Retroperitoneal perivascular epithelioid cell tumours: A case report and review of literature

Zisis Touloumis, Niki Giannakou, Christos Sioros, Argiro Trigka, Maria Cheilakea, Nikoletta Dimitriou, John Griniatsos

Abstract

BACKGROUND

The perivascular epithelioid cell tumour (PEComa) family of tumours mainly includes renal and hepatic angiomyolipomas, pulmonary lymphangioleiomyomatosis and clear cell “sugar” tumour of the lung. Several uncommon tumours with similar morphological and immunophenotypical characteristics arising at a variety of sites (abdominal cavity, digestive tract, retroperitoneum, skin, soft tissue and bones) are also included in the PEComa family and are referred to as PEComas not otherwise specified.

CASE SUMMARY

We present a 37-year-old female patient who underwent resection of an 8.5 cm × 8 cm × 4 cm retroperitoneal tumour, which eventually was diagnosed as PEComa of uncertain biological behaviour. Three years after the operation, the patient remains without any evidence of recurrence. A search was performed in the Medline and EMBASE databases for articles published between 1996 and 2018, and we identified 31 articles related to retroperitoneal and perinephric PEComas. We focused on sex, age, maximum dimension, histological and immunohistochemical characteristics of the tumour, follow-up and long-term outcome. Thirty-four retroperitoneal (including the present one) and ten perinephric PEComas were identified, carrying a malignant potential rate of 44% and 60%, respectively. Nearly half of the potentially malignant PEComas presented with or developed metastases during the course of the disease.

CONCLUSION

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Retroperitoneal PEComas are not as indolent as they are supposed to be. Radical surgical resection constitutes the treatment of choice for localized disease, while mammalian target of the rapamycin (mTOR) inhibitors constitute the most promising therapy for disseminated disease. The role of mTOR inhibitors as adjuvant or neoadjuvant therapies needs to be evaluated in the future.

**Key words:** Perivascular epithelioid cell tumour; Retroperitoneum; Mammalian target of the rapamycin inhibitors; Tuberous sclerosis complex; Case report; Treatment

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**Core tip:** The retroperitoneal space represents the third most frequent location for perivascular epithelioid cell tumours (PEComas) not otherwise specified development. Half were stratified as potentially malignant, and nearly half of the potentially malignant tumours presented with or developed metastases during the course of the disease. Thus, retroperitoneal PEComas are not as indolent as they are supposed to be. Radical surgical resection constitutes the treatment of choice for localized disease, while mammalian target of the rapamycin (mTOR) inhibitors constitute the most promising therapy for disseminated disease. The role of mTOR inhibitors as adjuvant or neoadjuvant therapies needs to be evaluated in the future.

**INTRODUCTION**

Perivascular epithelioid cell tumour (PEComa) was first included in the World Health Organization (WHO) classification of tumours as a distinctive entity in 2002, defined as “a mesenchymal tumour composed of histologically and immunohistochemically distinctive perivascular epithelioid cells”[1]. PEComa family tumours mainly included renal and hepatic angiomylipomas (AMLs), lymphangioleiomyomatosis (LAM), lymphangiomymoma and clear cell “sugar” tumour (CCST) of the lung. In 2004, the WHO classification of tumours subdivided AML further into classic AML and epithelioid AML, defining epithelioid AML as “a potentially malignant mesenchymal neoplasm, characterized by a proliferation of predominantly epithelioid cells”[2].

Currently, PEComas are considered a group of ubiquitous neoplasms sharing morphological, immunohistochemical, ultrastructural and genetic distinctive features[3], which typically express smooth muscle and melanocytic[4] as well as lymphatic vascular[5] markers. Several uncommon tumours with similar morphological and immunohistochemical characteristics arising at a variety of sites (abdominal cavity, digestive tract, retroperitoneum, skin, soft tissue and bones)[6] are also included in the PEComa family and are referred to as PEComas not otherwise specified (PEComas NOS)[7]. However, some authors[8,9] argue that the terminology used for non-pulmonary PEComas is confusing.

Although reviews for renal epithelioid AMLs, extrarenal AMLs, gastrointestinal PEComas and gynaecological PEComas have been published, a thorough review of retroperitoneal PEComas is missing. Regarding a case of retroperitoneal tumour resection that was postoperatively diagnosed as PEComa, we conducted a review of all published reports on retroperitoneal and perinephric PEComas, evaluating their biological behaviour in both sites, as well as possible differences between them.

**CASE PRESENTATION**

**Chief complaints**

A 37-year-old Caucasian female patient was investigated for persistently abnormal alkaline phosphatase (ALP) plasma values.
History of present illness
Although the patient remained asymptomatic, repeated liver function tests over a 9-mo period revealed persistently increased ALP plasma values.

History of past illness
The patient had a nonsignificant past medical history, no history of recent illness and/or trauma and was not receiving any medication at the time of referral.

Personal and family history
The patient was a nonsmoker and had no personal or family history of other diseases.

Physical examination upon referral
The clinical examination was unremarkable.

Laboratory investigation
All haematological and biochemical laboratory results were reported within normal limits except elevated ALP (> 500 IU/L). Tumour markers were reported as within normal limits.

Imaging investigation
A liver ultrasound scan revealed gallbladder sludge and multiple focal lesions in the hepatic parenchyma. An abdominal computer tomography (CT) scan disclosed multiple focal lesions of the liver enhancing during the arterial phase and as an incidental finding an 8.5 cm × 8 cm × 4 cm solid and heterogeneous retroperitoneal mass anterior to the right psoas muscle and posterior and inferior to the right kidney, which encapsulated the right ureter in its whole length and inferiorly to the level of the right lobe of the liver, abutting the right kidney anteriorly and laterally (Figure 1).

TREATMENT
A pig-tail catheter was first placed in the right ureter, after which the patient underwent exploratory laparotomy through a midline incision under general endotracheal anaesthesia. Cholecystectomy and excision of the retroperitoneal mass were performed, while multiple Tru-cut biopsies from the liver lesions were taken. Her postoperative course was uneventful, and she was discharged on the 5th postoperative day.

FINAL DIAGNOSIS
The gallbladder’s sludge was considered the aetiology for the abnormal ALP, while the malignant nature of the retroperitoneal tumour could not be excluded based on imaging findings.

Histology and immunohistochemistry report
Pathological examination with haematoxylin and eosin staining of the retroperitoneal mass revealed a completely resected encapsulated tumour composed of polygonal or spindle cells with eosinophilic cytoplasm and mildly atypical nuclei arranged in bundles around compressed, thin-walled vascular channels. Less than 1 mitosis per 10 high-power field (HPF) was present, while necrosis was absent. The immunohistochemical staining results were as follows: Desmin (+ diffuse), SMA (+ diffuse), HMB-45 (+ focal), PgR (+ diffuse), melan-A (-), CD34 (-), CD117 (-), S-100 (-), ER (-), Ki67 < 2%. The tumour was classified as “retroperitoneal PEComa of uncertain biological behaviour” (Figure 2).

Histological examination of the gallbladder disclosed “chronic cholecystitis”, while the biopsies from the liver were diagnostic of “focal nodular hyperplasia”.

OUTCOME AND FOLLOW-UP
After three years from the initial operation, the patient remains asymptomatic without any evidence of local or distant recurrence.

DISCUSSION
Abdominal computed tomography scan findings. Selective coronal views of the abdominal computed tomography scan with intravenous and oral contrast material at 1.3 mm intervals. A solid, heterogeneous, retroperitoneal mass, anterior to the right psoas muscle, posterior to the right kidney, inferior to the right lobe of the liver, extending down to the level of the caecum, and pushing the right kidney anteriorly and laterally, is documented.

Review of the literature

The Medline and EMBASE databases were searched using as key words the terms “perivascular epithelioid cell tumour(s)”, “PEComa(s)”, “retroperitoneal PEComa(s)”, “perinephric PEComa(s)”, “extrarenal PEComa(s)”, “non-pulmonary PEComa(s)” and “PEComa NOS” in several combinations.

For assessment of the published reports, we used the following terminology: (1) Renal classic AML, for AMLs confined to the kidney; (2) Renal epithelioid AML, for AMLs with epithelioid variant confined to the kidney; (3) Extrarenal AML, for AMLs developed at any extrarenal site; (4) Retroperitoneal AMLs, for pure retroperitoneal AMLs completely separately from the kidney(s); (5) Gastrointestinal PEComas, for tumours developed in the abdominal cavity or the digestive tract; (6) Gynaecological PEComas; (7) Perinephric PEComas, for tumours developed between Gerota’s and Zuckerkanld’s fascia[10]; and (8) Retroperitoneal PEComas, for retroperitoneal tumours completely separately from the kidney(s) and with a histology report other than AML.

We included articles between 1996 and 2018; the final search was conducted in December 2018. All articles with at least an abstract in the English language were considered eligible for inclusion. Thirty articles were identified, and the following parameters were studied: Sex, age, maximum dimension of the tumour, histological and immunohistochemical characteristics of the tumour, follow-up and long-term outcome.

AMLs constitute the most common, well-described and well-studied member of the PEComa family of tumours. On the other hand, non-renal AMLs/non-pulmonary PEComas are seldom reported. Approximately 120 renal epithelioid AMLs[11], fewer than 100 extrarenal AMLs[6,9], 50 gastrointestinal PEComas[12] and 78 gynaecological PEComas[13] have been reported so far in the English literature. In the present review, 33 (34 including the present case) retroperitoneal and 10 perinephric PEComas cases were identified[44-47], making retroperitoneal space the third most frequent location for PEComas NOS development (Table 1).

PEComas are considered neoplasms of unknown origin. According to a hypothesis, PEComas derive from undifferentiated cells of the neural crest, since they express several melanocytic markers[3]. Another hypothesis proposed that they have a smooth muscle origin with possible molecular alterations, leading to the expression of melanocytic markers[44]. A third hypothesis supported that the expression of melanocytic markers is acquired and related to chromosomal translocations or mutations affecting the pathway of melanosomal protein expression during tumour development[45]. The most recent theory, however, addressed that both PEComas and gastrointestinal stromal tumours (GISTs) have a common origin from telocytes, since markers expressed in telocytes (e.g., S-100, SMA, VEGF) are also expressed in PEComas[46].
AML and LAM have been proposed to be strongly associated with tuberous sclerosis complex (TSC), an inherent autosomal dominant syndrome resulting from heterozygous mutations of either the TSC1 or TSC2 tumour suppressor gene, causing a multisystem development of benign tumours\[47\]. Although renal AMLs develop in > 50\% of TSC patients\[47\], less than 20\% of AML patients have underlying TSC\[48\]. Thus, most AML cases arise sporadically, a fact probably related to new mutations\[49\], inactivating mutations, or difficulties in detection of mutations by conventional methods in either gene or due to the presence of additional still unidentified causative (TSC) loci\[49\]. In three reports of the present study\[4,21,33\], cytogenetic analysis was performed, but only one\[4\] concluded a loss of heterozygosity in the TSC2 gene.

PEComas are composed of nests and sheets of mainly epithelioid and occasionally spindled cells with clear to granular eosinophilic cytoplasm. The proportions of the two parts may vary significantly. Epithelioid cells are located immediately perivascular, while spindle cells are located away from the vessel's wall. Usually, PEC surrounds the blood vessels, arranging radially around the lumen, forming bunch-and web-shaped structures, while in a minority of cases, it has a focal association with the blood vessel walls. In all cases, PEC replaces the normal smooth muscle and collagen in the muscular wall of the vessel\[17,38,41]\]. A sclerosing variant of PEComa with predominant sclerotic and hyalinized stroma has also been reported\[17,25,27,28,40\].

A diagnosis of PEComa is usually established postoperatively by histology. Based on the CT and magnetic resonance imaging (MRI) findings, however, an accurate preoperative diagnostic rate does not exceed 31\% and 40\%, respectively, for AMLs and is 0\% for any other histological subtype\[50\]. In particular, retroperitoneal PEComas are usually diagnosed preoperatively as well-differentiated liposarcomas\[36\].

The diagnosis is based on immunohistochemistry. Co-expression of melanocytic markers such as melan-A and/or HMB-45 (expressed in epithelioid cells) and smooth muscle markers such as smooth muscle actin, pan-muscle actin, muscle myosin, and calponin (expressed in spindle cells) is considered diagnostic\[14-43\].

The biologic behaviour of PEComas remains unclear. Folpe et al\[51\] proposed the following: (1) Tumour size > 5 cm; (2) Mitotic rate > 1/50 HPF; (3) High nuclear grade and cellularity; (4) Presence of necrosis; (5) Vascular invasion; and (6) An infiltrative growth pattern, as risk factors for malignancy, stratifying the biological behaviour of PEComas as (1) being benign (tumours < 5 cm with one risk feature), (2) having uncertain malignant potential (tumours > 5 cm with no other risk features), and (3)
| Author       | Ref. | Year | Localization | No. patients | Sex/age | Maximum diameter (cm) | Biological behavior stratification based on Folpe et al.[44] criteria | Follow-up (mo) | Long-term outcome                         |
|--------------|------|------|--------------|--------------|---------|-----------------------|----------------------------------------------------------------------|----------------|------------------------------------------|
| Audard       | [14] | 2004 | Retroperitoneal | 1            | M/45    | 21                    | Malignant                                                           | NA             | NA                                       |
| Gunia        | [15] | 2005 | Perinephric   | 1            | F/57    | 5.3                   | Uncertain                                                           | 8              | No recurrence                             |
| Shin         | [16] | 2008 | Retroperitoneal | 1            | F/47    | 19                    | Malignant                                                           | NA             | NA                                       |
| Hornick      | [17] | 2008 | Retroperitoneal | 10           | F/43    | 9                     | 10 sclerosing PEComas                                               | NA             | NA                                       |
| Lans         | [18] | 2009 | Retroperitoneal | 1            | F/28    | 15                    | Malignant                                                           | 5              | No recurrence                             |
| Koening      | [19] | 2009 | Retroperitoneal | 1            | F/27    | 10                    | Malignant                                                           | NA             | NA                                       |
| Sabhia       | [20] | 2010 | Retroperitoneal | 1            | F/58    | 17                    | NA                                                                  | 48             | Liver and lung metastases                |
| Wagner       | [21] | 2010 | Retroperitoneal | 1            | M/65    | 20                    | NA                                                                  | 36             | Multifocal retroperitoneal recurrence    |
| Suemitsu     | [22] | 2010 | Retroperitoneal | 1            | M/39    |                        | Confirmation of malignancy retrospectively                         | 216            | Lung metastases                          |
| deLeon       | [23] | 2010 | Retroperitoneal | 1            | F/76    | 15                    | Malignant                                                           | 48             | Brain, T-spine, sacrum metastases        |
| Kumar        | [24] | 2010 | Perinephric   | 1            | F/54    | 8                     | Malignant (=gross infiltration of IVC)                              | NA             | NA                                       |
| Valiathan    | [25] | 2011 | Perinephric   | 1            | F/50    | 8                     | Sclerosing PEComa                                                   | NA             | NA                                       |
| Alguraan     | [26] | 2012 | Perinephric   | 1            | F/43    | 12.8                  | Uncertain                                                           | NA             | NA                                       |
| Santi        | [27] | 2012 | Retroperitoneal | 1            | F/66    | 8.5                   | Sclerosing PEComa                                                   | NA             | NA                                       |
| Rekhi        | [28] | 2012 | Retroperitoneal | 1            | F/56    | 5                     | Uncertain                                                           | NA             | NA                                       |
| Yang         | [29] | 2012 | Perinephric   | 1            | F/21    | 2.5                   | Malignant                                                           | 3              | No recurrence                             |
| Theodosopoulos | [30] | 2012 | Retroperitoneal | 1            | NA      | NA                    | NA                                                                  | NA             | NA                                       |
| Wu           | [31] | 2013 | Retroperitoneal | 1            | F/55    | 7.5                   | Malignant                                                           | 7              | Liver metastases                         |
being malignant (tumours with two or more risk features). Although Folpe’s criteria have been criticized\cite{7}, they continue to have utility, especially in helping to categorize lesions with low malignant potential. Applying Folpe’s criteria, the present study revealed that among the 34 retroperitoneal PEComas, 15 were malignant (44%), 10 (29%) exhibited uncertain biological behaviour, and 2 (6%) exhibited benign behaviour, while in 7 cases, the status was not stated. Among the 10 perinephric tumours, 6 were malignant (60%), 3 (30%) exhibited uncertain biological behaviour and 1 (10%) exhibited benign behaviour. There are clearly no differences in the malignant potential between the published retroperitoneal and perinephric PEComas. The literature addresses that the biological behaviour of the non-pulmonary PEComa family tumours varies widely. Renal classic AML constitutes an otherwise benign lesion, although rare cases of sarcomatous transformation have been described\cite{52}. Renal epithelioid AML resembles the biological behaviour of renal cell carcinoma with a 17% recurrence rate, 49% metastatic rate and 33% death rate\cite{53,54}. Extrarenal AML only occasionally develops malignant biological behaviour\cite{8}; 52% of gastrointestinal\cite{12} and 50% of gynaecological PEComas\cite{55} have malignant potential, while sclerosing PEComa pursues an indolent course, unless associated with a frankly histologically malignant component\cite{17}.

The present study adds to our knowledge that 45% of retroperitoneal and 60% of perinephric PEComas have malignant potential. Moreover, 7 out of 15 (47%) potentially malignant retroperitoneal PEComas presented with or developed metastases in the course of the disease, while 2 out of the 6 (33%) potentially malignant perinephric PEComas developed metastases. Based on the above, we postulate that retroperitoneal PEComas are not as indolent as they are supposed to be, since 20%-21% of all reported cases presented with or developed metastases in the course of the disease. The above findings should be taken into consideration in
designing therapeutic strategies and surveillance.

Since retroperitoneal PEComas cannot easily be differentiated from sarcomas and because half of them may develop a potentially malignant biological behaviour, radical surgical resection (usually organ sparing) constitutes the treatment of choice for localized disease. Chemo-, immune- and/or radiotherapy have little efficacy. Cytogenetic studies disclosed that the proteins encoded by the TSC1 (hamartin) and TSC2 (tubulin) genes are involved in cell proliferation and differentiation through the inhibition (negative regulation) of the mammalian target of the rapamycin (mTOR) kinase signalling pathway. Thus, loss of heterozygosity of the TSC1 and mainly TSC2 genes inactivates the tuberin/hamartin complex, leading to mTOR activation, further promoting translational initiation and cell growth. Kenerson et al. discovered activation of the mTOR cascade in 15 out of 15 sporadic AML cases, while Pan et al. found loss of heterozygosity, leading to mTOR activation, in 11 out of 12 PEComa patients. Activation of mTOR through loss of the TSC1/TSC2 complex seems to be a consistent and critically pathogenic event in PEComas, a finding that indicates a potential benefit from the use of mTOR inhibitors in patients with locally advanced, unresectable, metastatic or recurrent PEComas.

mTOR inhibitors act as cytostatic rather than cell death agents, regulating the cell cycle at the G1 phase, in several types of TSC1/TSC2 deficient cell lines in vitro. Currently, the effectiveness of mTOR inhibitors on non-AML/non-pulmonary PEComas of advanced stage, at any localization, is limited. In the only available review, Dickson et al. reported complete response in 5, partial response in 1 and progression of disease in 5 out of 11 enrolled patients. Later, Wagner et al. reported clinical response in 2 out of 3 enrolled patients, and Starbuck et al. also noticed clinical response in 2 out of 3 enrolled patients, while Batereau et al. reported complete response in both patients treated.

TFE3 gene rearrangements are increasingly described in PEComas, seen in 9 out of 38 cases studied from broad spectrum locations. Eighty percent of TFE3-negative PEComas harbour TSC2 mutations. However, PEComas harbouring TFE3 gene rearrangements are thought to form a morphologically similar but biologically distinctive subgroup, as they lack the TSC2 alterations characteristic of conventional ones. Lack of TSC2 involvement in TFE3 rearranged PEComas has been proposed as an explanation for the non-response to mTOR inhibitors.

In cases of retroperitoneal sarcomas, neoadjuvant chemotherapy is not the standard of care but can occasionally be considered when complete resection is uncertain. The present review, however, disclosed that this strategy has been applied only once in retroperitoneal PEComas. Administration of mTOR inhibitors as adjuvant therapy may be beneficial for patients at high risk for recurrence. Although the present study disclosed that half of the potentially malignant retroperitoneal PEComas will develop metastases, the rarity of the disease does not allow conclusive results because the “cost-benefit” analysis remains a major concern.

An optimal routine follow-up policy is also not available for PEComa cases. We propose a sensible approach to following the sarcoma guidelines for follow-up. Thus, high-risk patients may be followed every 3 mo for the first 3 years, then twice a year up to the fifth year and annually thereafter, while low-risk patients may be followed every 6 mo for the first 5 years and then annually.

**CONCLUSION**

Overall, 44 retroperitoneal PEComas have been reported in the English literature, making retroperitoneal space the third most frequent location for PEComas NOS development. Half were stratified as potentially malignant, and nearly half of the potentially malignant tumours presented with or developed metastases during the course of the disease. Thus, retroperitoneal PEComas are not as indolent as they are supposed to be. Radical surgical resection constitutes the treatment of choice for localized disease, while mTOR inhibitors constitute the most promising therapy for disseminated disease. The role of mTOR inhibitors as adjuvant or neoadjuvant therapies needs to be evaluated in the future.

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