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Case Report

An unusual complex karyotype in myopericytoma

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abstract

Introduction: Myopericytoma is a perivascular neoplasm commonly found in the skin and soft tissue of extremities. These lesions often exhibit concentric vascular proliferation of spindle shaped myoid cells.

Methods/Results: We present a case of a 76-year old male who was diagnosed with myopericytoma and subsequent cytogenetic analysis found a highly abnormal karyotype. This karyotype includes cytogenetic mutations that have not been described in previous case studies of myopericytoma.

Conclusions: Some of these aberrations occur on genes that are involved in hedgehog signaling as well as pericyte proliferation, indicating a potential pericyte origin for myopericytoma tumors.

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1. Introduction

Myopericytoma is a benign subcutaneous tumor with a prominent concentric perivascular growth pattern. Myopericytoma tumor cells usually exhibit oval or spindle-shaped morphology with multilayered growth surrounding blood vessels.¹ These tumors are predominately found within the subcutaneous tissues of distal extremities. Myopericytomas occur from the second decade of life onward, and with a reported slight male predilection.² Myopericytomas generally present as a painless slow growing nodule, less than 2 cm in diameter, and without invasion of adjacent structures.¹ On biopsy, their characteristic diagnostic feature is perivascular whorls of spindle to ovoid cells with eosinophilic cytoplasm.

Subendothelial proliferation of myopericytoma cells is frequently observed, and tumor cells predominantly bulging into the lumen of a vessel can be seen. Myopericytomas are generally well-circumscribed, however in some cases the spindle proliferation may extend along blood vessels outside of the demarcated lesion.¹ Most myopericytomas are immunoreactive for smooth muscle and muscle specific actin, with patchy desmin positivity.³ Investigators have argued that myopericytoma is part of a morphologic continuum with other perivascular tumors with smooth muscle differentiation, including myofibroma, angioleiomyoma, hemangiopericytoma, glomangiopericytoma, and glomus tumor. To our knowledge, only a single cytogenetic abnormality has been reported in myopericytoma: t(7;12) resulting in an ACTB-GLI1 fusion product.⁴ However, a complex karyotype has never been

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reported in myopericytoma. The present case is that of benign myopericytoma arising from the soft tissues of the knee. Cytogenetic analysis showed a complex karyotype with multiple balanced and unbalanced translocations, which may shed light on the biology of this relatively rare mesenchymal tumor.

2. Report of the case

A 76-year-old male presented with an enlarging mass in the anterolateral superficial soft tissue of his right knee. The lesion had been present for two years, and had recently grown in size. The patient denied any associated pain, limitations in mobility, or systemic symptoms. The patient had a history of follicular lymphoma (in remission for over four years), osteoarthritis, hypertension and hypercholesterolemia. The mass was imaged using X-ray and magnetic resonance imaging (MRI). Radiographs demonstrated a soft tissue mass without calcification. No bony destruction, erosion, periosteal reaction or joint space changes were seen. Subsequent MR imaging demonstrated a T1 isointense, T2 hypertense, well-circumscribed mass measuring 2.6×1.8 cm in the subcutaneous soft tissues just anterolateral to the tibial tubercle (Fig. 1). There was minimal surrounding edema and no evidence of invasion into adjacent structures.

Ultrasound guided percutaneous core needle biopsy was performed on the tumor. Hematoxylin and Eosin (H&E) stained samples of the biopsy showed a moderately cellular proliferation of relatively uniform ovoid to spindled tumor cells with plump nuclei and modest amounts of eosinophilic cytoplasm. Cells showed a solid to perivascular 'whorled' arrangement (Fig. 2A,B). Thin-walled vessels lined by bland appearing endothelial cells were numerous, with a sparse collagenous stroma. Mitoses were rare (1/20 high powered fields). No histologic features suggestive of malignancy were observed, including no significant cytologic atypia, no apoptotic bodies, no necrosis and no atypical mitotic figures.

Immunohistochemical staining demonstrated diffuse reactivity for α Smooth Muscle Actin (α SMA) (Fig. 2C,D) and focal patchy reactivity for Desmin (Fig. 2E,F). All other stains were negative including epithelial markers (Pankeratin cocktail), melanocytic markers (S100, HMB45 and MART1), and histiocytic markers (CD68 and CD163). Endothelial markers (CD31, CD34) were negative in tumor cells, and highlighted the numerous thin walled vessels. Based on the biopsy material, a diagnosis of myopericytoma was rendered.

Cytogenetic analysis of the biopsy specimen was performed, as is done routinely at our institution for all soft tissue tumors without a previous diagnosis. Results showed a complex karyotype in all cells analyzed. A stemline clone, 5 of 20 cells, exhibited $t(4;5)(p14;q33)$ (Fig. 3A). In addition to the stemline, 12 of 50 cells also exhibited: additional chromosomal material on the long arm of chromosome 3 (3q) (Fig. 3B); a balanced translocation involving the other copy of chromosome 4 and chromosome 21 [$t(4;21)$] (Fig. 3C); and a derivative chromosome 10 resulting from an unbalanced translocation between chromosomes 1 and 10 [$t(1;10)$] leading to trisomy 1q (Fig. 3D). Additionally, in 3 of 20 cells there was a balanced translocation between chromosome 13 and 22 [$t(13;22)$] (Fig. 3E). In summary the patient's karyotype was reported as: $46,XY,t(4;5)(p14;q33)[5]/$

Fig. 1 – Radiographic appearance. Magnetic resonance imaging demonstrated a well-circumscribed, soft tissue lesion without connection to the underlying tibia (see upper left corner of images). (A) T1 weighted image, demonstrating isointensity. (B) T2 weighted image, demonstrating hyperintensity.

$45-46,idem,add(3)(q21),t(4;21)(q31;q22),der(10)t(1;10)(q11;p15)[c p12]/46,XY,t(13;22)(q22;p13)[3]$. With the exception of $t(4;21)(q31;q22)$, which has been reported in cases of acute myeloid leukemia (AML)⁵ and T-cell acute lymphoblastic leukemia (T-ALL),⁶ none of the above abnormalities identified have been associated with neoplastic processes. As well, none of these cytogenetic abnormalities have been previously reported in myopericytoma.

Surgical excision was performed five months thereafter. The gross specimen showed a well-circumscribed, 3.0 cm, pink to tan solid mass. Routine histologic sections demonstrated a well-circumscribed, nodular neoplasm with numerous dilated, branching, 'hemangiopericytoma-like'

Fig. 2 – Histological appearance of biopsy. (A,B) H&E stained sections show spindled cells in a concentric, perivascular arrangement around thin-walled blood vessels. (C,D) α Smooth Muscle Actin (α SMA) immunohistochemistry showed strong, diffuse staining. (E,F) Desmin immunohistochemical staining showed patchy positive reactivity. Scale bar indicates 100 μ m.

thin-walled vessels (Fig. 4A). High magnification showed a similar cytomorphology to the biopsy specimen, without cellular atypia or atypical mitotic figures (Fig. 4B). Focally, blood vessels just outside the main tumor mass showed perivascular tumor nodules, as can be seen in myopericytoma (Fig. 4C, lower left). In addition, tumor nodules seeming to arise from a large vessel wall were also observed (Fig. 4D). In sum, the histologic features were again consistent with a diagnosis of myopericytoma.

3. Discussion

Myopericytoma is a relatively rare soft tissue perivascular neoplasm, which shares features of other tumors with pericytic/smooth muscle differentiation.⁷ In this case, other diagnostic possibilities were entertained, including glomus tumor, leiomyoma/angioleiomyoma, and PEComa. In the case of glomus tumor, the cells lacked the characteristic nuclear features of centrally placed, enlarged round to ovoid nuclei with granular chromatin and well-demarcated cell membranes. Although smooth muscle differentiation was observed by immunohistochemistry, the histologic appearance did not support a diagnosis of leiomyoma/

angioleiomyoma, as well formed fascicles of elongated tumor cells were not seen. Although PEComa was an initial consideration in this case, lack of melanocytic marker expression made the diagnosis of PEComa unlikely. Given the anatomic location, radiographic and histologic findings, we consider a diagnosis of myopericytoma to be most appropriate. The complex karyotype found in this case was unexpected, and to our knowledge without precedent in the literature.

In order to determine candidate genes affected by the cytogenetic abnormalities, we identified all coding genes on all loci involved by translocation or deletions in our case. Based on known function, genes with potential relevance were identified, and are discussed below.

As mentioned, myopericytoma and glomus tumor have been described as having pericytic differentiation. Although still unknown, the cellular origins of myopericytoma may well be vessel-lining pericytes themselves. In our case, one gene associated with pericytes was identified as falling within regions involved by the balanced translocation t(4;5)(p14;q33): PDGFRB (Platelet derived growth factor receptor β). PDGFRB (present on 5q33), although non-specific, is a defining marker of pericytes. PDGF ligands bind to PDGF receptor tyrosine-kinases which homo- or heterodimerize. PDGF/PDGFR β signaling has been shown to have a significant role in pericyte

Fig. 3 – Abnormal Karyotype. (A) Cytogenetic analysis found a translocation between chromosomes 4 and 5. (B) Cells also exhibited an addition on the long arm of chromosome 3, (C) a balanced translocation between chromosomes 4 and 21, (D) and a derivative chromosome 10 from an unbalanced translocation of chromosomes 1 and 10. (E) Additionally there was a balanced translocation between chromosomes 13 and 22.

proliferation and recruitment to blood vessels.⁸ Although there is no single marker that covers all pericyte types, the combination of PDGFR β and CD146 has been used successfully for the *in situ* identification of pericytes using immunohistochemistry.⁹ Moreover, the analysis and purification of pericytes via

flow cytometry and fluorescence activated cell sorting has been reported using these antigens.⁹ Although PDGFR β has important functions in pericytes, it is by no means specific and is expressed in a number of normal cell types, including fibroblasts,⁸ and diverse tumors such as meningioma,¹⁰ soft

Fig. 4 – Histological appearance of resection specimen. (A) H&E stained sections show a well-circumscribed, nodular tumor with prominent thin-walled, branching blood vessels, 40x. (B) High magnification show spindled cells in a concentric, perivascular arrangement, 200x. (C) Perivascular tumor nodules are apparent, lower left, 40x. (D) Perivascular tumor nodules are also seen to indent larger blood vessels, 40x.

tissue tumors (such as leiomyoma, leiomyosarcoma, and rhabdomyosarcoma),¹¹ and mesothelioma,¹² to name a few.

As mentioned, the only previously reported fusion product in myopericytoma is ACTB-GLI1.⁴ This fusion product results in activation of GLI1, one of three zinc finger GLI transcription factors and central mediators of the Hedgehog signaling pathway. Briefly, the hedgehog signaling pathway for Sonic Hedgehog (SHH) and Indian Hedgehog (IHH) proteins is a highly conserved three-step process: 1. hedgehog (HH) ligands are activated by protein cleavage and covalent lipid modifications¹³; 2. activated HH ligand binds to the receptor Patched (PTCH) an inhibitory regulator; 3. this binding releases the transmembrane protein Smoothened (SMO), which interacts with glioblastoma family of transcription factors (GLI1, GLI2 and GLI3).¹⁴ Hedgehog signaling dysregulation, due to a germline mutation of PTCH1, causes hereditary forms of basal cell carcinoma.^{15,16} Further proof for the role of PTCH1 as a tumor suppressor comes from PTCH1 knockout mice, who uniformly develop basal cell carcinoma by 16 weeks of life.¹⁷ In myopericytoma, a distinctive t(7;12)(p21-22;q13-15) karyotype results in ACTB-GLI1 fusion, with overamplification of a central mediator of the HH signaling pathway, the transcription activator GLI.^{18,19}

In our patient, a gene associated with Hedgehog signaling regulation was identified at the balanced translocation t(4;21)(q31;q22): HHIP (Hedgehog interacting protein). HHIP, a natural HH antagonist, inhibits PTCH1 induction by SHH by binding to the HH protein and a transcriptional target of HH signaling.²⁰ In various human carcinomas (including liver, lung, and colon), HHIP expression is downregulated when compared to normal tissues,²¹ potentially associated with tumor neovascularization. Conversely, HHIP is upregulated in basal cell carcinoma and has been investigated as a tumor associated antigen for immunoprevention of basal cell carcinoma in a mouse model.²² In summary, HHIP dysregulation has known roles in tumor biology; evidence from this unique patient karyotype suggests the further possibility of Hedgehog signaling derangement in myopericytoma.

In summary, we present a case of a myopericytoma with characteristic clinical, radiographic, and histologic findings, but with a complex karyotype. To our knowledge, this is the first description of a complex karyotype in myopericytoma. Candidate genes based on the regions of translocations have been identified, including gene markers of pericytes and regulatory elements in Hedgehog signaling.

Conflicts of interest

All authors have none to declare.

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