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CASE REPORT

Recurrent skeletal extra-axial chordoma confirmed with brachyury: Imaging features and review of the literature

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Abstract A small number of tumors bearing histological resemblance to axial chordoma arising from the bone or soft tissue outside the axial skeleton have been reported. These lesions have historically been referred to as parachordoma, chordoma peripheric um (CP), or extra-axial chordoma (EAC). With the introduction of the immunohistochemical stain brachyury, a sensitive and specific marker for notochordal origin, chordomas arising in extra-axial locations (i.e., CP, EAC), are now diagnosed with more accuracy and distinguished from parachordoma, which resembles chordoma on histology. The distinction between EAC and parachordoma is clinically important because EAC confirmed by immunoreactivity for brachyury tends to grow and recur with local bone destruction. Prior to the introduction of brachyury, the diagnosis of EAC was challenging and therefore the imaging features of EAC have not been comprehensively described. We report two cases of recurrent EAC confirmed by the expression of brachyury arising from the distal femur and distal tibia and describe the imaging findings from radiography and MRI at initial diagnosis and at recurrence.

Keywords Chordoma · Parachordoma · Chordoma peripheric um · Extra-axial chordoma · Myoepithelioma · Brachyury · Bone tumor · MRI · Radiography

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Introduction

Chordoma is a rare malignant primary bone tumor that shows notochordal differentiation [1]. A small number of chordoma-like tumors arising in the bone or soft tissue outside the axial skeleton have been reported and have historically been referred to as parachordoma, chordoma peripheric um (CP), or extra-axial chordoma (EAC). Although these chordoma-like tumors exhibit striking morphologic similarity to axial chordomas in histology, the difference in immunochemistry between chordoma-like tumors and axial chordoma has led to controversy as to whether these chordoma-like tumors are distinct entities or whether they fall within the spectrum of mixed tumor/myoepithelioma group of neoplasms [2, 3]. Recent advances in pathology suggest that brachyury is a sensitive and specific marker for chordoma [2, 4, 5] with the ability to differentiate EAC (also called CP) from other chordoma-like lesions such as parachordoma (also called myoepithelioma) [2]. The distinction between EAC and parachordoma/myoepithelioma is clinically important because EAC confirmed with brachyury immunoreactivity tends to grow and recur with local bone destruction, while parachordoma/myoepithelioma tends to be of low grade [2, 6].

The English-language literature includes eight reported cases of brachyury-positive skeletal EAC, three of which recurred locally [2]. Our aim is to report the fourth and fifth case of brachyury-positive locally recurrent EAC, and to document the imaging appearance of skeletal EAC at initial diagnosis and after local tumor recurrence.

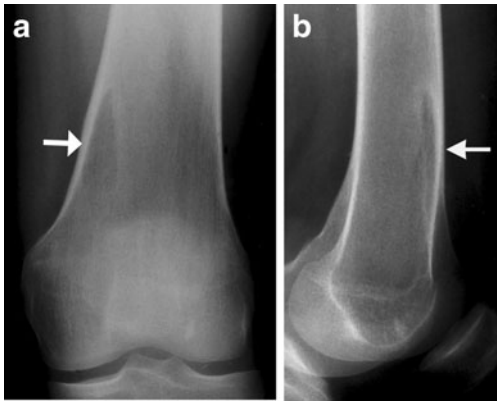

Fig. 1 AP (**a**) and lateral (**b**) views of the radiograph of the left knee demonstrate a lytic lesion (*arrows*) in the medial metaphysis of the distal femur

Case 1 report

A 21-year-old female with a 3-year history of constant knee pain presented to our institution for an orthopedic oncology consultation after a distal femoral lesion was seen on radiograph and MRI was performed at an outside institution. Physical exam revealed exquisite tenderness to palpation and soft tissue swelling at the anteromedial aspect of the distal femur. Her left thigh was asymmetrically atrophic.

Radiographs of the left knee showed an intracortical lytic lesion without sclerotic borders in the anteromedial cortex of the distal femur (Fig. 1). There was no cortical destruction or periosteal reaction. The referred MRI (Fig. 2) revealed an intracortical lesion in the distal femoral metaphysis hyperintense to muscle on proton density and STIR sequences. There was mild perilesional edema in the periosteal soft tissue and marrow. No intravenous contrast was administered. The differential diagnosis on imaging of this intracortical lesion included eosinophilic granuloma, periosteal chondroma, periosteal osteoblastoma, periosteal chondrosarcoma, Brodie's abscess, and metastasis.

An excisional biopsy of the lesion and bone grafting were performed. Morphologically, the lesion consisted of epithelioid cells in a myxochondroid matrix. Immunohistochemical stains showed cells that were strongly positive for S-100 protein, cytokeratin and EMA, while stains for CD31, SMA, and P53 were negative. MIB-1 immunohistochemical stain showed a low proliferative index and labeled only rare tumor cell nuclei. The final pathologic diagnosis was parachordoma.

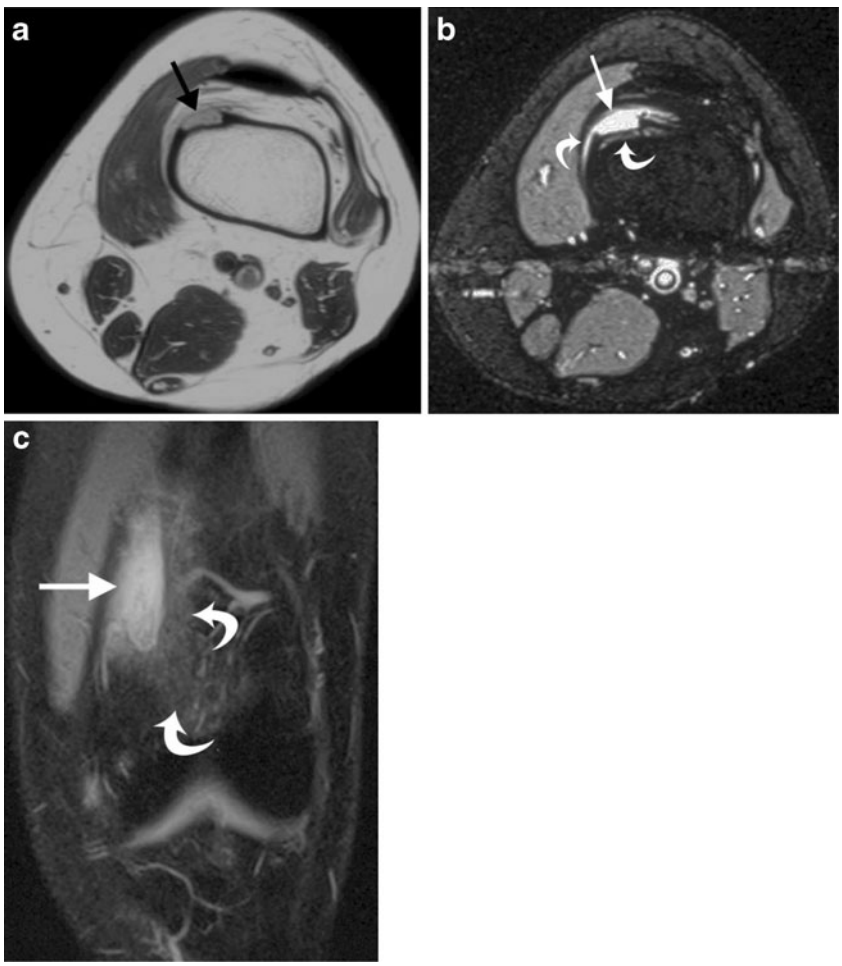

Fig. 2 Axial proton density (**a**), axial STIR (**b**), and a coronal STIR (**c**) images show that the lesion (*arrows*) is intracortical. There is mild endosteal bone edema and periosteal edema (*curved arrows*) adjacent to the lesion

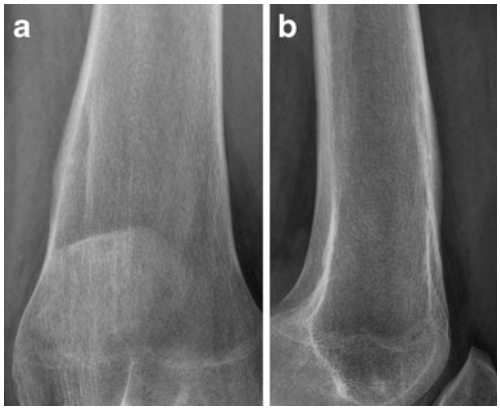

Fig. 3 AP (**a**) and lateral (**b**) views of the left knee radiograph 2 months after the initial surgery show incorporation of the bone graft in the distal femoral metaphysis. There is no new lesion

A whole-body MRI (not shown) performed at our institution revealed no additional lesions in the skull, spine, or proximal peripheral skeleton (ribs, humeri, femora, pelvis), thus excluding axial chordoma.

Two months after the surgery, a radiograph of the left knee (Fig. 3) showed incorporation of the bone graft. There was no evidence of recurrence. However, 2 years later, radiographs (Fig. 4) showed new cortical thickening with intracortical lytic foci. Five years after the surgery, the patient developed pain, and the intracortical lytic foci and cortical thickening in the distal femur had increased in the follow-up radiograph (Fig. 5). A subsequent MRI (Fig. 6) showed multiple enhancing intracortical and endosteal lesions in the distal femur. No bone marrow edema or soft tissue edema was identified. Because of the recurrent cortical involvement and concern for the risk of pathologic fracture, surgical resection was performed.

Histology of the re-excision specimen (Fig. 7) revealed a lobulated appearance with epithelioid cells in a myxochondroid matrix similar to the previous excision. Immunohistochemical

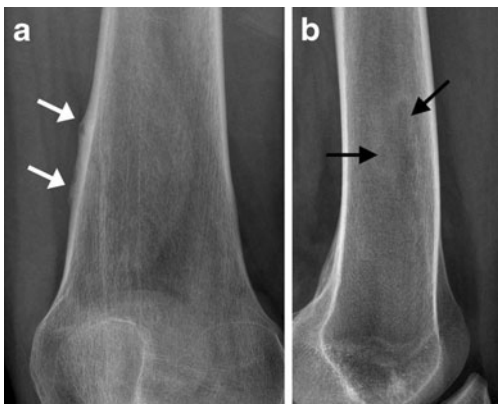

Fig. 4 AP (**a**) and lateral (**b**) views of the left knee radiograph 2 years after the initial surgery show new cortical thickening containing lytic foci (*arrows*) in the medial distal femoral metaphysis

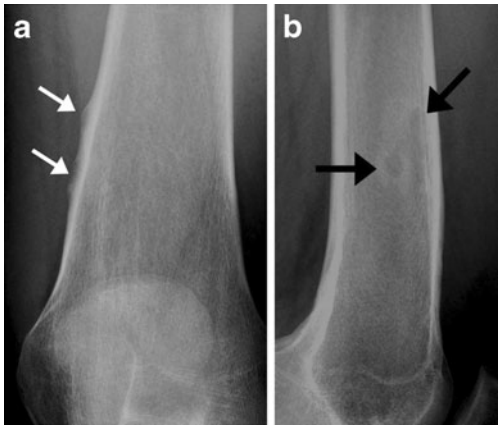

Fig. 5 AP (**a**) and lateral (**b**) views of the knee radiograph 5 years after the surgery show mildly enlarged lytic foci (*arrows*) and cortical thickening

stains showed cells that were strongly positive for S-100, Cytokeratin, and EMA and showed characteristic nuclear positivity for brachyury. The prior excision material was also analyzed for brachyury expression and showed nuclear positivity. These findings were diagnostic of recurrent EAC.

Case 2 report

A 21-year-old female with a 10-year history of right calf leg pain presented to our institution for orthopedic oncology consultation. The patient underwent surgical biopsy and curettage of a distal right tibia lesion at an outside institution a year prior to her consultation. Physical exam revealed a 5-cm incision over the lateral distal right calf with mild edema and minimal tenderness to palpation.

The outside preoperative right ankle radiographs (Fig. 8) showed an intracortical lytic lesion with cortical thickening and periosteal reaction in the distal tibial metadiaphysis as well as mild periosteal reaction in the adjacent fibula. Initial outside MRI (Fig. 9) showed an enhancing T2-hyperintense intracortical lesion in the distal tibial metadiaphysis with adjacent marrow edema pattern. There was also a small extraosseous extension of tumor with or without confinement by the periosteum. Imaging differential diagnosis of this intracortical lesion included Brodie's abscess, eosinophilic granuloma, periosteal chondroma, periosteal osteoblastoma, periosteal chondrosarcoma, and metastasis.

The histology of the surgical specimen was interpreted as chondroblastoma at the outside institution, and the patient subsequently underwent curettage and bone grafting. The post-operative radiograph (Fig. 10) performed 1 month after curettage showed a bone grafting within the curettage defect, residual cortical thickening, and periosteal reaction. However, radiographs (Fig. 11) 8 months after curettage revealed a recurrent lytic lesion, increased cortical thickening in the distal

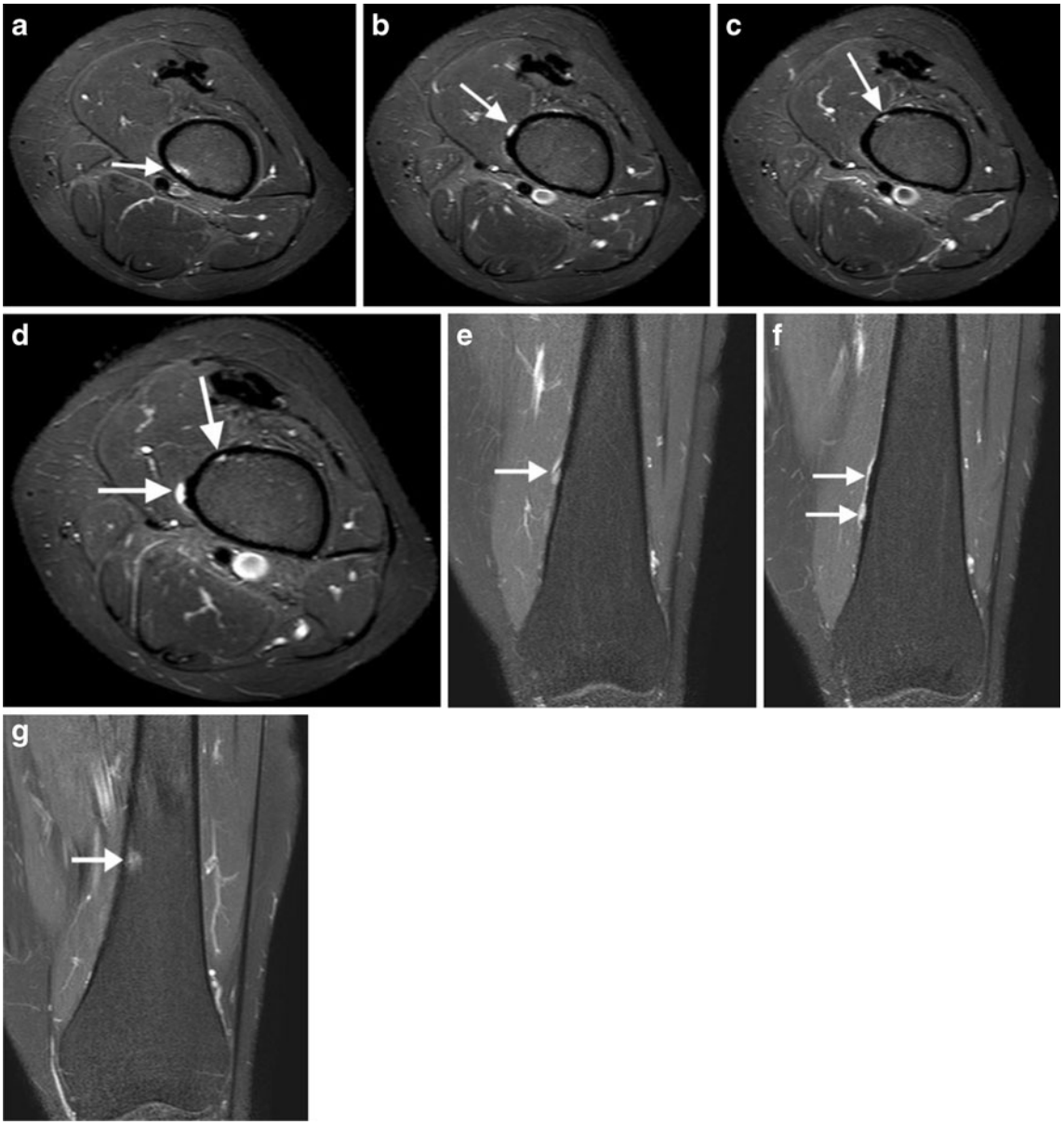

Fig. 6 Axial STIR images (**a**, **b**, **c**, **d**) show scattered intramedullary and intracortical lesions (*arrows*) in the post-surgical bed of the distal femur. Coronal fat-saturated post-contrast MR images (**e**, **f**, **g**) demonstrate diffuse contrast enhancement in the intramedullary and intracortical lesions (*arrows*) in the post-surgical bed of the femur

tibia, and increased periosteal reaction in the fibula. A follow-up MRI (Fig. 12) showed an enhancing intracortical lesion and new enhancing marrow signal abnormality in the distal tibia, increased fibula periosteal reaction, and new soft tissue adjacent to the interosseous membrane. These findings were consistent with a local tumor recurrence.

The pathology specimen of the initial curettage was reviewed at our institution and diagnosed as mesenchymal epithelioid neoplasm, and parachordoma was considered as a possible diagnosis. Immunohistochemical stains were positive for vimentin, cytokeratin cocktail, EMA and S100, while negative for CD1a and CD68. Given the recurrence at imaging, the patient underwent an en bloc resection of the distal lateral distal tibia, distal fibula, and the interosseous space in our institution.

Histology of the en bloc resection (Fig. 13) revealed a chondromyxoid neoplasm with cells arranged in a lobulated architecture. The tumor cells were round to epithelioid and embedded in the chondromyxoid matrix. The lesion showed characteristic nuclear positivity for brachyury (Fig 13), while negative for calponin and SMA. FISH analysis for rearrangement of the EWSR1 gene on 22q12 (Ewing's rearrangement) was negative. These findings were diagnostic of EAC involving the tibia, fibular periosteum, and

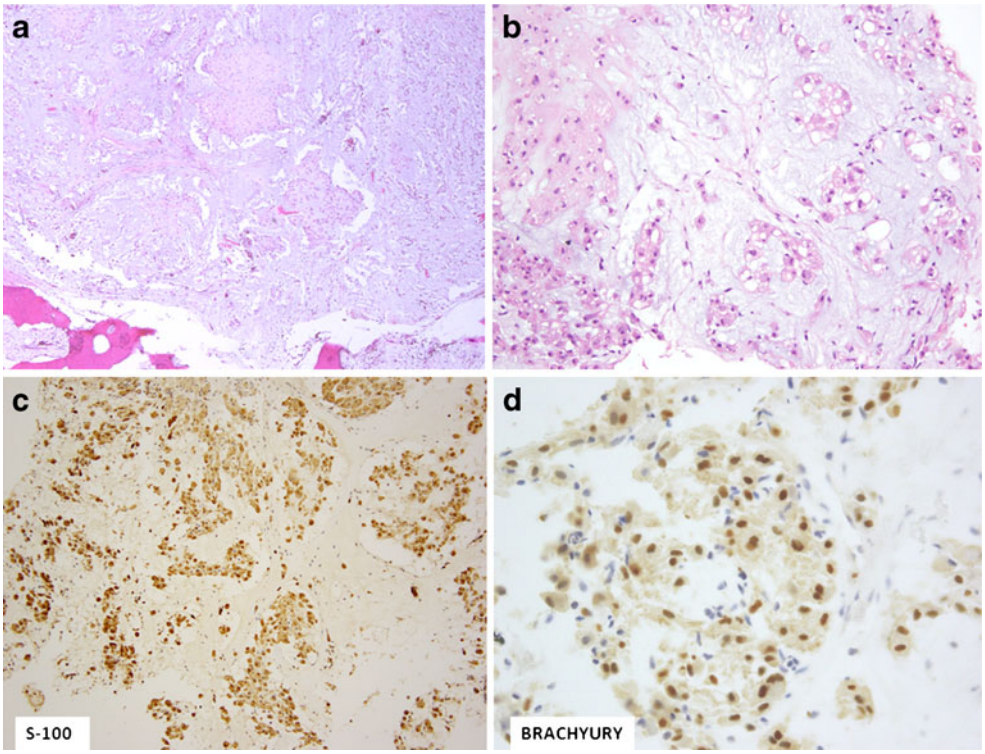

Fig. 7 Case 1. Histology and immunohistochemical stains. **a** H&E image demonstrates the lobulated appearance of the lesion (magnification, 40×). **b** Higher magnification H&E image of the same specimen shows epithelioid cells in a myxochondroid matrix. (magnification, 200×). **c** Immunohistochemical stain for S-100 shows diffuse positivity. **d** Immunohistochemical test for brachyury shows the characteristic nuclear positivity

adjacent soft tissues. The patient has been disease free 3 years after the en-bloc resection of the recurrent tumor.

Discussion

Laskowski first described chordoma peripheriсum in 1955 [7]. Later, Dabska coined the term parachordoma, presenting it as a new clinicopathologic entity, when she reported five cases of Dr. Laskowski's and five of her own, which were morphologically similar to axial chordomas but located outside the axial skeleton [8]. However, controversy exists over what defines true chordoma arising outside the axial skeleton [3, 9]. Although parachordoma, CP, and EAC appear morphologically similar to each other and to axial chordoma, immunohistochemistry has historically not supported the notion that they are simply the same entity in different locations [10]. Specifically, parachordoma does not express cytokeratin 1/10 and 19, which are expressed in axial chordoma [3, 10, 11]. Hornick et al. stated that because the immunophenotypes of parachordomas and myoepitheliomas overlap, parachordoma probably falls within the spectrum of myoepithelioma of soft tissue [6]. This notion is reflected by the classification of parachordoma by the World Health Organization as a soft tissue tumor of uncertain differentiation closely resembling mixed tumor/myoepithelioma [12] and more recent literature considers parachordoma and myoepithelioma as synonymous [13].

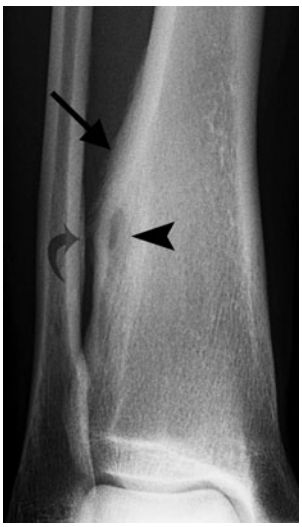

Fig. 8 AP radiograph of the right ankle shows an intracortical lytic lesion (*arrowhead*) and cortical thickening (*arrow*) in the distal tibial metadiaphysis. There is also a periosteal reaction in the adjacent fibula (*curved arrow*)

Recent advances in pathology suggest that positive nuclear reactivity for brachyury differentiates EAC from parachordoma/myoepithelioma [2, 3, 14]. Brachyury is a member of the T-box gene family and encodes a transcription factor required in posterior mesoderm formation and axial development [5, 14]; it is now a well-established marker for axial chordoma with high sensitivity (90–100 %) and specificity (100 %) [4, 5, 15]. Tirabosco et al. demonstrated that brachyury immunoreactivity can distinguish skeletal and soft tissue EAC from other entities

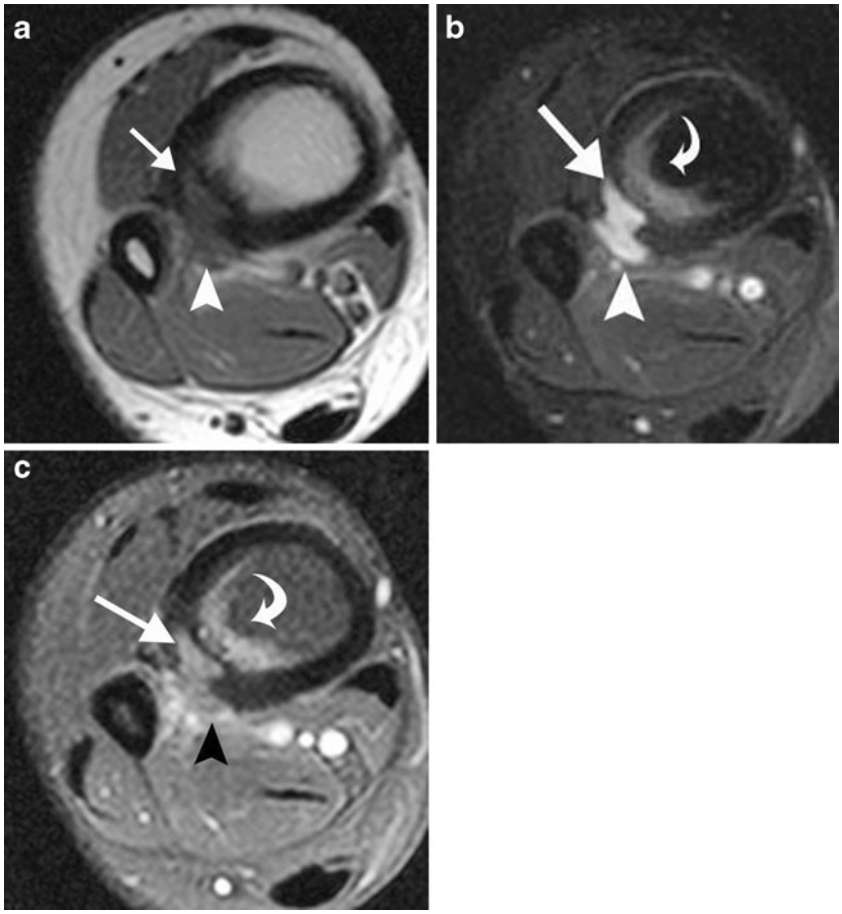

Fig. 9 Axial T1-weighted (**a**) and T2-weighted fat-suppressed (**b**) images show an intracortical lesion (*arrow*) with adjacent marrow edema (*curved arrow*) in the distal tibia and extraosseous extension (*arrowhead*). Post-contrast axial T1-weighted fat-suppressed image (**c**) shows the intracortical lesion (*arrow*) and contrast enhancement in the periphery of extraosseous extension (*arrowhead*) and marrow edema

such as parachordoma, carcinoma, and sarcoma; they proposed that chordoma-like lesions that are positive for brachyury and CK19 should be classified as extra-axial chordoma, whereas those that are negative for these stains should be categorized within the parachordoma/myoepithelioma/mixed tumor spectrum [2].

Our search of the English-language literature revealed 11 reported cases of skeletal EAC, apart from ours and Dabska's; eight of them were reported as brachyury-positive by Tirabosco et al. [2], while three were reported earlier by other

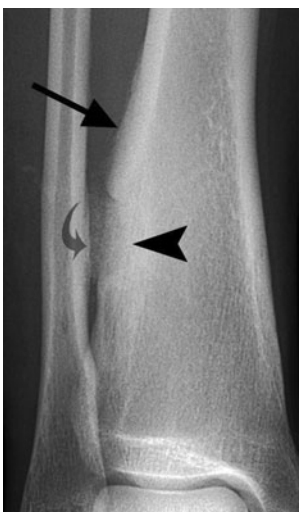

Fig. 10 AP radiograph of the right ankle 1 month after curettage shows a curettage defect containing bone graft (*arrowhead*), residual periosteal reaction in the fibula (*curved arrow*), and cortical thickening in the tibia (*arrow*)

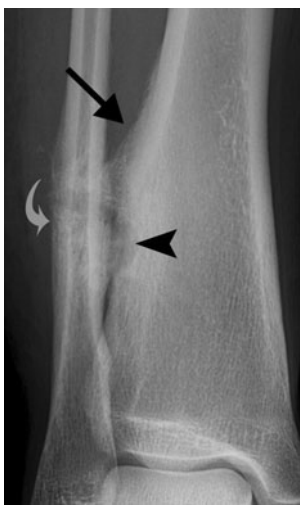

Fig. 11 AP radiograph of the right ankle shows a new lytic lesion (*arrowhead*) in the curettage bed of distal tibia and increased cortical thickening in the adjacent tibia (*arrow*) and fibula (*curved arrow*)

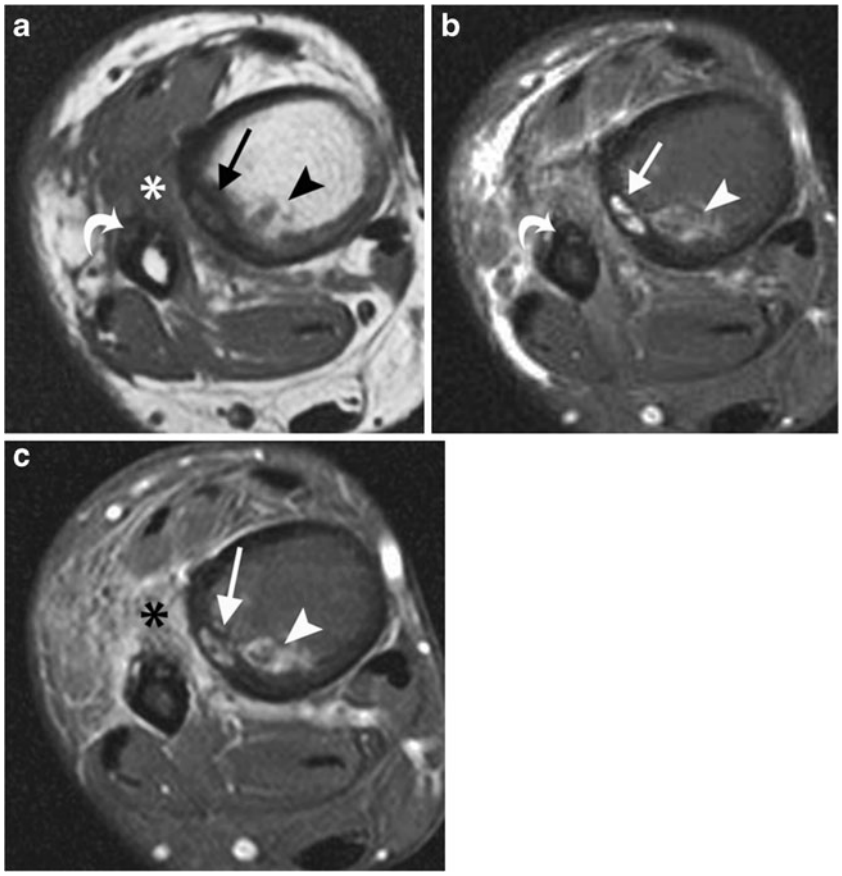

Fig. 12 Axial T1-weighted (**a**), T2-weighted fat-suppressed (**b**), and post-contrast T1-weighted fat-suppressed (**c**) images show an enhancing intracortical lesion (*arrow*) and new marrow signal abnormality (*arrowhead*) in the distal tibia. New enhancing soft tissue (*) adjacent to the interosseous membrane and increased periosteal reaction (*curved arrow*) in the adjacent fibula are also present

authors [16–18] and were not tested for brachyury expression (Table 1). Among the eight brachyury-positive cases, two were intracortical and six were intramedullary; three cases (two in the proximal tibia and one in the distal femur) showed local recurrence. Extraosseous extension was reported in four cases, one of which was located in the intramedullary canal of the distal femur and recurred twice. Our two cases are the ninth and tenth reported cases of brachyury-positive skeletal EAC and the fourth and fifth reported cases of locally recurrent brachyury-positive skeletal EAC, illustrating the rarity of this entity.

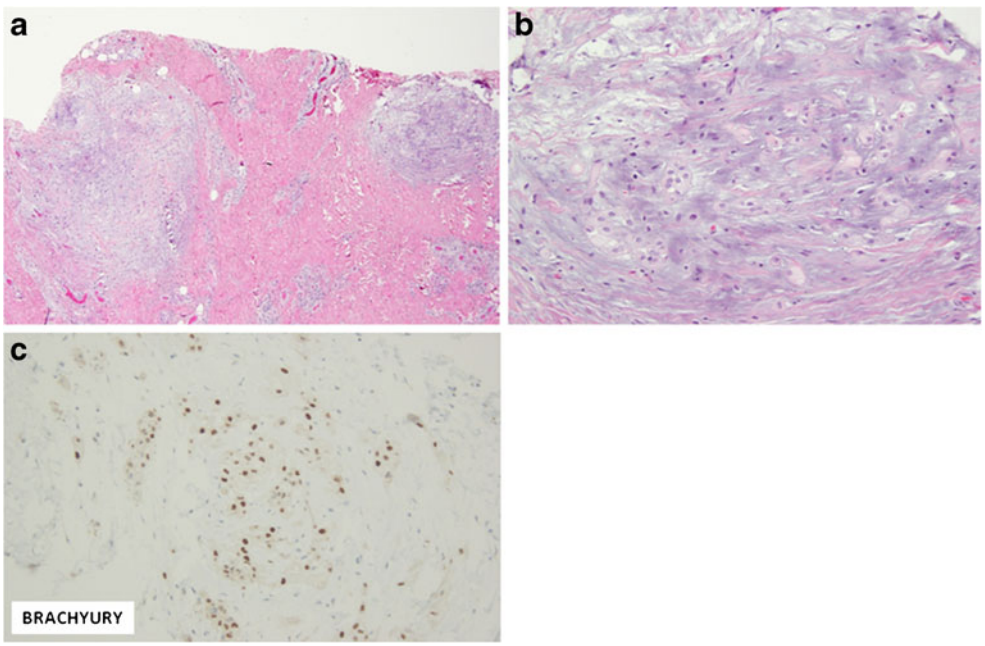

Fig. 13 Histology showing **a** the lobulated architecture of the lesion. (H&E, 100×) and **b** higher magnification showing uniform round to epithelioid cells in a chondromyxoid matrix. (H&E, 400×). **c** Immunohistochemical test for brachyury shows characteristic nuclear positivity

Table 1 List of the skeletal extra-axial chordoma cases in the English literature after Dabska's report

Authors	Year	Age	Sex	Site	Location	Extraosseous extension	Brachyury	CK 19	Local recurrence	Metastasis
Nielsen et al.[a] [24]	2001	36	M	Distal ulna	Intramedullary	Yes	+	+	None	None
DiFrancesco et al.[a] [25]	2006	41	F	Pubis	Intramedullary	Yes	+	+	None	None
O'Donnell et al.[a] [14]	2006	27	M	Proximal tibia	Intracortical	No	+	+	Yes (40 months)	None
van Akkooi et al.[a] [26]	2006	56	F	10th rib	Intramedullary	Yes	+	+	None	None
Tirabosco et al. [2]	2008	35	M	Mid tibia	Intracortical	No	+	+	None	None
		55	F	1st metatarsal	Intramedullary	No	+	+	None	None
		68	M	Distal femur	Intramedullary	Yes	+	+	Yes (9 months, 31 months)	None
		18	F	Proximal tibia	Intramedullary	No	+	+	Yes (<14 months)	None
Povysil et al. [16]	1985	NA	NA	Tibia	NA	NA	NA	NA	None	None
Koh et al. [17]	2000	64	M	Proximal tibia	Cortical erosion	Yes	NA	NA	Yes (1 year)	None
Hemalatha et al. [18]	2003	24	M	Proximal tibia	NA	NA	NA	NA	None	None
Case 1	2012	21	F	Distal femur	Intracortical	No	+	NA	Yes (5 years)	None
Case 2	2012	21	F	Distal tibia	Intracortical	Yes	+	NA	Yes (8 months)	None

NA not available (test not performed or reported)

[a] Re-analyzed by Tirabasco et al.

The two cases presented here may be the first two cases of skeletal EAC confirmed by the expression of brachyury to be reported with the radiographic and MRI findings at the initial diagnosis and at the time of local recurrence. Radiographic features in our two cases are lytic lesions located in long bone metadiaphyseal cortex. Periosteal reaction and cortical thickening were present in case 2 at the initial diagnosis and tumor recurrence. Although some of these features (lytic lesion, perilesional sclerosis) were previously reported in an intracortical proximal tibia metaphyseal EAC [14], they are not commonly seen in axial chordomas. At MRI, the high fluid-like signal intensity of the EAC is similar to that seen in axial chordoma, probably due to the rich fluid content of vacuolated cellular components in the tumor [19]. On the other hand, perilesional edema seen in both of our cases is an uncommon MRI feature in axial chordoma, despite frequent cortical destruction in the axial chordoma. Perilesional edema at MRI was also reported in skeletal EAC of the tibia [2, 14], and it is possibly due to early tumor extension, which causes periosteal reaction leading to adjacent bone and soft tissue edema. However, elucidation of this potential mechanism leading to perilesional edema will require the evaluation of more cases of skeletal EAC. At recurrence, the lesions were lytic at radiograph and multifocal, either involving the bone (case 1) or bone and soft tissue (case 2), similar to axial chordoma.

Generally, differential diagnosis of a juxtacortical lesion in long bone metadiaphyses with perilesional edema includes eosinophilic granuloma, periosteal chondroma, periosteal chondrosarcoma, periosteal osteoblastoma, osteoma, Brodie's abscess, and metastasis. A small eosinophilic granuloma is indistinguishable from skeletal EAC on imaging since it can exhibit perilesional edema in the early or active stage [20]. Perilesional edema is more frequently seen in periosteal chondrosarcoma, but it is uncommon in both periosteal chondrosarcoma and periosteal chondroma [21]. Periosteal osteoblastoma is rare, with a radiologic appearance that varies from a lytic lesion with internal calcification to a heavily calcified mass and with diffuse perilesional edema [22]. Intracortical osteoma is known for edema and periosteal reaction, but multifocal involvement as seen in case 1 at recurrence is unusual. Brodie's abscess was less likely in the absence of clinical constitutional symptoms despite long-standing pain and other imaging findings such as a sequestrum. Metastases were unlikely in both cases since both patients were young and without known primary malignancy. In case 1, metastasis (e.g., from chordoma or intracortical metastases from carcinoma such as lung or breast) [23] was also excluded by negative whole-body MRI and immunohistology. In case 2, metastasis is not entirely excluded given incomplete imaging of the axial skeleton, however, because the patient is clinically doing well without evidence of recurrence for 3 years, a solitary metastasis from an axial chordoma is considered less likely. Similarly, metastases from an axial chordoma in prior studies is not entirely excluded as well, though the largest series did have negative chest CTs and bone scans for all patients (2).

In summary, skeletal EAC is a rare entity that is identical to axial chordoma in histology, and its diagnosis is readily facilitated by brachyury immunohistochemistry. The imaging features of skeletal EAC include a lytic lesion on radiography at initial diagnosis and recurrence and high signal

intensity of the tumor on fluid-sensitive sequences on MRI; these are similar to the findings in axial chordomas. However, periosteal reaction and cortical thickening on radiograph and perilesional edema seen at MRI seen are not common findings reported in axial chordoma. The multifocal involvement in bone and soft tissue at local tumor recurrence in our skeletal EAC cases is similar to those seen with recurrent axial chordomas, and it underscores the importance of thoroughly examining the postsurgical bed at imaging so that all recurrent tumors can be properly resected.

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