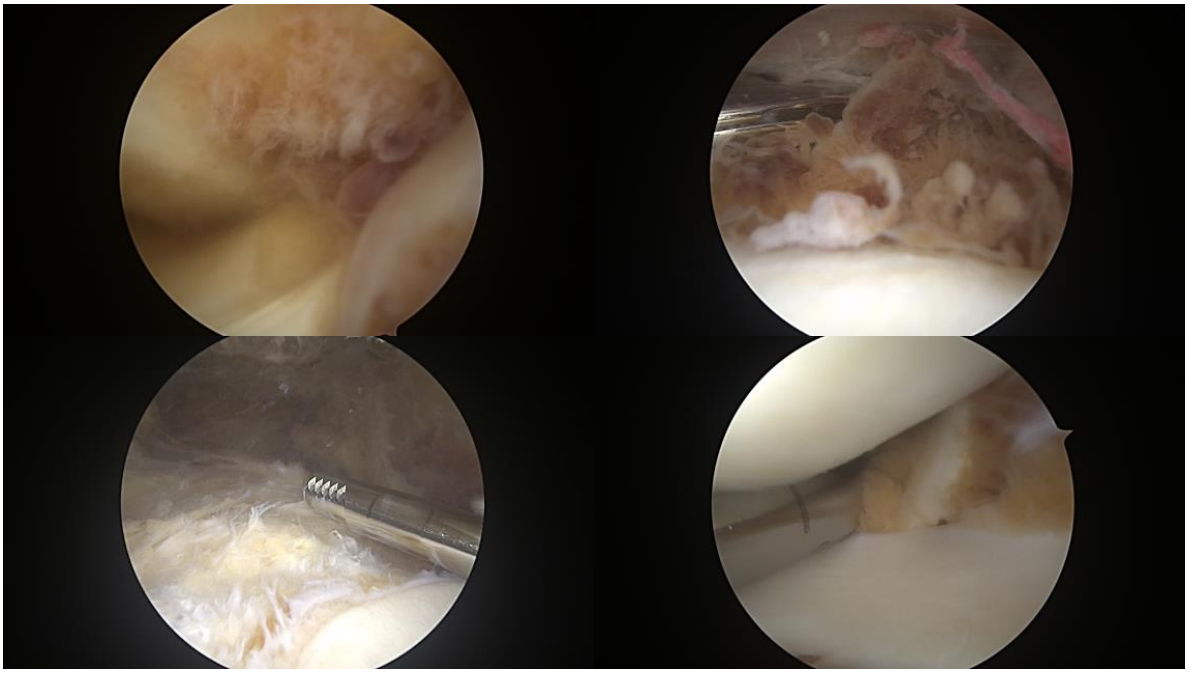

Figure 2. *Arthroscopy finding of DPVNS with brown colored lobulated hypertrophied synovium, before and after aggressive debridement.*

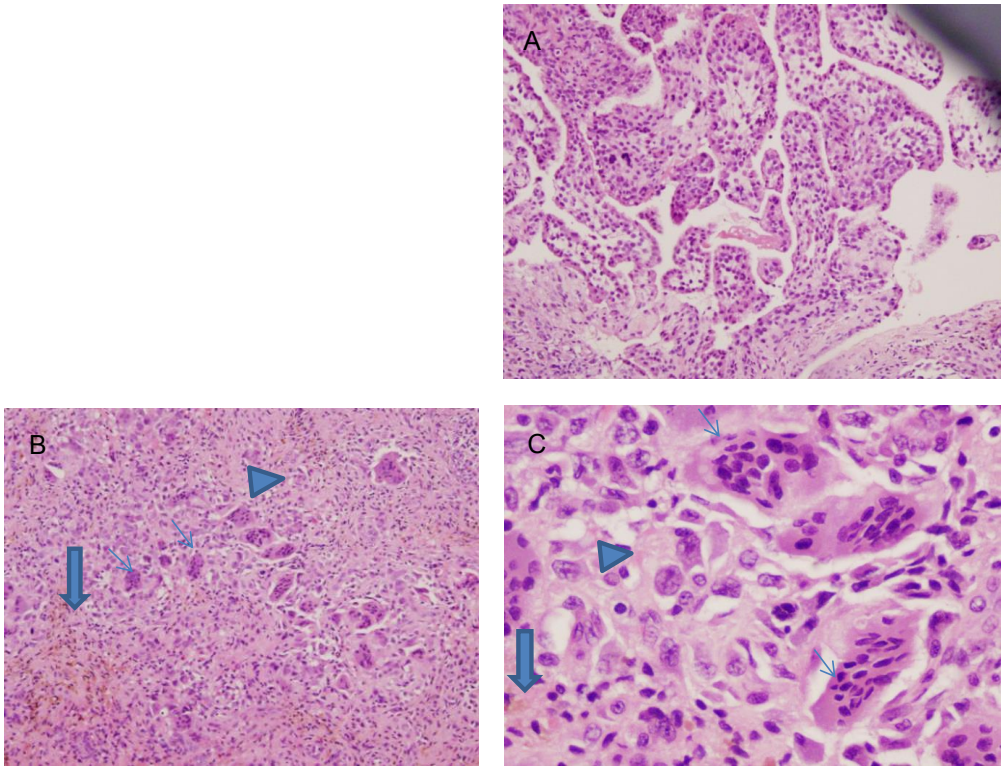

Figure 3. *Haematoxylin and Eosin staining x magnification histology specimens of the synovial membrane. (**A**) H&E X100 villous surface of the lesion. (**B**) H&E X100 osteoclastic-type giant cells (thin arrows), monocytoid cells (arrowhead), hemosiderin deposits (thick arrow). (**C**) H&E X200 osteoclastic-type giant cells (thin arrows), monocytoid cells (arrowhead), hemosiderin deposits (thick arrow).*

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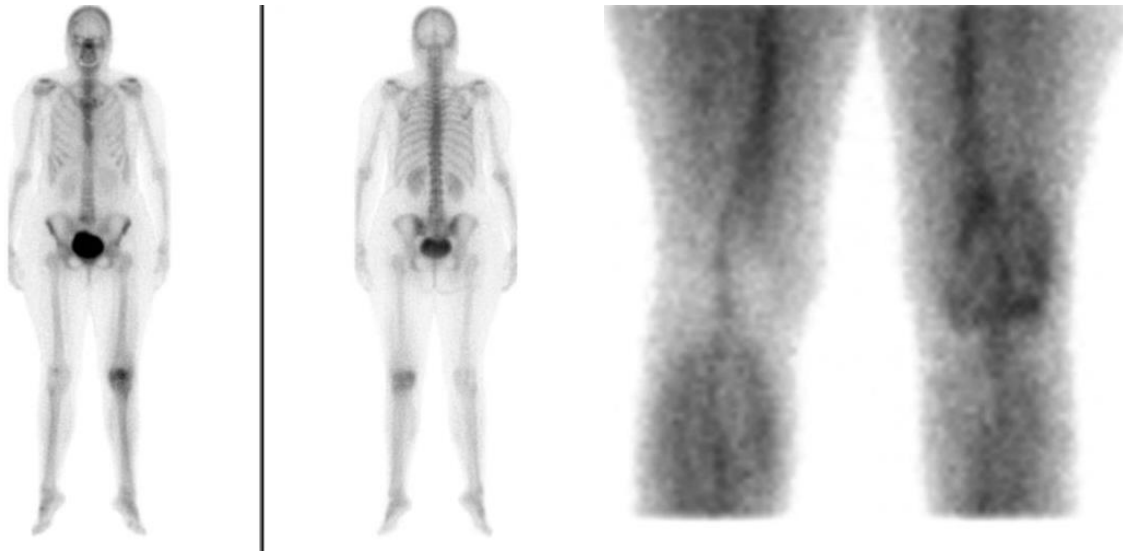

Figure 4. *Six weeks post-surgery a Tc-99m bone scan (blood pool phase) showed absence of any residual synovial reaction.*

bony tissues. When the tumor involves the tendons around the joint, or occurs in just one area of the joint, it is defined as Localized Pigment Villonodular Synovitis (LPVNS). When the condition is more widespread and involves an entire joint, the term Diffused Villonodular Synovitis (DPVNS) is used. The later, is also termed as Diffuse Type Tenosynovial Giant Cell Tumour in the most recent 5th edition of the WHO Soft Tissue and Bone Tumours classification.[1] It tends to be more aggressive and has increased recurrence rate and therefore, is more difficult to treat.

Young adults are mainly affected with the peak incidence observed between the second and fourth decade of life. The most frequently involved joint is the knee (28%-70%), followed by the hip, ankle, shoulder, and elbow joints.[2] The most common diffuse form has a reported recurrence rate up to 46%.[3] Microscopically, it is characterized by the presence of lipid-laden macrophages, multinucleated giant cells, hemosiderin deposits, and proliferation of fibroblasts and stromal cells. [4]

Because of its high local recurrence rate after surgery and the risk of osteochondral damage, there is growing interest towards novel therapeutic modalities that could be primary or adjuvant to surgical resection. The pattern of synovial gene and protein expressions in PVNS, similar to those in activated macrophages in rheumatoid arthritis, and the phenotype of multinucleated giant cells, characteristic of osteoclasts, suggest that there is a common autocrine mechanism in osteoclast differentiation in both diseases and indicate the potential utility of tumor necrosis factor (TNF)-alpha blockade. High synovial colony stimulating factor 1 (CSF1) messenger RNA (mRNA) expression in PVNS, unrelated to a chromosomal translocation involving CSF1 locus, may indicate that there is a synergic paracrine loop mediated by TNF-alpha and CSF1, as shown in both inflammatory and neoplastic conditions.[5] In 40 cases of PVNS, positivity of colony-stimulated factor 1 (CSF1), its receptor (CSF1R), and receptor activator of nuclear factor kappa-B ligand (RANKL) were immunohistochemically determined.[6] The relationship between the positivity and clinical outcomes was investigated. High positivity of CSF1 staining intensity was associated with an increased incidence of osteochondral lesions (bone erosion and osteoarthritis) ($p = 0.009$), but not with the rate of local recurrence. Positivity of CSF1R and RANKL

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staining was not associated with any clinical variables. The number of giant cells was not correlated with positivity of any of the three proteins, or with the clinical outcome. Particularly in knee cases, CSF1 positivity was also associated with the incidence of osteochondral change ($p = 0.02$). CSF1R positivity was high in cases which had local recurrence, but not significantly so ($p = 0.129$). It seems that determination of CSF1 and CSF1R expression may be useful as a prognosticator of the clinical course and/or outcomes of PVNS and especially of DPVNS. Additionally, the potential utility of tumor necrosis factor (TNF)-alpha blockade needs to be confirmed with larger controlled studies instead of rare reported cases in refractory PVNS.[7]

Arthroscopic synovectomy in DPVNS cases has gained popularity and seems to have several advantages over the open techniques especially in exclusively intra-articular cases.[8] In recent studies of arthroscopic synovectomy, the recurrence rate ranged from 16% to 50% at 5 years and up to 87% at 13 years. [9] Therefore, additional treatment options are deemed necessary to prevent local recurrence.

In the therapeutic algorithm of synovial disorders or persistent joint inflammation, radionuclide synovectomy or radiosynovectomy (RSV) with the use of radioactive agents is set between conservative treatment and operative procedures. In the case of pharmacotherapy failure, RSV is the radiopharmaceutical application of colloidal solution to joint cavities.[10,11] The most common indication for RSV is rheumatoid arthritis, although patients with seronegative spondyloarthropathies, unclassified arthritis, haemophilic arthropathy and other less common arthropathies such as pigmented villonodular synovitis benefit from this method.[12]

A commonly used radioactive agent for RSV is Yttrium-90 (^{90}Y). It is a colloid with 2.27 MeVw18x emitted β radiation with a natural half-life of 64 hours. Its maximum tissue penetration in the articular capsule and the adjacent cartilage is 11mm and 8.5 mm respectively. Regarding the mechanism of action, its diameter is small enough to be phagocytized, but big enough not to enter bloodstream via capillary fenestrations. After its intra-articular injection, ^{90}Y is phagocytized by type 2 synoviocytes (synovial macrophages) and captured in the external cell layers of the synovial membrane. The entrapped radioisotopes emit high energy β- radiation, which induces water hydrolysis, production of reactive oxygen species and cell apoptosis due to oxidative stress. With a half-life of 64 hours, ^{90}Y continuously emit radiation for a few weeks. In time, this leads to necrosis and subsequent fibrosis of the synovial membrane, a decrease in synovial fluid production and, clinically, reduction of inflammation symptoms. As mentioned, β- radiation has very limited tissue penetration, depositing more than 90% of energy within 10 mm from the point of origin, thus affecting almost exclusively the joint cavity. Most of the radiation is absorbed by the synovium, synovial fluid, superficial layers of cartilage and articular capsule. Subchondral bone and other para-articular tissues, in turn, receive negligible doses of radiation.[13]

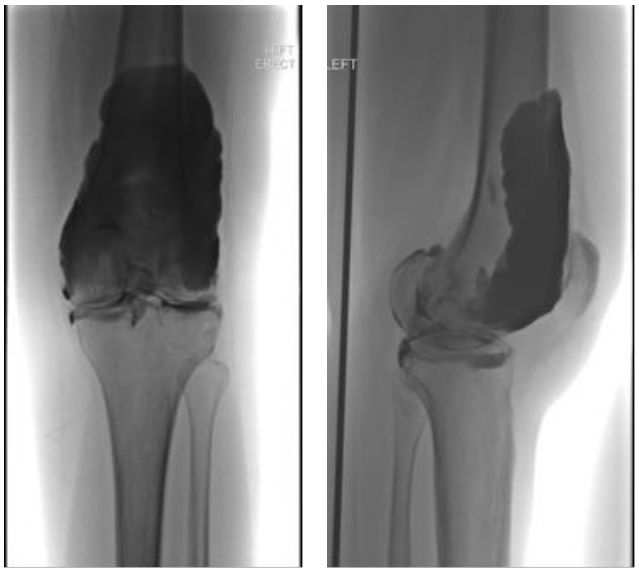

Figure 5. *Seven weeks post-surgery, arthrography of the affected knee before ^{90}Y administration ensured the integrity of the synovial capsule.*

^{90}Y intra-articular infiltration is used as adjuvant treatment along with the arthroscopic synovectomy in cases of PVNS in order to reduce the recurrence rates. Kollender et al, reported a 5% local recurrence rate in 20 patients treated with open or arthroscopic synovectomy followed by ^{90}Y admin-

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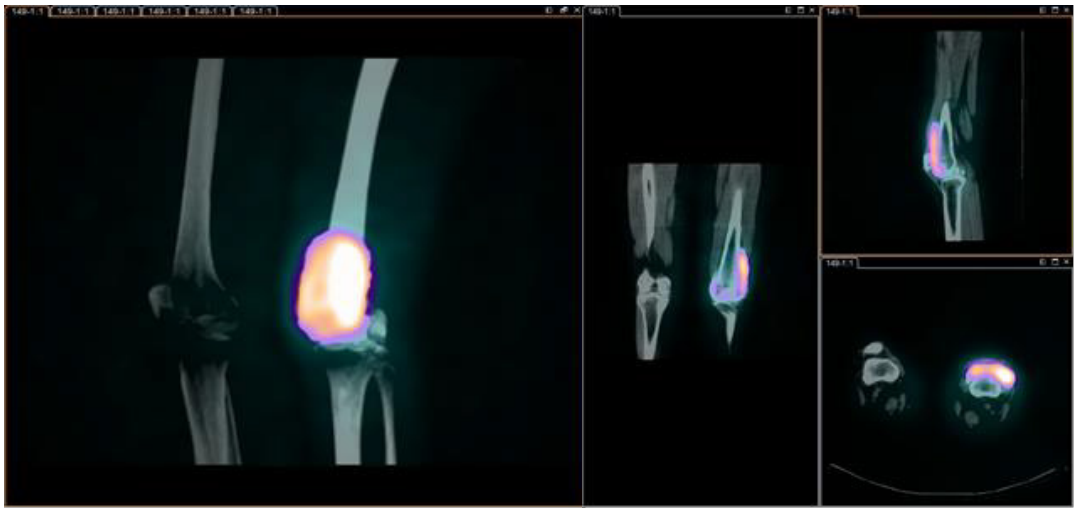

Figure 6. *PET scan, one hour after ^{90}Y administration, showed no leakage of the colloid into the extra-articular space.*

istration.[14] In a similar study by Oztemür et al, the recurrence rate was 0% over a follow-up period of 4.15 years.[15] Additionally, it seems that arthroscopic synovectomy in conjunction with ^{90}Y administration, increased patient-reported satisfaction rates.[16]

The safety profile of ^{90}Y is optimal as confirmed by direct post-administration scintigraphy. In a study of 30 cases, scintigraphy performed 24 hours post-^{90}Y administration, failed to identify any extra-articular leakage of the radiological agent. [3] In our case, we performed scintigraphy one hour after the radiotherapy for insurance cover reasons and for our patient's convenience.

In conclusion, meticulous arthroscopic synovectomy with adjuvant administration of ^{90}Y seems to be a safe method to prevent local recurrence in patients with PVNS. The adjuvant radio-synovectomy has no significant risks including environmental or extra-articular leakage. It is well tolerated by the patients with increased satisfaction rates and is also associated with decreased pain and improved joint function. Finally, it does not require hospitalization or prolonged rehabilitation.

It is necessary to mention that RSV is not a *panacea* and its therapeutic effects are considerably worse in patients with co-existent osteoarthritis and advanced joint degeneration. Therefore, meticulous patient selection is strongly recommended.

Despite its advantages, radionuclide synovectomy is not routinely used at present. Therefore, additional studies are necessary to assess the long-term efficacy of ^{90}Y adjunct treatment in controlling the recurrence rate of PVNS. There are no large series with long-term follow-up and a meta-analysis is still missing for safer conclusions. Regarding pharmaceutical targets, in the light of recent observations, CSF1/CSF1R interaction probably represents a more sensible therapeutic target than TNF-alpha blockade in the diffuse form of PVNS.[17]

The authors declared no conflicts of interest.

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