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Case Report

PEComa with Transcription Factor E3 Overexpression: A Diagnostic and Therapeutic Challenge

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Abstract
PEComa with transcription factor E3 overexpression, most commonly through gene rearrangement, represents a biologically distinct subset of disease. We present here an illustrative case to highlight its diagnostic and therapeutic challenge in the context of potential pathogenic signaling pathways.

Introduction

A 47-year-old female from Egypt presented with left-sided abdominal pain and was found on surgical exploration to have a left ovarian mass attached to the colon, originating from the retroperitoneum. Pathology at the time indicated alveolar soft part sarcoma. Three months later, a surveillance PET/CT showed recurrent disease and the patient underwent radical sigmoidectomy with pathology suggestive of high-grade malignant epithelioid leiomyosarcoma. She then received whole-pelvis radiotherapy with 4 courses of ifosfamide/Adriamycin followed by 4 courses of gemcitabine/docetaxel, with stable disease for the following year. However, she relapsed prior to coming to the US with new PET-avid intraabdominal lesions causing small bowel obstruction. On examination, she had a tender

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abdomen with very faint bowel sounds consistent with high-grade small bowel obstruction. She underwent exploratory laparotomy with near complete resection. The pathology features were similar to the previous specimen consisting of a malignant perivascular epithelioid neoplasm with nested pattern composed of pleomorphic cells with high mitotic activity and tumor necrosis. The differential diagnosis included a pleomorphic variant of alveolar soft part sarcoma, epithelioid leiomyosarcoma, and perivascular epithelioid cell tumor (PEComa). Immunohistochemical studies showed reactivity for smooth muscle actin, calponin, melan-A, and HMB45, consistent with PEComa. Immunostaining for transcription factor E3 (TFE3) showed diffuse reactivity (Fig. 1), which explains the previous consideration of alveolar soft part sarcoma, but which, in the context of all findings, is diagnostic of PEComa with TFE3 reactivity. The patient was started on adjuvant sirolimus at 4 mg daily based on the preclinical suggestion of dysregulation of the mTOR pathway in some PEComas. The patient did not respond, however, and new liver lesions appeared.

PEComas and TFE3

PEComas have recently been identified as having a subset with gene rearrangement of TFE3. This subset of PEComas show predominantly epithelioid cells arranged in nests or sheets separated by a delicate vascular network, with in 2 out of 3 cases nuclear atypia, mitotic figures, and necrosis [1]. This increasingly recognized group of TFE3-rearranged tumors includes TFE3 rearrangement-associated PEComas, melanotic Xp11 translocation renal cancers, or melanotic Xp11 neoplasms [2]. Subsequently, several case reports have highlighted the distinct entity of TFE3-associated PEComas with distinct malignant histological features and relatively aggressive clinical behaviors [3–5]. TFE3 is a member of the MiT family of transcription factors, which includes MiTF, TFEB, TFEC, and TFE3, which are important for mesenchymal cell differentiation [6].

Take-Home Message

Interestingly, recent observations have suggested that there is a different pathogenic mechanism in *TFE3*-rearranged PEComas which does not involve the *TSC2* gene. Thus, these *TFE3*-rearranged PEComas represent an entity which morphologically overlaps with conventional PEComas, but is biologically distinctive [7]. This concept has clinical translational importance in that mTOR1 inhibitors, such as rapamycin and everolimus, have been shown to be effective in a case series of 3 PEComas with TSC2 rearrangement [8]. As there is no TSC2 gene involvement in *TFE3*-rearranged PEComas, it is likely that these patients do not respond to mTOR1 inhibitors. Assessment for TFE3 gene expression in PEComas may identify this entity and aid therapeutic decisions. Therapeutic strategies targeting the MiT family of transcription factors where the TFE3 gene resides may aid in the treatment of this distinct entity.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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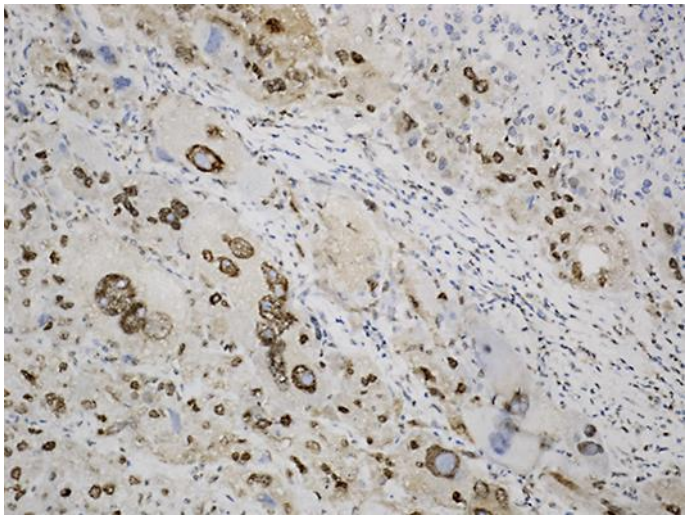

Fig. 1. Immunohistochemistry staining showing positive transcription factor E3 reactivity (brown).