Case report

**PIGMENTED/MELANOCYTIC MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMOR WITH TFE3-SFPQ(PSF) REARRANGEMENT — A CHALLENGING DIAGNOSIS OF PEComA FAMILY OF TUMORS**

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We here report a case of a distinct subtype of pigmented/melanocytic malignant PEComa with TFE3-SFPQ(PSF) rearrangement. The tumor involved the iliac region and clinically mimicked metastatic melanoma. The immunohistochemical assessment was supplemented with molecular studies including fluorescence in situ hybridization (FISH) and next-generation sequencing sarcoma panel (NGS). We also discuss the differential diagnosis of intraabdominal PEComas and emphasise the recent molecular reports on the TFE3 rearranged tumors.

Key words: perivascular epithelioid cell tumors.

Introduction

Perivascular epithelioid cell tumors (PEComas) are a distinct group of rare mesenchymal neoplasms with characteristics of both smooth muscle and melanocytic differentiation. Currently, the PEComa family of tumors includes a wide variety of malignancies: angiomyolipoma, primary extrapulmonary or pulmonary clear cell sugar tumor, lymphangiomyomatosis, and other tumors arising at various sites with a similar histopathological presentation together called not-otherwise specified PEComas [1]. The potentially malignant PEComa previously termed an abdominopelvic sarcoma of perivascular epithelioid cells retains the typical immunophenotype but according to Folpe classification requires fulfilling at least 2 of the grading criteria listed below: tumor size > 5 cm, infiltrative growth, high nuclear grade and hypercellularity, mitoses ≥ 1 per 50 high power fields (HPF), necrosis, variable clinical course [2]. The differential diagnosis of epithelioid PEComas needs to consider tumors with clear cell morphology, other epithelioid mesenchymal neoplasms including
Fig. 1. Histopathological presentation of PEComa. A) Heterogeneous appearance with fields of heavily pigmented cells (HE, 40×). B) Infiltrative growth (HE, 20×). C) Mitotic activity with scarce typical mitotic figures (HE, 600×). D) Immunohistochemically TFE3 positive subcapsular lymph node metastasis (TFE3, 40×). E-J) Histological spectrum of PEComa with pale, granular and melanin-packed epithelioid tumor cells arranged in typical nests surrounded by a delicate net of capillary vessels but also visible trabecular pattern and discohesive sheets of tumor cells (HE, E-G 100×; H-J 400×)
gastrointestinal stromal tumor, alveolar soft part sarcoma, rhabdomyosarcoma, myoepithelial tumor and all malignancies with positive melanocytic markers i.e. melanoma, clear cell sarcoma, adrenal cortical carcinoma, and finally renal and other carcinomas. The clinical presentation together with radiological images and morphological, immunohistochemical and molecular features should support the appropriate diagnosis. Molecularly, two subtypes of PEComas are defined [3]. The majority of the cases are characterized by loss of function of the TSC1/TSC2 complex which results in mTORC1 pathway activation. The second subtype harbors TFE3 (Xp11) rearrangements. The PEComas from this group exhibit distinct morphology known from other TFE3 rearranged neoplasms such as Xp11-translocation renal cell cancer and alveolar soft part sarcoma; they usually have an alveolar growth pattern and an epithelioid cytomorphology, additionally these entities lack PAX8 and smooth muscle antigens but maintain high cathepsin K expression [4, 5, 6, 7, 8].

Case report

Clinical and radiological presentation

A 61-year old female after initial exploratory laparotomy with partial tumor resection was admitted to Maria Skłodowska-Curie Institute-Oncology Cancer Centre for clinical and pathological consultation. The tumor mass of the 10 cm diameter was located in the iliac fossa region and was attached to large vessels. The radiological presentation as depicted in Fig. 2A. The tumor was surgically excised with R1 margin preservation. The intraperitoneal dissemination was described.

Histopathological findings

Macroscopically, a large poorly circumscribed brown tumor with infiltrative growth was found (Fig. 1A, B). The subcapsular lymph node metastases of 1 mm size were found (Fig. 1D). Microscopically, pale and melanin-packed epithelioid tumor cells were arranged in the nest but focally cords and sheets were observed as well. Occasionally, myxoid change, stromal microcysts, crystalline structures with various patterns, some resembling rexin granules and as well as pre-melanosomes or stage II melanosomes [9, 10]. Exceptionally, the melanin granules may be so abundant that those cases were separated into distinct subtypes called melanocytic or pigmented PEComa [7, 11, 12, 13]. The classical architecture consists of nests of ovoid cells which are closely associated with small thin-walled vessels. Sometimes PEComas may display cords of uniform epithelioid cells and trabecular or sheet-like pattern.

Fluorescence in situ hybridization and molecular findings

Fluorescence in situ hybridization analysis (TFE3 Break Apart FISH Probe Kit Cat No CT-PAC013) performed on formalin-fixed, paraffin-embedded tissue (FFPE) was positive for TFE3 gene rearrangement in 83% (83/100) of nuclei examined (Fig. 2B). Molecular studies using RNA from FFPE by targeted next-generation sequencing with FusionPlex Sarcoma Kit for Illumina, ArcherDx revealed SFPQ(PSF)(9)-TFE3(5) rearrangement. None of the remaining 25 fusion transcripts including ALK, CAMTA1, CCNB3, CIC, EPC1, EWSR1, FOXO1, FUS, GLI, HMGTA2, JAZF1, MEAF6, MCL2, NCOA2, NTRK3, PDGFB, PLAG1, ROS1, SS18, STAT6, TAF15, TCF12, TGF, USP6, YWHAE were observed.

Follow-up

The computed tomography of the lungs did not show metastatic disease. After 2 months from surgical treatment because of R2 resection and lymph node metastasis, the patient was qualified into systemic therapy with sirolimus which belongs to mTOR inhibitors.

Discussion

PEComas are rare mesenchymal tumors composed of epithelioid and pleomorphic cells with perivascular distribution, that express both melanocytic and smooth muscle markers. Usually, cells show a spectrum of morphological features including clear, eosinophilic, or granular cytoplasm, centrally located, round to oval nuclei, and inconspicuous nucleoli [1]. The different histological presentation corresponds to cytoplasmic glycogen and lipid droplets, crystalline structures with various patterns, some resembling rexin granules and as well as pre-melanosomes or stage II melanosomes [9, 10]. Exceptionally, the melanin granules may be so abundant that those cases were separated into distinct subtypes called melanocytic or pigmented PEComa [7, 11, 12, 13]. The classical architecture consists of nests of ovoid cells which are closely associated with small thin-walled vessels. Sometimes PEComas may display cords of uniform epithelioid cells and trabecular or sheet-like pattern. Occasionally, myxoid change, stromal microcysts, multinucleated cells, and “spider” cells or stromal hyalinization and sclerosis were reported [1, 8]. In our case all types of cells were seen – the clear, granular eosinophilic and melanin-loaded cells – mostly arranged in the nest but focally cords and sheets were observed as well.

Immunohistochemical staining shows that the PEComa tumor cells are positive for HMB-45, indicating
Fig. 2. A) Radiological presentation of PEComa (computed tomography) – the 10 cm diameter tumor was located in the iliac fossa region and was attached to large vessels; there was no connection to kidneys. B) TFE3 rearrangement in FISH; please note the fusion gene is located on Xp11 and the pattern with break-apart probe kit has different presentation between females and males (scheme: positive result in female patients consists of a fused or closely approximated green-red signal pair which represent the uninvolved X chromosome and another pair of split signals or a single green or red signal due to section truncation – it's the X chromosome involved in the translocation; TFE3 Break Apart FISH Probe, 40×). C) Cathepsin K (200×). D) PAX8 (200×). E) HMB-45 (200×). F) Progesterone receptors (200×). G) TFE3 (200×). H) Histochemical staining for iron (200×; please note internal control – erythrocytes in vessel lumen)
that the tumor cells have melanocytic features. In addition, they are usually positive for S100, SMA, and desmin, but negative for epithelial, other melanocytic and endocrine markers. The cathepsin K was thought to be a specific marker but it can be also found in melanocytic Xp11 translocation renal cell cancer (RCC) or in alveolar soft part sarcoma [1, 8]. The PEComas family of tumors including renal angiomylipoma and pulmonary lymphangioleiomyomatosis present increased estrogen and progesterone expression. The mechanism of action and role in the pathogenesis of hormone receptors remain still unclear. Single studies showed a beneficial effect of letrozole treatment on hormone-rich tumors [14, 15].

High-risk features include size of ≥ 5 cm, infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate of ≥ 1/HPF, as well as necrosis and vascular invasion [2]. The recent update for a malignant classification demonstrated that only a size of ≥ 5 cm and a mitotic rate of ≥ 1/HPF were significantly associated with potential malignant behavior and recurrence [16]. Consistent with this classification, our case was diagnosed as malignant because of size, infiltrative growth, and mitotic activity. The lymph node metastasis supported the malignant origin of that tumor.

In the differential diagnosis of intraabdominal PEComa, the Xp11 translocation RCC and Xp11 translocation RCC (members of the MiT family translocation RCC) and ASPS should be included [4, 8, 17]. The morphological and immunohistochemical differences between the neoplasms are reported. The histologic features of purely epithelioid cells, melanin pigment, the specific immunoprofile (PAX8, cathepsin K, HMB45/Melan-A), localization of the tumor and clinical behavior are the clues to the differential diagnosis. Xp11 translocation RCC are almost always PAX8(+), cathepsin K(−) in comparison to Xp11 translocation PEComas, melanocytic Xp11 translocation RCC and ASPS which are PAX8(−) and cathepsin K(+). Moreover young age, presence of psammoma bodies and minimal immunohistochemical reactivity for CAIX should suggest the Xp11 translocation RCC [8]. Our case did not exhibit any connection to the kidney and was located in the iliac region. The immunoprofile showed a positive reaction with HMB-45 together with cathepsin K and was negative for PAX8.

TFE3 protein, which gene rearrangement is a hallmark molecular feature for above neoplasms, belongs to the microphthalmia (MiFT/TFE) transcription factors along with TFEB, TFE3, and MITF, and triggers the Met receptor tyrosine kinase by direct transcriptional upregulation, leading to an activation of the downstream pathways, such as the PI3K/AKT/mTOR pathway [17, 18]. Xp11 translocation RCC harbors chromosome translocations characterized by TFE3 rearrangements with one of the fusion partners: ASPL, PRCC, NONO, SFPQ/PSF, CLTC, PARP14, LUC7L3, KHSRP, DVL2 and unknown genes on chromosomes 3 and 10 [1-9]. ASPL-, PRCC- and SFPQ-TFE3 are relatively most common fusion genes in Xp11 translocation RCC, resulting from t(X;1)(p11.2;q34), t(X;17)(p11.2;q25), and t(X;1)(p11.2;q21), respectively [18]. Alveolar soft part sarcoma is characterized only by ASPL-TFE3 gene fusion which is no longer specific for that entity and might be frequently found in Xp11 translocation RCC. Molecularly, most PEComas, including sporadic ones, are defined by a loss of function of the TSC1/TSC2 complex, in the majority of the cases the result of a LOH in the TSC2 gene, leading to increased mTORC1 activation and deregulated cell growth signaling. Additionally, a distinct small subset of PEComas harboring rearrangements of the TFE3 gene locus has been identified [19]. This subgroup also has no association with tuberous sclerosis and show SFPQ-, NONO- and DVL2-TFE3 gene fusions. Those observations open a discussion under the nature and relationship of these various tumors. All TFE3-positive tumors belong to a molecularly defined group of neoplasms which tends to share some microscopic features i.e. an alveolar or nesting growth pattern of large eosinophilic cells with clear cytoplasm [4, 8].

The review of clinical follow-up remains difficult since these neoplasms are rare and no common therapeutic guidelines for malignant PEComas do not yet exist. Our patient was treated according to the existing sarcoma protocol with wide local excision with lymph node excision. The current treatment for most PEComas consists of mTOR inhibitors [20, 21]. The case report studies showed sirolimus as a potential targeted therapy agent in PEComas defined by a loss of TSC1/2. In the TFE3 rearranged tumors the efficacy of mTOR inhibitors is largely unknown. Alternative drugs, such as crizotinib and tivantinib (MET inhibitors) are being explored in other TFE3-overexpressed sarcomas (i.e. alveolar soft part sarcomas) [20, 22]. In case of further progression with additional metastases, systemic therapy with mTOR-inhibitors might be a therapeutic option. On the other hand, TFE3 fusion-positive ASPS can be efficiently controlled with sunitinib, a small-molecule inhibitor of several receptor tyrosine kinases. The favorable responses, including single cases with persistent complete response, were also found in both adult and pediatric cases of metastatic RCC with TFE3 translocation [23, 24].

In conclusion understanding, molecular pathways and pathogenesis of PEComa and other TFE3 rearranged tumors may lead to the reclassification of that group. Since that tumors are rare, the multi-institutional study on a larger group of patients is required to present more informative clinical and pathological conclusions. If it is accessible, we suggest, to include
results of genetic diagnostics into the routine histopathological report of PEComa, because in the near future the molecular profile may be a key factor of therapy planning.

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References


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