World Journal of Surgical Oncology

CORRESPONDENCE

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Diagnostic challenges in imaging and immunohistopathological profiles in extraskeletal osteosarcoma

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Abstract

This correspondence addresses the article published by Nie et al. titled "Primary extraskeletal osteosarcoma of sigmoid mesocolon: a case report and a review of the literature". Their report highlighted an extremely rare case of extraskeletal osteosarcoma (EO) in the sigmoid mesocolon that was diagnosed through imaging and histopathological findings. Diagnosing EO has certain challenges; one of them being the lack of characteristic image findings of EO and the other being the lack of appropriate immunohistochemical (IHC) markers in the histopathological findings. Recently, special AT-rich sequence-binding protein 2 (SATB2) has been proposed as an IHC marker for osteoblastic differentiation; however, it has low specificity. Some cases of EO may show findings such as mouse double minute protein 2 expression and deletion of histone H3 lysine 27 trimethylation (H3K27me3), which are similar to those of other soft tissue sarcomas. Therefore, it is essential to consider other soft tissue sarcomas, especially dedifferentiated liposarcoma, before the accurate diagnosis of EO.

Keywords Extraskeletal osteosarcoma, Imaging, SATB2, MDM2, Dedifferentiated liposarcoma

Dear Editor,

Extraskeletal osteosarcoma (EO) is a rare malignant mesenchymal neoplasm characterized by the production of neoplastic osteoids and bone without any direct association with the skeletal system [1]. The age at which EO occurs is different from that at which conventional osteosarcoma (COS) occurs; however, the predilection site for the lower limb is similar for both EO and COS [1, 2]. We read with great interest the article titled "Primary extraskeletal osteosarcoma of sigmoid mesocolon: a case report and a review of the literature" published in the *World Journal of Surgical Oncology* [3]. The case report suggests that special caution is needed in the diagnosis of EO because (i) few characteristic imaging findings often overlap with those of other tumors [4]; (ii) histopathologically, EO shows broad morphology with no specific immunohistochemical (IHC) markers [1].

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Recent studies have shown that IHC findings of special AT-rich sequence-binding protein 2 (SATB2) have been useful in the diagnosis of EO and COS [1, 2]; however, its low specificity poses diagnostic pitfalls [5]. Additionally, mouse double minute protein 2 (MDM2)-positive EOs are associated with dedifferentiated liposarcoma (DDLPS) [6]. We will introduce the imaging details, the significance of SATB2 in histopathology, and its relationship with DDLPS for a better understanding of EO.

Clinical Features of EO

EO is an extremely rare soft tissue sarcoma accounting for less than 1% of all malignant soft tissue tumors and approximately 4% of COS [1]. The predilection age of 50–70 years, with a slight male prevalence in EO, differs from COS, which is more common in teenagers and females [1, 2]. The predilection site is the lower limbs, especially the thigh, which is similar to COS, and other sites including the buttocks, shoulders, and retroperitoneum have been reported [1, 2]. Most cases occur in the deep layer, and 10% of cases occur in the superficial layer [7]. Most cases develop de novo but some cases have been associated with radiation, previous trauma, and preceding EO [1, 7, 8].

Imaging of EO

Calcification in the EO was observed on X-ray and computed tomography (CT), although the incidence was estimated to be approximately 50–60%. In addition, 46% of these cases show calcification of less than 10% of the tumor volume, suggesting that the positivity is not high [4]. However, calcification is associated with a worse prognosis [4]. In the case published by Nie et al., calcification was difficult to estimate because of the lack of preoperative CT and limited magnetic resonance imaging (MRI) slices. On MRI, necrotic changes, hemorrhagic changes, heterogeneous T2, and contrast effects (to varying degrees) are reported in 97%, 38%, 100%, and 100% of cases, respectively [4]. These MRI findings are often positive for synovial sarcoma, suggesting that the specificity is low [9]. In Nie's case, although not definitive due to the lack of contrast-enhanced MRI, fat-suppressed T1WI showed a higher signal than the muscle, and T2WI showed a heterogeneous signal and multilocular cystic formation and fluid level, suggesting that these findings may indicate hemorrhage and cyst formation. Furthermore, the formation of multilocular cysts is not typically accompanied by necrosis. Considering the MRI findings and the occurrence of the sigmoid mesocolon, the differential diagnosis, including Gastrointestinal stromal tumor, liposarcoma, leiomyosarcoma, and angiosarcoma, was very broad, and a definitive diagnosis from MRI is extremely difficult.

IHC Features of SATB2

IHC methods are useful and commonly used for the histopathological diagnosis of various diseases, yet no specific markers exist for EO or COS [1, 2]. The use of SATB2 as an IHC marker has been developed recently [5, 10]. SATB2 has recently been recognized as a nuclear transcription factor and its roles in stemness, epithelial-mesenchymal transition, Wnt/β-catenin signaling pathway, microRNA regulation, and others are diverse [11]. SATB2 expression was initially found in the healthy lower gastrointestinal epithelium and was subsequently used clinically as a marker for colorectal cancer, resulting in a 95% correct diagnosis rate when used in concert with CK20 [11]. SATB2 expression is upregulated in various cancers, including pancreatic, breast, ovarian, and liver [11]. SATB2 is also known as a nuclear transcription factor that regulates osteoblast differentiation. Targeted knockout of SATB2 expression in mice reduced osteoblast differentiation and craniofacial skeletal defects [5]. The positivity rate of SATB2 in OS is reported to be more than 90%, whereas that in Ewing's sarcoma and chondrosarcoma is 0% [5], which may be useful in differentiating malignant bone tumors. However, its positivity has low specificity for differentiating OSs from other high-grade primary bone sarcomas [10]. Furthermore, SATB2 expression has been reported to be 100% in osteoid osteoma, fibrous dysplasia, and osteoblastomas and >80% in giant cell tumors of bone [5], suggesting difficulty in differentiating EO from benign and intermediate bone tumors. Regarding soft tissue sarcoma, the positivity rate of SATB2 in EO has been reported to be 89%. However, in soft tissue sarcomas with heterogeneous osteogenic differentiation, the positivity rates of SATB2 in leiomyosarcoma, malignant peripheral nerve sheath tumors (MPNST), and DDLPS were reported as 20%, 22%, and 100%, respectively [5]. In summary, SATB2 has both high sensitivity and low specificity in the diagnosis of COS and EO, which is a diagnostic dilemma. Therefore, we suggest a combination of SATB2 and other IHC markers as well as a careful examination of histological findings.

Relationship Between EO and DDLPS

As mentioned earlier, the reported case was not retroperitoneal; however, given the differential diagnosis by MRI and the IHC positivity of SATB2, considerable attention should be paid to differentiate EO from DDPLS. Both DDLPS and well-differentiated liposarcoma/atypical lipomatous tumors share the genetic amplifications in the chromosomal region 12q13-15, which includes several genes, such as *MDM2* and Cyclin-dependent kinase 4 (*CDK4*) [12]. Among the diagnostic features of DDLPS, MDM2 in the IHC method and fluorescence in situ hybridization (FISH) and CDK4 in the IHC method have high sensitivity, which is advantageous for making

a correct diagnosis [12]. However, MDM2-positive cases have been reported of myxofibrosarcoma, undifferentiated pleomorphic sarcoma, and EO, suggesting that its sensitivity is not high [6, 12].

Although the degree of staining varied, 32% of EO cases showed MDM2 IHC expression and amplification of *MDM2* in FISH; these EOs were also positive for CDK4 [6]. Thus, in cases of MDM2-positive EO, especially those with deep development and low-grade components, differentiating EO and DDLPS requires careful attention [6]. Furthermore, histone H3 lysine 27 trimethylation (H3K27me3) deletion, which is often observed in malignant peripheral nerve sheath tumors (MPNST) has also been found in a few cases of EO [6]. Collectively, differentiating EO from soft tissue sarcomas with osteogenic differentiation, presents significant challenges, even with careful diagnosis. Nonetheless, it is crucial to recognize that EO, despite exhibiting positive IHC results typical of other soft tissue sarcomas, is characterized by neoplastic osteoid production and the absence of histological co-existence with other malignant neoplasms. Nevertheless, further studies are warranted to unveil the pathogenesis of EO and the relationship between EO and other soft tissue sarcomas.

Treatment

The primary treatment for EO is surgery, and chemotherapy demonstrates no advantages for local recurrence or overall survival, suggesting that routine chemotherapy is not recommended in localized cases [13]. Chemotherapy regimens used for OS tend to offer better disease-free survival than those for soft tissue sarcomas [14]. However, the continuous administration of these regimens for OS seems to be difficult when considering hematological, renal, and hepatic toxicity and other factors; hence, new agents are urgently needed. We anticipate that an MDM2 inhibitor for which clinical trials of DDLPS have been conducted [15] will help develop a treatment option for MDM2-positive EO. Radiotherapy has contributed to a decrease in local recurrence but not overall survival [13]. In some cases of mesenteric origin, such as in this case, or of retroperitoneal origin, achieving R0 surgical resection can be particularly challenging due to the proximity of vital organs such as the kidneys and intestinal tract. Therefore, a multimodal approach combining surgery and radiotherapy may be reasonable. Thus, advancing chemotherapy options is essential for improving the prognosis of patients with EO.

Conclusions

This correspondence addresses the difficulties in diagnosing EO using imaging and histopathological analyses. Relying solely on imaging for diagnosis is extremely difficult. In the evaluation of histopathological findings, some cases of EO occasionally showed positivity for markers associated with other sarcomas, indicating that differential diagnosis should include other soft tissue sarcomas, particularly DDLPS. To achieve a comprehensive understanding of EO in rare locations, such as the case presented by Nie, more detailed imaging techniques, such as CT and contrast MRI and histopathological findings, should be employed in combination with IHC staining of markers like SATB2 and MDM2. This approach will further underscore the importance and relevance of case reports in elucidating the complexities of EO diagnosis.

Abbreviations

COS	Conventional osteosarcoma
EO	Extraskeletal osteosarcoma
FISH	Fluorescence in situ hybridization
MDM2	Mouse double minute protein 2
CDK4	Cyclin-Dependent Kinase 4
MPNST	Malignant Peripheral Nerve Sheath Tumor
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
IHC	Immunohistochemical
SATB2	Special AT-rich sequence-binding protein 2
DDLPS	Dedifferentiated liposarcoma

Acknowledgements

The authors thank Ms. Kahori Sano and Ms. Azusa Sakamoto for their secretarial assistance.

Author contributions

Conceptualization: all authors acquisition: J.I., T.K., K.O., K.A., and H.Formal analysis: J.I., T.K., K.O, M.W., S.O., and H.Interpretation: J.I., T.K., K.O., K.A., T.O., and H.Writing: original draft preparation, all authors; writing: review and editing, all authors.All authors have read and agreed to the published version of the manuscript.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 14 September 2024 / Accepted: 5 November 2024
Published online: 20 November 2024

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