

CLINICAL VIGNETTE

Extraskelatal Myoid Chondrosarcoma: Case Presentation of a Rare Soft Tissue Sarcoma

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Case Presentation

A 67-year-old male presented with gross hematuria. He had previously been seen at an urgent care center and started on ciprofloxacin for a presumed urinary tract infection. The patient denied any associated dysuria, fever, chills, nausea, vomiting, or weight loss at the time, but did report mild bilateral flank pain. His past medical history is significant for Whipple procedure for intraductal papillary mucinous neoplasm, dyslipidemia, prediabetes, and atrial fibrillation status post ablation on chronic anticoagulants.

Family history includes primary lung cancer with brain metastasis in his mother, coronary artery disease in his father, and lung cancer in his sister. He has a 40-pack-year smoking history, quitting 12 years ago, without significant alcohol or drug use. Current prescription medications include alprazolam 1 mg daily at bedtime, atorvastatin 20 mg daily at bedtime, metoprolol succinate 50 mg every morning and 25 mg daily at bedtime, rivaroxaban 20 mg daily, and the ciprofloxacin. Vital signs were remarkable for a pulse of 48 bpm, but were otherwise within normal limits. On physical examination, the patient was noted to have slight bilateral costovertebral angle tenderness. The rest of the physical examination was unremarkable. Point-of-care urine dipstick performed in the office showed small bilirubin, 3+ blood, and 1+ protein.

Additional labs included serum potassium 5.5, chloride 108, and glucose 107. BUN and creatinine were normal. A CT urogram with and without contrast showed no renal, ureteric, or bladder stones and no hydronephrosis. Bilateral cysts were noted with a maximum size of 4.5 cm on the left kidney. Postsurgical changes of his prior Whipple procedure were noted. A few mildly enlarged mesenteric and portal lymph nodes were noted. Most importantly, a region of hypoattenuation within the anterior right thigh was found demonstrating linear regions of enhancement measuring up to 6.7 x 5.7 x 8.0 cm in maximum diameter. This finding was concerning for a possible underlying mass and a dedicated contrast-enhanced MRI of the region was recommended for further evaluation.

A subsequent MRI of the right femur with and without contrast confirmed the presence of a 10.6 cm mass, within the iliopsoas muscles of the right hip corresponding to the CT abnormality. The mass appeared well-circumscribed, without invasion of the adjacent hip joint, femur, or muscles of the hip girdle. However, enhancement was noted particularly along the multiple internal

septations, and due to the large size and atypical appearance, tissue sampling and excision was recommended.

Several days later, the patient underwent a CT-guided core needle biopsy of the right anterior thigh mass. Pathology report revealed extraskelatal myxoid chondrosarcoma and the FISH report was positive for EWSR1 rearrangement. Hematology/oncology and orthopedic surgery were urgently consulted and the patient initiated neoadjuvant radiotherapy. Unfortunately, follow-up MRI showed minimal response and he underwent radical resection the soft tissue sarcoma of the right proximal thigh and pelvis requiring complex 30cm closure of the right proximal thigh without any soft tissue rearrangement.

Postoperatively, the patient required intensive physical therapy to regain ambulation. Subsequent surveillance imaging has showed no signs of recurrence or metastatic disease and the patient is now able to walk 5 miles. He continues with periodic MRI surveillance of the femur and CT imaging of the chest/abdomen/pelvis every 6 months.

Discussion

Sarcomas are malignant tumors generally arising from skeletal/extra skeletal connective tissues which can include the peripheral nervous system. Approximately 76% arise from soft tissue, and the rest from bone. Etiology is not clearly defined but there are a number of associated or predisposing factors including gene mutation, genetic predisposition, radiation/chemotherapy, and chemical carcinogens. In addition, there is an association between viral infection and sarcoma which is often seen in HIV and HHV-8 in Kaposi's sarcoma.¹

Extraskelatal myxoid chondrosarcoma is a rare translocation-associated soft tissue sarcoma of uncertain differentiation. More than 90% of EMC have a characteristic translocation that involves the NR4A3 gene on chromosome 9; the most common fusion partner is the EWSR1 gene on chromosome 22, but alternative translocations involving the TAF15, TFG or TCF-12 genes have also been described.² The EWSR1-NR4A3 and TAF15 fusion proteins have been characterized as transcription factors but the molecular consequences of the observed translocations have only been partly elucidated. EMC usually presents as a gradually enlarging painless mass. The most common sites are the thigh, groin, or buttock region in nearly

half of the cases. EMC is generally characterized by indolent growth rate but has strong tendency for local recurrence and metastatic spread, usually to the lungs. Histologic examination is essential for accurate diagnosis and treatment planning. Radiographic studies assist in determining the extent of primary tumor prior to surgical resection as well as detecting the presence/absence of metastatic disease. Well-differentiated versus higher grade variants and even dedifferentiated cases have been described.² Wide local excision is the only potentially curative treatment. Cytotoxic chemotherapy with drugs commonly used in other sarcomas such as ifosfamide, doxorubicin, cyclophosphamide, docetaxel or gemcitabine has generally shown little or no activity in metastatic EMC. Occasional responses to chemotherapy have been described however: 4 out of 10 patients for example, experienced a partial response to an anthracycline alone or combined to ifosfamide, in a recent series (2/4 PR in patients with metastatic disease).³⁻⁵ No drug is specifically approved by the FDA for this disease. Check-point inhibitors have occasionally shown clinical activity in other chondrosarcoma subtypes: for example, one PR to first line nivolumab was observed in a patient with a metastatic dedifferentiated chondrosarcoma in a retrospective series and one PR in a phase 2 study with pembrolizumab after prior systemic treatment.^{6,7} In a retrospective report from Kostine et al., PD-L1 expression was associated with the number of tumor-infiltrating lymphocytes and HLA class 1 expression in 11 out of 21 dedifferentiated chondrosarcoma (52%).⁸ Data on PD-L1 expression or other factors that may be potentially predictive of response to checkpoint inhibitors such as tumor mutational burden or microsatellite instability status in EMC is very limited. Davis et al. used a next-generation sequencing approach to genomically profile 6 patients with EMC; similar to other translocation-associated sarcomas and in the case presented here, the mutational profile was limited beyond the pathognomonic translocation. None of the other genomic aberrations found were recurrent or considered clinically relevant. Significant overexpression of RET compared to other types of sarcomas, was observed ($p < 0.0002$); additionally, the folate receptor was found to be overexpressed in 2 patients.⁹ Tyrosine kinase inhibitors may have better activity than chemotherapy in this challenging disease. Clinical benefit from sunitinib has been observed in 8 out of 10 patients with the EWSR1–NR4A3 translocation (6 PRs). Elevated expression and activation of RET, a known target of sunitinib, was noted in this study.¹⁰ Some studies suggest a more aggressive phenotype and possibly clinical behavior for EMC with alternative fusions but data is limited.^{10,11} A phase 2 trial of pazopanib in NR4A3 positive advanced EMC recently enrolled 24 patients. One patient out of 20 had a PR, 17 patients had stable disease and 2 patients had progression. At median follow-up of 13 months, the median progression free-survival was 13 months (range 1.6–25.1) with 29% of patients free of progression at 18 months.¹²

It is important to carefully assess any patient that presents with a palpable soft tissue mass by performing a thorough history, including time onset of when the mass was first noticed, how quickly it has been growing, and whether or not any presence

of symptoms to suggest distal neurovascular compromise. The physical exam should focus on size, depth, any fixation to adjacent structures, and associated edema or signs of nerve impingement. The most common reason for delayed diagnosis of a soft tissue sarcoma is patients' not seeking medical attention due to the painless nature of the tumor as well as physicians' assumption of benignity.¹

REFERENCES

1. **Ryan C, Meyer J.** Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma. Post TW, ed. UpToDate, Waltham, MA: UpToDate Inc. <http://www.uptodate.com> (Accessed on 09/09/2020.)
2. **Fletcher CDM, Bridge JA, Hogendoorn PCW, et al.** World Health Organization (WHO) classification of tumors of soft tissue and bone: pathology and genetics. Lyon: IARC Press; 2013. p. 218-20.
3. **Patel SR, Burgess MA, Papadopoulos NE, Linke KA, Benjamin RS.** Extraskelletal myxoid chondrosarcoma. Long-term experience with chemotherapy. *Am J Clin Oncol.* 1995 Apr;18(2):161-3. doi: 10.1097/00000421-199504000-00014. PMID: 7900708.
4. **Drilon AD, Popat S, Bhuchar G, D'Adamo DR, Keohan ML, Fisher C, Antonescu CR, Singer S, Brennan MF, Judson I, Maki RG.** Extraskelletal myxoid chondrosarcoma: a retrospective review from 2 referral centers emphasizing long-term outcomes with surgery and chemotherapy. *Cancer.* 2008 Dec 15;113(12):3364-71. doi: 10.1002/cncr.23978. PMID: 18951519; PMCID: PMC2779719.
5. **Stacchiotti S, Dagrada GP, Sanfilippo R, Negri T, Vittimberga I, Ferrari S, Grosso F, Apice G, Tricomi M, Colombo C, Gronchi A, Dei Tos AP, Pilotti S, Casali PG.** Anthracycline-based chemotherapy in extraskelletal myxoid chondrosarcoma: a retrospective study. *Clin Sarcoma Res.* 2013 Dec 18;3(1):16. doi: 10.1186/2045-3329-3-16. PMID: 24345066; PMCID: PMC3879193.
6. **Paoluzzi L, Cacavio A, Ghesani M, Karambelkar A, Rapkiewicz A, Weber J, Rosen G.** Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. *Clin Sarcoma Res.* 2016 Dec 30;6:24. doi: 10.1186/s13569-016-0064-0. PMID: 28042471; PMCID: PMC5200964.
7. **Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA, Movva S, Davis LE, Okuno SH, Reed DR, Crowley J, Butterfield LH, Salazar R, Rodriguez-Canales J, Lazar AJ, Wistuba II, Baker LH, Maki RG, Reinke D, Patel S.** Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017 Nov;18(11):1493-1501. doi: 10.1016/S1470-2045(17)30624-1. Epub 2017 Oct 4. Erratum in: *Lancet Oncol.* 2017 Dec;18(12):e711. Erratum in: *Lancet Oncol.* 2018 Jan;19(1):e8. PMID: 28988646.
8. **Kostine M, Cleven AH, de Miranda NF, Italiano A, Cleton-Jansen AM, Bovée JV.** Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates

potential for response to immunotherapy specifically in the dedifferentiated subtype. *Mod Pathol*. 2016 Sep;29(9):1028-37. doi: 10.1038/modpathol.2016.108. Epub 2016 Jun 17. PMID: 27312065.

9. **Davis EJ, Wu YM, Robinson D, Schuetze SM, Baker LH, Athanikar J, Cao X, Kunju LP, Chinnaiyan AM, Chugh R.** Next generation sequencing of extraskeletal myxoid chondrosarcoma. *Oncotarget*. 2017 Mar 28;8(13):21770-21777. doi: 10.18632/oncotarget.15568. PMID: 28423517; PMCID: PMC5400622.
10. **Stacchiotti S, Pantaleo MA, Astolfi A, Dagrada GP, Negri T, Dei Tos AP, Indio V, Morosi C, Gronchi A, Colombo C, Conca E, Toffolatti L, Tazzari M, Crippa F, Maestro R, Pilotti S, Casali PG.** Activity of sunitinib in extraskeletal myxoid chondrosarcoma. *Eur J Cancer*. 2014 Jun;50(9):1657-64. doi: 10.1016/j.ejca.2014.03.013. Epub 2014 Apr 2. PMID: 24703573.
11. **Agaram NP, Zhang L, Sung YS, Singer S, Antonescu CR.** Extraskeletal myxoid chondrosarcoma with non-EWSR1-NR4A3 variant fusions correlate with rhabdoid phenotype and high-grade morphology. *Hum Pathol*. 2014 May;45(5):1084-91. doi: 10.1016/j.humpath.2014.01.007. Epub 2014 Jan 28. PMID: 24746215; PMCID: PMC4015728.
12. **Stacchiotti S, Ferrari S, Redondo A, Palmerini E, Hindi N, Angeles Vaz M, Frezza AM, Gutierrez A, Lopez-Pousa A, Grignani G, Italiano A, Dumont S, Blay J-Y, Penel N, Bernabeu D, de Alava E, Ranchère-Vince D, Collini P, Cruz J, Broto JM.** International single-arm phase II trial of pazopanib in advanced extraskeletal myxoid chondrosarcoma: a collaborative Spanish (GEIS), Italian (ISG) and French (FSG) Sarcoma Groups study. *J Clin Oncol*. 2017;35(15):11062 (Abstract)