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Case Report

A rare manifestation of extraskeletal myxoid chondrosarcoma with a huge expanding hematoma

Toshinori Omori [a], Tomohiro Fujiwara [a, b, *], Toshiyuki Kunisada [a, c], Ken Takeda [a, d], Joe Hasei [a], Aki Yoshida [a], Hiroyuki Yanai [e], Toshifumi Ozaki [a]

[a] Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan
[b] Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan
[c] Department of Medical Materials for Musculoskeletal Reconstruction, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan
[d] Department of Intelligent Orthopaedic System Development, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Science, Okayama, Japan
[e] Department of Diagnostic Pathology, Okayama University Hospital, Okayama, Japan

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1. Introduction

Extraskeletal myxoid chondrosarcoma (EMC) is a rare and morphologically distinct soft tissue sarcoma. It is characterized by multinodular architecture, with cords or clusters of chondroblast-like cells in an abundant background of myxoid matrix [1]. Recent molecular cytogenic studies have confirmed its distinct nature, exhibiting a unique and characteristic chromosomal translocation, typically t(9; 22)(q22; q12.2), resulting in the fusion of *EWSR1* with *NR4A3* (genes formerly termed *EWS* and *CHN*, *TEC*, or *NOR1*, respectively) [2–4]. EMC usually arises in the deep soft tissue of proximal extremities [5]. In the initial growth phase, EMC tumors are typically asymptomatic. Pain and tenderness is reported in some cases, and tumors that are located around joints may restrict motion. Large or superficial tumors are even known to ulcerate the skin. Although imaging characteristics are nonspecific, most EMC tumors appear lobulated, and highly myxoid tumors show up as a homogeneous and elevated signal on a T2-weighted magnetic resonance (MR) image [6]. Although intratumoral hemorrhage and localized necrosis is seen in some cases of EMC, an EMC tumor with a large hematoma is uncommon [7].

Here we report a case of EMC in an elderly woman presenting a substantially large hematoma. This observation lays the premise for this rare tumor to be included in the differential diagnosis of hematoma-like tumors. The molecular analysis of *EWSR1–NR4A3* was useful in the differential diagnosis. Since the clinical presentation in this case was extremely unusual, and demographic data are an essential part of diagnosis, the present report adds new information to existing knowledge and has implications for diagnosis of EMC in patients presenting with a huge expanding hematoma. The patient provided an informed consent for the use of data concerning the case for this publication.

2. Case report

A 75-year-old woman presented with a 5-year history of asymptomatic swelling on the medial side of her left knee and with no contributing medical or family history. On physical examination, an elastic but firm mass was palpable from the medial to the popliteal area of her left knee (Fig. 1). Contrast-enhanced computed tomography (CT) revealed a 15 × 14 × 13-cm soft tissue mass without calcification or invasion into the surrounding bone (Fig. 2). Magnetic resonance (MR) imaging demonstrated a lobulated tumor, with high signal intensity relative to skeletal muscle on T1-weighted images, heterogeneous intermediate-to-high signal intensity on T2-weighted images, and gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement on tumor margin (Fig. 3). ^{201}Thallium scintigraphy showed increased accumulation on the tumor edges in the early phase (Fig. 4A), which was not washed out in the delayed phase (Fig. 4B). A needle biopsy discovered a hematoma with no tumor cells present. Thereafter, the patient was carefully followed up.

* Corresponding author. Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan. Fax: +81 86 223 9727.
E-mail address: tomomedvn@gmail.com (T. Fujiwara).

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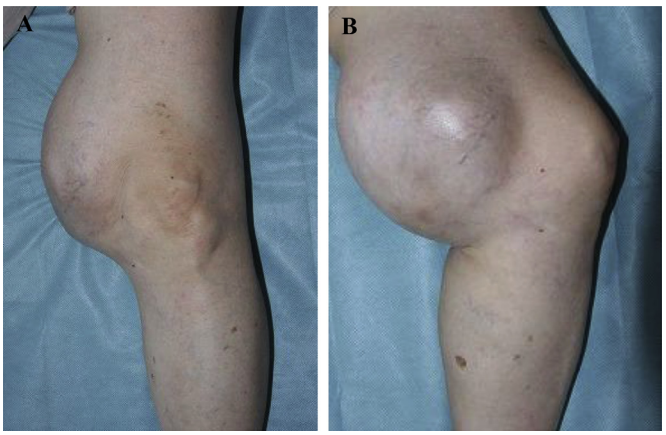

Fig. 1. Appearance of the medial part of the knee at the first visit. (A) Anterior view. (B) Lateral view. An elastic but firm mass was palpable from the medial to the popliteal area of left knee.

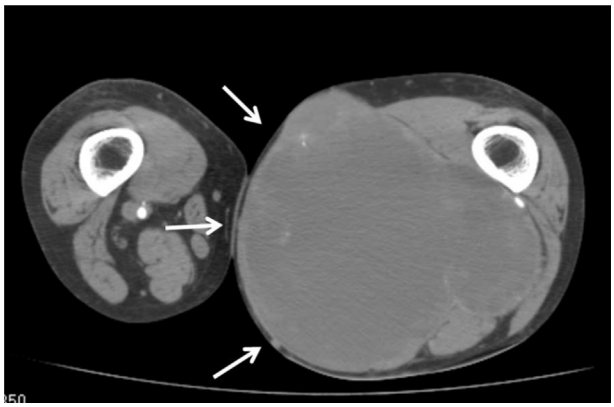

Fig. 2. Contrast-enhanced computed tomography (CT) imaging. Axial CT image revealed a 15 × 14 × 13-cm soft tissue mass, suggesting a homogeneous tumor without calcification. A mild contrast was identified at the wall of the tumor (arrow).

Since the tumor size gradually increased in the eight months following needle biopsy, the possibility of a chronic expanding hematoma or soft tissue tumor was considered and surgical resection was performed. Since the intraoperative pathological evaluation identified no malignancy in frozen specimens, marginal resection was performed. Macroscopically, the resected specimen revealed a grayish white component at the tumor wall (Fig. 5A). Microscopic evaluations showed proliferating spindle-shaped cells and oval cells with eosinophilic cytoplasm surrounded by abundant myxoid matrix (Fig. 5B and C). Moreover RT-PCR analyses revealed transcripts of the *EWSR1—NR4A3* fusion gene, and these analyses were confirmed by direct sequencing (Fig. 6). Therefore, we diagnosed this to be a case of EMC with a rare manifestation of a huge expanding hematoma. Considering the microscopic negative margins and advanced age, the patient was followed up without any adjuvant treatment. The postoperative course was uneventful for three years without any signs of local recurrence or metastasis.

3. Discussion

Extraskeletal myxoid chondrosarcoma is a rare tumor that accounts for approximately 3% of all soft tissue sarcomas [1]. It occurs more frequently in men than in women (at a 2:1 ratio), with 50% of all cases occurring during the fifth or sixth decade of life [8]. Recent cytogenetic studies have demonstrated the distinct molecular nature of EMC, involving a unique and characteristic chromosomal translocation, typically t(9; 22)(q22; q12.2), which results in the fusion of *EWSR1* with *NR4A3* [9]. Panagopoulos et al. reported that 15 of 18 analyzed EMC samples had *EWSR1—NR4A3* fusion transcripts [10]. In our case, the detection of the transcripts of the *EWSR1—NR4A3* fusion gene determined the diagnosis of EMC. Tateishi et al. have reported a low rate of intratumoral hemorrhage in EMCs (1 in 19 cases), and no hematoma formation [11]. To our knowledge, an EMC accompanied by a huge hematoma has never been reported in scientific literature published in the English language.

Although diagnoses of acute soft tissue hematoma are usually relatively easy, it is often difficult to distinguish between soft tissue tumors and chronic soft tissue hematomas [12—14], particularly when hematomas grow despite the lack of evident trauma. In 1980, Reid et al. used the term “chronic expanding hematomas” to describe lesions that grew progressively for over a month after onset [14,15]. History of trauma is an important diagnostic factor for chronic hematomas. Accordingly, reports of chronic expanding hematomas in lower limbs were identified in the Medline database for the period 1980—2010, and history of trauma was reported in 12 of 28 cases [16]. When soft tissue masses with calcification are identified using plain radiography, differential diagnoses include myositis ossificans, hemangioma, heteroplastic chondroma, or osteoma, or the presence of chronic abscesses or parasitic/infective cysts [16]. The present patient had no history of trauma and did not show calcification in radiological images. Currently, the etiology of chronic expanding hematoma is not well understood, although Labadie et al. suggested that breakdown of leukocytes, hemoglobin, platelets, and fibrin leads to inflammatory processes that damage capsule capillaries, increase permeability of vascular walls, and cause bleeding from dilated microvessels beneath fibrous capsules [17]. In agreement, Nishida et al. showed that 2-[^{18}F]fluoro-2 deoxy-D glucose is taken up by not only malignant tumor cells but also macrophages and tissues with granulation or inflammation, indicating limited diagnostic value of this imaging method [18]. Among soft tissue sarcomas, liposarcoma, undifferentiated/unclassified sarcoma, leiomyosarcoma, synovial sarcoma, extraskeletal Ewing sarcoma, and angiosarcoma are most commonly associated with the formation of hematomas [19—21]. Recently, Burgert-Lon et al. and Miyazaki et al. reported the development of angiosarcomas in chronic expanding hematomas [22,23], and Imaizumi et al. reported six cases of malignant fibrous histiocytomas, synovial sarcomas, leiomyosarcomas, and extraskeletal Ewing sarcomas that mimicked hematomas [21]. These authors concluded that MR imaging is more useful than CT for characterization and distinction between sarcomas and hematomas. Specifically, hematoma in sarcoma lesions appear as homogeneous signal patterns on T2-weighted images, either in entire tumors or in portions of tumors that have constant blood supply [21]. In contrast, chronic hematomas that are caused by trauma appear as a heterogeneous signal patterns throughout lesions. During MR imaging, signals from lesions generally vary with time, likely reflecting changes in hemoglobin levels. Accordingly, high-intensity T1-enhanced signals are attributable to methemoglobin levels in hematomas. However, phasic changes in MR imaging signatures of hematomas can hamper distinctions from malignant soft tissue tumors that are identified according to clinical and radiological findings [8]. Hence, when a soft tissue tumor cannot be ruled out, open biopsy or intensive and meticulous follow-up should be performed, even when the needle biopsy is negative, and subsequent surgical R0 resection should be conducted without delay.

EMC are distinguishable from other myxoid sarcomas such as myxoid liposarcoma and myxofibrosarcoma, warranting differential diagnosis. In the present case, proliferating spindle-shaped cells

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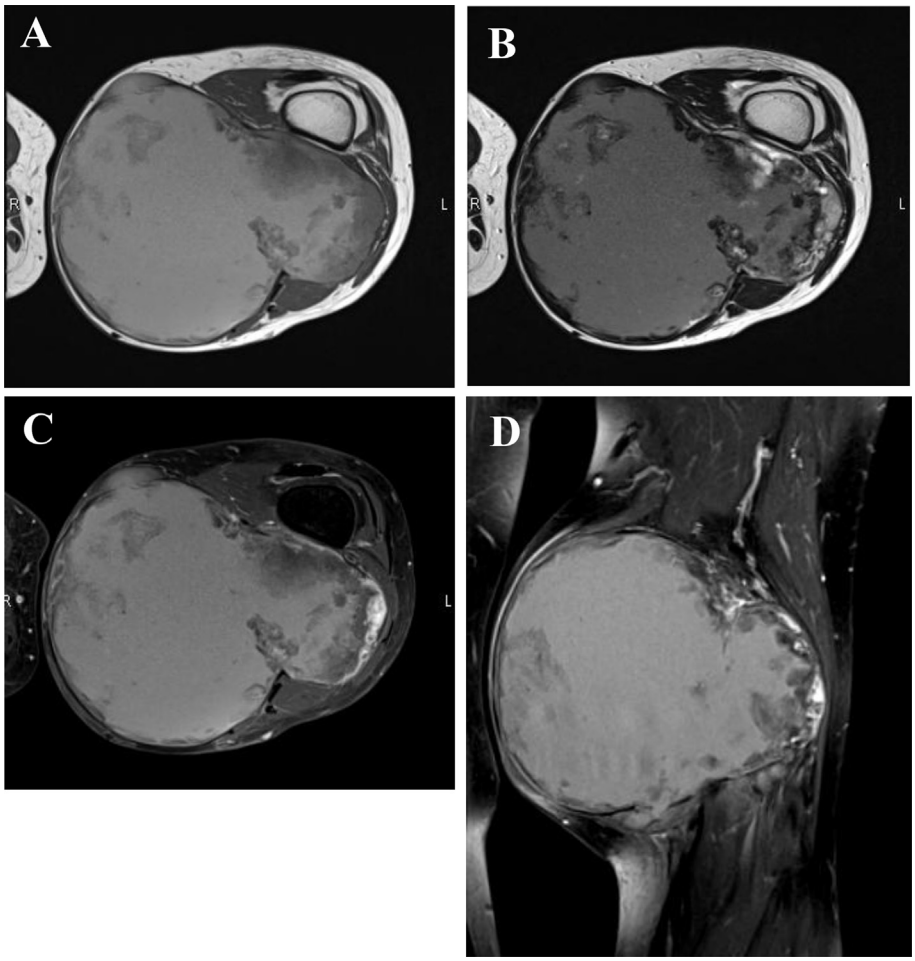

Fig. 3. Magnetic resonance (MR) imaging. (A, B, and C) Axial view of T1-weighted image (A), T2-weighted image (B), and gadolinium-enhanced T1-weighted image (C). (D) Coronal view of gadolinium-enhanced T1-weighted image.

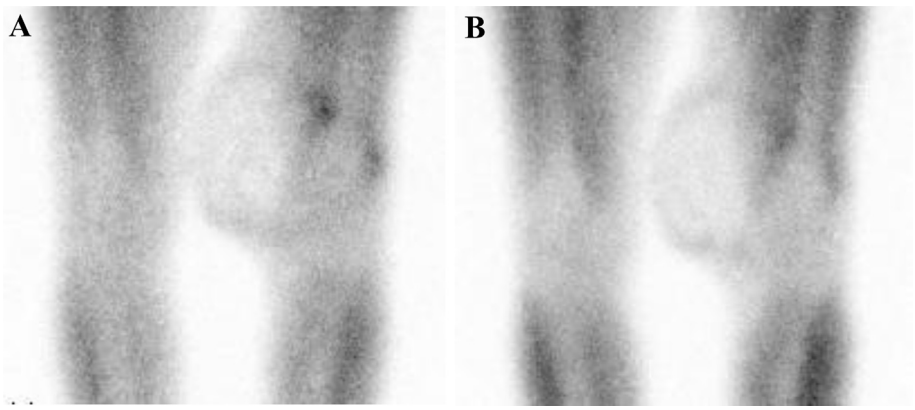

Fig. 4. Thallium scintigraphy. (A and B) Early phase (A) and delayed phase (B) are shown. Thallium scintigraphy showed mild uptake on the tumor margins in both the early and delayed phase.

and oval cells with eosinophilic cytoplasms were surrounded by abundant myxoid matrix, which was identified in a macroscopically grayish white component at the tumor wall. In addition, plexiform and reticular capillary vasculature and lipoblasts were absent, thus excluding myxoid liposarcoma. Moreover, atypical pleomorphic spindle cells or pseudolipoblasts that are characteristic of myxofibrosarcoma were absent. Most importantly, the diagnosis of EMC was confirmed by the presence of the *EWSR1—NR4A3* fusion gene transcripts in RT-PCR and direct sequencing analyses. Cytogenic studies have confirmed the unique and characteristic chromosomal translocations in EMCs, typically t(9; 22)(q22; q12.2) and in a other studies, in between t(9; 17)(q22;

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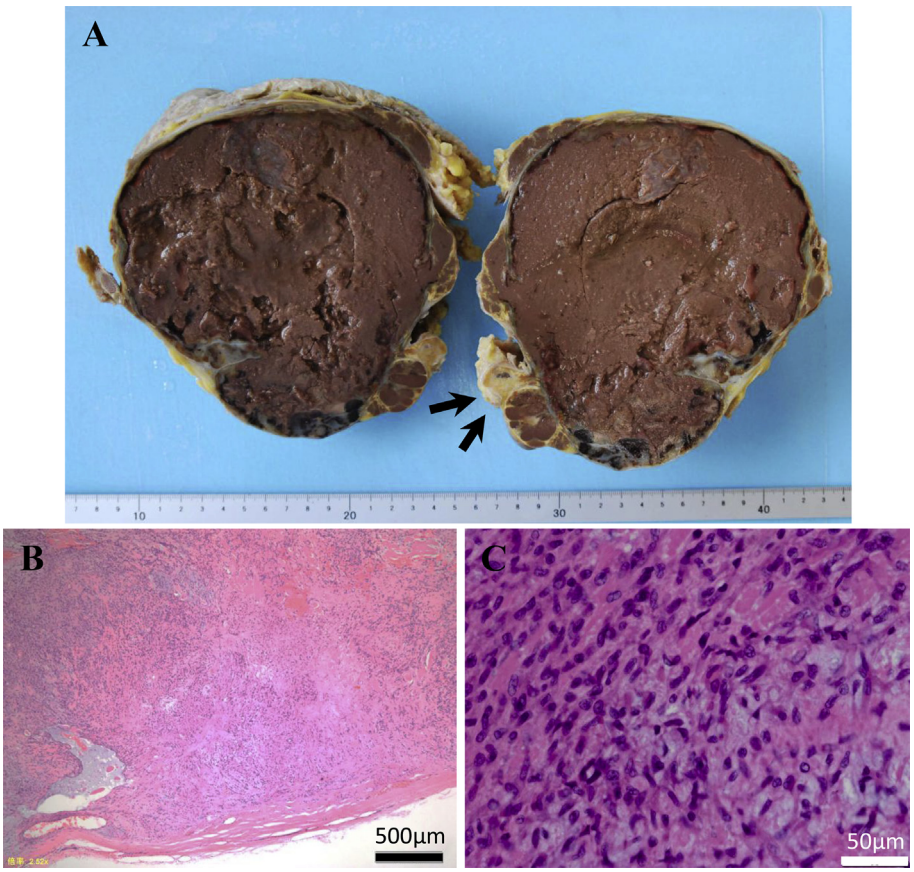

Fig. 5. Histopathology of the resected specimens. (A) Macroscopic view. (B and C) Hematoxylin and eosin stained areas shown by arrows in (A), 20× (B) and 40× (C) magnification. Microscopic evaluation revealed proliferation of spindle-shaped cells and oval cells with eosinophilic cytoplasm at the wall of the tumor (C).

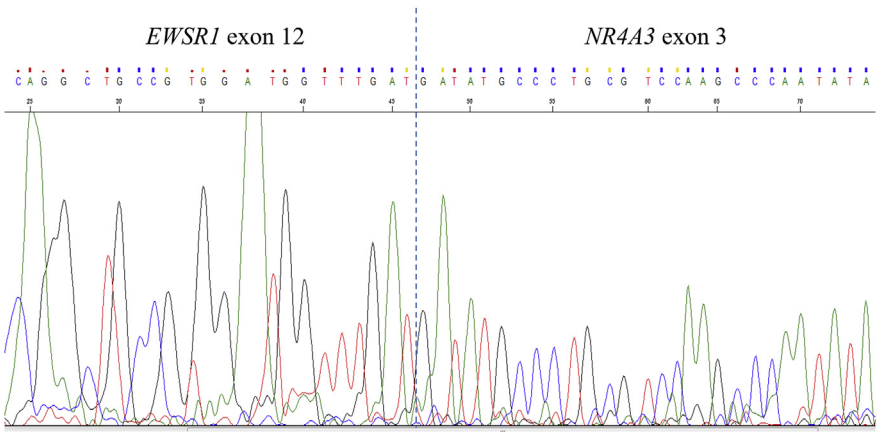

Fig. 6. Direct sequencing of *EWSR1-NR4A3* gene using samples from the resected tumor; gene fusion was confirmed between exon 12 of *EWSR1* and exon 3 of *NR4A3*.

q11) and t(9; 15)(q22; q11) [12,13]. Moreover, fusion of *EWSR1* and *NR4A3* genes is coincident in 85% of all EMC cases. Recently, Hisaoka et al. reported one case with expression of both *NR4A3* and *SIX3* but no *NR4A3* fusion [24]. NR4A3 is an orphan nuclear receptor that acts as a transcription factor after binding its putative coactivator *SIX3*. Because the *NR4A3* fusion protein has been implicated in oncogenesis of EMC, a small fraction of EMC lacks detectable rearrangements of the *NR4A3* gene or 9q22. Similarly, *SIX3* expression is specifically confined to the developing eye and fetal forebrain, although the expression of *NR4A3* is largely ubiquitous. Hence, these reports suggest that aberrant coexpression of *NR4A3* and *SIX3* is a potential alternative mechanism for the development of EMC. The present RT-PCR analyses showed the presence of the typical EMC fusion gene *EWSR1—NR4A3* in the tumor, and confirmed our diagnosis of EMC with a huge expanding hematoma.

Early and accurate diagnosis followed by definitive surgery is important for the cure of EMC. Drilon et al. have reported the poor response rate of EMC to chemotherapy and emphasize on aggressive control of localized disease as the primary approach for treatment [8]. Radiotherapy seems to be beneficial in an adjuvant

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setting and also for palliation of metastatic disease [25]. In our case, we performed initial surgery with R0 resection. Although adjuvant radiotherapy after resection of primary EMC may have been beneficial, our patient preferred instead regular follow-ups. During this three-year follow up period, we did not detect any distant metastases or local recurrence. Ogura et al. have reported that while clinical behavior of EMC is somewhat indolent, the disease has a high propensity for local recurrence and metastases over longer periods of ≥5 years [25]. Therefore, patients should be carefully monitored over a prolonged period.

In conclusion, we reported a rare case of EMC accompanied a large hematoma located on medial thigh of a 75-year-old woman, mimicking chronic expanding hematoma. The molecular detection of the *EWSR1–NR4A3* fusion gene was useful in confirming our diagnosis. We also propose that EMC should be included as one of the differential diagnoses when a large and expanding hematoma is detected in a soft tissue.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

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