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Ewing Sarcoma of Phalanx—A Common Tumor with an Uncommon Presentation

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Introduction

Ewing sarcoma (ES) is a small, blue, round cell tumor usually affecting long bones. In 90% of the cases, it occurs in patients aged from 5 to 25 years. While the incidence shows a peak during the second decade of life, it is extremely rare after the third decade of life.[1,2] The disease shows a slight predilection for males (male to female ratio of 1.6:1.0).[3] It rarely arises in fingers. Here, we present a case of ES of phalanx in an adult.

Case Report

A 46-year-old woman presented to our hospital with a 10-month long history of local swelling and 5 months history of pain involving right middle finger. There was no history of fever, loss of weight, or trauma. The swelling was nearly 7 cm × 7 cm x 11 cm in dimensions, firm, tender, immobile with no local rise of temperature. The range of motion of the second, third, and fourth metacarpophalangeal joint was restricted (►**Figs. 1** and **2**).

X-ray of the right-hand revealed bone destruction along with sclerosis of proximal phalanx and involvement of soft tissue component (►**Fig. 3**). Laboratory findings including complete blood counts and biochemistry were within normal limits except for the levels of serum lactate dehydrogenase that was elevated to almost three times the normal. Magnetic resonance imaging (MRI) of right hand revealed altered signal intensity in soft tissue lesion circumferential to third metacarpal, proximal, and middle phalanx with areas of cortical breach. Bone marrow examination showed that it was not involved. The histopathological examination revealed dense cellularity with small, round cells uniformly arranged in sheets along with areas of necrosis (►**Fig. 4**).

Tumor cells were immunonegative for transducer-like enhancer of split 1, epithelial membrane antigen (EMA), cytokeratin, and desmin. Tumor cells were immunopositive for CD99 (►**Fig. 5**), NKX2.2 (►**Fig. 6**), and faintly positive for FLI (►**Fig. 7**), while negative for EMA (►**Fig. 8**). Fluorescence in situ hybridization (FISH) revealed 72% tumor cells showing EWSR1 gene or t(12q22) gene rearrangement (►**Fig. 9**). CD99 and FLI-1 are sensitive however poorly specific IHC markers. In fact, combined NKX2.2 and CD99 positivity has highest specificity. The morphological and immunohistochemical profile was indicative of ES.

Contrast-enhanced tomography of chest and whole-body bone scan showed no evidence of metastatic disease. She was administered two cycles of neoadjuvant chemotherapy with inj. vincristine 1.5 mg/m^2, inj. doxorubicin 75 mg/m^2, inj. cyclophosphamide 1.2 g/m^2 (day 1) alternating with inj. ifosfamide 1.8 g/m^2, inj. etoposide100 mg/m^2 (day1–day 5) every 3 weeks. As clinically there was no improvement, response assessment was done post two cycles that suggested stable disease. The patient is planned for amputation at right wrist joint followed by adjuvant chemotherapy with the same regimen.

Discussion

Question 1: What is the clinical differential diagnosis of such presentation in this age group?

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Fig. 1 Clinical photograph depicting swelling involving the third phalanx on dorsal surface of hand.

Fig. 2 Clinical photograph ventral surface of hand showing swelling involving third phalanx.

Answer 1: Soft tissue or bone sarcoma including epithelioid sarcoma, melanoma, mucormycosis, and giant cell tumor of tendon sheath.

Question 2: What is the differential diagnosis of small round blue cell tumors?

Answer 2: Primitive neuroectodermal tumors, lymphoma, rhabdomyosarcoma, and synovial sarcoma.

Question 3: Which chromosomal abnormalities are seen in ES?

Fig. 3 Radiograph revealing bone destruction with sclerosis of proximal phalanx of middle finger and involvement of soft tissue component.

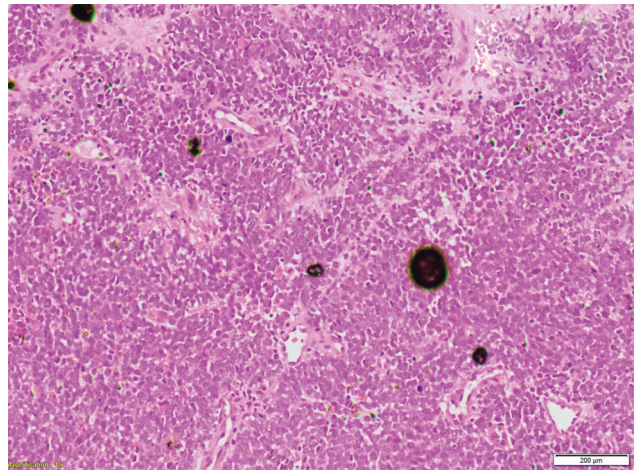

Fig. 4 Hematoxylin and eosin staining showing dense cellularity with small round blue cells uniformly arranged in sheets along with few areas of necrose.

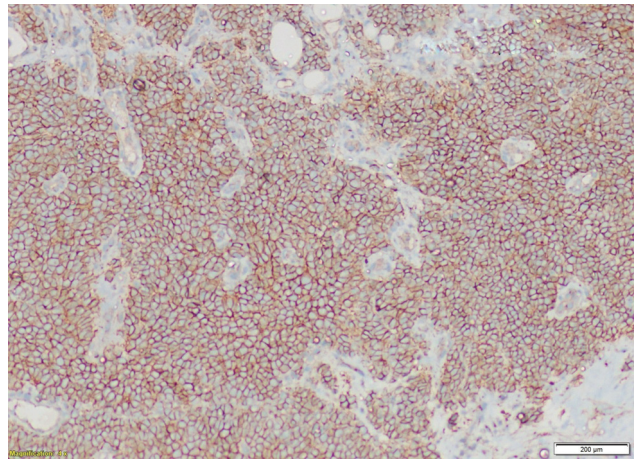

Fig. 5 Immunohistochemistry (IHC) showing neoplastic cells showing membrane positivity for CD99.

Answer 3: Distinct nonrandom chromosomal translocations involving the Ewing sarcoma gene (EWS) on chromosome number 22- t(11;22)(q24;q12) involving EWSR1-FLI1

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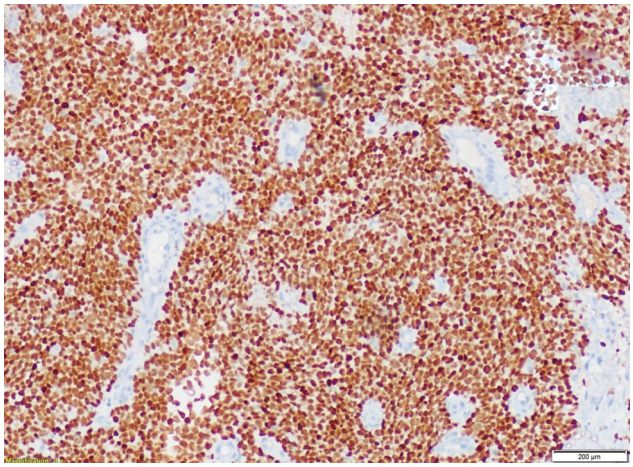

Fig. 6 Immunohistochemistry (IHC)-showing neoplastic cells positive for NKX 2.2.

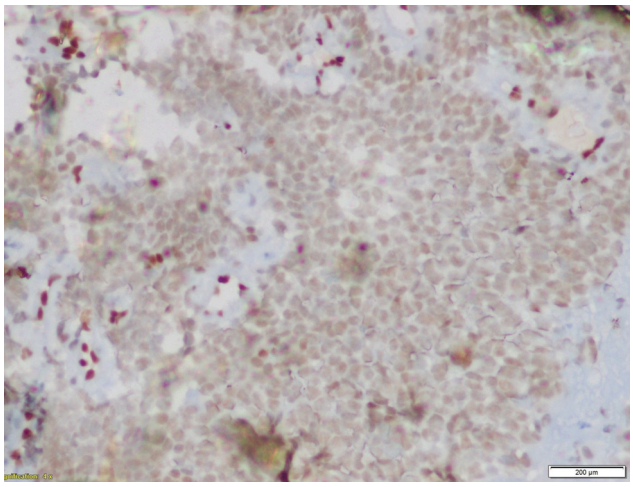

Fig. 7 Immunohistochemistry (IHC)-showing neoplastic cells positive for FLI-1.

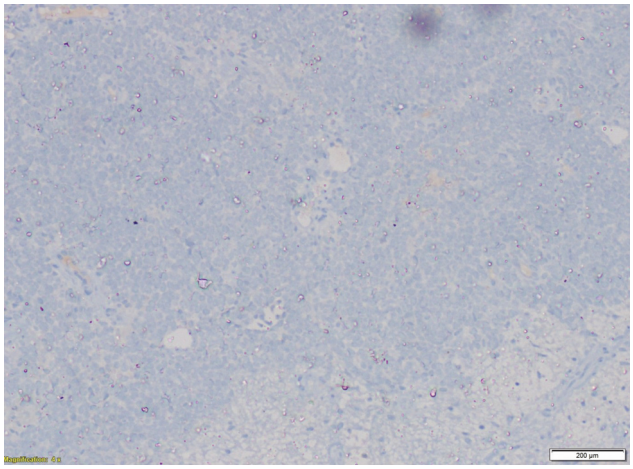

Fig. 8 Immunohistochemistry (IHC)-showing neoplastic cells positive for epithelial membrane antigen (EMA).

in more than 80% cases, while t(21;22)(q24;q12) involving EWSR1-ERG is seen in 10 to 15% cases.

Alternate events include fusions of 22q12 with other erythroblast transformation-specific (ETS) gene partners—7p22, 17p22, 17p22,2q33 (ETV1, ETV4, FEV, PATZ1) in nearly 5% of cases.

Question 4: Which techniques can be used to diagnose chromosomal abnormalities in ES?

Answer 4: EWSR1 gene rearrangement by break apart FISH or reverse-transcription polymerase chain reaction.

ES is a part of the Ewing sarcoma family of tumors (EFT). Previously, it was considered primitive neuroectodermal cell in origin,[4] now believed to arise from mesenchymal stem cells.[5]

Question 5: What comprises ES family of tumors (EFT)?

Answer 5: It includes extraosseous ES, primitive neuroectodermal tumor, malignant small round tumor of thoracopulmonary region (Askin tumor) and atypical ES.

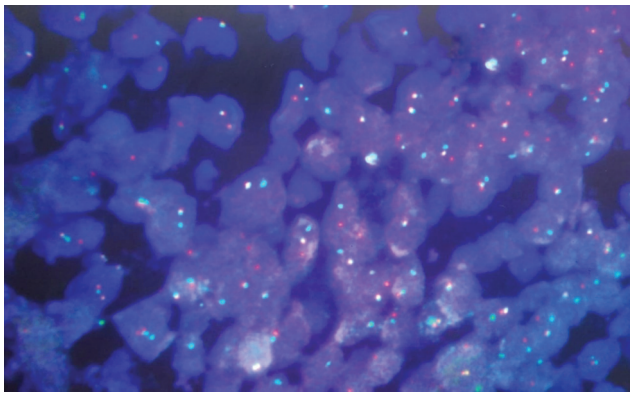

Fig. 9 Fluorescence in situ hybridization (FISH) showing 72% of tumor cells positive for EWSR1 gene rearrangement.

In 20% of patients, tumors are extraosseous and this occurs more frequently in adults.[6,7]

Patients present with localized pain and swelling. A pathological fracture is reported in 10 to 15% of cases, and nonspecific constitutive symptoms, including fever, weight loss, night sweats, and fatigue, may be present. Blood tests may show elevated levels of alkaline phosphatase and serum lactate dehydrogenase.[8]

Common sites according to incidence of cases include bones of lower extremities (40–45%), pelvis (20–25%), chest wall (15–20%), and upper extremities (10%). Extra skeletal sites may include gastrointestinal tract, kidneys, and skeletal muscle. Metastasis to lungs, bones or bone marrow may be present in around 25% of cases. Nodal or liver involvement is rare.[9]

Hand and wrist involvement represents less than 1% of all ES. Metacarpal and proximal phalanges of the thumb (28%) and middle finger (28%) are the most affected locations in the hand.[10,11]

On radiographs, there are multiple, confluent, and lytic bone lesions collectively called “moth eaten appearance” are observed. Subperiosteal growth gives rise to the “Codman’s triangle” and the “onion peel” that represent the displaced periosteum and resulting the proliferative reaction.

Induction chemotherapy is given for four cycles followed by local therapy at 12 weeks. Maintenance in the form of adjuvant chemotherapy with or without radiotherapy is recommended following surgery with the total duration of chemotherapy

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being 28 to 49 weeks. If the tumor is inoperable, local irradiation is given. Early studies suggested vincristine, doxorubicin, dactinomycin, and cyclophosphamide were active in treating ES.[12–14] The chemotherapy protocols have evolved over time as North American intergroup trial INT-OO91 established that adding IE (ifosfamide etoposide) to vincristine, doxorubicin, and cyclophosphamide (VDC) that improved 5-year event-free survival (EFS: 54 vs. 69%) for localized disease.[15] The current approach of interval compressed VDC/IE every 2 weeks was established by Children's Oncology Group AEWS0031 protocol that demonstrated better EFS of 73 versus 65% for 2 weeks as opposed to 3 weeks.[16]

Literature review on ES reveals seven cases with finger involvement in adults. To the best of our knowledge, this is the eighth case. Baccari et al reported two cases of phalanx with a literature review of 15 cases in which only 6 were adults.[10] In a 22-year-old female with ES of index finger reported by Wolthuizen et al, in 2019, treatment was index-ray amputation followed by adjuvant chemotherapy.[17]

Conclusion

Preoperative chemotherapy is generally prescribed for the limb except for amputation surgery candidates. The response rates for primary tumor are minimal, for those who require amputation. Such patients should immediately undergo surgery.

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None

Declarations
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity but anonymity cannot be guaranteed.

Competing Interests
None of the authors have any competing interests.

Authors' Contributions
SB and AC contributed to the conception of the study.SV, LAJ, LD, and SS were responsible for the acquisition. SA, LAJ, SBMC, LKN, AHR, and LKR drafted the work. LD, LAJ, and LKR substantively revised it. All authors have read and approved the manuscript.

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