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Original research

Perivascular epithelioid cell neoplasm (PEComa) of the uterus: A systematic review

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HIGHLIGHTS

- Perivascular epithelioid cell neoplasms represent a rare entity.
- Surgery represents most adopted primary treatment for PEComas.
- Role of systemic treatment is not well established yet.

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ABSTRACT

Background: Perivascular epithelioid cell neoplasm (PEComa) is a rare mesenchymal tumor. Gynecological PEComas account for just over one-fourth of the overall PEComa cases reported in the literature. Surgery is the most recommended primary treatment while adjuvant therapy is generally reserved for high-risk cases. However, the best management of this neoplasia has not been well established, primarily because of the paucity of cases described to date.

Objectives: The aim of this systematic review is to summarize what is known thus far regarding the etiopathogenesis, clinical and pathologic features of PEComas, focusing also on the most valid treatment options for uterine cases.

Data sources: Pubmed articles on PEComas published in various journals over the past 70 years were analyzed.

Conclusions and key findings: Although the optimal treatment of gynecological PEComas is controversial, surgical resection remains the cornerstone. The use of adjuvant treatment is warranted in high risk patients to increase disease control. A multidisciplinary approach should be key in treatment decision-making regarding gynecological PEComas.

1. Introduction

Perivascular epithelioid cell neoplasm (PEComa) is a rare mesenchymal tumor originating from the perivascular epithelioid cell (PEC) line. PEC was first described in 1943 by Apitz et al. [1] and it was designated as an "abnormal myoblast" in renal angiomyolipoma. In 1992 Bonetti et al. [2] proposed the term "perivascular epithelioid" to identify the morphologically and immunohistochemically unusual cell type with a perivascular distribution. More specifically, these cells are immunoreactive for melanocytic markers, have an epithelioid appearance and a clear-acidophilic cytoplasm, and show a perivascular distribution [2]. Subsequently, this designation was applied to a family of distinctive neoplasms at various anatomic locations, including angiomyolipoma, clear cell sugar tumors, lymphangioleiomyomatosis, clear

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cell myomelanocytic tumor of the falciform ligament and other unusual clear cell tumors. The progressive enlargement of the PEC family led the World Health Organization (WHO) to define PEComa as: "a mesenchymal tumor composed of histologically and immunohistochemically distintive perivascular epithelioid cells" [3].

Approximately 65 cases of gynecological PEComas have been described in the English-language literature to date; most as case reports or studies on small series of patients [4–9]. Owing to the paucity of cases, there have been many controversies over the most adequate management and prognosis of this neoplasm. For this reason, we conducted a detailed systematic literature review, focusing on the knowledge available to date regarding the genesis, treatment options and prognosis of gynecological PEComas.

2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed to perform this review. The final search was conducted in October 2014. Electronic medical databases (Pubmed, Medline) were searched for "gynecological PEComas" or "uterine PEComas" and "PEComas of uterus" in the title and abstract.

Pubmed filters were set to find all articles on PEComas written in the English language and published over the past 70 years. Studies reporting on gynecological PEComas were reviewed. Two independent reviewers selected the identified studies based on the title and abstract; in cases where the study topic could not be clearly ascertained from the title or abstract, the full-text version was retrieved for evaluation. From all the studies included, the following data were collected: first author's surname, publication year, sample size of cases, treatment strategies, morphological and immunohistochemical characteristics of the PEComa, duration of follow-up, and clinical outcome.

3. Results: epidemiology, clinical development, classification

The literature search identified a total of 62 potentially relevant articles on uterine PEComa out of more than two thousand seven hundred publications on the pathology. Six articles were excluded because they were not written in the English language. The reviewed article types included case reports, case series and literature reviews; no randomized trials were found.

3.1. Epidemiology

Gynecological PEComas accounted for just over one-fourth of the overall PEComa cases reported in the literature [10]. About 65 cases of uterine and cervix uteri PEComas have been described to date.

The age of patients affected ranged from 9 to 79 years, with a peak of incidence falling within the fourth decade of life. An association between all types of PEComas and tuberous sclerosis complex (TSC) was reported in 10% of cases. Even when PEComas at other sites are excluded, the rate of gynecologic PEComas TSC–associated remains at 9% [11–13]. This association is related to genetic mutations attributable to the inactivation of genes TSC1 or TSC2. Although TSC1/2 inactivation is much more pronounced in angiomyolipoma and lymphangioleiomyomatosis than in gynecological PEComas [14], the occurrence of this genetic disorder is related to high aggressiveness.

3.2. Clinical development

Clinical presentation of gynecological PEComa is non-specific and a correct diagnosis is difficult to make. The vast majority of tumors arise in the uterine corpus, while the cervix is less frequently involved [15–17]. Clinical manifestations vary in relation to the dimension, location, and diffusion of the tumor. Generally, small non-symptomatic tumors are accidentally discovered. However, the most common signs and symptoms of clinically evident lesions include: abnormal vaginal or peritoneal bleeding, abdominal pain and uterine symptoms, such as rupture of the uterus and hemoperitoneum.

Like clinical manifestations, the radiological appearance is extremely variable, in relation to PEComa texture, dimensions and local or distal diffusion. It may present either as a small benign smooth cell neoplasm, or as a large, heterogeneous mass [18–20].

The lack of specific clinical and radiological findings makes the diagnosis and the management of PEComa challenging, causing some delay in treatment in some cases.

3.3. Classification

Criteria to classify PEComa were recently proposed by Folpe et al. [11] (Table 1). Six high-risk criteria are recognized: tumor size $\geq$ 5 cm, infiltrative growth pattern, high nuclear grade cellularity, mitotic rate > 1/50 high power fields (HPF), necrosis and vascular invasion. Based on these criteria, three categories of PEComas were delineated [11,21]: benign, uncertain malignant potential and malignant. "Benign" is defined as tumors without features typically associated with malignancy. Tumors of "uncertain malignant potential" are defined as having only a single histological feature including nuclear pleomorphism or multinucleated giant cells or a size $\geq$ 5 cm. Tumors are classified as "malignant" if they clearly show 2 or more of the above-mentioned atypical criteria. There is a significant association between these criteria and consequential aggressive disease behavior. Given the rarity of these tumors, evidence of some atypical nuclear features, without showing other worrying histological criteria, should still be considered as "uncertain malignant potential", even if it is probable that only a benign condition exists.

4. Morphological and immunohistochemical features

4.1. Morphological features

Most of the morphological features of PEComas of the uterus are common with those of other anatomical sites. As originally

Table 1
Classification of gynecological PEComas.

Category	Criteria
Benign	None of: Size $\geq$ 5 cm Infiltrative growth pattern High nuclear grade cellularity Mitotic rate > 1/50 HPF Necrosis Vascular invasion
Uncertain malignant potential	One of: Nuclear pleomorphism Multinucleated giant cell Size $\geq$ 5 cm
Malignant	Two or more: Size $\geq$ 5 cm Infiltrative growth pattern High nuclear grade cellularity Mitotic rate > 1/50 HPF Necrosis Vascular invasion

HPF: high power fields.

described, PEC has an epithelioid appearance with clear to eosinophilic and granular cytoplasm, centrally located, round to oval nuclei with a nucleolus. The tumor cells typically grow in sheets or nests, and the cells are often intimately associated with a prominent vascular component. This perivascular distribution is a distinctive feature and it led initial observers to speculate a probable origin from blood vessel walls. Since this classic description, histological variants of PEComas are now known to occur and include tumors with a variable and often prominent spindled tumor cell component – as described in clear cell myelomelanocytic tumors of the falciform ligament – as well as tumors with extensive stromal hyalinization or so-called sclerosing PEComas [22]. The epithelioid component seems to be predominant in most cases, generally characterized by a nested growth pattern or, more rarely, by a fascicular or diffuse evolution [23,24].

Irrespective of the growth pattern, gynecological PEComas showed variable amounts of stromal hyalinization. In some cases, this was so significant that it made the epithelioid cells seem immersed in a hyalinized-fibrotic background [6,23,24]. Uterine PEComas can be well or partially circumscribed, or they can diffusely infiltrate the myometrium [6,15]. Vascularization of PEComas often presented characteristic features, composed generally of a network of small vessels distributed throughout the tumor [6].

4.2. Immunohistochemical features

PEC expresses a myomelanocytic phenotype, being immunoreactive for melanocytic and smooth muscle markers. Immunoreactivity for HMB-45 and certain other melanocytic markers was widely demonstrated [25–29]; the most relevant ones were microphtalmia transcription factor (MTF), MelanA/Mart-1 and HMSA-1 [30]. In approximately 70% of cases, immune reaction for SMA was reported, while an immuno-positivity for vimentin and/or desmin was observed, though less frequently [6,12,31]. Cathepsin K expression was also reported to be useful in the diagnosis of PEComas [32].

In a recent literature review conducted by Fadare et al [15], the following immunophenotype was found: HMB45: 100% positive, smooth muscle actin 73% positive, vimentin 56% positive, CD10 25% positive, Melan-a 24% positive, CD117 9% positive, CD34 5% positive, S100 3% positive, keratins 3% positive as well as antimembrane antigen, inhibin and chromogranin 0% positive.

Taking into account these constant morphological and immunohistochemical features and the variety of the anatomical distribution together with the absence of a normal counterpart, many efforts have been made to research the origin of these tumors among multipotential primitive cells, in particular those located in perivascular areas. Recently, several hypotheses have been proposed [34]. One theory is that undifferentiated cells of the neural crest, able to express melanocytic and smooth muscle phenotype, represent the PEC cells of origin. Secondly, it has been proposed that PEC may derive from pericytic elements. Moreover, it has been suggested that PEC should have a myoblastic and smooth muscle origin with acquired melanocytic marker expression [33]. Nevertheless, further investigations are needed to better understand PEComa histogenesis.

5. Differential diagnosis

Some morphological overlap exists between PEComas and epithelioid smooth muscle tumors of the uterus (ESM), in particular, both tumors may display clear cells, epithelioid cells, stromal hyalinization and multinucleated giant cells. A delicate vascular network characterizes PEComas, but not ESM. Both affect patients in the same age group. Both can probably be classified as malignant if there is coagulation necrosis and/or > 10 HPF. Moreover, keratin positivity may be found in both, but it is more frequent in ESM [34,35] and desmin positivity is present in about 50% of both ESM and PEComas [34,36].

ESM and uterine PEComas display a substantial immunophenotypical overlap that is at least indicative of their shared lines of differentiation. However, most PEComas can be morphologically distinguished from classical ESM tumors by their distinctive network of capillaries [37]. Nonetheless, these lesions may exist at different points on a single clinical-morphological spectrum [38], and distinguishing between them may be difficult. Future studies should evaluate a series of archived ESM tumors in order to determine whether cases that are morphologically and immunophenotypically more consistent with PECcomas are identifiable, and whether these cases are prognostically distinct from others.

6. Treatment

To date, no optimal management strategy for gynecological PEComas has been established.

Surgery represents the cornerstone of treatment, however, a unanimously accepted approach has not been proposed for lesions with high-risk features and a variety of therapeutic strategies, including chemotherapy and radiation, are employed in clinical practice through the world.

The lack of unanimous consensus regarding the treatment of gynecological PEComas is due to several factors, such as the small number of cases reported in the literature, the lack of randomized studies, and the poor results achieved with the variety of therapeutic strategies used, especially regarding non-surgical patients. Moreover, in a set of patients, diagnosis is not made until surgical resection is performed, thus delaying the start of therapy and reducing the efficacy of treatment. Neo-adjuvant treatment was employed in a limited number of cases in the literature without relevant benefits in arresting tumor growth and progression. Various adjuvant chemotherapy schedules were employed, mostly demonstrating poor efficacy. Several series of patients who underwent adjuvant therapy presented a higher incidence of recurrences compared with those who did not undergo post-surgical treatment [39]. However, this could be ascribed to the aggressive behavior of some gynecological PEComas, leading to distal metastasis and death, as could be expected with high-grade sarcomas.

6.1. Surgery

Primary surgical excision, with the aim of negative margins, represents the mainstay treatment in gynecological PEComas. Independently of surgical procedure, a complete resection is paramount to evaluate tumor histopathological risk factors.

The vast majority of patients affected by uterine PEComas in this study received a total hysterectomy with or without bilateral salpingo-oophorectomy [6], even though one successful case of fertility-sparing surgery was described [40].

6.2. Chemotherapy

Heterogeneous results were achieved with chemotherapy treatment of gynecological PEComas. Cases of complete, partial or absent responses were described. Different drugs were tested (dacarbazine, ifosfamide, doxorubicin, vincristine), as well as different combinations of these [41–44]. In this scenario, with a paucity of cases reported, it is difficult to identify the real impact and the best chemotherapy schedule in uterine PEComas.

6.3. Radiation therapy

A subgroup of malignant gynecological PEComas exhibits aggressive behavior. The histological features of malignancy show a high mitotic index and multiple areas of necrosis. While necrosis is associated to radio-resistance, a high mitotic index and rich vascularization, typical of this kind of neoplasm, are related to high cellular sensitivity to radiation. This evidence could support the use of ionizing radiation as a rational therapeutic agent in patients with PEComas.

Nowadays, the role of radiation therapy remains unclear. It was explored in several patients affected by this pathology, but only a few technical details were reported in each case [41]. The lack of a comprehensive radiation treatment plan makes it impossible to perform a critical evaluation. However, for reasons mentioned above, radiotherapy could show clinical efficacy in local disease control and needs additional investigation.

7. Metastatic disease

PEComas tend to recur locally [45] or to develop distal metastases, most commonly in the lung [46,47]. Metastatic spread may be a late occurrence, presenting even 7 years after curative surgery [48,49]. No definite therapy has been described in the literature to date. Surgery seems to represent an optimal treatment option when feasible, especially in oligometastatic patients. Several protocols of systemic chemotherapy were used with little efficacy. Surprisingly, good survival rates for up to one year from diagnosis, without any treatment, were also reported [50].

Targeted therapies, especially with mTOR inhibitors seem to provide encouraging results. Recent immunohistochemical and biochemical analyses demonstrated TSC1/2 inactivation and hyperactivation of the mTOR pathway in non-TSC PEComas [6,11]. Therefore, inhibition of mTOR resulted in significant clinical activity in patients with PEComas. Gennatas et al [46] presented a case of a retroperitoneal PEComa with lung metastasis treated with an oral mTOR inhibitor. The disappearance of lung lesions and a significant reduction of the abdominal mass after 12 weeks of treatment, without severe side effects, were reported. Additionally Italiano et al [51] reported promising results with the use of mTOR inhibitors in two patients with malignant PEComa.

Based on the above promising data, mTOR inhibitors warrant additional investigation in prospective studies for the treatment of gynecological PEComas.

8. Discussion

Some questions remain unanswered regarding this distinctive tumor; for example, what is the best treatment approach for high-risk patients and what are the real benefits of target therapy in term of survival? Although the optimal management of PEComas is still controversial, surgical resection remains the treatment of choice. Surgery alone seems to be appropriate in non-aggressive PEComas, but preoperative or adjuvant treatment seems to be necessary in high-risk patients [39]. Several series reported a high rate of local control with a multimodal approach. Jeon et al. [41] reported a favorable response by combining surgery, radiotherapy and chemotherapy, with a disease free survival of 18 months after resection. Similarly Ong et al. [37] described no evidence of disease 6 months after surgery; whereas Folpe et al [11], in a series of 26 patients affected by PEComas of soft tissue and the gynecologic tract, reported a disease-free survival reaching 36 months after surgery for gynecological PEComas, as well as Vang and Kempson reporting no evidence of disease after two years from surgery [44]. However, owing to the small series reported, the lack of randomized trials and to the heterogeneity of therapeutic strategies adopted, no definitive information regarding the most adequate management is available yet. Therefore, as a result of potential bias in our review regarding the types of articles selected, no conclusive treatment observations can be drawn. A trial to prove the most adequate management should be performed, despite the obvious difficulties related to the rarity of this pathology.

Regarding target therapy, it appears that lowering the rate of local and distal progression is of great importance in patients presenting metastatic disease. Treatment with mTOR inhibitors has been shown to improve, albeit limited to a handful of case reports, the rate of long-term response in this subgroup of patients [52]. Considering the lack of benefit of traditional cytotoxic therapy, mTOR inhibitors should be considered as a valid alternative in metastatic disease.

9. Conclusion

Gynecological PEComa is a rare pathology and its prognosis is variable and dependent on histological features. The variety of therapeutic strategies used with heterogeneous results, as well as the lack of established guidelines, highlights the need for randomized trials. Although the optimal treatment is controversial, surgical resection remains the cornerstone of therapy. The addition of adjuvant treatment should be considered to increase disease control in patients with high-risk features. A multidisciplinary approach should be the most promising approach to treatment decision-making in gynecological PEComas.

Conflicts of interest

All authors declare no conflict of interest.

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