CASE REPORT

Extra-axial dedifferentiated chordoma: A case report with brachyury immunohistochemical confirmation, literature review and pathologists’ perspective

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Abstract: Dedifferentiated chordoma is a rare and aggressive malignant bone tumor. It is known as a variant of conventional chordoma, which possesses additional high-grade sarcomatous elements. Dedifferentiated chordoma is commonly identified in axial location as recurrences, or following radiation therapy of primary tumors. Prognosis is poor and there is a potential risk for metastasis. There have been only a few reports of primary dedifferentiated chordoma. Owing to its rarity, especially when it is in an unusual extra-axial location, primary dedifferentiated chordoma presents a diagnostic challenge. Brachyury, a recently described immunohistochemical marker specific for chordoma, has improved the diagnostic accuracy of chordoma and its variants in extra-axial sites. We herein report an exceptional case of extra-axial dedifferentiated chordoma confirmed by the expression of brachyury, the first case report of this kind. The review of relevant literature and discussion of practical diagnostic approach from sarcoma pathologists’ perspective are intended to provide an update of this topic.

Keywords: chordoma; brachyury; pathology; dedifferentiated


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Introduction

Chordoma, a malignant tumor showing notochordal differentiation, chiefly arising within the axial skeleton, has a reported incidence of 0.08 per 100,000 people[1-3]. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute reported that in the axial skeleton, 32% of the cases were cranial-based, and 32.8% and 29.2% occur in the mobile spinal and sacrococcygeal bones, respectively[1,4]. There is a small subset of tumors that have been identified outside of the axial skeleton, referred to as extra-axial chordomas[1,5-13]. Extra-axial chordomas exhibit an identical histological resemblance to conventional chordomas found within the axial skeleton.

A rare, aggressive variant of conventional chordoma, known as dedifferentiated chordoma, harbors sarcomatous areas as well as areas resembling conventional chordoma. The sarcomatous areas commonly appear as high-grade undifferentiated spindle cell sarcoma; however, other histomorphologies have also been reported such as fibrosarcoma, osteosarcoma, or rhabdomyosarcoma[14-26]. It is usually diagnosed in recurrences and following radiation therapy, but there have been reports of de novo development[24,26-28]. In the era of personalized medicine,
the need to generate accurate diagnosis including tumor type and grade information on small biopsy is becoming a norm, with the size of the tumor biopsy decreasing. This presents a special challenge when a tumor is heterogeneous such as the dedifferentiated chordoma and when only the dedifferentiated area is sampled. We have the opportunity to report a case of extra-axial dedifferentiated chordoma presenting as a foot mass. A discussion of solution design to approach this diagnostic challenge and an update on literature review is intended to provide practical information for practicing pathologists.

Case Report

Clinical presentation

For about two years, a 68 year-old female with a history of celiac disease and neuropathy had suffered from burning pain in her feet, as well as tightness and swelling with purple discoloration of her feet. In 2013, she was evaluated at an outside facility, which initially diagnosed her with plantar fasciitis but after failure to improve her ailment with conservative management, imaging studies were obtained. A magnetic resonance imaging (MRI) from the outside facility reported the presence of a 4.8 × 4.0 × 4.0 cm lobulated soft tissue mass on the plantar aspect of the right foot, located along the inferior aspect of the talonavicular and navicular cuneiform joints, and along the medial aspect of the calcaneal body and cuboid bone deep to the flexor digitorum longus tendon. The mass has caused erosion to the anterior calcaneal body and the proximal aspect of the cuboid bone. The mass had completely encased the flexor hallucis longus tendon along the lateral aspect. This was subsequently excised (the pathology report and slides were unavailable for review). She constantly bore the pain following surgery over the next six months and tried physical therapy without benefit.

In 2014, an outside MRI report indicated the presence of a multi-lobulated and erosive mass, 4.5 cm in its greatest dimension, in the medial posterior right foot involving both the calcaneus and soft tissue inferior to the calcaneus. A core needle biopsy of the right plantar foot mass was performed at an external hospital and the pathology results showed the possibility of dedifferentiated chondrosarcoma. However, the case was passed over for consultation at another facility which diagnosed the lesion as an epithelioid malignant neoplasm, favoring carcinoma over epithelioid sarcoma. At this time, the patient came to Moffitt Cancer Center for a secondary suggestion.

An additional MRI obtained of the patient’s right lower extremity demonstrated a 6.4 × 3.8 × 4.9 cm plantar soft tissue mass involving several tarsal bones, particularly the anterior calcaneus, and several flexor tendons and muscles along the plantar aspect of the foot (Figure 1). Physical exam showed a well-healed plantar medial incision and a diffuse, firm mass over the plantar aspect of the foot. There was mild tenderness to palpation. Additional imaging studies did not reveal any evidence of metastatic disease. Clinicians deduced that the mass was a high-grade primary malignancy and performed a right below-the-knee amputation. The patient’s surgery was complicated by wound dehiscence of her right stump two months later. At that time, the patient agreed to a debridement of the wound dehiscence of the right stump. Wound cultures showed a positive result for Escherichia coli. The patient received appropriate antibiotic therapy and the right below-the-knee amputation stump completely healed. A year later, the patient is doing well and has no evidence, clinically or on follow-up MRI lower extremity imaging, of local recurrence.

Pathological findings

Core biopsy

The core biopsy was reviewed. The histological sections revealed a poorly differentiated malignant neoplasm comprised of spindle-shaped and epithelioid-appearing neoplastic cells containing large, irregular nuclei and abundant eosinophilic cytoplasm (Figure 2a). Frequent mitoses were observed, including atypical mitotic figures. Necrosis was absent. A small focal population of cells was identified with clear and vacuolated cytoplasm embedded within an extracellular myxoid-like matrix (Figure 2b). There was no chondroid or osteoid matrix identified. What could be the pertinent differential diagnoses of tumor at this location with this morphology? At this point, carcinoma, melanoma, and sarcoma were all fair diagnoses.

On immunohistochemical staining, the tumor cells exhibited strong and diffuse positivity for pancytokeratin,
Figure 2. Core biopsy of foot mass. (a) The biopsy is composed of spindle and epithelioid shaped neoplastic cells with large, irregular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm (hematoxylin and eosin, 400X), (b) Focal population of cells with clear, vacuolated cytoplasm is identified (hematoxylin and eosin, 400X), (c) Strong nuclear positivity with brachyury (200X)

epithelial membrane antigen (EMA), and CD10. The tumor cells were focally positive for CD99. Tumor cells showed focal patchy positivity for CD31 and multifocal positivity for p63. Tumor cells were negative for cytokeratin 7, cytokeratin 20, bcl-2, CD68, CD34, S100, HMB-45, PAX2, CD56, GFAP, INI-1, and desmin. This immunostain panel does not support epithelioid sarcoma, melanoma, angiosarcoma, malignant peripheral nerve sheath tumor, renal cell carcinoma, or leiomyosarcoma.

Upon further and closer examination of the core biopsy, small groups of cells that had clear and vacuolated cytoplasm with myxoid matrix reminiscent of a chordoma were observed. The strong and diffuse positivity for pancytokeratin and epithelial membrane antigen (EMA) could be seen in a chordoma. S100 expression can be seen in 80%–90% of cases of chordoma[29-34]. A brachyury immunostain was performed for confirmation (Figure 2c) (stain performed at PhenoPath Laboratories; polyclonal clone), which revealed uniform and diffuse nuclear positivity. Given the morphology and immunophenotype, a diagnosis of dedifferentiated chordoma, extra-axial type, was rendered. This case was reviewed at another institution and a similar diagnosis by an expert soft tissue pathologist was rendered. The repeated immunostain of brachyury by the external pathology consultant provided a similar positive report.

The patient’s clinical team was informed about this surprising diagnosis but deemed that surgery would still be the best treatment. This is owing to the fact that the tumor was fungating out of the patient’s skin, which would cause substantial wound care issues and she would continue to lose function of her lower extremity.

Surgical resection

A 6.0 × 4.0 × 3.5 cm mass was identified in the right foot, deep to the patient’s prior incisional scar, involving 30%–40% of the foot with concentration on the plantar aspect. The mass involved the calcaneus, cuboid, navicular, and lateral cuneiform bones, including surrounding soft tissue, muscle, and tendons. The skin was not involved. The cut surface of the tumor showed a multi-loculated appearance with hemorrhage and necrosis, including a solid, tan-white lobulated area (Figure 3). Microscopic examination revealed a lobulated tumor with areas of necrosis. The tumor was predominantly composed of spindle-shaped and epithelioid-like cells, exhibiting a sarcomatoid appearance with moderate to marked nuclear pleomorphism and eosinophilic cytoplasm. Rare scattered small foci of tumor cells with abundant clear and vacuolated cytoplasm were identified, admixed with sarcomatous-like tumor cells (Figure 4a). Immunohistochemically, tumor cells were positive for brachyury (Figure 4b). Specifically, the recognizable chordoma-like areas were brachyury-positive while the dedifferentiated areas were negative. Additional immunohistochemical stains were performed in order to compare the pattern of staining in the resection to the prior biopsy. Similar to the biopsy, tumor cells in the resection specimens exhibited strong and diffuse positivity for pancytokeratin, EMA, and CD10. Tumor cells were focally positive for CD99 and CD31. Tumor cells demonstrated multifocal positivity for p63 (Figure 5a–5f). The histomorphology and immunohistochemical staining pattern, including the positive brachyury nuclear expression, were identical to the findings in the core biopsy supporting the diagnosis of dedifferentiated chordoma, extra-axial type.

Discussion

There were 10 reported cases of brachyury-positive skeletal extra-axial chordoma in English-language scientific literature[35,36]. Based on our knowledge, this report is the first to report an extra-axial dedifferentiated...
Figure 3. Foot mass surgical resection. Gross image of the right foot mass (left), and axial T1-weighted (right) showing the soft tissue mass (*) involving the bones and soft tissue of the right foot

Figure 4. Foot mass surgical resection. (a) On the right side of the image, neoplastic cells with abundant, clear, vacuolated cytoplasm is present and on the left side of the image, neoplastic cells with sarcomatoid morphology with moderate to marked nuclear atypia and eosinophilic cytoplasm is seen (hematoxylin and eosin, 200X), (b) Strong nuclear positivity with brachyury (200X) on the right side of image; dedifferentiated area shows negative staining on the left side of image

Figure 5. Foot mass surgical resection immunostains. (a) CKAE1/3 CAM (200X), (b) Epithelial membrane antigen (EMA) (200X), (c) CD10 (200X), (d) CD99 (200X), (e) CD31 (200X), (f) p63 (200X)
brachyury-positive chordoma. Dedifferentiation occurs in 2%–8% of chordomas, which may develop at the onset of the disease or later[37]. Prognosis is poor owing to the aggressive nature of this tumor, culminating in distant metastases and rapid demise. In rare instances, patients with small foci of dedifferentiation demonstrate longer survival than patients with multiple significant foci of dedifferentiation[27]. Recently, brachyury was identified as a sensitive and specific marker for chordoma with the ability to discern between extra-axial chordoma and other chordoma-like lesions such as parachordoma/myoepithelioma[30,35,38,39]. Given that extra-axial chordomas are rare and our case of extra-axial dedifferentiated chordoma is even rarer, brachyury is extremely useful in confirming the diagnosis.

Brachyury, a transcription factor within the T-box complex of genes encoded by the T gene, is a diagnostic marker for chordomas[40,41]. According to recent ies, brachyury nuclear expression has been shown in most axial and skull-based chordomas, ranging between 89.7% and 100%, including dedifferentiated and metastatic ones[30,38,42]. The expression of brachyury as well as cytokeratin, EMA, and S100 are not seen in the areas of dedifferentiation[30,38]. In our case, the dedifferentiated component was negative. A few cases of conventional chordomas and chordoid chordomas demonstrated the absence of brachyury staining, which was presumed to be due to inadequate fixation of tissue and poor antibody penetration[30,42]. Brachyury expression has reportedly not been observed in chondrosarcoma, liposarcoma, myoepithelial tumors, germ cell tumors, or clear cell renal cell carcinoma[35,38,42,43]. However, Miettinen et al. immunohistochemically evaluated 5,229 different tumors for nuclear brachyury expression (rabbit monoclonal antibody; 1:2,000 antibody dilution) and had shown that brachyury expression is prevalent in embryonal carcinoma, seminoma, and small cell carcinoma of the lung, but very rarely in common carcinomas such as ductal carcinomas of the breast or adenocarcinomas of the prostate, sarcomas, and melanoma[30]. Additionally, all chordomas (75/76), except a sarcomatous one, were positive while chondrosarcomas were negative[39]. Overall, brachyury appears to be a sensitive and fairly specific marker for chordoma, useful in distinguishing chordomas, including those occurring in extra-axial sites, from their histological mimics[30,38,39,42,46].

Although rare, it is of immense importance to recognize extra-axial skeletal and soft tissue chordomas as the treatment of this neoplasm and patient prognosis differs from that of other neoplasms, which it could be mistaken for. Histopathologically, chordomas including their histologic subtypes (chondroid chordoma and dedifferentiated chordoma) harbor areas exhibiting classic features characterized by physaliphorous cells embedded in myxoid/chondromyxoid matrix. However, it is difficult to diagnose chordoma, let alone dedifferentiated chordoma, at extra-axial sites with histology demonstrating paucity or absence of physaliphorous cells, variable chondromyxoid matrix, and spindle to epithelioid cells with mild to marked atypia. The differential would include other primary bone/soft tissue tumors such as parachordoma/myoepithelioma, chondrosarcoma, and extra skeletal myxoid chondrosarcoma, as well as metastasis such as metastatic renal cell carcinoma or metastatic mucinous adenocarcinoma, or tumor arising from skin/adnexal structures involving soft tissue such as melanoma or mucoid/pseudomyxoid carcinoma (Table 1). When confronted with a neoplasm from a bone or soft tissue specimen with an epithelioid appearance and diffuse expression of cytokeratins, it is important to review clinical and radiological findings to determine if the neoplasm represents a metastatic carcinoma, but if history does not indicate metastasis and tumor of unknown origin is raised, an panel of immunostains including brachyury would be of value. Given the differential described above, melanoma rarely expresses cytokeratin but other melanocytic markers (Melan A, HMB-45, MITF, etc.) would exclude this diagnosis. Meanwhile RCC, CD10, PAX-2, and PAX-8 would help rule out renal cell carcinoma metastasis, especially if the tumor does not show prominent clear cell features.

Chondrosarcomas lack cytokeratin expression. Extraskeletal myxoid chondrosarcomas generally lack cytokeratin expression with a minority of cases exhibiting S100 expression. They possess the t(9;22)(q22;q11) translocation[47]. Parachordoma/myoepithelioma typically coexpress cytokeratin (or EMA) and S100. Like extraskeletal myxoid chondrosarcoma, parachordoma/myoepithelioma show rearrangements involving the EWSR1 locus[48]. Fluorescence in-situ hybridization (FISH) for NR4A3 gene, rearranged in extraskeletal myxoid chondrosarcoma but not to date in myoepithelioma, may be helpful in differentiating the two[49,50]. Again, brachyury would be diagnostically valuable in this situation because expression is not seen in melanoma, renal cell carcinoma, chondrosarcoma, extraskeletal myxoid chondrosarcoma, or parachordoma/myoepithelioma. Cytokeratin is still the most accurate ancillary stain in discriminating chordoma from chondrosarcoma, though the addition of brachyury in a panel-based approach does slightly improve accuracy and serves as a useful confirmatory marker. Interestingly, brachyury may be lost in more histologically and clinically aggressive chordomas[42]. In other words, dedifferentiated chordomas may lose the expression of brachyury and in small core biopsies where the
dedifferentiated component is the only area biopsied and viewed microscopically, the diagnosis would be missed and likely interpreted as an undifferentiated sarcoma since the dedifferentiated area of dedifferentiated chordomas do not stain with brachyury.

**Conclusion**

In summary, we herein report an exceptionally rare case of extra-axial dedifferentiated chordoma confirmed by the expression of brachyury. We have discussed the differential diagnosis and reviewed the relevant literature.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**


