Case Report

Proximal Type of Epithelioid Sarcoma: A Rare Aggressive Tumor Presenting Simultaneously in Spine and Pelvis

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ABSTRACT

A 40-year-old female presented with bilateral lower limb weakness with bladder and bowel incontinence. MRI study revealed a destructive lesion involving the D7 vertebral body and a large tumor in the gluteal muscles invading the right iliac blade. A histological examination demonstrated a tumor comprising of rounded to ovoid pleomorphic epithelioid cells with marked cytological atypia. Tumor cells expressed CD34, vimentin and focally pancytokeratin but were negative for CD31, EMA, SMA, WT1 and LCA. A D6-7 laminectomy with posterior decompression was done. Postoperatively, external beam radiotherapy was given. However, the patient deteriorated rapidly with no neurological improvement. Epithelioid sarcomas and their recently described proximal variant, by virtue of being an exceedingly unusual tumor are often misdiagnosed or diagnosed late beyond the stage of salvage. This report highlights the histopathology and immunohistochemistry of this tumor and the differentials that need to be analyzed to correctly diagnose this entity.

KEY WORDS: CD31, CD34, epithelioid sarcoma, proximal variant

INTRODUCTION

The term epithelioid sarcoma (ES) was first described in 1970 by Enzinger, recognizing it as a distinct neoplastic entity simulating both a granuloma and a carcinoma[1]. Although there is still no consensus as to the line of cellular differentiation of this tumor, it has been suggested that ES is a tumor of primitive mesenchymal cells with fibroblastic and histiocytic differentiation. It is the most common primary sarcoma of the hand and wrist, prevalent in patients between 10 - 39 years of age with a male predominance[2,3]. Guillou in 1997 described a new variant of this tumor arising from axial locations such as the pelvis, perineum and genital tract and designated it as the "proximal type of epithelioid sarcoma" (PES). This proximal variant is characterized by a more aggressive behaviour and a histological picture showing predominance of large epithelioid cells with marked cytological atypia and intracytoplasmic hyaline inclusions, imparting a rhabdoid appearance to the tumor cells[4]. This variant has an immuno-phenotype similar to that of the classic ES.

CASE REPORT

In February 2011, a 40-year-old Muslim female housewife presented to us with a history of insidious onset and gradually progressing weakness in both lower limbs of one month duration. At presentation this culminated into an upper motor neuron type paraplegia with bladder and bowel involvement. On examination, the sensory level was at D9 - 10. There were no local signs of swelling, deformity or tenderness in the spine. Other associated complaints were significant weight loss and anorexia. The patient was a known diabetic on insulin therapy. There was also a history of total hysterectomy done seven years ago for an obstetric indication.

Radiographs of the dorso-lumbar spine revealed no abnormality. MRI study of the spine (Fig. 1 A - E) revealed altered signal intensity in the right half of the D7 vertebral body and its posterior elements. The lesion, predominantly in the posterior vertebral elements, measured 2.2 x 1 x 1 cm and was hyper-intense on STIR and hypo-intense on T1 weighted images. This lesion extended up to the epidural space.
compressing the right lateral aspect of spinal cord. Focal hyper-intense signals were seen in the spinal cord on T2 weighted images at this level. Screening through the pelvis revealed a large 1.4 x 5.8 x 8.0 cm sized tumor arising from the right iliac bone and invading the right glutei and the iliacus muscles. It was hyper-intense on STIR and hypo-intense on T1 weighted images.

Hematological investigations showed an elevated erythrocyte sedimentation rate (ESR, 60 mm at the end of 1hr). Hepatic and renal function tests were essentially within normal limits. Serum immunoglobulin levels were normal. Bence-Jones proteinuria was absent. Serology for antibodies against HIV, HbsAg and HCV antigens was negative. A chest radiograph obtained at time of presentation was also normal.

CT-guided biopsies from the involved D7 vertebra and right ilium were performed. Multiple tissue fragments were examined. Histopathology (Fig. 2 A - C) revealed spindle cells infiltrating collagenized tissue, with interspersed round to ovoid epithelioid cells showing nuclear pleomorphism. Large cells with vesicular nuclei, prominent nucleoli and abundant cytoplasm were also seen. These large cells showed occasional intra-cytoplasmic inclusions reminiscent of a ‘rhabdoid’ morphology. Focal areas of tumor necrosis were observed. Frequent mitoses were also noted. On

Fig. 1A - C: T2 and T1 weighted MRI images depicting the tumor involving the bodies and posterior elements of D6-7 vertebrae. 1D - E: T2 and T1 weighted MRI images of the right pelvic location of tumor involving the glutei and extending medially across the ilium.
immuno-histochemistry, the tumor cells expressed CD 34, vimentin and focal pancytokeratin positivity. They were immunonegative for CD31, WT1, EMA and SMA, LCA.

Considering the severe neurological deficit that the patient presented with, a D6 - 7 laminectomy with posterior decompression was done. Post-operatively external beam radiotherapy was administered. The patient showed no symptomatic improvement despite these measures. One month later, the patient expired at home (i.e., within four months of onset of initial symptoms. Correlating immuno-histochemistry findings with the histopathological picture and clinical presentation a diagnosis of a PES variant was made retrospectively.

DISCUSSION

ES, as a rare group of tumors, have been a curious pathological entity ever since their first description by Enzinger. The proximal type, first reported by Guillou in 1997 has frequently been confused with tumors such as synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, extraskeletal -c¡˜'ȱ Œ'˜—›˜œŠ›Œ˜–Šøjȱ ž—'ěŽ›Ž—'ŠŽȱ
carcinomas and epithelioid angiosarcoma.

Oval to polygonal cells arranged predominantly in cohesive sheet like pattern with interspersed large epithelioid cells with intra-cytoplasmic inclusions and prominent nucleoli resembling a rhabdoid morphology has been the classical description for the PES[4]. This was the picture seen in our case too. But a similar histopathological picture can also be seen in the above mentioned differentials.

Immunohistochemistry marker studies were performed to differentiate between these entities. The characteristic immuno-profile of ES is the co-expression of keratin and vimentin[5]. Cytokeratin is expressed in over 75% cases using older immunohistochemistry techniques, whereas in more recent series it has been reported in upto 94% of cases[5]. EMA is expressed in 50 - 96% of tumors but its pattern of reactivity demonstrates variability within the same lesion[5-7]. About 60% of cases have been shown to be positive for CD34 expression[5,7,8]

ES with a pseudovascular pattern may mimic epithelioid angiosarcomas, both of which are frequently positive for cytokeratin and CD34[9]. Also, many epithelioid angiosarcomas have a diffuse sheet-like growth pattern, and a vasoformative architecture is often not present. However, they have positive immunoreactivity for a sensitive and specific marker for endothelial differentiation, CD31[10].

Synovial sarcomas display an epithelial immunophenotype positive for both cytokeratin and EMA[11]. But, synovial sarcomas are consistently
negative for CD34 and usually show, at least focally, a biphasic pattern allowing correct diagnosis[10].

Epithelioid morphology can occasionally be seen in both rhabdomyosarcomas and leiomyosarcomas. It has also been reported that approximately 30% of leiomyosarcomas are immunoreactive for cytokeratin and EMA. However, ES are easily distinguished from these by the lack of a representative area, showing fascicles of elongated tumor cells with blunt-ended “cigar-shaped” atypical nuclei, and greater frequency of negativity for desmin and SMA[15].

High-grade large epithelioid cells and a rhabdoid phenotype observed in extraskeletal myxoid chondrosarcomas may cause confusion with ES[13]. The presence of the lobular architecture and typical appearance of cords and strands of eosinophilic chondroblasts embedded in a myxoid matrix readily distinguish extraskeletal myxoid chondrosarcoma from ES.

Distinction between PES and undifferentiated carcinoma also needs consideration. The occurrence of tumors in the subcutis or deep soft tissues without any connection with the overlying epidermis or cutaneous adnexa, the absence of histological features of squamous or glandular differentiation, and presence of CD34 reactivity favour the diagnosis of ES over undifferentiated carcinoma. The latter are negative for CD34 in most cases[10].

Another close differential diagnosis, which was entertained, was malignant extra-renal rhabdoid tumor (MERT). In terms of its biological behavior, MERT is quite aggressive and lethal. MERT is known to show inactivating mutations / deletions of both the alleles of tumor suppressor genes hSNF5/INI1 on chromosome 22q11.2. Similar deletion has also been noted in PES[14]. On this basis, it has been proposed that PES might actually be representing a form of a “complex” rhabdoid tumor. However, MERT is an entity known to occur more commonly in young children.

Recently, deletion of the SMARCBI/INI1 gene with gene inactivation was reported in the proximal type of ES[14]. Immunohistochemical expression of INI1 was recently studied in 260 epithelioid malignant tumors, including 96 cases of ES, and showed a loss of expression in about 90% of distal and proximal ES cases[15]. Immunostaining for INI1 can be used to confirm the diagnosis of ES as a complement to epithelial markers and CD34[13]. However, in view of financial and infrastructural constraints, the above mentioned study could not be obtained in our case.

In this way, a diagnosis of PES was deduced in our case based on the presence of rhabdoid cells with an epithelioid morphology, exhibiting a polyphenotypic expression with mesenchymal markers (vimentin, CD34), along with an epithelial marker (CK). The importance of identifying this subtype lies in its aggressive behaviour, which was seen in our patient, who, despite adjuvant RT did not show improvement or regression of the tumor and expired within four months of the onset of symptoms.

Reported adverse prognostic features for epithelioid sarcoma in general include male gender, proximal / axial tumor location, large tumor size (> 5 cm), deep tumor location, high mitotic index, hemorrhage, necrosis and vascular invasion[5]. Moreover the presence of rhabdoid features is related to an aggressive behaviour, multimodal therapy resistance, and rapidly fatal outcome[16]. Our patient also had some of these associated poor prognostic factors. It would be worthwhile to identify more of such rare cases and their clinical outcomes.

Treatment of ES in general includes amputation or wide en bloc resection as well as radiation and chemotherapy. Unfortunately, PES is often resistant to multimodal therapy, and death from disease is seen more frequently compared to the classic form.

CONCLUSION

We conclude that PES are rare soft-tissue sarcomas of adults, with epithelioid features and a frequent rhabdoid phenotype. The importance of identifying this tumor relates to its aggressive behaviour and the possibility of improving survival with early diagnosis and initiation of appropriate therapy. A range of differentials needs to be kept in mind and ruled out on the basis of the clinical profile, morphology and a wide panel of relevant immunohistochemistry markers.

REFERENCES