

UNRESECTABLE PIGMENTED VILLONODULAR SYNOVITIS (PVNS)

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CASE PRESENTATION

A 42 year old male with no comorbidities presented in the OPD of Plastic Surgery complaining of swelling in left ankle for 3 to 4 years and associated with pain for 2 to 3 years.

According to the patient, the swelling was initially smaller over the medial aspect of ankle which then gradually increased in size extending up to the lateral aspect during the 3-4 years period associated with on and off dull pain on movement. The patient had an incisional biopsy of the swelling done outside LNH, showing pigmented villonodular synovitis. It was done in December 2012.



Fig. 1. Gross specimen

On examination, the swelling appeared on medial aspect of ankle extending upto the lateral side. It was soft, non-compressible, non-pulsatile and non-reducible. overlying skin colour was normal. Sensations were intact and incisional biopsy wound was seen on the medial aspect.

The patient underwent surgery for excision of whole swelling and wound coverage. The wound was covered with a rotation flap + SSG. Tissue was sent for histopathology. MRI was done in February 2013 postoperatively after 4 weeks.

HISTOPATHOLOGY DETAILS

GROSS EXAMINATION

Specimen was received in formalin in two containers coded as medial malleolus and lateral malleolus, consisting of multiple irregular grayish brown pieces of tissue measuring 7cm in aggregate from container A and approximately 6cm in aggregate from container B (Fig.1).

MICROSCOPIC EXAMINATION

Microscopic sections examined from specimen coded as medial and lateral malleolus revealed multiple fragments of synovial tissue with papillary projections on the surface and marked synovial hyperplasia. Granulation tissue, dense lymphoplasmacytic infiltrate and sheets of polygonal cells with abundant eosinophilic cytoplasm, foamy and hemosiderin laden histiocytes

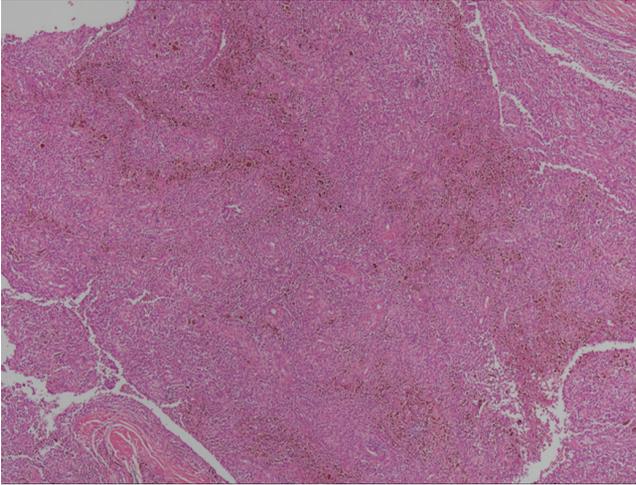


Fig. 2. Pigmented villonodular synovitis H & E - 4x

were appreciated. Scattered foci of multinucleated giant cells were also seen. Occasional mitosis i.e. 0-1/10HPF was noted. No evidence of infiltrative growth pattern, significant cytological atypia, necrosis or increase mitoses (cut off >10/10HPF) was seen (Fig.2).

DIAGNOSIS

Pigmented Villonodular Synovitis (PVNS)

RADIOLOGY DETAILS

Patient had Magnetic Resonance Imaging (MRI) of left ankle done which showed lobulated synovial based soft tissue mass along the posterior aspect of ankle joint adjacent to flexor hallucis longus tendon associated with extensive synovial thickening and nodularity around ankle joint. It showed abnormal signals appearing hypointense on all pulse sequences. Posteriorly, it was extending in between peroneus brevis and flexor hallucis longus muscles, abnormal signals were also identified in adjacent bones, predominantly in subchondral region of tibia, talus bone, lateral malleolus of fibula and calcaneum. These represent bony erosions secondary to synovial proliferations.

MRI typically shows mass-like synovial proliferation with lobulated margins in Pigmented Villonodular Synovitis. This may be extensive in the diffuse form or limited to a well-defined single nodule in the localized form. MR imaging findings of prominent low signal intensity masses on T(1)-weighted (T1WI) and

T(2)-weighted (T2WI) are nearly pathognomonic of this diagnosis. These lesions are best seen on Fast Field Echo (FFE) sequence.

TUMOUR BOARD DISCUSSION

Participants included plastic surgeon, rheumatologist, histopathologist, radiologist and radiation oncologist.

How should this patient be managed further?

- a. Additional Surgery
- b. Chemotherapy
- c. Radiotherapy
- d. Observation with imaging

The operative findings were unusual in that the lesion was in thin polythene like sac with jelly like liquid material simulating a bunch of grapes. This was extending into intra-articular spaces and causing erosions. It encased the hemovascular bundles all around the ankle and extended into the muscle plane up to 5-8cm above the ankle joint. Thus, complete excision was not possible without compromising vital structures. Hence, for surgical excision to be meaningful, joint excision or amputation below the knee would have been required.

Histopathological comment on excision was not possible as the specimen was received in multiple pieces which did not include bone and bony invasion could not be determined. However, post-operative MRI showed slight worsening with re-growth of the lesion. Surgical resection, which is usually curative, in this case was complicated by the location of the lesion. Due to the rarity of Pigmented Villonodular Synovitis (PVNS), extensive studies are not available, however, case series reporting improvement with Radiation therapy after incomplete surgical resection are found. Usually the outcome of post radiation is excellent without the requirement of high doses of radiation and the joint function remains uncompromised. Therefore, Radiation therapy was a strongly recommended option.

The other option was based on the tissue biology of PVNS. In this lesion, there was synovitis involving fibroblast proliferation and macrophage infiltration. These cells are also involved in Rheumatoid arthritis which is treated with immunosuppressive agents

such as methotrexate. However, there is no literature available on the use of such chemotherapy in PVNS. Systemic or intra-articular methotrexate should be an option worth considering.

OVERVIEW

1. RHEUMATOLOGIST'S PERSPECTIVE

Research into Pigmented Villonodular Synovitis (PVNS) is difficult because of the rarity of the disorder and most series have had very few patients or have grouped cases from different anatomical sites. In 1941 Jaffe, Lichtenstein, and Sutro introduced this term to describe a 'yellow-brown tumour-like tenosynovial lesion'[1]. The salient histological features they described were: deposition of haemosiderin and infiltration of histiocytes and giant cells in a fibrous stroma within the synovium of tendon sheaths and large joints. There is synovial fibroblast proliferation as described in our patient. PVNS falls in the category of tenosynovial giant cell tumours (TGCT) which are uncommon pathologic entities affecting the synovium and tendon sheath in young adults. These benign neoplasms can be divided into the localized or nodular type and diffuse type. Localized or nodular type affects the smaller joints of the fingers and is generally extra-articular. Diffuse type affects larger joints and is often

intra-articular, infiltrative and includes PVNS[2].

In the absence of any clear knowledge of the pathogenesis, or of any large prospective studies, treatment of PVNS has been predominantly surgical. Since it is a non-malignant disorder, radical treatment is not indicated, however suboptimal treatment leads to recurrence (30 to 50%)[3]. In our case where total excision was not possible, we used additional combined treatment approach with radiotherapy and chemotherapy.

Radiotherapy has been used with good results, mostly for recurrences but also for primary disease[4,5]. Isotopic synoviorthesis using Yttrium 90 or Rhenium 186 has been reported as adjunctive therapy to surgical resection[5]. We went further and treated the patient with systemic methotrexate (25mg/week subcutaneously) as well. We planned to continue this therapy for six months. Though there is no evidence of this in the literature, the extent of our patient's disease and difficulty of resection combined with high probability of recurrence necessitated this measure. This decision was based on the pathogenic similarity between PVNS and rheumatoid arthritis (RA) where macrophages and synovial fibroblast proliferation is involved. Interestingly, radiation synovectomy has previously been used in rheumatoid arthritis as well[6]. Methotrexate was chosen due to its effectiveness in rheumatoid arthritis (RA) and its affordability.

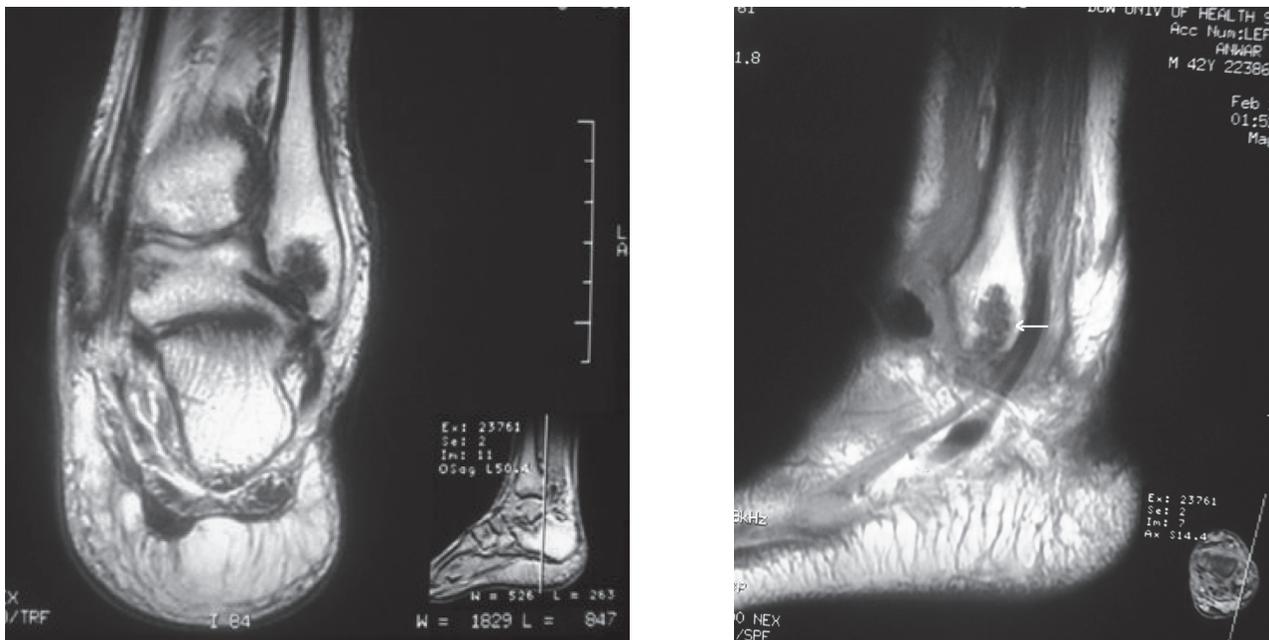


Fig. 3 a, b. MRI ankle coronal and sagittal TIW images showing lobulated low signal intensity masses causing pressure erosions along lateral malleolus

Patient would be monitored for improvement with musculoskeletal ultrasound (MSKUS).

Immunohistology of the synovial tissue of a patient with PVNS demonstrated an infiltrate mainly consisting of CD68+ macrophages with abundant presence of TNF- α [7]. The treatment of this patient with Infliximab, a monoclonal antibody inhibiting TNF- α , resulted in remission of the disease after 5 months of therapy. Interestingly, methotrexate 10mg/week was given in combination with infliximab[7].

PVNS is thought to be driven by the overexpression of colony stimulating factor-1 (CSF1), expressed by a minority of proliferating cells, which, in turn attract inflammatory cells that express CSF1 receptor (CSF1R) through a paracrine effect[8]. Imatinib has been shown to block CSF1R[9] and through this mechanism, treat locally advanced PVNS[10].

Intra-articular radioisotope therapy after surgical resection with injections of P_{32} in PVNS have also shown success in an institutional trial with local control of the disease ranging from 70% - 88%[11]. Similarly, intraarticular adalimumab and etanercept have been shown to cause clinical and radiological regression of PVNS[12,13]. In our patient, if systemic methotrexate would not be effective on MSKUS monitoring, we plan to give intra-articular methotrexate. Anti-TNF- α agents may also be considered if clinically indicated and economically feasible for the patient.

2. RADIATION ONCOLOGIST'S PERSPECTIVE

PVNS and radiation therapy

Pigmented villonodular synovitis is an uncommon proliferative disorder of uncertain aetiology of synovial membranes with invasive and expansive growth patterns. Radical synovectomy is the treatment of choice but because of high rate of recurrence, adjuvant radiation therapy (RT) has been evaluated with positive results.

Due to the rarity of this disease, there have been no randomized trials but German Cooperative Group on Radiotherapy in Benign Diseases (GCG-BD) conducted national patterns of care (PCS) study in 2008-2009. Structured questionnaire was mailed to all 227 radiation therapy institutions in Germany to assess all treatments, the radiation therapy indication and

techniques, the rate of local control, the functional outcome and possible adverse effects related to radiation therapy. Ten per cent of the 227 institutions (22 institutions) presented clinical experience with the use of radiation therapy for PVNS. From this database, a total of 41 treated sites from [14] institutions were evaluated for long term analysis. The primary therapeutic approach was cyto-reductive surgery in all cases and in cases of residual disease or complete resection of extensive local recurrence, radiation therapy was applied in 39 cases (95.1%). An excellent or good functional outcome was noted in 34 cases (82.9%). The use of RT was not associated with early or late toxicity greater than RTOG Grade II[14].

Literature search from international electronic databases identified 19 published studies from 1940-2009 which represented 140 cases. After a follow up ranging from 1-250 months and administration of radiation dose in the range of 1600cGy-5000cGy, the overall rate of local control was 84.5%. Literature review demonstrates that radiation therapy is a very safe and effective treatment option for the prevention of disease progression or recurrence in pigmented villonodular synovitis after primary surgical interventions[15]. The planned treatment volume should include the whole synovial space and eventually all invasive components of the disease.

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