Sclerosing Epithelioid Fibrosarcoma – A Rare Sacral Lesion and Literature Review

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Abstract
Sclerosing epithelioid fibrosarcoma (SEF) is a singular entity, recognized as malignant fibroblastic sarcoma variant, which deviates from classic type due to the indolent progression and late metastasis. Typically occurring in middle aged adults, it presents a predilection for deep soft tissues, particularly skeletal muscle. It often involves the fascia or periosteum, and less frequently it may invade or arise from bone. Diagnosis and recognition are critical, as the generally bland appearance or when intraosseous similarity with an osteoid lesion, can lead to misdiagnosis. We herein present a case showing an unusual location and challenging radiological morphological and surgical features.

Keywords: Fibrosarcoma; Sarcoma; Epithelioid; Sacral region

Introduction
Sarcomas can be classified into 2 broad categories: soft tissue sarcomas (STS), and sarcomas of the bone (commonly seen in the paediatric population) [1]. In the former group, sarcomas that have histologic resemblance to fat, muscle, nerve sheath, and blood vessels are included and are named accordingly. In 1995, by Meis-Kindblom et al. [2], it was first described as a different entity, among the STS, named sclerosing epithelioid fibrosarcoma (SEF). It’s a rare mesenchymal neoplasm that has been classified as a low-grade sarcoma, which is nowadays considered an obsolete terminology, regarding its malignant behaviour [3]. With a median age of diagnosis between 50 and 60 years-old [4,5], only 10% of patients are younger than 20 years at the time of diagnosis. There is no gender predominance in the SEF [1,2]. The mean interval from first symptoms to diagnosis is 33 months, with approximately one quarter of the cases with synchronous metastatic disease [6]. These tumours present a typical location on deep soft tissue of the limbs, limb girdles, trunk, neuroaxis, pelvis, head and neck. Primary SEF in visceral organs or bone lesions are exceedingly rare [2]. The first description of SEF with bone origin was found in 2002 by Abdulkader et al. [4] that reported a case of an iliac SEF as a primary bone tumour. To our knowledge, on literature (Embase®, NCBI-Pubmed® and Google Scholar®), from around 20 cases of SEF arising from bone [7-9], five cases were allocated to the axial skeleton, but there is only one report of sacrum involvement, by Chow et al. [10]. Here we describe a rare case of SEF arising from sacral bone tissue, an unusual origin and location for such a relatively rare lesion.

Case Presentation
A 38-year-old female patient was presented with persistent and incapacitating sacral ant buttock pain. Local evaluation and neurological examination results were entirely normal. Laboratory tests and her past medical history were unremarkable. Lumbosacral spine MRI (Figure 1) and CT (Figure 2) denoted an expansible lesion, with 5 cm × 4 cm × 3 cm in diameter, implanted on the posterior wall of the sacrum, with bone erosion, neural foramen and soft tissue involvement. The mass presented a moderate enhancement after endovenous administration of the contrast agent. Staging CT scans doesn’t reveal any other lesion.

Figure 1: Sagittal T1 gadolinium and axial TSE - Expansive and lytic lesion on S1 and S2 body, with contrast enhancement and soft tissue component on sacral canal.

Figure 2: Axial CT - Preoperative image with invasive sacral soft tissue mass, and obliteration of sacral canal.
Due to large size and ill-defined margins at CT examination (Figure 3) a malignant soft tissue tumour was suggested.

Needle biopsy diagnosis was inconclusive for tissue characterization. It was presented the diagnosis of sarcoma, without subtype definition. The Department decision, after histological confirmation, was to propose the patient to surgical tumour-based resection. A posterior approach with sacral laminectomy and subtotal resection was performed, in piece-meal type, from a very soft and fragile lesion. To avoid any neurological damage, the lesion was treated with close surgical margins due to the great difficulty imposed by location and tumour size. Despite the risk of regrowth, the main objective was to get the larger area with negative margins and maximum preservation of neurological structures. The tumour was poorly circumscribed and showed an infiltrative edge, with destruction of the surrounding lamellar cortical bone. Complementary histopathological review of large surgical piece confirmed the diagnosis of SEF.

Postoperative MRI scans demonstrated residual disease, mostly on lower aspect of the sacrum and around S2 and S3 foramen. The postoperative course of the patient was uneventful. After three months of clinical followup no local recurrence was observed, but with the patient consent, we decide to reoperate, and remove the remaining tumour. Based on preoperative MRI (Figure 4), the same approach was performed; extending sacral residual tumour remained adjacent to the S3 roots, impossible to dissect from a much attached lesion.

Patient developed a CSF fistula that needed surgical repair at day 4. She was discharged from hospital at day 12, and resumed her usual daily activities after one to two months of rehabilitation. Patient was proposed to adjuvant external-beam radiotherapy, with 2 Gy daily fractions to a total dose of 60 Gy on target areas. The course of treatment was uneventful. Patient reports episodic paresthesia in the right L5 dermatome, without motor limitation, and maintains detrusor underactivity, but with spontaneous voiding, without considerable residual volume. At the end of the first year of follow-up she attends daily activities on a regular basis, without limitation, but did not return to work. There is no evidence of tumour regrowth.

Histology

The surgical specimen was submitted for histological examination and revealed an heterogeneous mesenchymal tumour with areas showing a prominent hyalinised and sclerotic collagenous stroma with small epithelioid cells, showing small nucleoli and clear cytoplasm, arranged in cords or nests, typical of SEF, and areas of spindle shaped cells, with mild to moderate pleomorphism arranged in a storiform or herringbone pattern, suggestive of conventional fibrosarcoma (Figures 5 and 6).

Focal areas of necrosis were identified and the mitotic count was 4 mitotic figures per 10 high-power fields. Immunohistochemistry with antibodies to AE1-AE3, CAM5.2, S100 protein, HMB45, Desmin, EMA, GFAP, INI1 and CD99, showed immunoreactivity of neoplastic cells for CD99 (membrane) S100 protein (focal and cytoplasmic), with preservation of INI1 expression and lack of immunoreactivity for other antibodies are studied. The case was sent for consultation to Professor

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Christopher Fletcher, the Harvard University and the Hospital Brigham and Women's, Boston, USA, whose opinion corroborated our impression, classifying this legion as a cellular variant of sclerosing epithelioid fibrosarcoma, highlighting the immunoreactivity of neoplastic cells to MUC4 in immunohistochemical study in his lab."

Discussion

Sarcomas are rare malignant tumours of mesenchymal origin, accounting for less than 1% of all new cancer diagnoses [10] SEF represents a small subtype of soft tissue sarcomas, that is often linked to low-grade fibromyxoid sarcoma (LGFM) and hyalinizing spindle cell tumour with giant rosettes (HSCTGR) [8,11,12].

Albeit their histologic and immunohistochemically resemblance to various entities catalogued as malignant, it has been described as a low-grade sarcoma for many years [2,8]. The slow growth pattern and indolent course of the entity, support this statement, with descriptions of the presence of the lesion for several months or years before diagnosis [13]. However, concerning this controversial definition, recently, WHO "Classification of Tumours of Soft Tissue and Bone" review (2013), includes sclerosing epithelioid fibrosarcoma, on malignant Fibroblastic/Myofibroblastic tumours, along with adult fibrosarcoma, myxofibrosarcoma and low-grade fibromyxoid sarcoma [3]. A propensity for local recurrence and late metastasis, findings of necrosis and large anaplastic figures, and an accumulation of p53 by immunohistochemistry that is paradoxically always found, corroborate this classification [9,13,14].

Criteria for the diagnosis of SEF are primarily histological: small to medium-sized ovoid cells with pale cytoplasm arranged in cords separated by dense, collagenous stroma [15]. Differential diagnoses are generally ruled out by the clinical data, the morphology and the immunohistochemical study [13].

Giving emphasis on radiological and pathological features, in our case, CT and MRI were clearly consistent with a densely cellular or calcifications, and, after endovenous administration of the contrast, mild homogeneous enhancement, usual to a moderately vascularized mass. Those features were not specific. The typical image of SEF with bone involvement is predominantly lytic and poorly marginated [5,10]. Accordingly, the following mainly tumours were included in the differential diagnosis: osteosarcoma, liposarcoma, assorted mesenchymal neoplasms that may exhibit epithelioid appearances, metatstatic carcinoma, sclerosing hematomymphoid tumours, and malignant melanoma. Osteosarcoma can be suggested by a higher prevalence, age of diagnosis, and radiographic appearance [12]. Regarding the location, SEFs mainly present as tumours of the lower extremities (39%), followed by the trunk (21%) and upper extremities (14.5%) [16]. The thigh is the most common location for soft tissue sarcoma [1].

Histopathologic features a conglomerate of epithelioid cells arranged in strands, cords, nests, and sheets embedded in a sclerosed and hyalinized stroma [17]. It may resemble infiltrating carcinoma, sclerosing lymphoma, and other sarcomas [4,5], and it may contain areas of conventional fibrosarcoma or minor areas resembling a low-grade fibromyxosarcoma, with transition to higher-grade fibrosarcoma, especially in recurrent cases [18]. Ultrastructurally shows fibroblastic or myofibroblastic differentiation [4]. Greater cytological atypia, and the epithelioid appearance can lead to an improper diagnosis of metatstatic carcinoma [5]. This is particularly difficult to the diagnosis on visceral organs because of its rarity and its epithelioid appearance, closely mimicking carcinomas [18]. A strong and diffuse cytoplasmic reactivity for vimentin is a characteristic feature of sclerosing epithelioid fibrosarcoma, and 70% of the cases show MUC4 positivity [7,14,16,17]. It lacks immunoreactivity for epithelial membrane antigen; cytokeratins (CAM5.2 or AE1/3), HMB-45, neurospecific enolase, desmin, smooth muscle actin, or muscle common actin (HHF-35) [8]. Focal and weak immunostaining for EMA, S-100 protein and more rarely for cytokeratins may be seen in a minority of cases [19]. Despite this uncommon report, other entities, like clear cell sarcoma and malignant peripheral nerve sheath tumour may need to be distinguished from SEF given that all these tumours may express S-100 protein [4,14].

As presented in this case, MUC4 and SATB2 were considered on immunohistochemistry. They were recently characterized as immunohistochemical markers for SEF and osteosarcoma, respectively [5]. The first marker is important to another entity that was essential to exclude, the low-grade fibromyxoid sarcoma (LGFM). Due to a subset of overlapping morphologic and immunohistochemical features, related members in the fibroblastic family, both display hyalinized spindle cell tumours with giant rosetes [7,16,17,20]. LGFMS is characterized by expression of the MUC4 protein, like SEF, and about 90% of cases show a distinctive t (7; 16) (q33;p11) that results in FUS-CREB3L2 gene fusion [3,11,17,21]. The use of MUC4 immunostaining and molecular techniques to identify FUS and EWSR1 rearrangements has clear utility in the recognition of SEF, despite the reports of immunoexpression in up to 70% of cases suggesting that at least a subset are related to LGFMS [3,20]. MUC4 upregulation results on a tumorigenic effect elicited through interactions with ERBB2 (HER2) to enhance the proliferation, motility, and tumorigenic capacity of epithelial cell and fibroblastic cells [17]. Concerning cytogenetic findings on bone lesions, immunohistochemistry for SATB2, a recently described marker for osteoblastic differentation could present a useful weapon, with wildtype presentation on SEF [5,17]. MUC4 has not been systematically studied in SEF arising from bone [5,17,20]. SEF typically displays wide-spread immunoactivity for this antiapoptotic Bcl-2 proto-oncogene [2], something that wasn't evaluated on this case.

Recommended treatment is total resection, and complementary action with chemotherapy or radiotherapy is not consensus [2,6,18,19]. Subtotal resection may represent a strong weapon to control tumour recurrence or to contain local disease. Given the singularity of the tumour, an usual referred problem to the surgical planning, is the preoperative unsuspected image of malignancy, which intraoperatively may resemble a benign circumscribed tumour, that will recommend a less radical procedure [4]. Persistent disease and local recurrence is probably related with inadequate surgical excision [2,4]. There isn’t established concrete value, but it may present an incidence of 30%, despite the margins of surgical resection [6].

Tumour dissemination usually occurs to the lungs, the pleura, chest wall, or bone [7,8,22]. Metastatic rate reports range from 40% to 86% and the interval ranged from synchronous with the primary diagnosis to 14 years [6,7,23]. The median interval to the first local recurrence was 4.8 years (range, 2.3–11 years) and that to metastasis was 7.7 years (range, 4.7–14 years) [2,10,22]. There are several descriptions of metastatic lesions at the time of presentation [23]. One important concern was the reference to a much higher proliferative activity on metastatic tumour cells (60%), when comparing the staining positivity for the proliferation marker Ki-67 versus the primary tumour (7% to 8%) [22]. One important discrepancy, when reviewing all series, is...
mortality evaluation, with rates from 35% to 60% [5,7,10]. On the comprehensive report of Ossendorf et al. [6], that included 90 patients, twenty-three patients (34%) died from their disease after a mean of 46 months.

Concerning our case, after the definitive histological diagnosis, surgical planning was managed by benefit and risk analysis and patient opinion. From our point of view, the decision to perform a less aggressive procedure was more rational than to advance to a radical resection, or even total sacrectomy. On a 38 years-old neurologically intact patient, the disability due to sacral root lesion, with possible motor and sensitive impairment, and anal and urethral sphincters denervation or persistent pain, can be deleterious. It adds to the vascular risk associated with surgical procedure, wound and infectious complications. Despite a possible better prognosis and disease-free survival, the option for a subtotal resection was also based on the fact that literature absences on evidence that the presence of residual disease is associated with the occurrence of distant metastases, obviously concerning the regional recurrence. In this regard, it was crucial to establish if tumour is confined to the sacral region, which was confirmed. However, with the extensive literature available about sarcoma treatment, we should have in concern that a positive margin of resection still had a high risk of local recurrence, despite the addition of radiotherapy.

The decision of complementary chemotherapy is questionable. Regarding bone relation, an option is to plan neoadjuvant chemotherapy treatment, based on the EURAMOS-1 protocol [16]. It consists of chemotherapy elements with Doxorubicin, Cisplatin, and high-dose Methotrexate [24]. Lack of evidence remains, with only a few cases reporting the use of this protocol [6,24] and without any valuable evidence to date.

This case report emphasizes the rarity of SEF, and necessity of diagnosis alertness, especially when presenting bone involvement [9,10]. Like it's presented by Chow et al. [10], we expect a similar valuable evidence to date.

Conclusion

This case confirms that SEF may occur in an unusual site, representing a potential diagnostic pitfall. Clinical awareness and removal capability is essential to survival, maintaining a correct judgment on the morbidity associated with a more radical procedure. Systemic therapy remains controversial, but radiotherapy it is recommended on subtotal resection. Although this unusual variant of fibrosarcoma exhibits some alarming radiological and morphological features, the correct diagnosis can be confidentially achieved by the Pathologist. Typical slow progression underscores the importance of a long-term follow-up, with an expected survival better than most of other soft tissue sarcomas.

References
