Pigmented villonodular synovitis

Monoclonality and metastasis—a case for neoplastic origin?

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We report a 48-year follow-up of a case of recurrent pigmented villonodular synovitis of the knee. Subcutaneous metastasis to the contralateral thigh was an unusual finding. Histology demonstrated fibroblastic and histiocytic proliferation, as well as increased mitotic activity in recurrent lesions. Cytogenetic analyses demonstrated monoclonality and chromosomal abnormalities. Our findings support a neoplastic origin of this lesion.

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Case report

A 35-year-old woman presented at another hospital in 1943 with minor symptoms and a swelling in her left popliteal fossa. At operation a multilobulated structure resembling a ganglion occupied the whole popliteal fossa. The mass was excised without subsequent histological examination.

In 1945, she presented with discomfort in her left knee. A hard 1 cm mobile intraarticular mass was found on the medial aspect of her left knee. In addition, a larger mass was felt on the lateral aspect of the knee. At arthrotomy a 2 cm oblong, pedunculated growth was seen medially and excised from the synovium. A larger lateral mass, similar to the first, was also excised through a separate arthrotomy. No other abnormalities were noted. Both specimens were submitted for histological examination and a diagnosis of giant cell fibrosarcoma was made (Figure 1). Consequently, the patient received 10 treatments with radiotherapy. The dose, however, was not mentioned in the medical records.

In 1947, a new growth was excised from the left knee in the region of the patella. Histological examination revealed inflammatory and giant cells with no malignancy and the patient remained symptom-free for the next 34 years.

In 1981, at the age of 74 years, the patient was referred to our institution with a lump in the popliteal fossa of her left knee. Fine needle biopsy suggested the presence of an osteoclastoma or giant cell tumor of the tendon sheath. Subsequently, a 2 × 2 cm tumor was marginally excised from the posterior capsule of the knee (Figure 2).

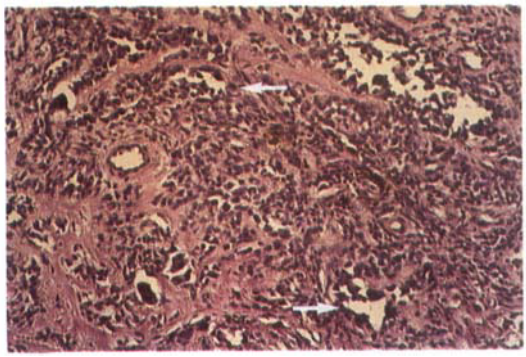


Figure 1. Giant cell tumor biopsy from 1945 with pseudoglandular spaces (arrows). HE ×185.

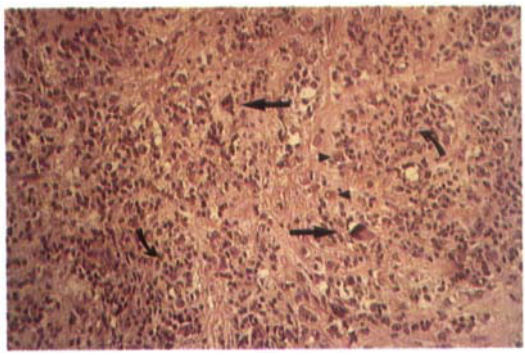
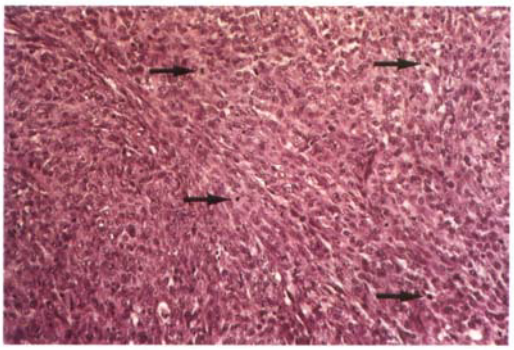


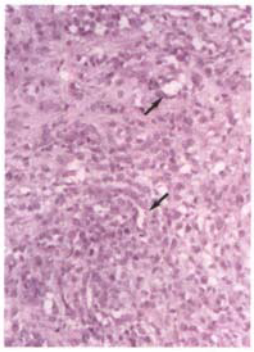
Figure 2. Recurrent tumor (1981) with histiocytes (arrow heads), fibroblasts (curved arrows) and multinucleated giant cells (straight arrows). HE ×185.

In 1984, the patient again noticed swelling of her left knee and examination revealed a 4 × 5 cm soft tissue mass with a diffuse border situated medially

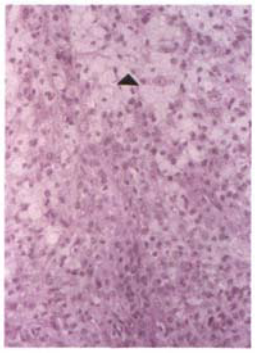
Figure 3. Second local recurrence in right thigh (1993). HE ×185.



High cellularity and mitotic activity (arrows).



Regular fibroblasts, pseudoglandular spaces (arrows).



Numerous foamy histocytes (arrowhead). HE ×185.

over the tibial tuberosity. Fine needle biopsy showed giant cells with no evidence of malignancy. Exploration of the knee revealed an extensive soft tissue tumor that was fixed to the back of the knee joint and femur with skin and intramuscular extensions. The popliteal vessels and nerves lay plastered to the tumor. The tumor was firm and lobulated, with an appearance of pigmented villonodular synovitis (PVNS). The intimate relationship between the tumor and vital structures precluded extirpation and therefore only a confirmatory biopsy was performed.

The patient refused amputation for the control of her disease and agreed to radiotherapy instead. She received 20 Gy in 2 Gy fractions between April and May of 1984. This failed to control progression of her disease and in November of 1985, the patient received 185 MBq of intraarticular Yttrium-90. A subsequent knee arthroscopy showed fibrotic changes in the suprapatellar pouch as well asa reddish-brown and hypertrophic synovium lining the intercondylar notch. In addition, there were many osteoarticular erosions in the intercondylar notch. The tumor continued to enlarge and in 1987 the patient agreed to an above-knee amputation. Dissection of the amputated specimen revealed massive intra- and extraarticular tumor with intraosseous and soft tissue extension. There were several satellite lesions within the proximity of the tumor.

5 years (1992) after amputation, the patient returned with a recurrence on her amputation stump. This was marginally excised. Several months after this, the patient reported a 2 × 2 cm, firm, smooth, subcutaneous lump in the lateral aspect of her contralateral thigh. It was not fixed to underlying tissue or overlying skin. Aspiration cytology of the mass was consistent with PVNS. The lesion was marginally excised and the previous diagnosis of PVNS remained unchanged.

1 year later, the patient, now aged 83 years, noted a further subcutaneous lesion at the site of the previous surgery on her right thigh. The second lesion was firm, oval-shaped, measuring approximately 2 × 3 cm and was fixed neither to the skin nor to the underlying deep fascia. It was not tender and there was no overlying skin reaction or edema. No inguinal lymphadenopathy was noted. The lesion was again marginally excised and found to be composed of 3 distinct nodular masses (Figure 3).

Investigations and results

Histology

8 biopsy specimens between 1945 and 1993 were available for diagnostic re-evaluation. 6 biopsies (1945–1992) were from the left knee region, including the amputation material (1987) and the recurrence in the amputation stump (1992). The last biopsies came from the right thigh (1992 and 1993). The histological sections were stained with hematoxylin eosin and van Gieson (Table 1).

Electron microscopy from the latest tumor (1993) revealed numerous fibroblast-like cells with dilated rough endoplasmic reticulosis. A great number of histiocytes containing lysosomes and vacuoles were also present. Both types had long slender filopodia. A few cells had single membrane-bound bodies containing hemosiderin. No cell contacts were observed.

Clonality studies

Frozen operative tissue samples from the amputated limb in 1987 and the contralateral soft tissue recurrence in 1993 were available for DNA extraction and X chromosome inactivation analysis (Vogelstein et

Table 1. Summary of histological, clonality and cytogenetic analyses

Sample year	Site	Histological characteristics									Histopathology[a]	Clonality analyses	Cytogenetic analyses
		A	B	C	D	E	F	G	H	I			
1945	(L) Knee (Figure 1)	+++	+++	–	+++	+	–	+++		+++	NS		
1981	(L) Knee (Figure 2)	+++	+++	+++	+	+++	+++	+++	+	+++	VNS	–	–
1984	(L) Knee	+++	+++	–	+++	+	–	–		+	NS	–	–
1986	(L) Knee	+++	+++	+++	+++	+	+++	+		+++	VNS	–	–
1987	(L) Above knee amputation	+++	+++	+++	+	+	+++	–	+	–	Diffuse VNS	X chrom inactivation	Normal karyotype
1992	Amputation stump	+++	+	+++	+	+	–	–		+	Diffuse VNS outside a joint	–	Poor growth
1992	(R) Thigh	+++	+++	+++	+	++	+	–	+	–	Diffuse VNS outside a joint	–	–
1993	(R) Thigh (Figures 3 and 4)	+++	+	+	+	+++	+++	–	+	–	NS outside a joint	X chrom inactivation (same as 1987)	Abnormal karyotype[b]

A Fibroblasts and histiocytes, B Giant cells, C Foamy histiocytes, D Collagen, E Mitoses, F Necrosis, G Hemosiderin deposits, H Normal tissue infiltration, I Vascularity; + occasional, ++ several, +++ many

[a] NS nodular synovitis, VNS villonodular synovitis

[b] 47,X,-X,del(1)(p32), add(3)(q21),+der(5)t(5;8)(p15;q22),+i(7)(q10),der(8)t(1;8)(p13;q11),der(13)t(5;13)(q11;p11), add(16)(p11),der(21), t(8;21)(q13;q22)[13]/46,idem,–10,add(19) (q13)[3]/46,XX[7]

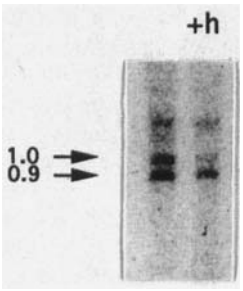


Figure 4. Southern blot analysis of tissue from PVNS. 3 bands are visible in each lane. The PGK probe hybridized with 1.0 (upper arrow) and 0.9 kb (lower arrow) DNA fragments. The 1.0 kb fragment represents the active X chromosome. The lane labeled +h represents DNA that received additional enzyme digestion with HpaII. Note the almost complete elimination of the 1.0 kb signal in lane +h. The residual signal reflects contamination of normal polyclonal tissue. Each lane contains 5 µg DNA.

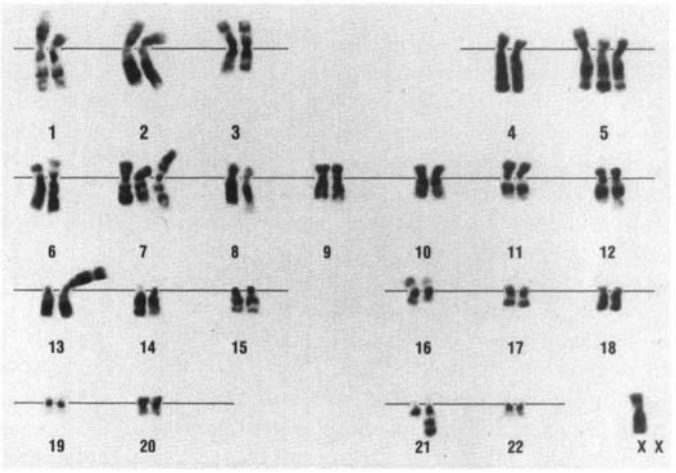


Figure 5. Representative karyogram from the largest subclone.

al. 1987). DNA was subjected to digestion with the restriction enzymes PstI and BstXI revealing a polymorphism of the X chromosomal gene, PGK. Samples from the two recurrences were then divided into two aliquots, one of which was further digested with the methylation-sensitive enzyme HpaII. After agarose gel electrophoresis and Southern transfer, the filters were hybridized to a probe from the PGK gene. The findings indicate a monoclonal origin at both tumors (Figure 4; Table 1)

Cytogenetic analysis

Cytogenetic studies were performed on fresh operative samples in 1987, 1992 and 1993. Short-term cultures (Mandahl et al. 1988) were initiated and chromosome preparations made after 3–10 days. G-banding was obtained with Wright's stain and any chromosomal aberrations were classified according to the ISCN (1991). A massively rearranged genome was found in the third sample (Figure 5; Table 1).

Discussion

Scant reports of PVNS do not help to resolve the etiology of this condition, though the majority of articles suggest an inflammatory pathogenesis. Jaffe and co-workers (1941) concluded that their observation of hyperplastic stromal cells in a milieu of hyalinized collagen was consistent with an inflammatory process. Electron microscopic evidence of hemosiderin-laden macrophages and fibroblasts synthesizing collagen and proteoglycan lend further support to this concept (Hirohata 1968). In contrast, Rao and Vigorita (1984) demonstrated the presence of a centrifugal growth pattern of the PVNS tissue as well as distinct differences between the lesional tissue and the adjacent hyperplastic synovial tissue. They concluded from these findings that PVNS was a true neoplastic process.

There were histological similarities between this case and those reported by Rao and Vigorita (1984). We found both microscopic and ultrastructural evidence of proliferating synovial fibroblasts or primitive mesenchymal cells as well as histocyte-like cells (Figure 2). In addition, we saw greater mitotic activity in recurrent lesions (Figure 3). While many have classified PVNS as inflammatory, we concur with Rao and Vigorita that the peripheral nature of inflammatory changes, together with the nodular appearance, mitotic activity and propensity for recurrence after inadequate removal, contradicts this classification.

The diagnosis of giant cell fibrosarcoma in 1945 was reassessed and a revised diagnosis of nodular synovitis was made (Figure 1). The multiple manifestations of PVNS and, in particular, abnormalities of the fibrous stroma and presence of giant cells are known to mimic sarcomatous tumors. Subsequent histological findings of soft tissue giant cell tumor, without evidence of malignancy in this case, support the overall diagnosis of PVNS.

There was no histological evidence of malignant change during any stage of treatment. Therefore, it was particularly striking to find tissue consistent with PVNS in a distant nonsynovial site long after the initial diagnosis and subsequent amputation of the primary site. Metastasis has been noted in one previous report of PVNS, but only following malignant change to a malignant giant cell tumor of the tendon sheath on its second recurrence (Ushijima et al. 1985).

Clonality studies have suggested a monoclonal origin of most types of various human neoplasms (Fialkow 1971). Cytogenetic evidence of clonality in PVNS was first alluded to by Ray and co-workers (1990) who observed trisomy 7 in 35 percent of metaphases obtained from short-term in vitro cell cultures. In our study, evaluation of operative tissue from 1987 and 1993 showed an X-chromosome inactivation pattern consistent with monoclonality. Another case of PVNS studied by the same technique was reported to be of polyclonal origin (Sakkers et al. 1991). The authors concluded that PVNS is more likely to be a reactive process than a true neoplasm because of their findings. They, however, did not comment on the possibility that polyclonality may be the result of a large number of cells contaminating the tissue analyzed. Our findings raise the possibility of monoclonality in this disease which, lends weight to the case for a neoplastic origin.

The normal karyotype at the first cytogenetic analysis may be interpreted either as PVNS cells with submicroscopic mutations or as the karyotype of dividing stromal cells. We believe our findings are more in keeping with the latter explanation because overgrowth of fibroblasts is a common phenomenon in cultures of solid tumors. The massively rearranged genome detected by the third analysis is highly suggestive of aberrations from a monoclonal neoplastic cell population. In this regard, Fletcher and co-workers (1992) demonstrated non-random aberrations in uncultured cells of PVNS, while Mertens and coworkers (1993) demonstrated other clonal structural and numerical chromosomal aberrations in 3 of 5 tenosynovial giant cell tumor specimens. Thus, the only recurrent aberrations detected in tenosynovial giant tumors to date are +5 and +7. However, this information should be used with caution, as there have been reported cases of clearly non-neoplastic tumors presenting with chromosomal anomalies involving +7 (Guerneri et al. 1991, Johansson, et al. 1993). Nevertheless, it is interesting to speculate whether the trisomic alterations of the short arm of chromosome 5 and tetrasomy of the long arms of chromosome 5 and 7 that were found in our case also evolved from cells showing only +5 and +7. We could not demonstrate other cytogenetic denominators common to the present and previously reported cases.

Radiotherapy is a recognized tumorigenic agent. Our patient received 3 separate courses of radiation as part of her treatment. One may speculate that the 35 years between her first course of radiotherapy in 1946 and her presentation in 1981 might have given sufficient time for any malignant change to become evident. However, at no stage following this course did the tissue from the irradiated sites exhibit malignant change. Considering the limited dosages used in 1984 and 1985, it would be reasonable to assume

that the time between these 2 radiation treatments (1984 and 1985) and her subsequent above-knee amputation (1987) was insufficient for any malignant change to occur. Although the chromosomal changes observed in the sample from 1993 accord with the previously described cytogenetic patterns in PVNS, it is possible that the radiotherapy may have influenced the karyotype. Only one other report refers to a case of PVNS treated with radiotherapy where the patient was followed for 48 years (Kindblom and Gunterberg 1978). There was no evidence of histological evolution to a more malignant character in that case either. The lack of reports about these changes, specifically in PVNS, makes a more definite conclusion difficult, though it seems unlikely that radiation was an etiological factor in the genetic aberrations noted.

Acknowledgements

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