

Primary multicentric angiosarcoma of bone: true entity or metastases from an unknown primary? Value of comparative genomic hybridization on paraffin embedded tissues

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Abstract

Multicentric primary angiosarcoma of bone has been described as a distinct entity from bone metastases from angiosarcoma. Bone angiosarcoma accounts for less than 1% of sarcomas. It has dismal prognosis overall, but the multicentric expression does not confer worse prognosis. We describe the case of an old male with bone angiosarcoma of the extremities with multicentric presentation. He soon after had soft tissue angiosarcoma of the head and neck. Histology and immunohistochemistry were consistent with the diagnosis of high-grade angiosarcoma. Comparative genomic hybridization on paraffin-embedded samples of the bone and head and neck samples suggested additional abnormalities in the bone fragment, thus suggesting that bone lesions were indeed metastatic from his head and neck angiosarcoma; although these preliminary analyses warrant confirmation in other similar rare cases. The patient died after 3 years of relapsed acute leukemia with progressive angiosarcoma.

Introduction

Angiosarcomas are intermediate/high-grade

vascular tumors.^{1,2} Bone and head and neck angiosarcomas both account for $\leq 2\%$ of sarcomas. Risk factors include prior radiation therapy, Paget's disease or metallic implants. Angiosarcomas are observed at any age with a peak between 60 and 80 years.¹ There is a male predominance and a predilection for bones of the hands and feet (74%). A third of bone angiosarcomas are multicentric at diagnosis.^{3,4} It is unknown whether multicentric bone angiosarcoma represents a metastatic entity or a true synchronous multifocal exclusively osseous disease.^{5,6} We present here the case of a multicentric bone angiosarcoma with metachronous head and neck soft-tissue angiosarcoma.

Case Report

A 69-year-old man with previous myeloid splenomegaly presented secondary acute myeloid leukemia (AML)(CD33+, 47XY, +9 and 49XY, +8, 10) in 2008. He underwent induction chemotherapy (aracytin/idarubicin), consolidation following remission, and allograft without total body irradiation. He underwent cyclosporin and steroid therapy for cutaneous graft versus host disease for six months. In April 2009, the patient, on remission from his AML, presented with painful swelling of the inferior extremity of his ulna. X-rays showed a destructive lytic mass with irregular borders and cortical erosion, complicated with spontaneous fracture. He underwent surgical biopsy, gross resection (curettage) and cementoplasty. Whole-body diagnostic work-up included X-rays of painful areas, blood tests, chest-abdomino-pelvic CT and bone scan. He had two other soap-bubble lytic lesions of his wrists (Figure 1) on X-rays, inT1-weighted hyposignal on MRI (Figure 1, right insert). Pathological specimen showed a high-grade tumor. On microscopy, round epithelioid tumor cells were separated by collagenous tissue, forming dense vascular channels and solid nests without necrosis (Figure 2A). Cells harbored enlarged nuclei of irregular shape and size with numerous mitoses and scant basophilic cytoplasm. Immunohistochemistry showed strong diffuse anti-CD31 (Figure 2B), CD34, FLI1 expression in tumor cells with Ki67 60%. Tumor cells were negative for anti-pancytokeratin antibodies AE1, AE3, EMA, desmin, protein S100, CD20, CD3, HHV8, LMP and D2.40. Centrally-reviewed diagnosis, within the French Sarcoma Group (FSG), was epithelioid high-grade angiosarcoma of bone. The patient, WHO performance status 1, underwent hypofractionated radiation therapy with concomitant low-dose weekly paclitaxel (25 mg/m²) on bone tumors. The patient experienced symptomatic relief and grade 2 radioder-

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matitis. One month later, the patient had a round centimetric lymphadenopathy in the submandibular area, metastatic on biopsy from his angiosarcoma. The patient had worsening limited mouth opening. CT and MRI revealed unresectable contrast-enhanced masses of the right parapharyngeal space. Histology showed poorly-differentiated angiosarcoma (Figure 2C) phenotypically comparable with his bone angiosarcoma (Figure 2D). Comparative Genomic Hybridization (CGH) performed on paraffin-embedded tissues, as previously described,⁷ upon patient consent and FSG approval, revealed gain of chromosomes 8 and 9, consistent with angiosarcoma. Genomic profiles were similar in bone and head and neck soft-tissue lesions (Figure 3A, B) suggesting tumor clonality. The bone fragment however presented additional 12p and 18p losses (Figure 3B, arrow) (Figure 3A). There was neither cMyc (8q24) amplification nor additional genomic instability. Profiles showed full chromosomes or chromosome arm alterations, rather indicated mitotic segregation instability.

The patient underwent conformal irradiation on gross head and neck disease with a complete response. He subsequently underwent 12 courses of radiation therapy on long bones, always with durable pain relief and consolidative effect. He had monthly zoledronate

therapy for eight months. He then developed multifocal destructive lesions of the extremities and skin nodules in October 2011. He underwent 3 cycles of doxorubicin with progressive disease. AML relapsed in June 2012. He died of AML in July 2012, 36 months after the diagnosis of angiosarcoma, which was progressive at last follow-up.

Discussion

Bone angiosarcomas can affect any portion of the skeleton: 33% occur in the axial skeleton, 33% in long tubular bones, and the remaining lesions in the small bones of the hands and feet, often involving multiple bones of the same extremity. The multicentric pattern of involvement of contiguous bones in primary bone angiosarcomas suggests a vascular origin for these tumors. The prognostic of primary angiosarcomas is poor (five-year survival 10-30%) but multicentricity does not seem to worsen it.^{8,9} Here, the patient presented with bilateral multicentric bone angiosarcoma of the extremities of the upper limbs. Bone angiosarcomas are usually not associated with soft-tissue lesions. Most angiosarcomas involve the skin or soft tissues, of which only 1-4% in the head and neck. Since 1977, <50 cases of head and neck angiosarcomas have been reported but seldom with bone metastases,¹⁰ and more favorable outcomes than other sites. Here the patient developed head and neck angiosarcoma, with metastatic node (observed in 45% of angiosarcomas).¹¹ Contrasting with median one-year survival of primary bone angiosarcomas, the patient survived three years. The *quasi*-coincidence of his multifocal bone lesions at onset and his head and neck lesions raised the question of two distinct entities. Histology was indeed consistent with angiosarcoma in both sites. Further, CGH analyses, performed on paraffin-embedded tissues,⁷ suggested that the bone lesions were indeed metastases of his head and neck primary. The multifocal bone angiosarcomas entity may be worth reassessment in light of the current case. In particular, whole-body imaging may be recommended in multiple angiosarcomas apparently limited to bone. The angiosarcoma arose in a heavily-pretreated patient (dose-intense chemotherapy without irradiation). Series of soft-tissue angiosarcomas showed altered expression of p53, p16, K-RAS and VEGFR2. c-MYC amplification is found in half angiosarcomas in irradiated tissues.¹² Our CGH analyses revealed gain of chromosomes 1q, 8 and 9 and alterations specific to bone lesion were loss of 12p and 18p entire regions. Altogether such alterations do not target specific genes and rather revealed mitotic defect. CGH analysis is of limited inter-



Figure 1. Soap bubble lesions, left (L) and right (R), where cement can be seen.

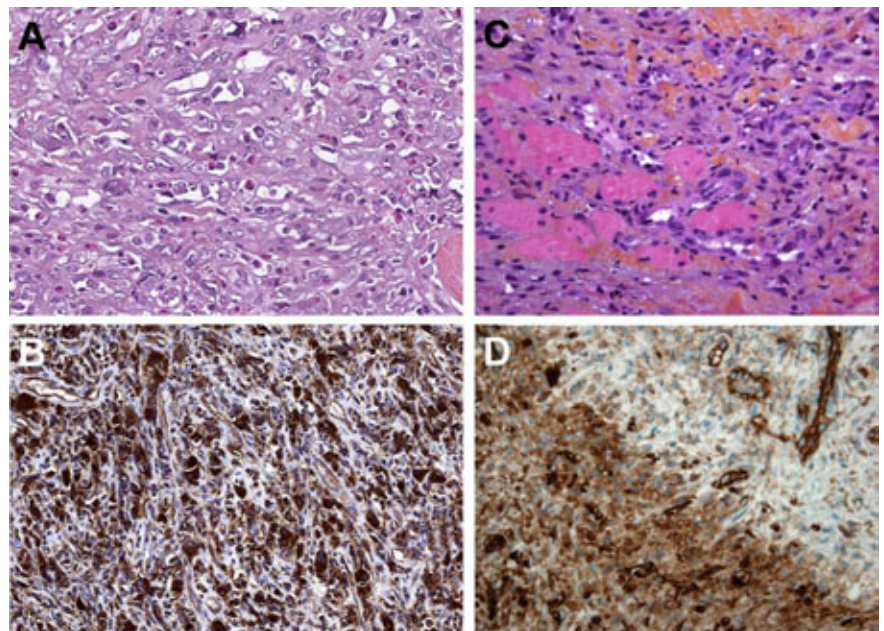


Figure 2. A) HES 200x; B) anti-CD31 100x; C) HES 40x; D) CD31 40x.

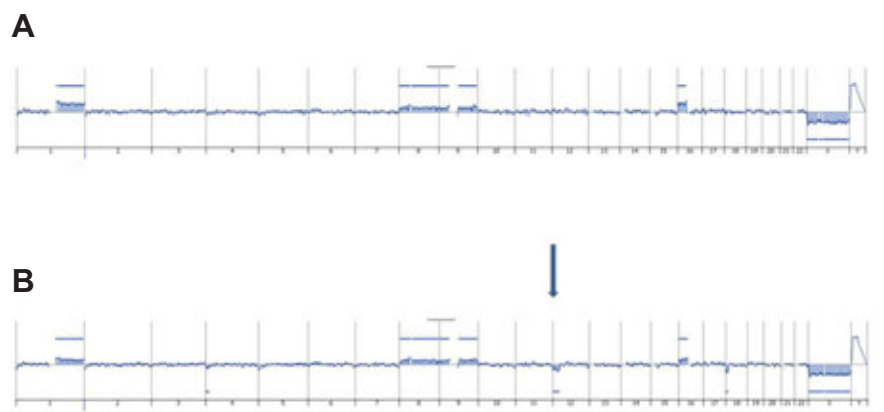


Figure 3. Comparative genomic hybridization; A) head and neck lesion; B) bone lesion.

est here to detect driver alterations since only quantitative alterations are detected by this approach and those alterations involve many genes. To go further in this analysis, high-throughput sequencing, *i.e.* exome sequencing or RNA sequencing, and search of t(1;14)(p21;q24) translocation could be a powerful alternative to detect point mutations and/or translocation.¹³

The optimal local treatment for multicentric bone angiosarcoma is not well defined. Chemotherapy consisted of paclitaxel and doxorubicin.¹⁴ The patient had excellent response at all irradiated sites. Such good response to definitive radiation therapy is rare in angiosarcomas.^{15,16} It has been described for some subtypes of sarcomas such as Kaposi sarcoma. The molecular reasons for his good response remain unknown. Also, his survival by far exceeds the median eight months survival of metastatic angiosarcomas, survival being however better if primary is from the head and neck region.

Conclusions

In conclusion, this case revealed metachronous occurrence of multicentric bone angiosarcoma and head and neck angiosarcoma. It calls into question the relevance of the multifocal bone angiosarcoma entity described in the literature and rather suggests that bony lesions are metastases of an occult angiosarcoma primary thus warranting whole-body diagnostic work-up.

References

1. Verbeke SL, Bertoni F, Bacchini P, et al. Distinct histological features characterize primary angiosarcoma of bone. *Histopathology* 2011;58:254-64.
2. Brouchet A, Amoretti N, Penel N, et al. Primary vascular tumors of bone. *Encyclopedie Medico-Chirurgicale* 2012;7:1-12.
3. Kakouri E, Whelan JS, Coltart S, et al. Multi-focal, multi-centric angiosarcoma of bone. *Sarcoma* 1997;1:183-7.
4. Mitsuhashi T, Shimizu Y, Ban S, et al. Multicentric contiguous variant of epithelioid angiosarcoma of the bone. A rare variant showing angiotropic spread. *Ann Diagn Pathol* 2005;9:33-7.
5. Santeusano G, Bombonati A, Tarantino U, et al. Multifocal epithelioid angiosarcoma of bone: a potential pitfall in the differential diagnosis with metastatic carcinoma. *Appl Immunohistochem Mol Morphol* 2003;11: 359-63.
6. Wang C, Rabah R, Blackstein M, et al. Bone marrow metastasis of angiosarcoma. *Pathol Res Pract* 2004;200:551-5.
7. Lagarde P, Przybyl J, Brulard C, et al. Chromosome instability accounts for reverse metastatic outcomes of pediatric and adult synovial sarcomas. *J Clin Oncol* 2013;31:608-15.
8. Volpe R, Mazabraud A. Hemangioendothelioma (angiosarcoma) of bone: a distinct pathologic entity with an unpredictable course? *Cancer* 1982;49:727-36.
9. Deshpande V, Rosenberg AE, O'Connell JX, et al. Epithelioid angiosarcoma of the bone: a series of 10 cases. *Am J Surg Pathol* 2003;27:709-16.
10. Carr RJ, Green DM. Oral presentation of disseminated angiosarcoma. *Br J Oral Maxillofac Surg* 1986;24:277-85.
11. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. *Am J Surg Pathol* 1998;22:683-97.
12. Manner J, Radlwimmer B, Hohenberger P, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. *Am J Pathol* 2010;176:34-9
13. Dunlap JB, Magenis RE, Davis C, et al. Cytogenetic analysis of a primary bone angiosarcoma. *Cancer Genet Cytogenet* 2009;194:1-3.
14. Palmerini E, Maki RG, Staals EL, et al. Primary angiosarcoma of bone: a retrospective analysis of 60 patients from 2 institutions. *Am J Clin Oncol* 2013 Mar 4. [Epub ahead of print].
15. Mark RJ, Poen JC, Tran LM, et al. Angiosarcoma. A report of 67 patients and a review of the literature. *Cancer* 1996; 77:2400-6.
16. Sasaki R, Soejima T, Kishi K, et al. Angiosarcoma treated with radiotherapy: impact of tumor type and size on outcome. *Int J Radiat Oncol Biol Phys* 2002;52:1032-40.