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Review

Pigmented Villonodular Synovitis: A Critical Review

Christopher D. Bernard, M.D.[1,2], Jacob L. Rooker, B.S.[1], Tucker D. Morey, M.D.[1], Rachel E. Long, B.S.[1], Kyle R. Sweeney, M.D.[1,2], Benjamin C. Powers, M.D.[1,3], Bryan G. Vopat, M.D.[1,2]

[1]University of Kansas School of Medicine-Kansas City, Kansas City, KS

[2]Department of Orthopedic Surgery

[3]Department of Medical Oncology

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INTRODUCTION

Pigmented villonodular synovitis (PVNS), also recognized as tenosynovial giant cell tumor (TGCT) or giant cell tumor of the tendon sheath (GCTTS), represents a benign, but locally aggressive neoplastic process that involves the synovial lining of joints. PVNS, TGCT, and GCTTS are essentially identical in clinical presentation and histology. This disease process likely occurs along a spectrum of severity; however, it is typically categorized into a local or diffuse form. Localized disease is often considered to comprise a well circumscribed soft tissue mass involving only a portion of the synovium; in diffuse disease, an ill-defined soft tissue mass is observed with involvement of most or all the joint synovia. The proliferation of synovial tissue and inflammation that occur with this condition most often presents with swelling, pain, decreased range of motion, and stiffness. This can produce rapid destruction of the articular cartilage and lead to early osteoarthritis (OA).

Believed to be the first reported case of TGCT, Chassaignac in 1852 described a nodular lesion of the synovial membrane of the flexor tendons in the fingers. This was originally thought to be a neoplastic process given its growth pattern and capacity to erode surrounding bone and joint tissue, as well as a high recurrence rate after resection. However, that assumption was brought into question in 1941 when Flandry et al.[1] and Tyler et al.[2] described this disease as an inflammatory process and proposed the term pigmented villonodular synovitis. More recent studies demonstrating clonal chromosomal aberrations have established the pathogenesis as neoplastic in origin.[3,4]

Etiology

In 2006, West et al.[5] provided a breakthrough in understanding the etiology and pathogenesis contributing to PVNS by confirming that translocations involving 1p11-13 are present in most patients with PVNS and demonstrated that colony stimulating factor-1 (CSF-1) is the gene located at this chromosome breakpoint. West et al.[5] found that 23 of 30 patients with TCGT and 5 of 8 patients with PVNS had a CSF-1 translocation, but only 2 - 16% of the tumor cells carried the translocation and expressed CSF-1. This suggests that only a minority of cells are neoplastic and that the majority of intratumoral cells are reactive, non-neoplastic cells, recruited by the local overexpression of CSF-1. A better understanding of the molecular pathways involved with PVNS has led to potential targets for medical management of this disease. Further understanding may generate future molecular targets for medications.

Clinical Presentation and Natural History

PVNS can be found throughout the body, but it is usually the large joints that are chiefly involved.[6,7] Of the large joints, the knee is the most frequently affected by a significant margin. In a study of 237 consecutive patients with a PVNS diagnosis, Xie et al.[7] demonstrated that 74% of cases involved the knee, 18% involved the hip, 3% involved the ankle or wrist, and 1% involved the shoulder or elbow. Rare locations for PVNS include the temporomandibular joint (TMJ) and the spine.[8,9] Localized PVNS in the knee can present in any area of the synovial tissue, however, most lesions will arise in the suprapatellar pouch, or Hoffa's fat pad.[10] For diffuse disease, lesions are predominantly found intra-articularly and mainly affect the knee.[6,7,10] Patients typically present in the third to fifth decades of life with an insidious onset of joint pain, swelling, and stiffness. Recurrent hemarthroses may also occur.[6,11] Rarely patients may present with mechanical symptoms. For superficial locations, a soft mass may be palpable on exam. Occasionally, a history of localized trauma may be reported. Gender predominance has varied in the literature. Initial radiographs often are normal in the early stages of disease, and with nonspecific symptoms, patients may be symptomatic for extended periods of time before diagnosis. One study found a mean delay from symptom onset to diagnosis to be 55 months.[12] This demonstrates the importance of considering PVNS in the differential for patients who present with joint swelling and/or joint pain.

PVNS may become symptomatic, thus limiting the activity and function of patients. The localized form typically is considered less aggressive than the diffuse type, and greater success has been observed when treating localized disease. In contrast, the diffuse type tends to be more aggressive, having a more rapidly destructive course, resulting in a poorer prognosis. While the continued presence or recurrence of PVNS in any joint can lead to cartilage destruction, this is more apparent in the hip joint. The progression of cartilage destruction and lytic lesions on both sides of the joint ultimately leads to significant arthritis.[11]

Diagnosis

Accurately diagnosing PVNS often is challenging as patients typically present with nonspecific symptoms of joint pain and swelling, and the prevalence of PVNS is low compared to other conditions that result in identical presenting symptoms. Patients routinely are misdiagnosed with other conditions, such as rheumatologic disorders, trauma, meniscus injuries, or infection, prior to a diagnosis of PVNS. Flandry et al.[13] found that only 17% of patients were correctly diagnosed with PVNS prior to referral. In general, PVNS should be considered in the differential in any inflammatory arthritis. If patients do not respond to initial treatment, more diagnostic workup should be considered to rule out PVNS.[14]

Multiple imaging modalities are frequently used to help diagnose PVNS, while excluding other conditions to narrow the diagnosis. Radiographs often are the first imaging study obtained (Figure 1). In most cases, radiographs reveal nonspecific features including soft tissue swelling, joint effusion, degenerative joint disease, or a normal appearance.[15-18] Well defined erosions with relative preservation of joint

space may be noted in early phases of the disease. Cystic lesions, often symmetric on either side of the joint line in a non-weight-bearing region of the joint, or at the capsular insertion site, without calcification, may be suggestive of PVNS. With progression of the disease, joint space narrowing may occur concentrically, especially when involving joints with minimal volume capacity such as the hip.[5,17]

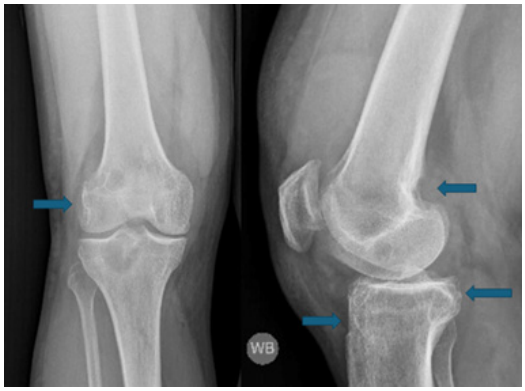

Figure 1. X-ray of right knee demonstrating pigmented villonodular synovitis. Anterior-Posterior (Left) and Lateral (Right) views demonstrating multiple erosions in the lateral femoral condyle and proximal tibia, large joint effusion, and degenerative changes.

Magnetic resonance imaging (MRI) often is the imaging study of choice to further evaluate a patient with nonspecific symptoms of joint pain, intermittent swelling, and possible mechanical symptoms. Not only can an MRI assist in ruling out more common etiologies for these nonspecific symptoms at presentation, but there are pathognomonic features present on MRI which highly suggest PVNS as the diagnosis (Figure 2). The signal characteristics observed on MRI reflect the histological composition of the diseased tissue, particularly the hemosiderin deposition, lipids, fibrous stroma, and inflammatory cells. This is represented as nodular masses with heterogeneous low signal intensity on both T1 and T2 weighted sequences with blooming artifact. This "blooming artifact," which is most characteristic of PVNS, is best appreciated on gradient echo sequences and represents the increased signal dropout from the presence of hemosiderin. MRI also plays an instrumental role in determining localized versus diffuse forms, as well as the extent and specific location of the lesion. This information is important for treatment strategy and possible surgical planning.[15,18,19] Although MRI can be extremely helpful in suggesting the diagnosis of PVNS, histologic confirmation with a tissue biopsy remains the gold standard.

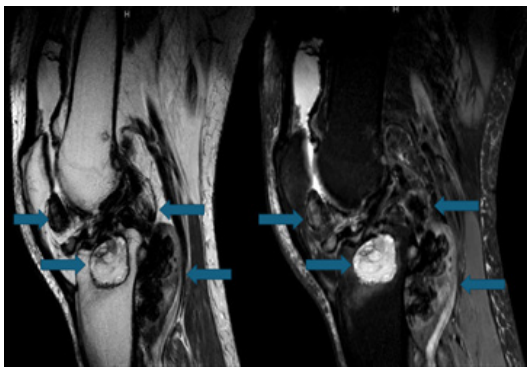

Figure 2. MRI of right knee demonstrating pigmented villonodular synovitis. T1 (Left) and T2 (Right) sagittal sequences showing nodular masses diffusely in both the anterior and posterior compartments of the knee with heterogenous low signal intensity. A large joint effusion and large tibial cyst are also noted.

Management

Surgical

Localized PVNS. Numerous treatment regimens exist in the management of localized PVNS, including observation with serial imaging, open excision, arthroscopic excision, or combined arthroscopic and open excision. With advancements in arthroscopic techniques, arthroscopic partial synovectomy is considered the preferred surgical option. The primary aim of surgical management is to resect all the diseased synovium to prevent local recurrence and reduce the risk of OA. Much of the current literature focuses on treatment outcomes for the knee as this is the most involved joint. Multiple studies involving surgical treatment of the knee have demonstrated excellent results. A systematic review performed by Auregan et al.[20] demonstrated low recurrence rates of disease (8.7% and 6.9%) and low complication rates (<1% and 0%) with no significant differences between open synovectomy and arthroscopic synovectomy, respectively. A more recent case series by Patel et al.[10] similarly demonstrated no significant difference in recurrence rates between open and arthroscopic synovectomy, respectively (8.7% vs 9.1%). Additionally, excellent functional results are likely to be observed after surgical treatment. Dines et al.[21] showed a mean post-operative Lysholm score of 95.4 for patients treated with arthroscopic synovectomy at least five years of follow-up. All patients had full range of motion of their knee and had no concerns of pain, locking, clicking, or swelling. Despite low recurrence rates with arthroscopic treatment, concern for recurrence exists, principally with posterior based lesions. This is a result of the technically challenging nature of an arthroscopic posterior synovectomy due to anatomical blind spots when viewing this space from an anterior portal. However, newer arthroscopy techniques have been described to help visualize the knee's posterior compartment.[22] In localized disease of the posterior compartment of the knee in 10 patients who underwent arthroscopic synovectomy, Shekhar et al.[23] demonstrated no recurrence of disease or symptoms and a mean International Knee Documentation Committee subjective score of 85 post-operatively. For surgeons with less arthroscopy experience, an arthroscopic assisted mini open partial synovectomy can be considered as a safe alternative. Georgiannos et al.[24] compared an arthroscopically assisted mini open technique to an all-arthroscopic technique and found similar post-operative Lysholm scores, as well as recurrence rates between the techniques.

Treatment efficacy in other joints with localized PVNS have not been as well studied to date as the knee. However, available studies have demonstrated similar results to that found for arthroscopic treatment of lesions in the knee.[25-27] In a recent large multicenter database study by Mastboom et al.[28] on localized PVNS of large joints, they demonstrated no significant difference in recurrence rates on multivariate analysis when comparing arthroscopic to open treatment. A lesion size of >5 cm was found to result in a significant increase in recurrence of disease.

Overall, both open and arthroscopic excision of localized PVNS lesions produce good to excellent outcomes with low recurrence and

complication rates. Initial treatment with arthroscopy, however, may tend to be favored in many cases with an experienced arthroscopist as lower rates of morbidity, pain, and stiffness may be associated with arthroscopic compared to open treatment.

Diffuse PVNS. Best treatment practices for diffuse PVNS of large joints remain controversial. Higher rates of disease recurrence are routinely reported despite varying surgical treatment options when compared to treatment of localized disease. In a meta-analysis by Mollon et al.,[29] they demonstrated that patients with localized PVNS treated surgically had a recurrence rate of 7% compared to 28% in patients treated surgically with diffuse disease. Several studies have sought to determine the efficacy of arthroscopic versus open versus a combined approach with results having varied significantly throughout the literature. Regardless of treatment approach, complete resection is required to reduce the likelihood of recurrence. Patel et al.[10] demonstrated in 102 patients treated operatively for diffuse PVNS of the knee, a significantly higher rate of recurrence with arthroscopic treatment compared to open synovectomy (83.3% vs 44.8%). It also was noted that most complications occurred in patients who underwent an open procedure. In contrast, multiple case series have demonstrated good to excellent results following arthroscopic treatment for diffuse PVNS of the knee, with low recurrence and complication rates reported at final follow up.[30,31] It is important when performing an arthroscopic synovectomy for diffuse disease to utilize multiple accessory portals. The advantages of performing an isolated arthroscopic synovectomy include minimizing post-operative stiffness, shorter rehabilitation period, and fewer wound complications.[32] Other comparison studies have demonstrated no significant difference in recurrence rates between arthroscopic and open synovectomy. A systematic review by Auregan et al.[20] for diffuse PVNS of the knee found no significant difference in recurrence rates between arthroscopic compared to open synovectomy (16.1% vs 22.6%), with a significant difference in complication rates which favored arthroscopy (0 vs 19%). A more recent meta-analysis by Chandra et al.[33] demonstrated a 1.56 times higher rate of recurrence for diffuse PVNS of the knee when treated arthroscopically compared to an open approach. Some surgeons have performed a combined arthroscopic and open approach which has demonstrated potentially more promising results for diffuse disease. Mollon et al.[34] demonstrated a recurrence rate of 13% in 15 patients with good to excellent outcomes in all patients treated with combined arthroscopic and open synovectomy for diffuse disease. Colman et al.[35] compared a series of patients treated with combined arthroscopy and open synovectomy to patients treated with just arthroscopy or open synovectomy alone and found that recurrence rate for the combined group was significantly lower at 9% compared to 62% and 64%, respectively.

Again, limited data are available for treatment outcomes of PVNS involving other large joints. Nazal et al.[26] reported on a small series of five patients with diffuse type PVNS of the hip treated with arthroscopic synovectomy. No recurrence of disease was reported, and outcome scores were lower than patients treated arthroscopically for localized disease, however, this was not significantly different. Byrd et al.[25] reported good to excellent outcomes in patients treated arthroscopically for PVNS of the hip. The mean Harris Hip Score (HHS) improved from 62 pre-op to 89 post-op (scores <70 poor, 70 - 80 fair, 80 - 90 good, 90 - 100 excellent). Three of these patients had diffuse PVNS with a mean improvement of 38 points in the HHS. A systematic review by Siegel et al.[27] evaluating patients with PVNS of the foot and ankle treated with either open or arthroscopic synovectomy demonstrated a recurrence rate of 21% which is comparable to the results for other joints in the literature. However, the complication rate was higher than that seen in other joints at 24%. One explanation for the increased complications in treatment of the foot and ankle may be related to the poorer blood circulation compared to other large joints which may impact the healing potential. Additionally, there is a tendency to perform an open rather than arthroscopic procedure which may trend towards an increase in the complication rate.

Radiation

Radiation therapy either alone or as an adjuvant therapy following operative treatment may be considered in an attempt to reduce recurrence rates of disease. Results have been mixed, and the side effect profile of radiation must be considered as well. O'Sullivan et al.[36] published one of the earlier reports on utilizing external beam radiation in patients with PVNS. In this study the recurrence rate was 7% which is comparable or better than other studies in the literature. Additionally, most patients experienced good to excellent functional outcomes. Similar results were found by Chien et al.[37] in patients with diffuse PVNS of the knee treated with open synovectomy followed by moderate radiation dose therapy in which the recurrence rate was 8.3% compared to 57% in patients treated with open synovectomy alone. These results, however, were not reproducible for their patients treated with arthroscopic synovectomy. Sun et al.[38] compared outcomes of patients with PVNS of the hip who underwent arthroscopic synovectomy to those who underwent arthroscopic synovectomy plus adjuvant radiotherapy. They found that hip outcomes scores and Visual Analog Scale pain scores were comparable between the two groups and no patients who underwent adjuvant radiotherapy converted to total hip arthroplasty (THA) compared to 38% in the group without radiotherapy. Despite some promising results, caution must be taken when considering this adjunct as radiation is not a benign therapy. Radiation induced sarcoma or significant wound complications can develop.[37,39] It is unknown whether the potential benefit of radiation therapy following synovectomy outweighs its potential complications in the treatment of a benign process.

Medical Management

With significant advances in molecular biology and an improvement in the understanding of underlying molecular pathways involved in various conditions, medicines are being developed to act specifically on these targets. The discovery of overexpression of CSF-1 as the etiology which chiefly contributes to the development of PVNS, has provided a molecular target for potential medical management of this condition.

Pexidartinib. Pexidartinib acts as a CSF-1 receptor inhibitor, thereby restricting PVNS growth.[40-42] In a phase three randomized

clinical trial[41] (ENLIVEN study) of 120 patients (61 receiving pexidartinib, 59 receiving Placebo) with symptomatic, advanced PVNS in which surgery was not recommended, patients who received pexadartinib demonstrated improved outcomes of their disease compared to placebo. The overall response rate of the disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) was 39% in the pexidartinib group compared to 0% for placebo at 25 weeks. Additionally, the pexadartinib group demonstrated a significant improvement in physical functioning compared to placebo.[41] Given these notable benefits, this became the first FDA approved drug specifically for the treatment of PVNS. Despite significant benefits, adverse events occurred in 98% of patients who received pexidartinib with the most common event being hair color changes. Grade three (severe) or four (life-threatening) adverse events did occur in 44% of patients, which were often increases in liver enzymes. Serious hepatotoxic side effects were experienced by eight people taking pexidartinib, however, three people recovered after discontinuing the medication.[41] As a result, this medication is currently only available in the U.S. via the Risk Evaluation and Mitigation Strategy (REMS) Program.[40]

Patients considered candidates for this medication are predominantly those with inoperable diffuse disease or in which surgical resection would be associated with worsening function and would likely cause severe morbidity.[41,43] This medication is available as an oral capsule, with a recommended dosage of 250 mg twice daily.[44,45] Continued use of pexidartinib is indicated until evidence of either disease progression or drug toxicity occurs. Ongoing monitoring via frequent liver testing is required.[40-42] Studies evaluating outcomes following operative management with adjuvant medical therapy have yet to be performed.

Imatinib. Imatinib acts as an inhibitor of macrophage colony stimulating factor (M-CSFR) activation of non-neoplastic PVNS cells.[46] Most commonly utilized for chronic myeloid leukemia and gastrointestinal stromal tumors, the effect of imatinib on PVNS was first reported on a single patient. Blay et al.[46] first reported the use of imatinib in a patient with PVNS with promising initial results from a case report demonstrating complete remission by the fifth month after starting imatinib. The course of treatment was interrupted a few months later with observed disease relapse, but a second complete remission was documented shortly after re-introducing imatinib.[46] In a study of 62 patients with PVNS, Verspoor et al.[47] demonstrated an overall response rate of disease based on RECIST of 31% in those taking imatinib. Additionally, symptom improvement was found in 78% of patients.

Use of this medication is reserved for those with symptomatic recurrence of PVNS following surgery, or in instances where surgical re-excision would detrimentally affect function.[46-48] It is available as an oral tablet, with recommended dose of either 100 mg, 400 mg, or 600 mg once daily. Optimal treatment duration has yet to be elucidated. Continued use is indicated without progression of disease or evidence of drug toxicity. The most common adverse effects are edema, muscle cramping, musculoskeletal pain, abdominal pain, nausea, vomiting, diarrhea, rash, or fatigue.[47,48]

Salvage. The goal of treatment in patients with PVNS is to reduce symptoms, improve clinical outcomes, minimize recurrence rates, and decrease the risk of cartilage and soft tissue destruction that leads to early OA and ultimately worsening pain and function. Total joint arthroplasty can be considered as a salvage option for significant recurrent disease with associated degenerative changes and if all other options have failed.[49,50] While data are limited, some promising results have been observed following hip and knee arthroplasty in patients with PVNS.[51,52] Houdek et al.[51] presented a series of 48 patients with PVNS who underwent total knee arthroplasty (TKA). The local recurrence rate of disease was 13%. They found that patients who had undergone at least two procedures to remove PVNS from the knee were significantly more likely to have recurrence following TKA. The overall 10-year revision free survival rate was 80%. Revisions were most performed for tumor recurrence and component loosening. The complication rate of 52% is notably higher compared to patients who undergo TKA for primary OA with most complications being related to joint stiffness.[51] Casp et al.[53] also demonstrated a significantly increased rate of stiffness in patients with PVNS who underwent TKA compared to a control matched cohort of patients with primary OA (6.8% vs 4.7%), although the overall rates were significantly lower than the previously mentioned study. The infection rate also was found to be higher at two years at 3.3% in patients with PVNS compared to 1.5% in the OA group, although rates of ER visits, hospital readmission, revision TKA at two years and death at one year were not found to be significantly different between the matched groups.[53]

Despite a paucity of literature, results of THA in patients with hip PVNS are encouraging. Xu et al.[54] compared 19 patients with PVNS who underwent a THA to matched controls and found no significant difference between groups with respect to revision rates and HHS at final follow-up. Additionally, there was no evidence of recurrence of disease in the PVNS cohort.[54] Tibbo et al.[11] also demonstrated good outcomes in 25 patients with PVNS who underwent THA. Only one patient was noted to have disease recurrence, which was determined at 24 years post-operatively. However, a high complication rate was noted in this study, which was most commonly aseptic loosening. All patients with aseptic loosening were noted to have uncross-linked polyethylene components. In contrast, all patients with highly cross-linked polyethylene liners did not demonstrate any loosening for a survivorship free of revision at 10 years of 100%. The mean HHS at final follow-up was 78, significantly improved from pre-operative scores.[11] Overall, the available literature demonstrates good outcomes in patients with PVNS who undergo total joint arthroplasty as a salvage option for treatment. However, surgeons should remain cautious about complications, as this has routinely been found to be higher in this patient population.

Summary

PVNS represents a benign neoplastic process that involves the synovial lining of joints, most commonly affecting the knee when involving the large joints. This disease process occurs along a spectrum of severity, divided into localized and diffuse forms. The proliferation of synovial tissue and inflammation that occurs with this condition may present with swelling, pain, and stiffness. These non-specific symptoms, as well as the limited occurrence of this disease process, often leads to a delay in

initial diagnosis and treatment. Advanced imaging with MRI is helpful in suggesting a diagnosis of PVNS, but histology is necessary to confirm the diagnosis.

Best management practices for the treatment of PVNS have yet to be elucidated at this time and may vary depending on the extent of the disease. Both arthroscopic and open synovectomy have been found to be effective for the treatment of localized disease, with a potential preference to arthroscopic synovectomy given low complication rates and good functional outcomes after the procedure. Controversy remains for diffuse disease treatment as outcomes have varied amongst studies. Medical therapy with pexidartinib or imatinib may be considered as stand-alone therapy, an adjunct therapy to surgery, or for patients who are not surgical candidates. More investigation is required to optimize their effect while minimizing the side effect profile. If these methods fail to treat the disease process, promising results have been observed with total joint arthroplasty in patients who develop severe or recurrent disease and progress to significant OA, although a higher rate of complications has been observed compared to total joint arthroplasty for primary OA.

REFERENCES

[1] Flandry F, Hughston JC. Pigmented villonodular synovitis. J Bone Joint Surg Am 1987; 69(6):942-949. PMID: 3597511.
[2] Tyler WK, Vidal AF, Williams RJ, Healey JH. Pigmented villonodular synovitis. J Am Acad Orthop Surg 2006; 14(6):376-385. PMID: 16757677.
[3] Nilsson M, Höglund M, Panagopoulos I, et al. Molecular cytogenetic mapping of recurrent chromosomal breakpoints in tenosynovial giant cell tumors. Virchows Arch 2002; 441(5):475-480. PMID: 12447678.
[4] Sciot R, Rosai J, Dal Cin P, et al. Analysis of 35 cases of localized and diffuse tenosynovial giant cell tumor: A report from the Chromosomes and Morphology (CHAMP) study group. Mod Pathol 1999; 12(6):576-579. PMID: 10392632.
[5] West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A 2006; 103(3):690-695. PMID: 16407111.
[6] Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented villonodular synovitis: A retrospective single-center study of 122 cases and review of the literature. Semin Arthritis Rheum 2011; 40(6):539-546. PMID: 20884045.
[7] Xie GP, Jiang N, Liang CX, et al. Pigmented villonodular synovitis: A retrospective multicenter study of 237 cases. PLoS One 2015; 10(3):e0121451. doi: 10.1371/journal.pone.0121451. PMID: 25799575.
[8] Roguski M, Safain MG, Zerris VA, et al. Pigmented villonodular synovitis of the thoracic spine. J Clin Neurosci 2014; 21(10):1679-1685. PMID: 24938389.
[9] Wang DD, Luo HY, Guo CB, Meng JH. Clinical and immunohistochemical analysis of diffuse tenosynovial giant cell tumour of the temporomandibular joint. Int J Oral Maxillofac Surg 2020; 49(7):882-888. PMID: 32014315.
[10] Patel KH, Gikas PD, Pollock RC, et al. Pigmented villonodular synovitis of the knee: A retrospective analysis of 214 cases at a UK tertiary referral centre. Knee 2017; 24(4):808-815. PMID: 28442184.
[11] Tibbo ME, Wyles CC, Rose PS, Sim FH, Houdek MT, Taunton MJ. Long-term outcome of hip arthroplasty in the setting of pigmented villonodular synovitis. J Arthroplasty 2018; 33(5):1467-1471. PMID: 29352684.
[12] Ma X, Shi G, Xia C, Liu H, He J, Jin W. Pigmented villonodular synovitis: A retrospective study of seventy-five cases (eighty-one joints). Int Orthop 2013; 37(6):1165-1170. PMID: 23503697.
[13] Flandry F, Hughston JC, McCann SB, Kurtz DM. Diagnostic features of diffuse pigmented villonodular synovitis of the knee. Clin Orthop Relat Res 1994; (298):212-220. PMID: 8118978.
[14] Willimon SC, Busch MT, Perkins CA. Pigmented villonodular synovitis of the knee: An underappreciated source of pain in children and adolescents. J Pediatr Orthop 2018; 38(8):e482-e485. PMID: 23503697.
[15] Al-Nakshabandi NA, Ryan AG, Choudur H, et al. Pigmented villonodular synovitis. Clin Radiol 2004; 59(5):414-420. PMID: 15081846.
[16] Friedman T, Chen T, Chang A. MRI diagnosis of recurrent pigmented villonodular synovitis following total joint arthroplasty. Hss j 2013; 9(1):100-105. PMID: 24426852.
[17] Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res 2017; 103(1s):S91-s97. PMID: 28057477.
[18] Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: Radiologic-pathologic correlation. Radiographics 2008; 28(5):1493-1518. PMID: 18794322.
[19] Lin J, Jacobson JA, Jamadar DA, Ellis JH. Pigmented villonodular synovitis and related lesions: The spectrum of imaging findings. AJR Am J Roentgenol 1999; 172(1):191-197. PMID: 9888766.
[20] Aurégan JC, Klouche S, Bohu Y, Lefèvre N, Herman S, Hardy P. Treatment of pigmented villonodular synovitis of the knee. Arthroscopy 2014; 30(10):1327-1341. PMID: 24999007.
[21] Dines JS, DeBerardino TM, Wells JL, et al. Long-term follow-up of surgically treated localized pigmented villonodular synovitis of the knee. Arthroscopy 2007; 23(9):930-937. PMID: 17868831.
[22] Moran J, Miller MD, Schneble CA, Yalcin S, Katz LD, Medvecky MJ. Arthroscopic synovectomy for tenosynovial giant cell tumor/pigmented villonodular synovitis in the posterior knee using the posterior trans-septal portal technique. JBJS Essent Surg Tech 2022; 12(1). PMID: 35685235.
[23] Shekhar A, Patil SS, Dixit C, Tapasvi SR. Localized pigmented villonodular synovitis of posterior compartment of the knee. J Orthop Surg (Hong Kong) 2017; 25(3):2309499017727923. PMID: 28847242.
[24] Georgiannos D, Boutsiadis A, Agathangelidis F, Papastergiou S, Karataglis D, Bisbinas I. Arthroscopically-assisted mini open partial synovectomy for the treatment of localized pigmented villonodular synovitis of the knee. A retrospective comparative study with long-term follow up. Int Orthop 2017; 41(5):925-930. PMID: 27866235.
[25] Byrd JW, Jones KS, Maiers GP, 2nd. Two to 10 Years' follow-up of arthroscopic management of pigmented villonodular synovitis in the hip: A case series. Arthroscopy 2013; 29(11):1783-1787. PMID: 24209675.
[26] Nazal MR, Parsa A, Gibbs JS, Abraham PF, Martin SD. Mid-term results of arthroscopic synovectomy for pigmented villonodular synovitis of the hip. Arthroscopy 2020; 36(6):1587-1598. PMID: 32061973.
[27] Siegel M, Bode L, Südkamp N, et al. Treatment, recurrence rates and follow-up of tenosynovial giant cell tumor (TGCT) of the foot and ankle-A systematic review and meta-analysis. PLoS One 2021; 16(12):e0260795. PMID: 34855875.
[28] Mastboom MJL, Staals EL, Verspoor FGM, et al. Surgical treatment of localized-type tenosynovial giant cell tumors of large joints: A study based on a multicenter-pooled database of 31 international sarcoma centers. J Bone Joint Surg Am 2019; 101(14):1309-1318. PMID: 31318811.
[29] Mollon B, Lee A, Busse JW, et al. The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee: an individual patient meta-analysis. Bone Joint J 2015; 97-b(4):550-557. PMID: 25820897.
[30] Cheng YH, Lin YH, Tseng IC, Chan YS. A case series of intra-articular diffuse pigmented villonodular synovitis of the knee: Prognosis of complete synovectomy under arthroscopic surgery. J Orthop Surg (Hong Kong) 2021; 29(2):23094990211022042. PMID: 34114516.
[31] Keyhani S, Kazemi SM, Ahn JH, Verdonk R, Soleymanha M. Arthroscopic treatment of diffuse pigmented villonodular synovitis of the knee: Complete synovectomy and septum removal-midterm results. J Knee Surg 2019; 32(5):427-433. PMID: 29727868.
[32] Chang JS, Higgins JP, Kosy JD, Theodoropoulos J. Systematic arthroscopic treatment of diffuse pigmented villonodular synovitis in the knee. Arthrosc Tech 2017; 6(5):e1547-e1551. PMID: 29354472.
[33] Chandra AA, Agarwal S, Donahue A, Handorf E, Abraham JA. Arthroscopic versus open management of diffuse-type tenosynovial giant cell tumor of the knee: A meta-analysis of retrospective cohort studies. J Am Acad Orthop Surg Glob Res Rev 2021; 4(12). PMID: 34882586.
[34] Mollon B, Griffin AM, Ferguson PC, Wunder JS, Theodoropoulos J. Combined arthroscopic and open synovectomy for diffuse pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc 2016; 24(1):260-266. PMID: 25308157.

[35] Colman MW, Ye J, Weiss KR, Goodman MA, McGough RL, 3rd. Does combined open and arthroscopic synovectomy for diffuse PVNS of the knee improve recurrence rates? Clin Orthop Relat Res 2013; 471(3):883-890. PMID: 22996360.
[36] O'Sullivan B, Cummings B, Catton C, et al. Outcome following radiation treatment for high-risk pigmented villonodular synovitis. Int J Radiat Oncol Biol Phys 1995; 32(3):777-786. PMID: 7790264.
[37] Chien JC, Wei YP, Chen CY, et al. Long-term functional outcomes of diffuse pigmented villonodular synovitis of knee: The role of adjuvant radiotherapy. Medicine (Baltimore) 2021; 100(12):e23794. PMID: 33761628.
[38] Sun H, Ju XD, Huang HJ, Zhang X, Wang JQ. Clinical outcomes of endoscopic synovectomy with adjuvant radiotherapy of pigmented villonodular synovitis of the hip: A case series of single center. BMC Musculoskelet Disord 2022; 23(1):192. PMID: 35236301.
[39] Bickels J, Isaakov J, Kollender Y, Meller I. Unacceptable complications following intra-articular injection of yttrium 90 in the ankle joint for diffuse pigmented villonodular synovitis. J Bone Joint Surg Am 2008; 90(2):326-328. PMID: 18245592.
[40] Palmerini E, Longhi A, Donati DM, Staals EL. Pexidartinib for the treatment of adult patients with symptomatic tenosynovial giant cell tumor: Safety and efficacy. Expert Rev Anticancer Ther 2020; 20(6):441-445. PMID: 32297819.
[41] Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): A randomised phase 3 trial. Lancet 2019; 394(10197):478-487. PMID: 31229240.
[42] Van De Sande M, Tap WD, Gelhorn HL, et al. Pexidartinib improves physical functioning and stiffness in patients with tenosynovial giant cell tumor: Results from the ENLIVEN randomized clinical trial. Acta Orthop 2021; 92(4):493-499. PMID: 33977825.
[43] Spierenburg G, van der Heijden L, van Langevelde K, et al. Tenosynovial giant cell tumors (TGCT): Molecular biology, drug targets and non-surgical pharmacological approaches. Expert Opin Ther Targets 2022; 26(4):333-345. PMID: 35443852.
[44] Benner B, Good L, Quiroga D, at al. Pexidartinib, a novel small molecule CSF-1R inhibitor in use for tenosynovial giant cell tumor: A systematic review of pre-clinical and clinical development. Drug Des Devel Ther 2020; 14:1693-1704. PMID: 32440095.
[45] Monestime S, Lazaridis D. Pexidartinib (TURALIO™): The first FDA-indicated systemic treatment for tenosynovial giant cell tumor. Drugs R D 2020; 20(3):189-195. PMID: 32617868.
[46] Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol 2008; 19(4):821-822. PMID: 18296418.
[47] Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. Sci Rep 2019; 9(1):14551. PMID: 31601938.
[48] Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer 2012; 118(6):1649-1655. PMID: 21823110.
[49] Tan YC, Tan JY, Tsitskaris K. Systematic review: Total knee arthroplasty (TKA) in patients with pigmented villonodular synovitis (PVNS). Knee Surg Relat Res 2021; 33(1):6. PMID: 33632334.
[50] Yoo JJ, Kwon YS, Koo KH, Yoon KS, Min BW, Kim HJ. Cementless total hip arthroplasty performed in patients with pigmented villonodular synovitis. J Arthroplasty 2010; 25(4):552-557. PMID: 19356895.
[51] Houdek MT, Scorianz M, Wyles CC, Trousdale RT, Sim FH, Taunton MJ. Long-term outcome of knee arthroplasty in the setting of pigmented villonodular synovitis. Knee 2017; 24(4):851-855. PMID: 28552192.
[52] Lin W, Dai Y, Niu J, Yang G, Li M, Wang F. Pigmented villonodular synovitis does not influence the outcomes following cruciate-retaining total knee arthroplasty: A case-control study with minimum 5-year follow-up. J Orthop Surg Res 2020; 15(1):388. PMID: 32894157.
[53] Casp AJ, Browne JA, Durig NE, Werner BC. Complications after total knee arthroplasty in patients with pigmented villonodular synovitis. J Arthroplasty 2019; 34(1):36-39. PMID: 30266323.
[54] Xu C, Guo H, Bell KL, Kuo FC, Chen JY. Pigmented villonodular synovitis does not influence the outcome following cementless total hip arthroplasty using ceramic-on-ceramic articulation: A case-control study with middle-term follow-up. J Orthop Surg Res 2018; 13(1):294. PMID: 30458820.

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