Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Pigmented/melanocytic malignant perivascular epithelioid cell tumor with *TFE3-SFPQ(PSF)* rearrangement – a challenging diagnosis of PEComa family of tumors

Anna Szumera-Ciećkiewicz[1,2], Olga Kuczkiewicz-Siemion[1,2], Katarzyna Seliga[1], Magdalena Grabowska-Kierył[1], Andrzej Tysarowski[1], Michał Wągrodzki[1], Tomasz Świtaj[3], Monika Prochorec-Sobieszek[1,2], Piotr Rutkowski[3]

[1]Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie Institute-Oncology Centre, Warsaw, Poland
[2]Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[3]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute-Oncology Centre, Warsaw, Poland

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

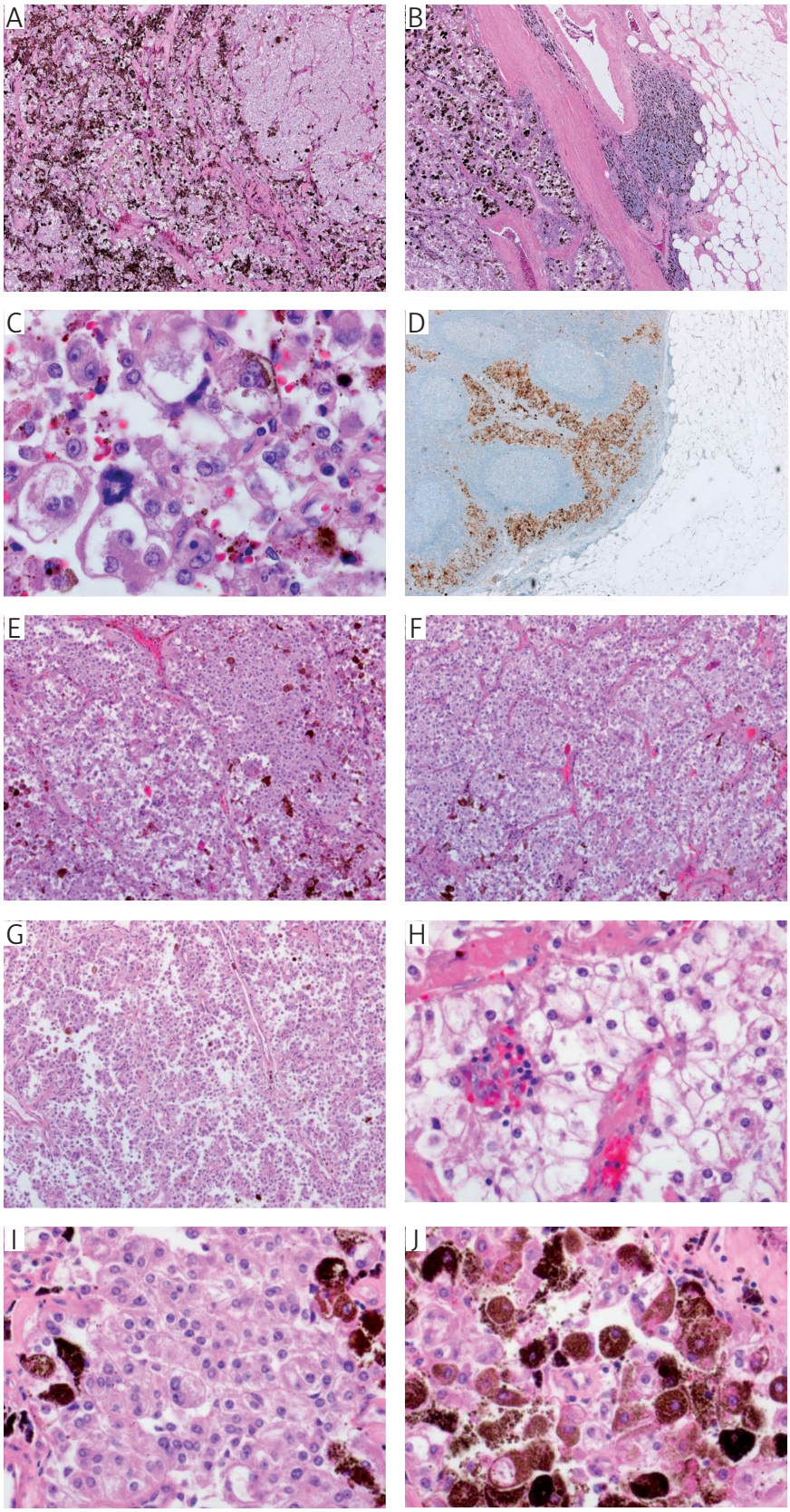

Fig. 1. Histopathological presentation of PEComa. A) Heterogeneous appearance with fields of heavily pigmented cells (HE, 40×). B) Infiltrative growth (HE, 20×). C) Mitotic activity with scarce typical mitotic figures (HE, 600×). D) Immunohistochemically TFE3 positive subcapsular lymph node metastasis (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 typical nests surrounded by a delicate net of capillary vessels but also the discohesive sheets of tumor cells were seen (Fig. 1E-J). The nuclear grade was low. Two mitoses per 50 HPF were found (Fig. 1C). The foci of necrosis comprised no more than 5% of the tumor. Immunohistochemically the tumor showed strong expression for HMB45, Cathepsin K, TFE3, progesterone receptors but was negative for the other markers including: PAX8, CD10, RCC, CAIX, CKAE1/AE3, CK7, CK20, Inhibin, MiTF, Melan A, S100, WT1, tyrosinase, BRAF, SMA, desmin, h-caldesmon, chromogranin, synaptophysin, calretinin, estrogen receptors (Fig. 2C-H).

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, HMGA2, JAZF1, MEAF6, MKL2, 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 renin 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

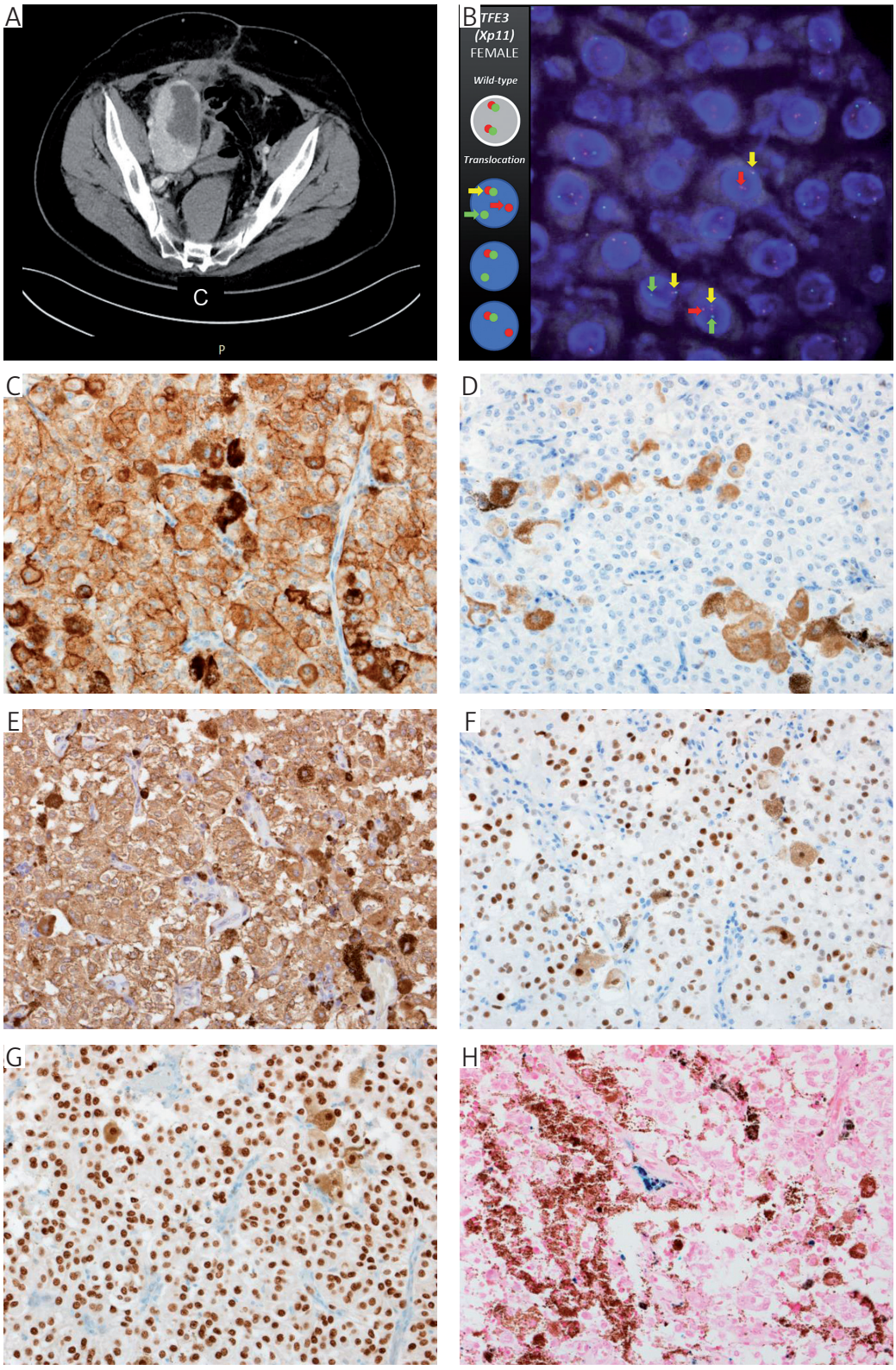

Fig. 2. A) Radiological presentation of PEComa (computed tomography) – the 10 cm diameter tumor was located in the iliac fossa region and was attached to large vessels; there was no connection to kidneys. B) *TFE3* rearrangement in FISH; please note the fusion gene is located on Xp11 and the pattern 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 angiomyolipoma 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 und 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, TFEC, 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.

This work has been implemented using the Project infrastructure POIG.02.03.00-14-111/13 funded by Operational Programme Innovative Economy 2007-2013, Priority II. R&D Infrastructure, Measure 2.3. Investments connected with development of IT infrastructure of Science.

The authors declare no conflict of interest.

References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone WHO/IARC Classification of Tumours. 4th Edition, Volume 5. 2013.
2. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 2005; 29:1558-1575.
3. Agaram NP, Sung YS, Zhang L, et al. Dichotomy of Genetic Abnormalities in PEComas With Therapeutic Implications. Am J Surg Pathol 2015; 39: 813-825.
4. Maloney N, Giannikou K, Lefferts J, et al. Expanding the histomorphologic spectrum of TFE3-rearranged perivascular epithelioid cell tumors. Human Pathol 2018; 82: 125-130.
5. Rao Q, Shen Q, Xia QY, et al. PSF/SFPQ is a very common gene fusion partner in TFE3 rearrangement-associated perivascular epithelioid cell tumors (PEComas) and melanotic Xp11 translocation renal cancers: clinicopathologic, immunohistochemical, and molecular characteristics suggesting classification as a distinct entity. Am J Surg Pathol 2015; 39: 1181-1196.
6. Shen Q, Rao Q, Xia QY, et al. Perivascular epithelioid cell tumor (PEComa) with TFE3 gene rearrangement: clinicopathological, immunohistochemical, and molecular features. V Arch Virchows 2014; 465: 607-613.
7. Argani P, Aulmann S, Karanjawala Z, et al. Melanotic Xp11 translocation renal cancers: a distinctive neoplasm with overlapping features of PEComa, carcinoma, and melanoma. Am J Surg Pathol 2009; 33: 609-619.
8. Argani P, Zhong M, Reuter VE, et al. TFE3-Fusion Variant Analysis Defines Specific Clinicopathologic Associations Among Xp11 Translocation Cancers. Am J Surg Pathol 2016; 40: 723-737.
9. Kaiserling E, Krober S, Xiao JC, et al. Angiomyolipoma of the kidney. Immunoreactivity with HMB-45. Light- and electron-microscopic findings. Histopathology 1994; 25: 41-48.
10. Park SH, Ro JY, Kim HS, Lee ES. Perivascular epithelioid cell tumor of the uterus: immunohistochemical, ultrastructural and molecular study. Pathology Int 2003; 53: 800-805.
11. Rasalkar DD, Chu WC, Chan AW, et al. Malignant pigmented clear cell epithelioid cell tumor (PEComa) in an adolescent boy with widespread metastases: a rare entity in this age group. Pediatric Radiol 2011; 41: 1587-1590.
12. Ribalta T, Lloreta J, Munne A, et al. Malignant pigmented clear cell epithelioid tumor of the kidney: clear cell ("sugar") tumor versus malignant melanoma. Human Pathol 2000; 31: 516-519.
13. McGregor SM, Alikhan MB, John RA, et al. Melanotic PEComa of the Sinonasal Mucosa With NONO-TFE3 Fusion: An Elusive Mimic of Sinonasal Melanoma. Am J Surg Pathol 2017; 41: 717-722.
14. Le P, Garg A, Brandao G, et al. Hormonal manipulation with letrozole in the treatment of metastatic malignant pecoma. Curr Oncol (Toronto, Ont) 2014; 21: e518-20.
15. Prizant H, Hammes SR. Minireview: Lymphangioleiomyomatosis (LAM): The "Other" Steroid-Sensitive Cancer. Endocrinology 2016; 157: 3374-3383.
16. Bleeker JS, Quevedo JF, Folpe AL. "Malignant" perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. Sarcoma 2012; 2012: 541626.
17. Gandhi JS, Malik F, Amin MB, et al. MiT family translocation renal cell carcinomas: A 15th anniversary update. Histol Histopathol 2019; 18159.
18. Calio A, Segala D, Munari E, et al. MiT Family Translocation Renal Cell Carcinoma: from the Early Descriptions to the Current Knowledge. Cancers (Basel) 2019; 11: (pii): cancers11081110.
19. Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. Ann Diagn Pathol 2015; 19: 359-368.
20. Stacchiotti S, Marrari A, Dei Tos AP, et al. Targeted therapies in rare sarcomas: IMT, ASPS, SFT, PEComa, and CCS. Hematol Oncol Clin North Am 2013; 27: 1049-1061.
21. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 2010; 28: 835-840.
22. Dickson MA, Schwartz GK, Antonescu CR, et al. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. Int J Cancer. 2013; 132: 1711-1717.
23. Chowdhury T, Prichard-Jones K, Sebire NJ, et al. Persistent complete response after single-agent sunitinib treatment in a case of TFE translocation positive relapsed metastatic pediatric renal cell carcinoma. J Pediatr Hematol Oncol 2013; 35: e1-3.
24. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol 2011; 22: 1682-1690.

Address for correspondence

Anna Szumera-Ciećkiewicz
Maria Sklodowska-Curie Institute – Oncology Centre
Department of Pathology and Laboratory Diagnostics
Roentgena 5
02-781 Warsaw, Poland
e-mail: szumann@gmail.com