Commentary

Ewing's sarcoma (ES) is a rare malignant bone or soft-tissue tumor of developmental origin that affects children, adolescents, and young adults. ES accounts for only 6%–8% of all primary malignant bone tumors although it is the second most common type encountered in pediatric patients, behind only osteosarcoma.[1] Although varied based on age, the most common primary sites for ES include the pelvis, femur, tibia, and ribs (for bone) and thoracic wall, gluteal muscle, pleural cavities, and cervical muscles (for soft tissue).[2] The exact histologic features of ES continue to be debated among pathologists, although the genetic characterization of this neoplastic disorder is well described.[2,3] Broadly, chromosomal translocations fuse members of the FET family of proteins (*FUS, EWSR1, and TAF15)* with members of the ETS (E26-specific, *FLI1*) family of transcription factors. These protein families are RNA-binding proteins involved in transcription and transcription factors involved in cell proliferation, differentiation, cell-cycle control, and apoptosis, resulting in ES's primary oncologic manifestations.[3,4]

Given the infrequency and nonspecific presentations of ES signs and symptoms, there can be delays in diagnosis. For this reason, 20%–25% of patients with ES present with metastatic disease. Unfortunately, with metastatic spread, ES can be resistant to therapy, making early diagnosis, and intervention critical.[5,6] Even with these interventions, the mortality rate is high, with an overall survival rate of <30%.[5] Spread of ES to the central nervous system, is very rare, with only 1%–2% of all metastatic presentations extending to the brain or spine.[6,7] Although the modality of extension can be diverse for metastatic tumors of the bone, ES is known to primarily metastasize to the skull bones although hematogenous spread is possible.[2,6-8] Following spread to the skull bones, and more specifically the skull base, direct extension can cause mass effect on local structures, leading to the bulk of primary neurologic presentations of metastatic ES.

In the case presented by Gupta *et al*.,[9] a 13-year-old female presented to an outpatient facility with headache, ptosis, diplopia, and ophthalmoplegia within 3 months of diagnosis and resection of a ES. This case aptly describes a presentation of cavernous sinus syndrome (CSS) wherein multiple cranial nerve palsies result in ophthalmoplegia, ptosis, and facial sensory loss due to the involvement of adjacent cranial nerves. Headaches, as presented in this case, frequently co-occur in CSS. The contents of the cavernous sinus include oculomotor nerve (cranial nerve three), trochlear nerve (cranial nerve four), abducens nerve (cranial nerve six), and the ophthalmic and maxillary branches of the trigeminal nerve (cranial nerve five). In addition, the space also contains the internal carotid artery although this high-pressure structure is less likely to cause pathology unless severe mass effect is present. In addition, the optic nerve (cranial nerve two) lies just above and outside the cavernous sinus, superior, and lateral to the pituitary gland on each side, which as in the case presented by Gupta *et al*., was also involved.[9]

In any patient, the differential diagnosis for CSS is broad including tumor, trauma, aneurysm/fistula, infection, inflammation, diabetes, or venous sinus thrombosis. However, in a patient with a recent or remote oncologic history and evidence of CSS, expedited neuroimaging (preferably magnetic resonance imaging [MRI]) with and without contrast should be obtained as the risk of neoplastic spread to the cavernous sinus or surrounding bony structures is high.[7,8] Obtaining an MRI with views of the venous architecture may also be relevant as venous sinus thrombosis (in both oncologic and nononcologic states) is on the differential and must be ruled out.

Although the ideal treatment for patients with neoplastic CSS is based on the tumor type, the vital structures in and around the cavernous sinus make full surgical or radiotherapeutic interventions of any type extraordinarily difficult. As in the case presented, chemotherapeutic therapy has a low rate of tumor suppression once ES becomes metastatic and many cases are fatal.[2,5,6] Although many novel therapeutic targets for ES are emerging (poly ADP ribose polymerase inhibitors, zoledronic acid, NAE inhibitors, and CD99 inhibitors), these treatments are still under investigation and can be risky to utilize in critically ill patients. As always, selection of the most appropriate management should be tailored to the individual, tumor location, and tumor type while also including the patient preferences with regard to goals of care. This important case serves as a reminder of the need for immediate evaluation and imaging in patients with an oncologic history and signs or symptoms indicating new onset CSS.

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Conflicts of interest

There are no conflicts of interest.

Jonathan Douglas Santoro, Taylor Nicole Santoro[1]

Department of Neurology, Massachusetts General Hospital, Boston, MA, [1]School of Professional Studies, Columbia University, New York, NY, USA

Address for correspondence: Dr. Jonathan Douglas Santoro, Department of Neurology, Massachusetts General Hospital, 55 Fruit St, ACC 708, Boston, MA 02114, USA.
E-mail: jdsantoro@mgh.harvard.edu

References

1. Gurney JG, Davis S, Severson RK, Fang JY, Ross JA, Robison LL. Trends in cancer incidence among children in the U.S. Cancer 1996;78:532-41.
2. Grünewald TG, Cidre-Aranaz F, Surdez D, Tomazou EM, de Álava E, Kovar H, *et al.* Ewing sarcoma. Nat Rev Dis Primers 2018;4:5.
3. Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, *et al.* Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature 1992;359:162-5.
4. Crompton BD, Stewart C, Taylor-Weiner A, Alexe G, Kurek KC, Calicchio ML, *et al.* The genomic landscape of pediatric Ewing sarcoma. Cancer Discov 2014;4:1326-41.
5. Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley MC, *et al.* Ewing sarcoma: Current management and future approaches through collaboration. J Clin Oncol 2015;33:3036-46.
6. Ladenstein R, Pötschger U, Le Deley MC, Whelan J, Paulussen M, Oberlin O. Primary disseminated multifocal Ewing sarcoma: Results of the euro-EWING 99 trial. J Clin Oncol 2010;28:3284-91.
7. Bekiesinska-Figatowska M, Duczkowska A, Duczkowski M, Bragoszewska H, Romaniuk-Doroszewska A, Iwanowska B, *et al.* CNS metastases from bone and soft tissue sarcomas in children, adolescents, and young adults: Are they really so rare? Biomed Res Int 2017;2017:1456473.
8. Porto L, Jarisch A, Zanella F, Du Mesnil R, Kieslich M, Schwabe D. The role of magnetic resonance imaging in children with hematogenous brain metastases from primary solid tumors. Pediatr Hematol Oncol 2010;27:103-11.
9. Gupta V, Aggarwal K, Nishant P, Arora RK. Rare case of sellar and suprasellar metastasis from ewing's sarcoma of Tibia. J Neurosci Rural Pract 2018;10:158-61.

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