Prometastatic CXCR4 and Histone Methyltransferase EZH2 are Upregulated in SMARCB1/INI1-deficient and TP53-mutated Poorly Differentiated Chordoma

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Introduction
Chordoma is a rare tumor most commonly arising in the sacrococcygeal region from notochord remnants. Usually, these tumors are locally invasive and recurrent, but do not have the capacity to metastasize. A newly described aggressive variant called poorly differentiated chordoma is different than conventional chordoma in that it does not have the well differentiated histologic appearance of conventional chordoma and also exhibits loss of SMARCB1/INI1. Herein, we describe a case of poorly differentiated chordoma with SMARCB1/INI1 loss, concurrent TP53 mutation and RB1 loss.

Materials and Methods
The patient is a 55-year-old man with a history of a previously resected sacrococcygeal chordoma 5 years ago. Imaging revealed new multiple hepatic (Figure 1), lung, and adrenal lesions. An ultrasound-guided biopsy of the liver revealed a poorly differentiated tumor with an epithelioid appearance. An extensive panel of immunohistochemical markers was used to attempt to identify the lesion. Once the key markers revealed the identity of the malignant neoplasm, a small panel of probes was applied to help elucidate the biological aggressiveness of the tumor. This panel included the marker CXCR4, which is a chemokine receptor, and the histone methyltransferase EZH2.

Results

The tumor was only positive for Cam5.2, EMA, and CD56. Brachyury (Figure 7) was performed due to the patient’s previous history and was positive. Genomic testing showed a SMARCB1 mutation, a TP53 mutation, and RB1 loss. Additional markers were performed and the tumor showed a Ki-67 proliferation index of approximately 80% (Figure 9), mutant p53 protein (Figure 8), loss of INI1 (Figure 10), and strong expression of prometastatic CXCR4 (Figure 11) and the histone methyltransferase EZH2 (Figure 12).

Conclusion
Thus far 53 cases of poorly differentiated chordoma with INI1 loss have been reported in the literature, but most occur in the pediatric population and develop de novo. However, our case occurred in an older patient after radiotherapy for a sacrococcygeal chordoma. This case of poorly differentiated chordoma also showed concurrent TP53 mutation and loss of RB1, which resulted in malignant transformation of patient’s prior conventional chordoma, with loss of differentiation, cell cycle progression, and up-regulation of prometastatic CXCR4 and the histone methyltransferase EZH2, causing aggressive behavior and metastasis.

Compared to other chordoma subtypes, poorly differentiated chordoma has a significantly decreased mean overall survival and should be treated aggressively with multimodality therapy.

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