Ewing Sarcoma in the Fifth Metacarpal of an Adult Woman

A Case Report

M. Chad Mahan, MD, Nicholas Frisch, MD, MBA, Broc Durrant, MD, Theodore Parsons III, MD, Tammy Woods, MD, and Michael Mott, MD

Investigation performed at the Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan

Abstract

Case: Atypical presentations of Ewing sarcoma (ES) can lead to misdiagnosis and delays in treatment. We present a rare case of ES in the hand of an adult woman who underwent multiple interventions prior to referral to our institution. At 22 months after definitive treatment, the patient remained pleased with the result and had no evidence of recurrence.

Conclusion: To our knowledge, ES of the hand in an adult woman has not yet been reported in the literature, and a lack of recognition of this condition might be secondary to the absence of features traditionally associated with malignant bone neoplasms. A broader differential diagnosis after intervention failures offers the opportunity for diagnosis and appropriate treatment.

Ewing sarcoma (ES) is a high-grade, malignant, small round cell neoplasm that commonly arises in the metaphysis of long bones or flat bones of the shoulder and pelvis in children and adolescents. An estimated 1 in 1 million individuals per year develops ES. ES in adults is rare; approximately 90% of cases are seen in patients <30 years of age[1]. ES in the hand is extremely rare, occurring in <0.2% of all cases of ES[2,3]. In the Intergroup Ewing Sarcoma Study, 2 of 1,351 cases involved the hands, and both of these cases were in children[4]. To our knowledge, only 29 cases of ES in the hand have been presented in the literature and ours is the first report of ES in the metacarpal of an adult woman[5]. When present in the hand, ES is most commonly seen in the metacarpal of the long finger[6]. Notably, ES in adults has a male preponderance, with 1 study showing an occurrence of only 31% in women[5].

ES symptoms at presentation can be nonspecific and include pain, swelling, fevers, and erythema, which may lead to errors in diagnosis. The erythrocyte sedimentation rate and C-reactive protein level may be elevated[2]. Radiographically, ES presents most commonly with permeative bone destruction, multilayered periosteal reaction, and flattening of the bone producing a cyst-like lesion, often accompanied by a soft-tissue mass or an expansile bone lesion[7].

Treatment of ES relies on a multidisciplinary approach, coupling intensive neoadjuvant and adjuvant chemotherapies with surgery or radiation therapy for control of the primary site and possible metastatic disease[8]. The optimal method of local

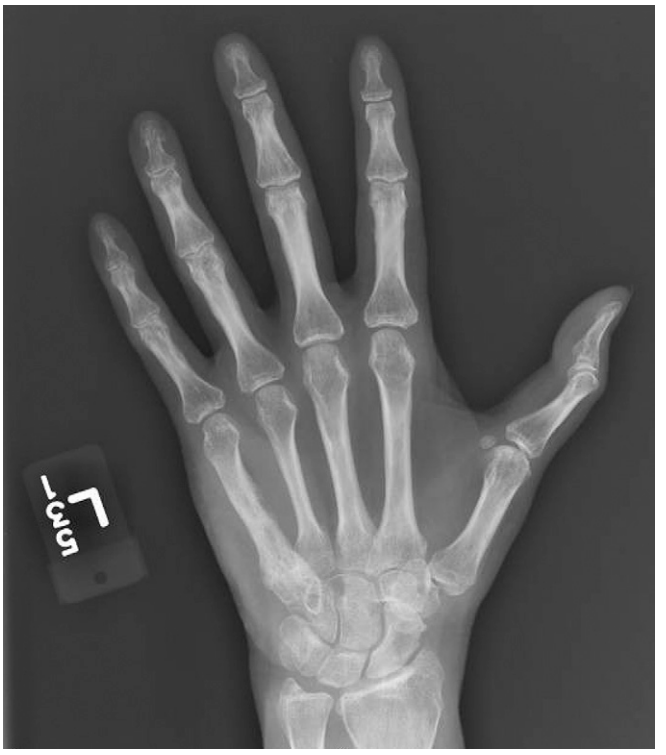

Fig. 1

Anteroposterior radiograph of the left hand demonstrating a soft-tissue mass, cortical irregularity, and osseous destruction.

Disclosure: The authors indicated that no external funding was received for any aspect of this work. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article.

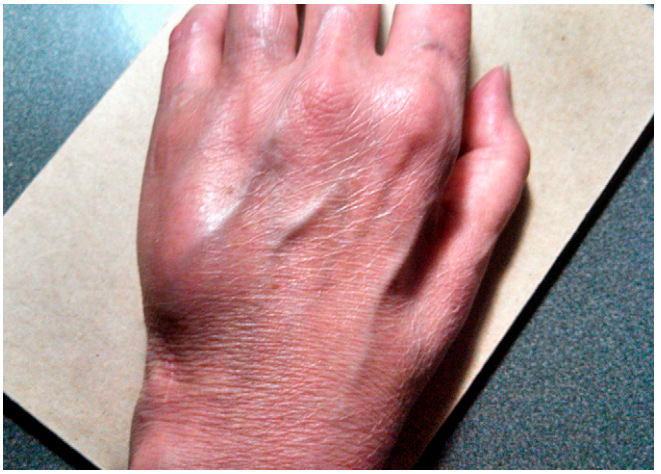

Fig. 2
Clinical photograph showing erythema and swelling over the ulnar aspect of the hand.

control is determined on an individual basis, depending on the location of the tumor and the potential functional outcome. Most current approaches are based on international collaboration guided by data from pediatric patients[8]. Because of its rarity, there is no standardized treatment recommendation for ES of the hand[3]. Prognosis for ES of the hand is similar to that of other sites, with local disease control achievable in 70% to 80% of cases and a 5-year survival rate of 50% to 60%[2]. Most surgeons favor limb salvage procedures as an alternative to amputation. Preservation of hand functionality can be difficult juxtaposed against the need for excision with negative margins[3].

The patient was informed that data concerning the case would be submitted for publication, and she provided consent.

Case Report

A 55-year-old right-hand-dominant woman with no noteworthy medical history initially had presented to an outside hospital in July 2012 with left ulnar-sided wrist pain attributed to a hypermobile fifth ray (Fig. 1). She had been treated with fifth carpometacarpal fusion, which had been supplemented with pin fixation and an allograft in June 2013. The pain persisted, and she developed a distal ulnar nerve palsy with loss of intrinsic function as well as a low ulnar claw hand, which originally was attributed to hardware migration. The patient next underwent nerve release with hardware and scar removal in November 2013 for presumed nerve entrapment. After returning again with pain, swelling, and erythema, she underwent operative debridement in April 2014 for suspected infection and osteomyelitis. No purulence was encountered intraoperatively, prompting a biopsy of noninfectious material for histopathologic examination.

To identify areas of tumor for enrichment, microscopic examination was performed by macrodissection in addition

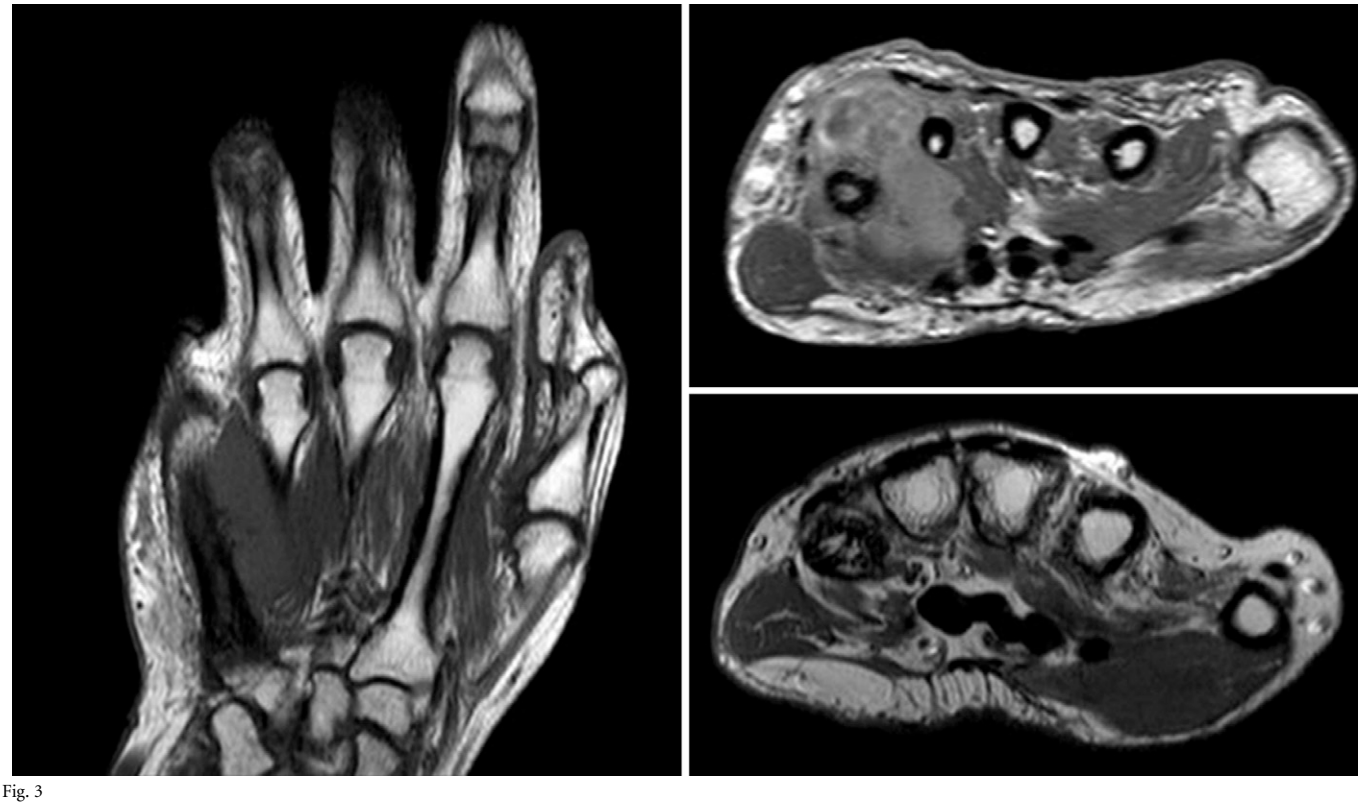

Fig. 3
T1-weighted MRI series demonstrating a mass occupying the intramedullary space with a large soft-tissue component abutting the fourth metacarpal. Note the abnormal intramedullary signal throughout the fifth metacarpal, suggesting an infiltrative, marrow-replacing process.

to mutation analysis of EWSR1 (ES breakpoint region 1)-FLI1 and EWSR1-ERG fusion transcripts using reverse transcriptase-polymerase chain reaction. The study confirmed neoplastic cells that were positive for CD99 and negative for desmin, SMA, CD3, CD20, TdT, CK OSCAR, TTF1, snaptophysin, NSE, EMA, CK7, CK AE1/AE3, chromogranin, and CD45. Validation studies showed the clinical sensitivity to be 91% and the specificity to be 100% for the diagnosis of ES.

The patient presented to our institution's sarcoma service for additional evaluation in May 2014, 2 years after the initial symptoms. Physical examination revealed swelling along the ulnar aspect of the dorsal part of the hand, muscle wasting most notable along the first dorsal interosseous

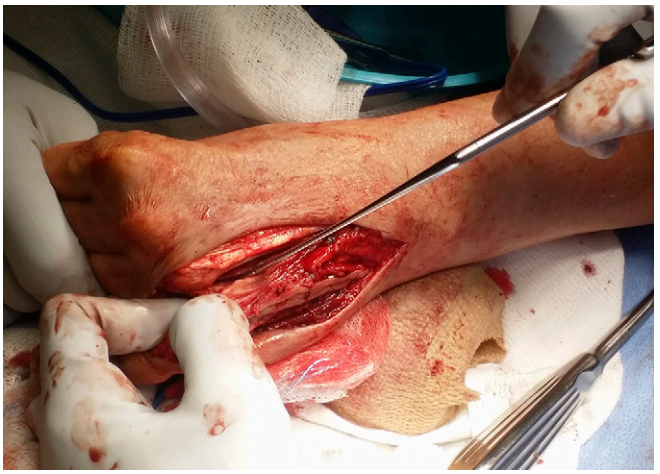

Fig. 4-A

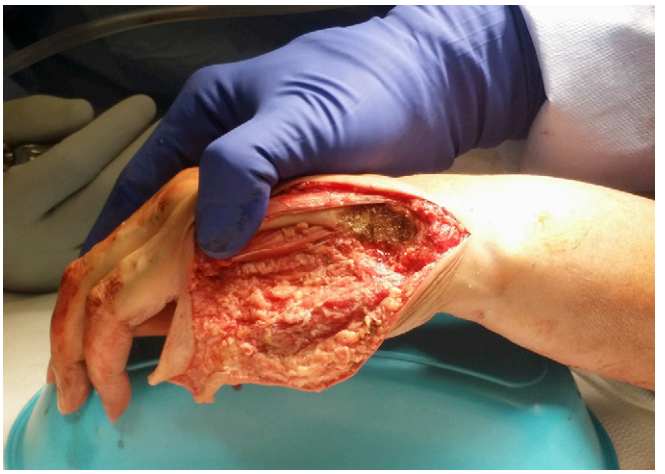

Fig. 4-B

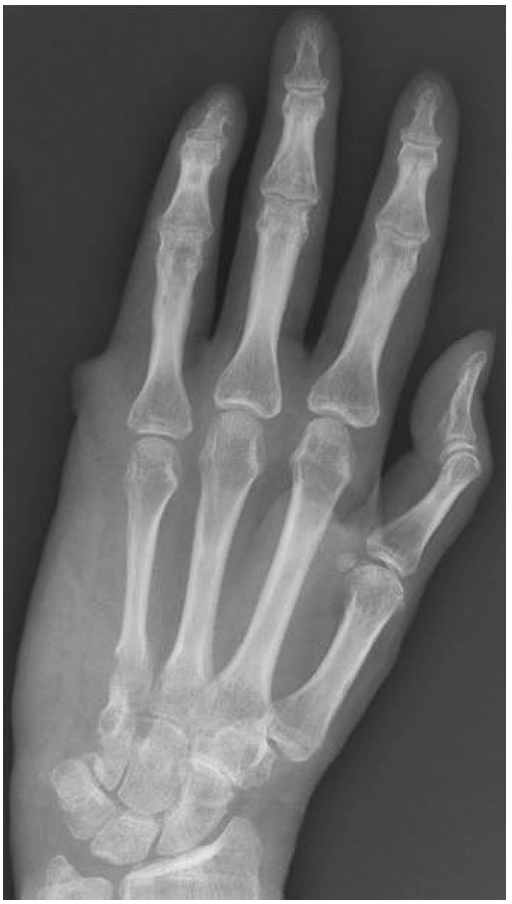

Fig. 4-C

Figs. 4-A, 4-B, and 4-C Intraoperative photographs and radiograph. **Fig. 4-A** Intraoperative photograph showing the development of the interval between the fourth and fifth metacarpals. Resolution of the soft-tissue mass, as a result of neoadjuvant chemotherapy, facilitated sparing of the fourth metacarpal. **Fig. 4-B** Development of the soft-tissue flap and reconstruction of the hypothenar eminence. **Fig. 4-C** Anteroposterior radiograph of the left hand demonstrating the extent of the resection.

muscle, and mild clawing of the ulnar digits (Fig. 2). Magnetic resonance imaging (MRI) demonstrated a mass with an epicenter along and radial to the fifth metacarpal (Fig. 3), and a bone scan demonstrated uptake in the ulnar aspect of the left hand.

The medical oncology service initiated a neoadjuvant chemotherapy regimen designed to treat possible metastases and to shrink the primary tumor. After 3 cycles of chemotherapy, physical examination showed less wasting of the interossei, decreased clawing, and nearly complete resolution of the ulnar-sided mass. Posttreatment MRI demonstrated a substantial decrease in the size of the mass. Given the excellent clinical response, we believed that the tumor could be resected via a fifth ray resection with tight margins of 0.5 to 1 cm and preservation of the fourth ray.

The patient underwent fifth ray resection in August 2014. The entire lesion was resected en bloc with the fifth ray (Figs. 4-A, 4-B, and 4-C). Particular attention was drawn to areas of possible contamination from previous incisions and procedures. The extent of the diseased tissue, combined with the previous carpometacarpal fusions, required sacrificing the insertions of the flexor carpi ulnaris and extensor carpi ulnaris muscles, and only thin dorsal skin was available to cover the ulnar border of the hand (Fig. 4-B).

Formal pathologic examination confirmed negative margins, with the closest margins being 0.4 cm at the base of the fourth metacarpal. The specimen showed good response to neoadjuvant treatment, with >95% fibrosis and an estimated 1% to 2% of viable tumor cells. Histologically, the tumor was arranged in sheets of small, round, uniform cells with small to moderate amounts of eosinophilic to pale cytoplasm with indistinct cell borders. The nuclei were round to oval and had small nucleoli. There were occasional mitotic figures and apoptotic cells, consistent with the original diagnosis of ES (Figs. 5-A and 5-B). Immunohistochemical labeling for CD99 was strongly positive, and the stain appeared in a solid pattern as opposed to the usual membranous appearance (Fig. 5-C).

The patient completed 13 cycles of chemotherapy, and at the 22-month follow-up, routine surveillance imaging showed no evidence of recurrence or metastatic disease. The patient was happy with the progress and pleased with the cosmetic

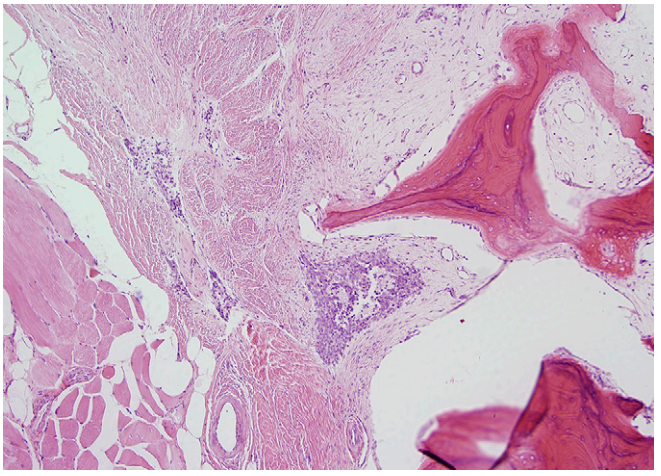

Fig. 5-A

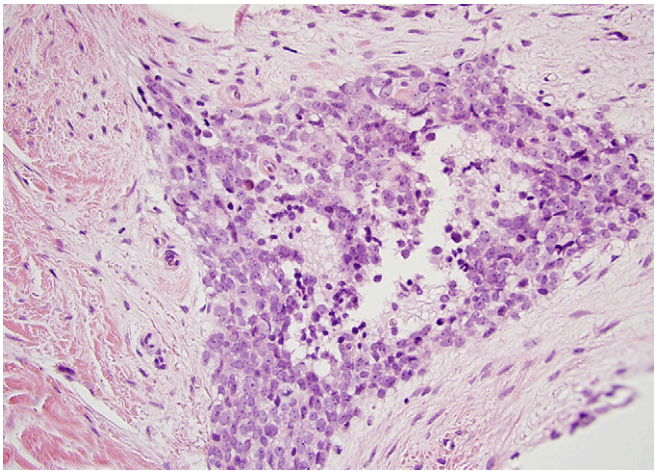

Fig. 5-B

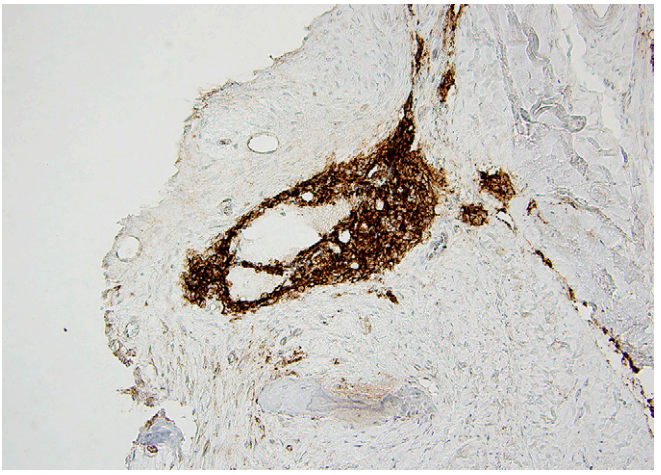

Fig. 5-C

Figs. 5-A, 5-B, and 5-C Surgical pathology from the resection of the fifth ray. **Fig. 5-A** Low-power micrograph demonstrating bone, fibrosis, and small foci of viable tumor (hematoxylin and eosin). **Fig. 5-B** High-power micrograph of viable tumor cells demonstrating round to oval nuclei with small nucleoli, occasional mitotic figures, and apoptotic cells. The tumor is arranged in sheets of small, round, uniform cells with small to moderate amounts of eosinophilic to pale cytoplasm with indistinct borders (hematoxylin and eosin). **Fig. 5-C** Immunohistochemical staining for CD99 is strongly positive in the areas of the small round blue cells.

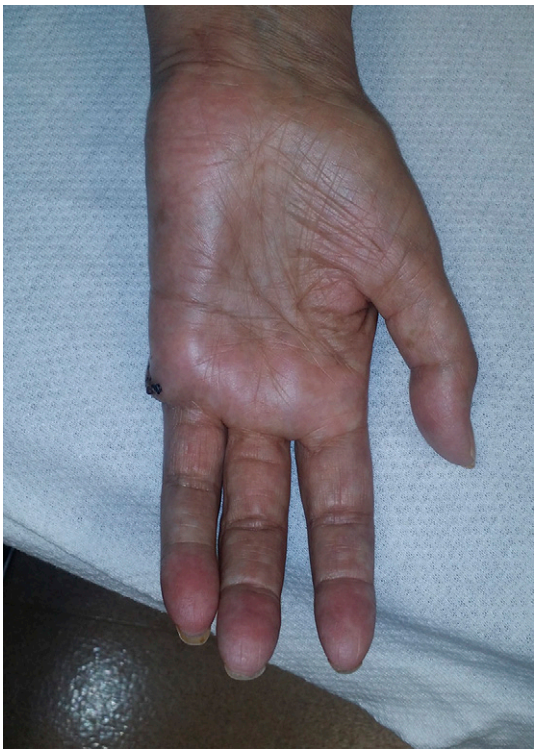

Fig. 6-A

Fig. 6-B

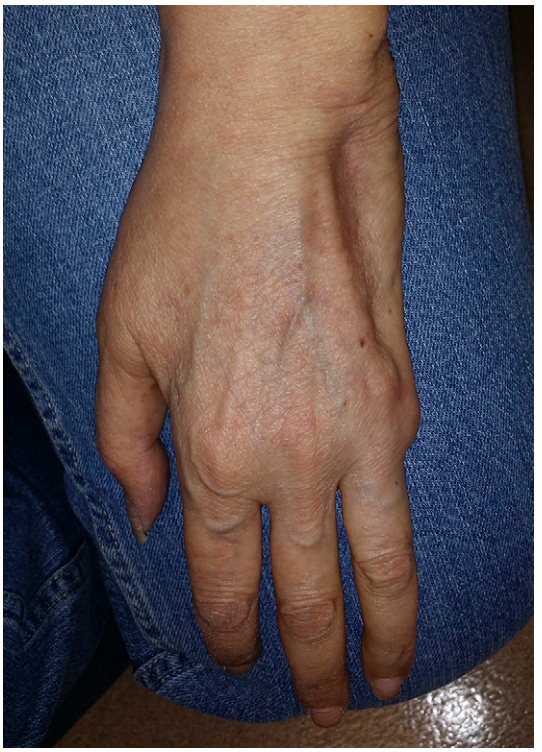

Fig. 6-C

Figs. 6-A, 6-B, and 6-C Postoperative clinical photographs. **Fig. 6-A** The volar aspect of the hand at the first postoperative visit. **Fig. 6-B** Improvement in function is evident at the first postoperative visit. **Fig. 6-C** Soft-tissue contraction over the fourth ray was evident 1 year postoperatively.

appearance and functionality of the hand (Figs. 6-A and 6-B). Hypersensitivity to pain around the thin dorsal skin had improved with time and was no longer limiting activity (Fig. 6-C). The altered wrist mechanics caused weakened grip strength and a mildly extended and radially deviated wrist position, which improved with therapy.

Discussion

ES presenting in the fifth metacarpal of an adult woman is exceedingly rare. The clinical and radiographic findings of ulnar-sided wrist pain with minor radiographic changes can generate a broad differential diagnosis. The similarities between ES and infection are well described; however, other benign and malignant tumors must be ruled out. Osteosarcoma, primary lymphoma, acute leukemia, undifferentiated high-grade pleomorphic sarcoma, and metastasis all may have similar clinical presentations. Morphologically, ES has a similar appearance to other small round blue cell tumors such as small-cell osteosarcoma, rhabdomyosarcoma, primitive neuroectodermal tumor, and other related tumors in the Ewing sarcoma family of tumors (EFT). It is important to consider information from the history, physical examination, radiographs, advanced imaging, and tissue biopsy with histologic, molecular, and immunohistochemical analysis.

The EFT includes a group of neoplastic diseases that share histologic/immunohistochemical characteristics and nonrandom chromosomal translocations. The majority of EFT neoplasms express a surface glycoprotein known as CD99. Although CD99 expression is a sensitive marker for EFT, it lacks specificity because other neoplasms, including rhabdomyosarcoma, and even normal tissue express this glycoprotein[9,10]. Much more specific to ES is a unique pattern of translocations involving the EWSR1 gene on chromosome 22. Up to 90% of the EFT expresses the recurrent translocation, t(11,22)(q24,q12), which fuses the 5′ end of the EWSR1 gene on chromosome 22 to the 3′ end of the FLI1 gene on chromosome 11[11,12].

Patients with atypical presentations of prolonged hand pain, including night pain and pain at rest, and/or destructive lesions with soft-tissue masses warrant a more advanced workup. The classic radiographic features of ES may not be present or may be more difficult to appreciate in the hand[9]. Soft-tissue masses with any bone changes mandate additional investigation with advanced imaging and biopsy. Noncystic solid masses without clinical symptoms of infection should raise the possibility of neoplasm. Because of the rarity and complexity of these tumors, sarcomas should be treated at institutions with multidisciplinary teams, and surgical treatment should be performed by an orthopaedic oncologist[8].

The workup of our patient included radiographs and MRI of the affected hand, bone scintigraphy, and computed tomography of the chest. The establishment of a definitive diagnosis was completed with biopsy specimens. With this patient, the biopsy was performed at an outside institution at the time of a planned debridement for infection. Fortunately, when apparently noninfectious material was encountered, the specimen was sent for histopathologic examination in addition to cultures.

Optimal treatment of upper-extremity bone tumors requires a careful balance of local tumor control and preservation of hand function[13]. With fifth ray resection, loss of subcutaneous padding on the ulnar border of the hand leaves only thin skin with subcutaneous bone, which can be symptomatic. At the 22-month follow-up, the patient was satisfied with the cosmetic appearance and functionality of the hand. ■

M. Chad Mahan, MD[1]
Nicholas Frisch, MD, MBA[1]
Broc Durrant, MD[1]
Theodore Parsons III, MD[1]
Tammy Woods, MD[1]
Michael Mott, MD[1]

[1]Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan

E-mail address for M.C. Mahan: mmahan3@hfhs.org

References

1. Eggli KD, Quiogue T, Moser RP Jr. Ewing sarcoma. Radiol Clin North Am. 1993 Mar;31(2):325-37.

2. Rajappa S, Menon PG, Sundaram S. Ewings sarcoma of the hand-a case report. J Hand Microsurg. 2010 Dec;2(2):82-4. Epub 2010 Oct 6.

3. Ramos-Pascua LR, Fernández-Hernández O, Sánchez Herráez S, Santos Sánchez JA, Flores Corral T. Ewing sarcoma of the first metacarpal with a 9-year follow-up: case report. J Hand Surg Am. 2013 Aug;38(8):1575-8. Epub 2013 Jun 25.

4. Reinus WR, Gilula LA, Shirley SK, Askin FB, Siegal GP. Radiographic appearance of Ewing sarcoma of the hands and feet: report from the Intergroup Ewing Sarcoma Study. AJR Am J Roentgenol. 1985 Feb;144(2):331-6.

5. Cook MA, Manfredi OL. Ewing sarcoma of the hand: a case report. Bull Hosp Jt Dis. 1996;55(2):75-7.

6. Euler E, Wilhelm K, Permanetter W, Kreusser T. Ewing sarcoma of the hand: localization and treatment. J Hand Surg Am. 1990 Jul;15(4):659-62.

7. Gökalp MA, Kaplanoğlu V, Unsal SS, Erten R. Ewing Sarcoma of the Finger. J Clin Imaging Sci. 2014;4:57. Epub 2014 Oct 27.

8. Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley MC, Kovar H, Grimer R, Whelan J, Claude L, Delattre O, Paulussen M, Picci P, Sundby Hall K, van den Berg H, Ladenstein R, Michon J, Hjorth L, Judson I, Luksch R, Bernstein ML, Marec-Bérard P, Brennan B, Craft AW, Womer RB, Juergens H, Oberlin O. Ewing sarcoma: current management and future approaches through collaboration. J Clin Oncol. 2015 Sep 20;33(27):3036-46. Epub 2015 Aug 24.

9. Fellinger EJ, Garin-Chesa P, Triche TJ, Huvos AG, Rettig WJ. Immunohistochemical analysis of Ewing sarcoma cell surface antigen p30/32MIC2. Am J Pathol. 1991 Aug;139(2):317-25.

10. Weidner N, Tjoe J. Immunohistochemical profile of monoclonal antibody O13: antibody that recognizes glycoprotein p30/32MIC2 and is useful in diagnosing Ewing sarcoma and peripheral neuroepithelioma. Am J Surg Pathol. 1994 May; 18(5):486-94.

11. Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, Kovar H, Joubert I, de Jong P, Rouleau G, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992 Sep 10; 359(6391):162-5.

12. Zucman J, Delattre O, Desmaze C, Plougastel B, Joubert I, Melot T, Peter M, De Jong P, Rouleau G, Aurias A, et al. Cloning and characterization of the Ewing sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints. Genes Chromosomes Cancer. 1992 Nov;5(4):271-7.

13. Henderson M, Neumeister MW, Bueno RA Jr. Hand tumors: II. Benign and malignant bone tumors of the hand. Plast Reconstr Surg. 2014 Jun;133(6): 814e-21e.