



## Primary perivascular epithelioid cell tumor (PEComa) in bone: A review of the literature and a case arising in the humerus with multiple metastases



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### ABSTRACT

**Introduction:** Perivascular epithelioid cell tumors (PEComas) are a family of mesenchymal tumors that rarely arise as a primary bone tumor.

**Material and methods:** We report a case of primary malignant bone PEComa. A literature review via PubMed, Embase and Web of Science databases with the keyword "PEComa" and "bone" was performed. **Results:** We reported a 33-year-old female with primary malignant bone PEComa in right distal humerus. The patient received an inhibitor of the mammalian target of rapamycin (mTOR) protein based on negative molecular investigation result of transcription factor E3 (*TFE3*) rearrangement, and additional therapies including palliative radiotherapy, anti-angiogenics and immunotherapy when the disease progression was detected. The patient was alive with the disease twenty-three months postoperatively. A total of nineteen related literature cases were retrieved and reviewed. Taking current case into account, ten males and ten females with median age of 24 years (range, 3–93 years) were identified, who were most frequently affected in tibia. The median follow-up duration of 24 months (range, 3–96 months). One patient died due to this disease, and six patients showed metastases. Three patients experienced recurrence, and two of them experienced twice and three times, respectively.

**Conclusion:** To our knowledge, this is the first case of primary malignant bone PEComa arising in humerus. Clinicopathological and radiological correlation is mandatory to the correct diagnosis and to determine its malignancy. More studies are required to understand the role of molecular test and imaging in selecting suitable treatment and mechanisms of treatment resistance.

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**Abbreviations:** <sup>18</sup>F-FDG, fluorine-18-fluorodeoxyglucose positron; ASPS, alveolar soft part sarcoma; CT, computed tomography; ECT, emission computed tomography; EMA, membrane antigen; HMB 45, human melanoma black 45; HPF, high-power fields; MITF, microphthalmia-associated transcription factor; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; PEComa, perivascular epithelioid cell tumor; PET/CT, positron emission tomography/computed tomography; SMA, smooth muscle actin; SUV<sub>max</sub>, maximum standard uptake value; TFE3, transcription factor E3.

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### 1. Introduction

Perivascular epithelioid cell tumors (PEComa) are a group of mesenchymal tumors that classically composed of distinctive cells that show a focal association with blood vessel walls and usually express melanocytic and smooth muscle markers [1–3]. In 1992, Bonetti et al [4] first observed this group of tumors. These tumors exhibit an epithelioid appearance, clear-cell acidophilic cytoplasm and a perivascular distribution, had an immunoreaction with melanocytic markers and were the most sensitive to human melanoma black 45 (HMB45) [1]. In 1996, the term "PEComa" was first used by Zamboni et al [5] to describe this family of lesions.

Since then, PEComas have been discovered in a wide variety of anatomical locations, most frequently in kidney, liver, pancreas,

uterine, etc. [1]. However, limited cases of primary bone PEComas have been documented in the literature, whose radiological features and pathological findings were rarely described. Immunohistochemical staining might provide clues for approaching the diagnosis, and recent advance in molecular testing showed potential in diagnosis and treatment selection [3]. Nonetheless, the diagnosis of PEComa was still of great difficulty.

Most PEComas behave as benign or indolent lesions with relatively good prognosis, but a minority of them have malignant potential. Folpe et al [6] defined malignant PEComas with a few criteria, such as a tumor size  $\geq 5$  cm, mitotic activity  $\geq 1/50$  high-power fields (HPF), cell necrosis, nuclear pleomorphism and an infiltrative growth pattern.

Histologically malignant PEComas often exhibit invasive behaviors, including metastases and recurrence, which require a more aggressive treatment plan and closer follow-up [1–3].

To increase the recognition of this rare disease, we reported our experience in diagnosing and treating a case of primary malignant bone PEComa. Moreover, we reviewed the related literatures to summarize diagnostic approach, clinical management, and prognosis information of this disease.

## 2. Material and methods

We retrospectively reviewed a case of malignant PEComa in detail. The diagnosis was established based on a biopsy and resected specimen by two experienced pathologists. Molecular investigations were performed to confirm the diagnosis. All images were collected from our picture archiving and communication system. Two radiologists reviewed all the images, and the tumor features were recorded based on consensus. The relevant clinical data was collected from electronic charts and telephone calls. The ethics committee of our institution approved this study and written consent was obtained from the patient included in this study. Our study conformed to the provisions of the Declaration of Helsinki.

The literature review was performed via the PubMed, Embase and Web of Science databases with “PEComa” AND “bone” as keywords until 28 Aug 2020. Detailed search strategy was described in Table 1. Studies in languages other than English, Japanese, German, French or Chinese were excluded. The titles and abstracts were screened after exclusion of duplicates to assess eligibility, and full-texts were read to determine their inclusion. The reference lists of the included studies were screened for additional potentially eligible articles. The process was performed by one reviewer who has expertise in five selected languages. In the case of uncertainties, the reviewer consulted other reviewers to reach final decision. The reviewer extracted and summarized data from included studies, which later checked by another reviewer. The data of

current cases were merged with the literature data during pooled analysis.

The literature review was performed with assistance of Endnote software version X9.2 (Clarivate Analytics, Philadelphia, PA, USA), while all analyses were performed using SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA). P-value  $< 0.05$  was recognized as statistical significance, unless otherwise specified.

## 3. Results

### 3.1. Case presentation

A 33-year-old female was admitted to a local hospital with a one-week history of right elbow pain. Radiography was performed and revealed a lesion and pathological fracture of the right distal humerus. The local hospital failed to remove the lesion at that time. The patient came to our institute for further treatment one week later.

Physical examination revealed mild right elbow pain, swelling and movement difficulty. No other signs or symptoms were present. The patient denied any tobacco or alcohol use. She did not have a significant medical or family history, except for a pulmonary bulla resection. Laboratory tests, including hematology, serology, and biochemistry, revealed no abnormal findings except for an elevated neuron-specific enolase value of 17.53  $\mu\text{g/mL}$ .

Radiography of the right elbow revealed an expansive lesion in the right distal humerus with pathological fracture (Fig. 1a). Further evaluation with computed tomography (CT) showed an expansile osteolytic lesion with destruction of the cortex and soft tissue expansion (Fig. 1b, c). Magnetic resonance imaging (MRI) detected a lesion with nodules infiltrating surrounding soft tissues (Fig. 1d–g). Technetium-99m emission computed tomography ( $^{99\text{m}}\text{Tc}$  ECT) demonstrated that the lesion had abnormal bone metabolism activity (Fig. 2a). Moreover, positron emission tomography with fluorine-18-fluorodeoxyglucose integrated with computed tomography ( $^{18}\text{F}$ -FDG PET/CT) showed that the lesion had weak  $^{18}\text{F}$ -FDG-avidity (Fig. 2b).

An incisional biopsy was performed and reported the lesion as a malignant PEComa based on its morphological and immunohistochemical features. The tumor showed positive for HMB45, Melan-A, smooth muscle actin (SMA) and TFE3, negative for desmin and S100 protein, with Ki-67 expression of 20%. The pathologists recommended the clinician to exclude the possibility that this lesion was a metastasis from another site. Thus, systemic examination was performed and analyzed. No other mass in the viscera or retroperitoneum was found by chest, abdominal or pelvis CT, and no evidence of a primary tumor was identified by ECT or PET/CT. However, PET/CT and CT scans revealed multiple osteolytic lesions

**Table 1**  
Search strategy for PEComa in bone.

| Database       | Search terms  | Articles retrieved |
|----------------|---|--------------------|
| PubMed         | #1 'perivascular epithelioid cell neoplasm' OR 'perivascular epithelioid cell tumor'<br>OR pecoma*                | 4,068              |
|                | #2 bone OR osteo* OR osseous  | 1,525,121          |
|                | #3 #1 AND #2  | 116                |
| Embase         | #1 'perivascular epithelioid cell neoplasm':ti,ab,kw OR 'perivascular epithelioid cell tumor':ti,ab,kw OR pecoma* | 1,048              |
|                | #2 bone OR osteo* OR osseous  | 1,855,281          |
|                | #3 #1 AND #2  | 84                 |
| Web of Science | #1 TS=('perivascular epithelioid cell neoplasm') OR TS=('perivascular epithelioid cell tumor') OR TS=(pecoma*)    | 1,382              |
|                | #2 TS=(bone) OR TS=(osteo*) OR TS=(osseous)   | 3,097,686          |
|                | #3 #1 AND #2  | 146                |

Note: Articles retrieved on 28 Aug 2020 via PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Embase ([www.embase.com](http://www.embase.com)) and Web of Science ([apps.webofknowledge.com](http://apps.webofknowledge.com)).



**Fig. 1.** Radiological findings at presentation. (a-c) Radiography and CT showed an expansile osteolytic lesion in right distal humerus with destruction of cortex, soft tissue expansion and pathological fracture, measuring 12.6 × 2.9 × 1.8 cm in size. (d, e) MRI demonstrated a homogeneous signal isointense lesion to muscle tissue on T1-weighted imaging and a heterogeneous signal hyperintensity on T2-weighted imaging. (f, g) After contrast administration, the lesion showed a significant homogeneous enhancement on T1-weighted imaging, except for a foci of low signal intensity similar to that on T2-weighted imaging. Enhanced nodules infiltrating surrounding soft tissues were detected.

in the right mandible, the thoracic, lumbar and sacral vertebrae and the right ilium, which did not exhibit an elevated <sup>18</sup>F-FDG-avidity. Since systemic examination revealed no evidence of a primary elsewhere, the primary lesion was thought to be a dominant large mass in the right distal humerus.

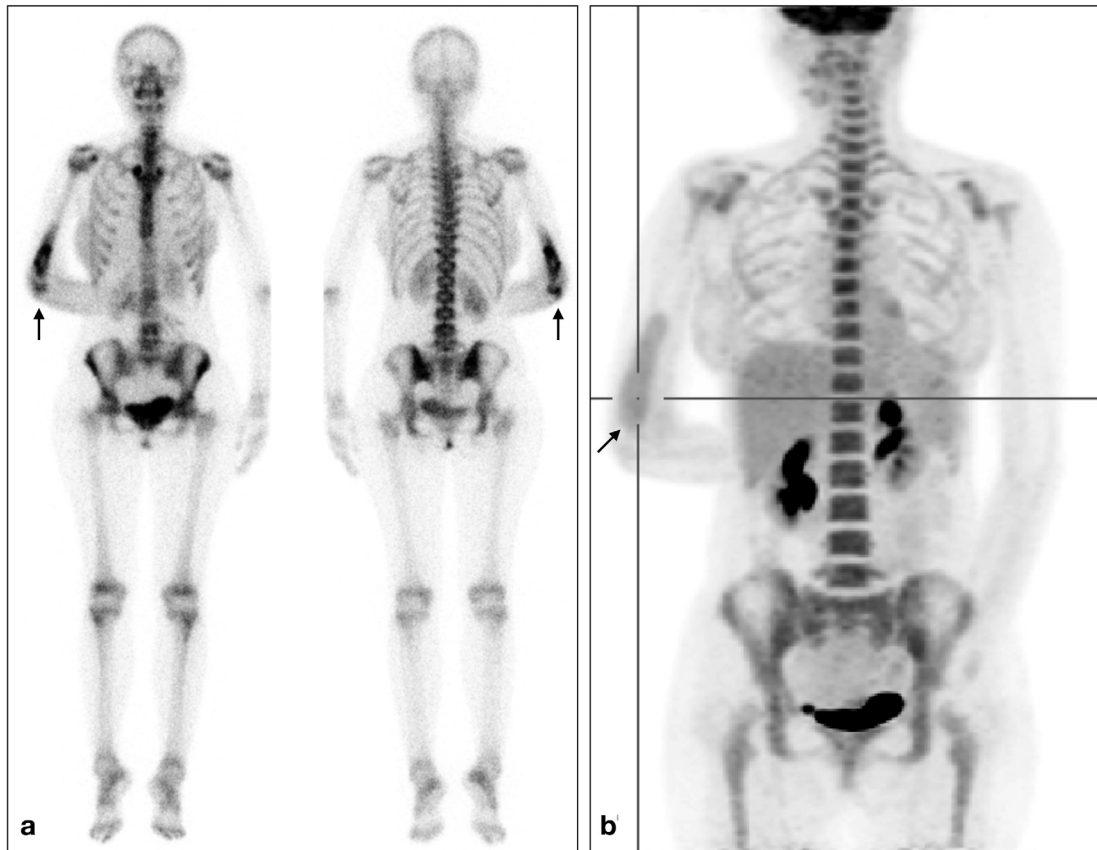
The patient was treated with one cycle of neoadjuvant chemotherapy (adriamycin 60mg d1 + isophosphamide 3.2g d1-4), but no sign of response was observed. The patient underwent a wide resection of the distal right humerus lesion and reconstruction of the right elbow joint to release her symptoms and to remove the lesion. The negative surgical margin was confirmed by frozen sections.

Grossly, the specimen from the right distal humerus measured 19.0 cm in length with a pathological fracture 5.5 cm from the resection margin. This specimen contained a gray-white mass that

measured 11.8 cm in length, and broke through the bone cortex and infiltrated surrounding soft tissue, resulting in several scattered nodules that ranged from 0.8 to 1.0 cm (Fig. 3a).

Histologically, the tumor was composed of epithelioid and spindle cells arranged in a nested pattern and displayed delicate arborizing capillaries. The tumor showed an infiltrative growth pattern that entrapped surrounding bone, muscle and soft tissue. The tumor cells showed a moderate to high degree of nuclear pleomorphism and cell necrosis with a clear to granular, lightly eosinophilic cytoplasm. Mitoses were readily encountered with a mitotic rate of more than 8/10 HPF (Fig. 3b-e).

Immunohistochemically, the tumor cells were positive for HMB45, SMA, desmin and caldesmon and were weakly positive for Melan-A (Fig. 3f, g). The nuclei of tumor cells were partially positive for TFE3 (Fig. 3h). The vascular network was clearly delin-



**Fig. 2.** Nuclear imaging findings at presentation. (a) ECT showed an abnormal radioactive concentrative lesion in right distal humerus (arrow). (b) PET/CT showed a  $^{18}\text{F}$ -FDG-avid lesion in the same site (arrow) with a maximum standard uptake value of 2.3.

eated using CD34 and CD31 staining. The tumor cells were negative for epithelial membrane antigen (EMA) and S100 protein. Ki-67 expression was found in more than 25% of the tumor cells (Fig. 3i). A diagnosis of a malignant PEComa was proposed based on the morphological features and the immunohistochemical profile.

As hypothesized, the PEComas with the *TFE3* rearrangement might be nonresponsive to the mammalian target of rapamycin (mTOR) protein inhibitor [7]; thus, further molecular assays were performed to help treatment selection. *TFE3* rearrangement was not identified on fluorescence in situ hybridization. These results provided a scientific basis to start everolimus therapy (10 mg/d) in this individual case. Meanwhile, she was given zoledronic acid (4 mg/month) to control multiple bone metastases.

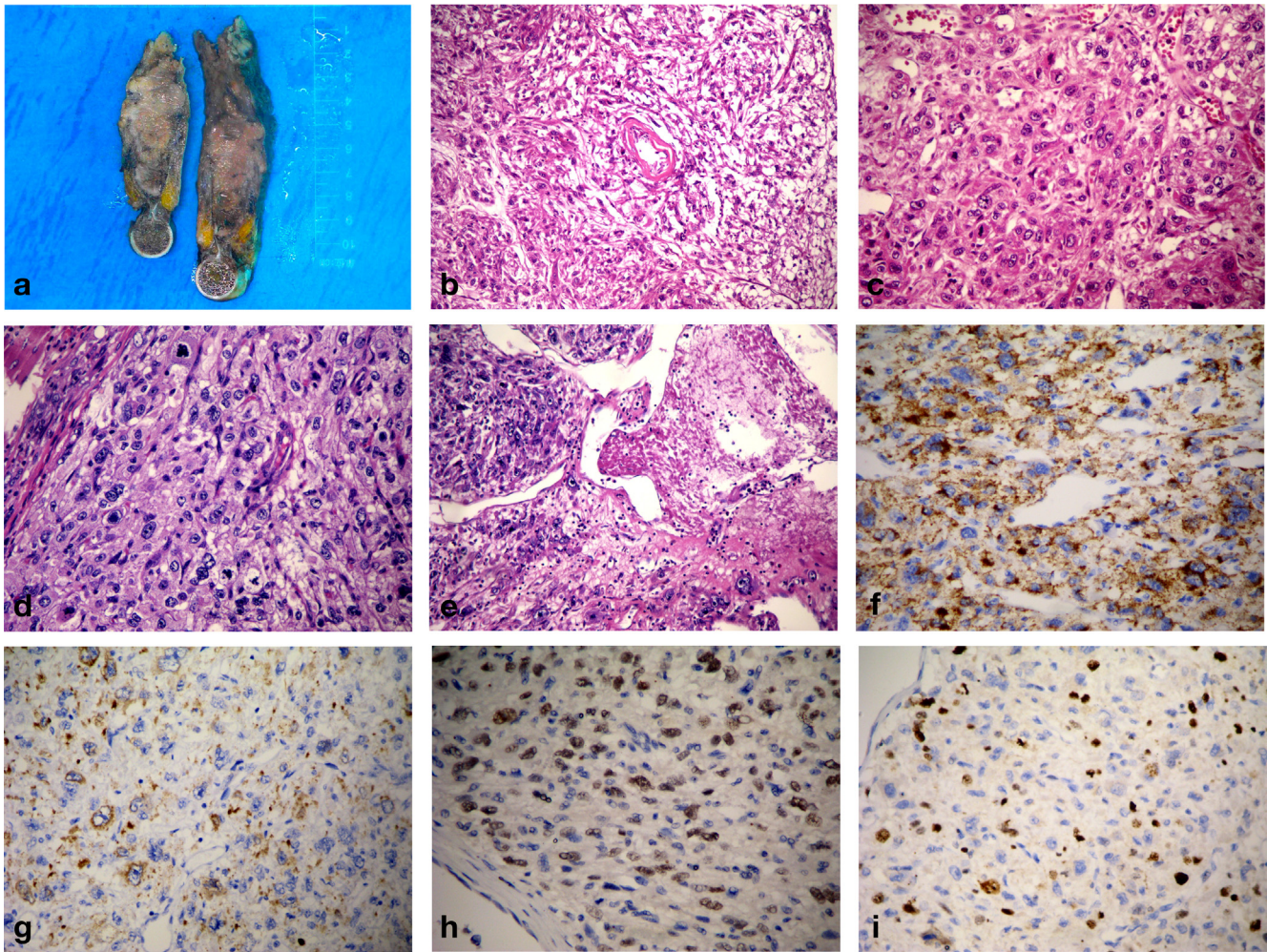
The disease had been stable for five months postoperatively, until she presented to our hospital complaining about lower back pain. PET/CT scans detected new-shown osteolytic lesions of the right clavicle, right 8th rib, cervical vertebrae, left superior pubic ramus and left proximal femur, which were thought to be newly developed metastases. Several lesions demonstrated an elevated  $^{18}\text{F}$ -FDG-avidity (Fig. 4a, b), indicating the malignancy. The patient received palliative radiotherapy to the cervical, lumbar and sacral vertebrae to release her pain. Additionally, the multiple tyrosine kinase inhibitor anlotinib (12mg d1-14 per 3 week) and zoledronic acid (4 mg/month) were given to retard the progression of the disease, and their effect was detected (Fig. 4c-e). However, due to further progression detected in regular followed-up, a combination of a vascular endothelial growth factor receptor inhibitor (apatinib; 250 mg/d) and an

anti-programmed cell death protein 1 (PD-1) antibody (camrelizumab [SHSR1210]; 200 mg/2 weeks) was introduced. Fortunately, no new metastases (Fig. 4f, g) or recurrences of the tumor at the primary site were found at later follow up (Fig. 4h, i). The patient later received a percutaneous vertebroplasty of fourth lumbar vertebra.

The patient is still alive with disease twenty-three months after the surgery and continued receiving everolimus and zoledronic acid.

### 3.2. Literature review

A total of sixteen studies with nineteen unique case reports with pathologically confirmed primary bone PEComas were available via PubMed, Embase and Web of Science (Fig. 5) [8–23]. Taking current case into account, ten males and ten females with a median age of 34 years, and a range from 3 to 93 years, were identified. The most common site of the tumor was tibia (4 of 17), and followed by fibula and femur (both 3 of 17). Table 2 and Fig. 6 summarized the details of these twenty patients with primary bone PEComas. Treatment selection varies among cases. Notably, mTOR protein inhibitor was first introduced to treat osseous PEComa in 2012 [15]. The median follow-up duration was 24 months, ranging from 3 to 96 months. One patient died due to this disease. Six patients showed metastases, four of which were in the lung. Three patients experienced recurrence, and two of them experienced twice and three times, respectively. The overall survival and disease-free survival were shown in Fig. 7.



**Fig. 3.** Pathological findings. (a) Surgical specimen of right distal humerus after formalin fixation showed the section of tumor, measuring 11.8 cm in length. (b) Epithelioid and spindle malignant tumor cells surrounding vasculature (HE  $\times 10$ ). (c) Nuclear pleomorphism was observed (HE  $\times 40$ ). (d) Nuclear mitoses was observed (HE  $\times 40$ ). (e) Area of necrosis present within the tumor (HE  $\times 10$ ). (f) Positive for HMB45 (EnVision  $\times 40$ ). (g) Weak positive for Melan-A (EnVision  $\times 40$ ). (h) Partial nuclear positive for TFE3 (EnVision  $\times 40$ ). (i) Ki-67 expression was found more than 25% of tumor cells (EnVision  $\times 40$ ).

## 4. Discussion

### 4.1. Anatomic locations and clinical features

Similar to PEComas involving other sites, primary bone PEComas most commonly occur in young to middle-aged adults [1]. Unlike PEComas involving other sites, which were markedly more frequent in females [1], primary bone PEComas were equal in both sexes; however, this finding could be due to the small sample size of primary bone PEComas.

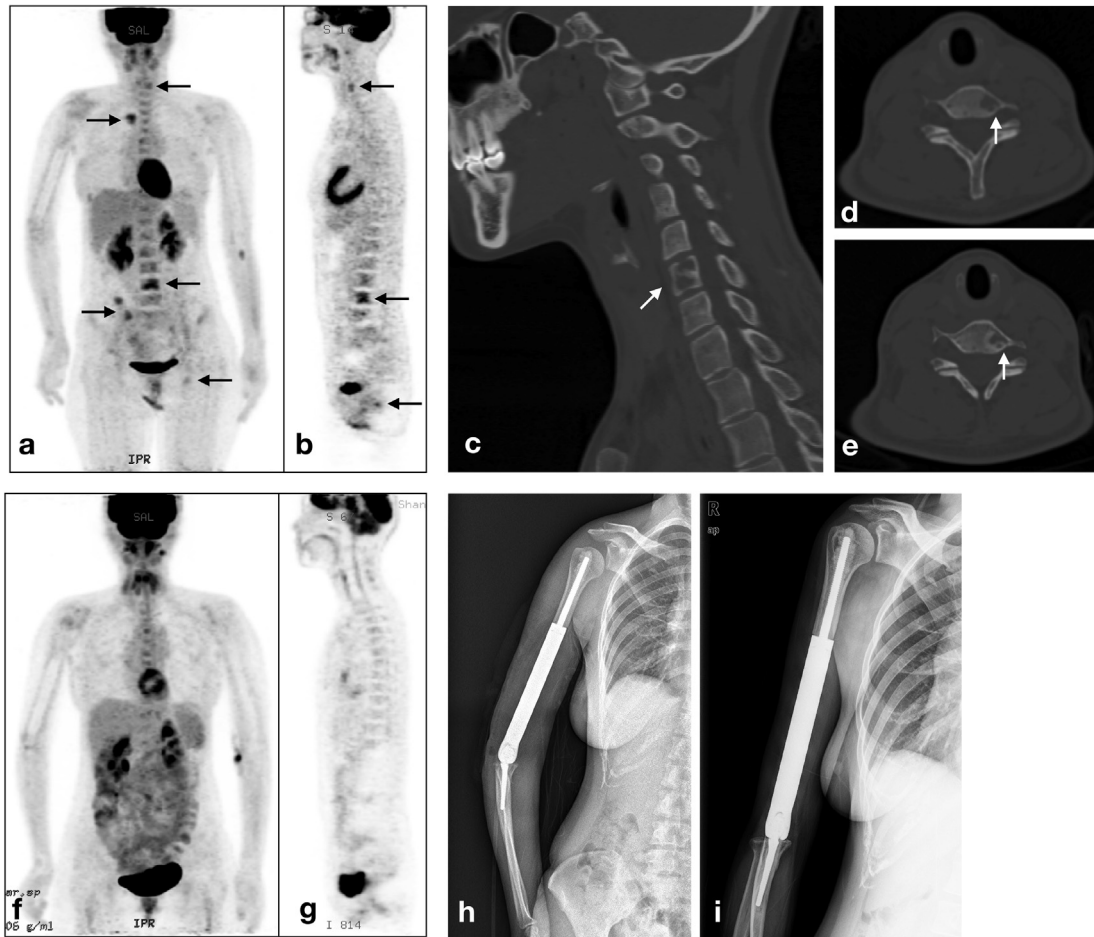
The sites of primary bone PEComa varies and the establishment of bone origin needs careful clinical review. In six PEComas presenting in bone described by Yamashita et al [13], three were included into our review. One case in left proximal humerus was determined as metastatic lesion, because the patient was subsequently discovered a history of malignant PEComa in uterus. The rest two cases in left scapula and left proximal femur were excluded, because multiple other lesions were identified and the primary site was unclear. In the former one, there was no dominant lesion; and in the later one, the dominant lesion was only 3 cm in size. We established the diagnosis in a similar manner as Yamashita et al [13] used. In our case, although multiple osteolytic lesions were found simultaneously, the dominant lesion was 11.8 cm in size. Further, no suspicious history was discovered,

nor did any other primary site become evident in follow up. To the best of our knowledge, we first reported a case of PEComa arising from an upper limb.

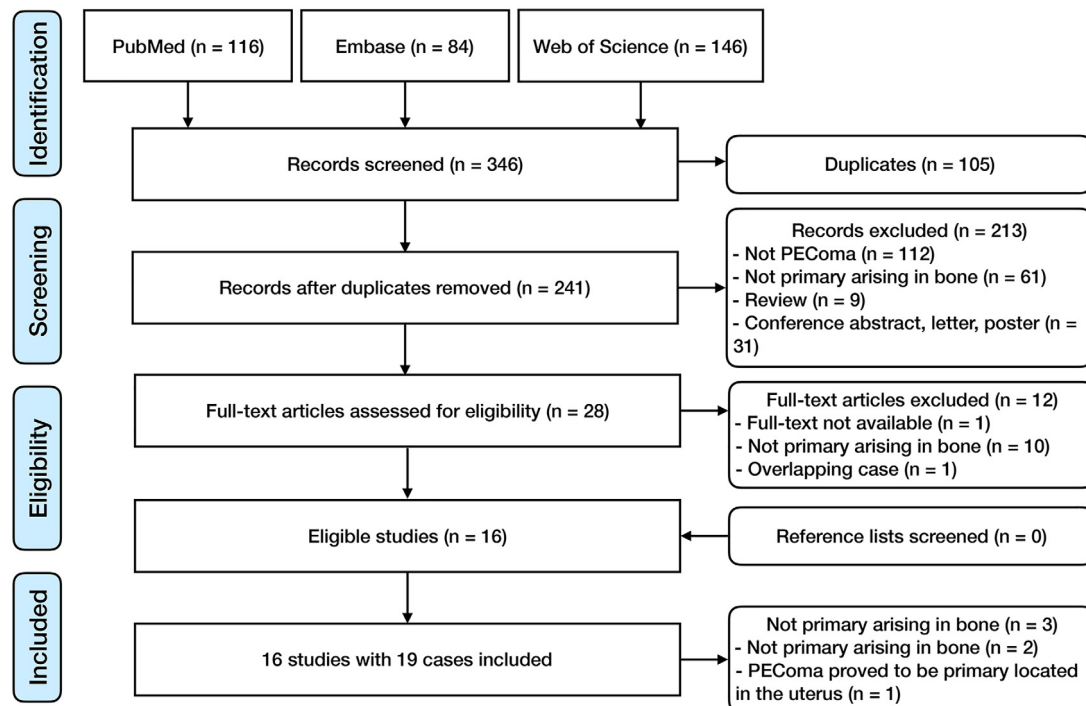
Clinically, in contrary to the usually painless PEComas in other sites, patients with bone PEComas typically present with pain [8,11,13,15,17–22]. Four cases reported swelling [12,17,18], one of which had pathological fracture of the fibula [15]. Two patients had PEComas of the vertebral column that resulted in leg weakness due to cord compression [13,14]. Generally, the laboratory data for these patients has all been within normal limits.

### 4.2. Radiological characteristics

Radiological characteristics of bone PEComas have rarely been reported (Table 3) [24–32]. Primary bone PEComas usually appear as osteolytic lesions with mixed lytic and sclerotic lesions sometimes. As for more aggressive tumors, the destruction of the bone cortex and the formation of soft tissue masses present [8,9,12–18,20,22]. On MRI, PEComas of the bone are likely to exhibit heterogeneous T1 signal hypointensity or isointensity and heterogeneous T2 signal hyperintensity [13,15,17,20,23], which is consistent with PEComas at other sites [25,26]. Intense enhancement on contrast CT and MRI are suggested as a feature of PEComas arising other than bone [25,26]; limited reports described similar



**Fig. 4.** Imaging findings during treatment. (a, b) Five months postoperatively, PET/CT showed several lesions with elevated <sup>18</sup>F-FDG-avidity, including right clavicle, cervical and lumbar vertebrae, right ilium and left proximal femur (arrow). (c, d) Osteolytic lesion of C6 vertebra was demonstrated as bone metastases (arrow). (e) Seloring rim of C6 vertebra lesion after regional RT suggested improvement (arrow). (f, g) Postoperative, PET/CT did not detect new metastases. Decreased <sup>18</sup>F-FDG-avidity was considered result of targeted therapy and immunotherapy. (h, i) Radiography after operation immediately and 23 months postoperatively showed no signs for recurrence, respectively.



**Fig. 5.** Flow diagram of included studies. Sixteen studies with nineteen unique cases with PEComa primary arising in bone were included into literature review.

**Table 2**  
Summary of twenty cases of PEComa in bone, including present case.

| No. | Age | Sex | Site                    | Size (cm)  | Presentation                       | Radiologic Features   | Histology-cell Types | IHC Markers                     | Treatment   | Follow-up                             | Folpe's classification        | Reference                |
|-----|-----|-----|-------------------------|------------|------------------------------------|---|----------------------|---------------------------------|---|---------------------------------------|-------------------------------|--------------------------|
| 1   | 30  | M   | Right proximal tibia    | 2          | Pain                               | Osteolytic with cortical destruction  | Epithelioid          | HMB-45                          | Local resection   | ANED, 12 mo                           | Benign                        | Insabato, 2002 [8]       |
| 2   | 9   | M   | Right calcaneus         | NA         | Trauma                             | Large, expansile lesion; thinned cortex with a solid, enhancing tumor mass                      | Epithelioid          | HMB-45, Melan-A, SMA, Desmin    | Local resection   | ANED, 1.5 y                           | Benign                        | Sawger, 2004 [9]         |
| 3   | 92  | F   | Right fibula            | NA         | NA                                 | NA  | Epithelioid          | HMB-45, CD10                    | Local resection   | NA                                    | Benign                        | Righi, 2008 [10]         |
| 4   | 28  | M   | Right 6th rib           | 2          | Pain                               | Osteolytic  | Epithelioid, spindle | HMB-45, SMA                     | Local resection   | ANED, not reported                    | Uncertain malignant potential | Torii, 2008 [11]         |
| 5   | 52  | F   | Right mid-shaft fibula  | 6.3        | Progressive swelling               | Extension through the cortex forming a soft-tissue mass   | Epithelioid          | HMB-45, CyclinD1                | Wide resection  | ANED, 3 mo                            | Malignant                     | Lian, 2008 [12]          |
| 6   | 35  | M   | 7th thoracic vertebra   | Large      | Bilateral leg weakness, back pain  | Osteolytic, destructive enhancing lesion; thoracic vertebrae and skull metastases at present    | Epithelioid, spindle | HMB-45, Melan-A, SMA            | CRT   | Pelvic bone metastases, AWD, 12 mo    | Malignant                     | Yamashita, 2010 [13]     |
| 7   | 39  | F   | Right proximal tibia    | 6.5        | Pain                               | Enhancing mass with areas of breakthrough of the cortex forming a soft-tissue mass              | Epithelioid, spindle | HMB-45, Melan-A, SMA            | Resection, RT   | ANED, 34 mo                           | Malignant                     | Yamashita, 2010 [13]     |
| 8   | 48  | F   | Right distal tibia      | Very small | Pain                               | Permeable destructive lesion with soft tissue extension (recurrent lesion)                      | Epithelioid, spindle | HMB-45, Melan-A, SMA            | Incisional biopsy, amputation                               | Recurred 3 times in 3 y, ANED, 3 y    | Uncertain malignant potential | Yamashita, 2010 [13]     |
| 9   | 26  | M   | 5th lumbar vertebra     | Large      | Lower back pain, left leg weakness | Destructive lesion with extra-osseous mass; lung and superior iliac spine metastases at present | Epithelioid          | HMB45, S-100                    | Conservative  | Lung metastases, ANED, not reported   | Uncertain malignant potential | Kazzaz, 2012 [14]        |
| 10  | 93  | F   | Right distal fibula     | NA         | Progressive pain, swelling         | Expansile lytic lesion, pathological fracture   | Epithelioid, spindle | HMB45                           | Local resection   | ANED, 2 y                             | Benign                        | Desy, 2012 [15]          |
| 11  | 29  | M   | Left acetabulum         | 5          | Progressive hip pain               | Extensive lytic with soft tissue expansion  | Epithelioid, spindle | Melan-A, Desmin, Vimentin       | Left hemipelvectomy, temsirolimus                           | Lung metastases, DOD, 8 mo            | Malignant                     | Desy, 2012 [15]          |
| 12  | 77  | M   | Left posterior mandible | 7.5        | Slow-growing mass                  | Mass involving the left mandibular ramus and body   | Epithelioid, spindle | Melan-A, Vimentin               | Wide resection  | ANED, 2 y                             | Malignant                     | Untrauer, 2014 [16]      |
| 13  | 47  | M   | Left distal femur       | 5.2        | Progressive pain, swelling         | Osteolytic mass, destruction of cortex forming a soft tissue mass; lung metastases at present   | Epithelioid          | HMB45 PNL2, TFE3, Vimentin, SMA | Resection, CRT  | Lung metastases, AWD, 3.5 y           | Malignant                     | Lao, 2015 [17]           |
| 14  | 65  | M   | Right distal femur      | 11.5       | Progressive pain, swelling         | Expansile lytic lesion with soft tissue expansion   | Epithelioid, spindle | HMB45, Melan-A, SMA             | Wide resection  | ANED, 28 mo                           | Malignant                     | Yu, 2016 [18]            |
| 15  | 25  | F   | Left ilium              | 8          | Pain                               | Lytic lesion infiltrating surrounding muscles   | Epithelioid          | HMB45, Melan-A                  | Resection, radiofrequency ablation, chemotherapy, sirolimus | Recurrence, lung metastases, AWD, 8 y | Malignant                     | Karpathiou, 2017 [19]    |
| 16  | 46  | F   | Right distal femur      | 7.3        | Pain                               | Mixed lytic and sclerotic lesion with soft tissue expansion                                     | Epithelioid, spindle | Melan-A, SMA, TFE3              | Wide resection  | ANED, 6 mo                            | Malignant                     | Sadigh, 2018 [20]        |
| 17  | 50  | F   | Right talus             | NA         | Progressive Pain                   | Osteolysis with central osteosclerosis  | Epithelioid          | HMB45                           | Local resection   | ANED, 65 mo                           | Benign                        | Gebhart, 2019 [21]       |
| 18  | 24  | M   | Right proximal tibia    | NA         | Pain                               | Osteolytic lytic lesion with soft tissue expansion  | Epithelioid          | None                            | NACT, local resection                                       | ANED, 2 y                             | Benign                        | Técualt-Gómez, 2019 [22] |

(continued on next page)

Table 2 (continued)

| No. | Age | Sex | Site                  | Size (cm) | Presentation                        | Radiologic Features   | Histology-cell Types | IHC Markers                        | Treatment   | Follow-up                       | Folpe's classification | Reference       |
|-----|-----|-----|-----------------------|-----------|-------------------------------------|---|----------------------|------------------------------------|---|---------------------------------|------------------------|-----------------|
| 19  | 3   | F   | craniofacial skeleton | 3.6       | Mass                                | Subgaleal transcranial mass   | Epithelioid          | HMB45                              | Local resection, sirolimus (TFF3 translocation), wide resection                                       | Recurrence twice, 6mo, 12 mo    | Malignant              | Diab, 2019 [23] |
| 20  | 33  | F   | Right distal humerus  | 11.8      | Pain, swelling, movement difficulty | Expansile lytic lesion with destruction of cortex and soft tissue expansion, pathological fracture; multiple bone metastases at present | Epithelioid, spindle | HMB-45, Melan-A, SMA, TFE3, Desmin | Incisional biopsy, NACT, Wide resection, RT, everolimus, anlotinib, apatinib, camrelizumab (SHR-1210) | Multiple metastases, AWD, 23 mo | Malignant              | Present Case    |

Abbreviations: ANED indicates alive with no evidence of disease, AWD alive with disease, CRT chemo-radiotherapy, DOD died of disease, EMA membrane antigen, HMB 45 human melanoma black 45, IHC immunohistochemical, NA, not available, NACT, neoadjuvant chemotherapy, RT radiotherapy, SMA smooth muscle actin, TFE3 transcription factor E3, mo months, y years

enhancement pattern of those in bone [14,15]. In the current case, significant homogeneous enhancement of the lesion was demonstrated after contrast administration.

Following the analysis of the local radiologic findings, patients often undergo systemic radiologic testing for staging and exclusion of metastatic disease [20]. Metastases were also detected at initial patient presentation in three of the primary bone PEComa cases, which included metastasis to the lung [14,17], superior iliac spine [14], thoracic vertebrae and skull [13]. <sup>18</sup>F-FDG PET/CT was useful here. Sun et al [30] summarized that benign PEComas are usually negative in PET/CT scans with a maximum standard uptake value (SUV<sub>max</sub>) lower than 2.0; on the other hand, malignant ones are always positive in both primary site and metastases with an SUV<sub>max</sub> ranging from 3.19 to 72. In our case, the initial PET/CT scan detected avidity in right distal humerus, in accordance with the pathological findings. However, only a part of other lesions showed avidity on follow up PET/CT scans, encouraging further studies on the relation between PET/CT avidity and malignancy of PEComas.

#### 4.3. Pathological findings

Pathology is mandatory for the correct diagnosis. Histologically, most bone PEComas are composed of epithelioid perivascular cells that exhibit a characteristic nesting or organoid arrangement [17]. In ten cases, including our case, a composition consisting of both epithelioid and spindle cells was observed [11,13,15,16,18,20]. The diagnostic criteria for a benign, borderline or malignant PEComas was not initially determined. Folpe et al [6] established a few criteria for diagnosing a malignant PEComa, but it is important to note that malignancy classifications based on Folpe's criteria may not always align with malignancy classifications based on clinical aggressiveness, though almost all of the prior cases that involved metastatic disease were histologically classified as malignant [20].

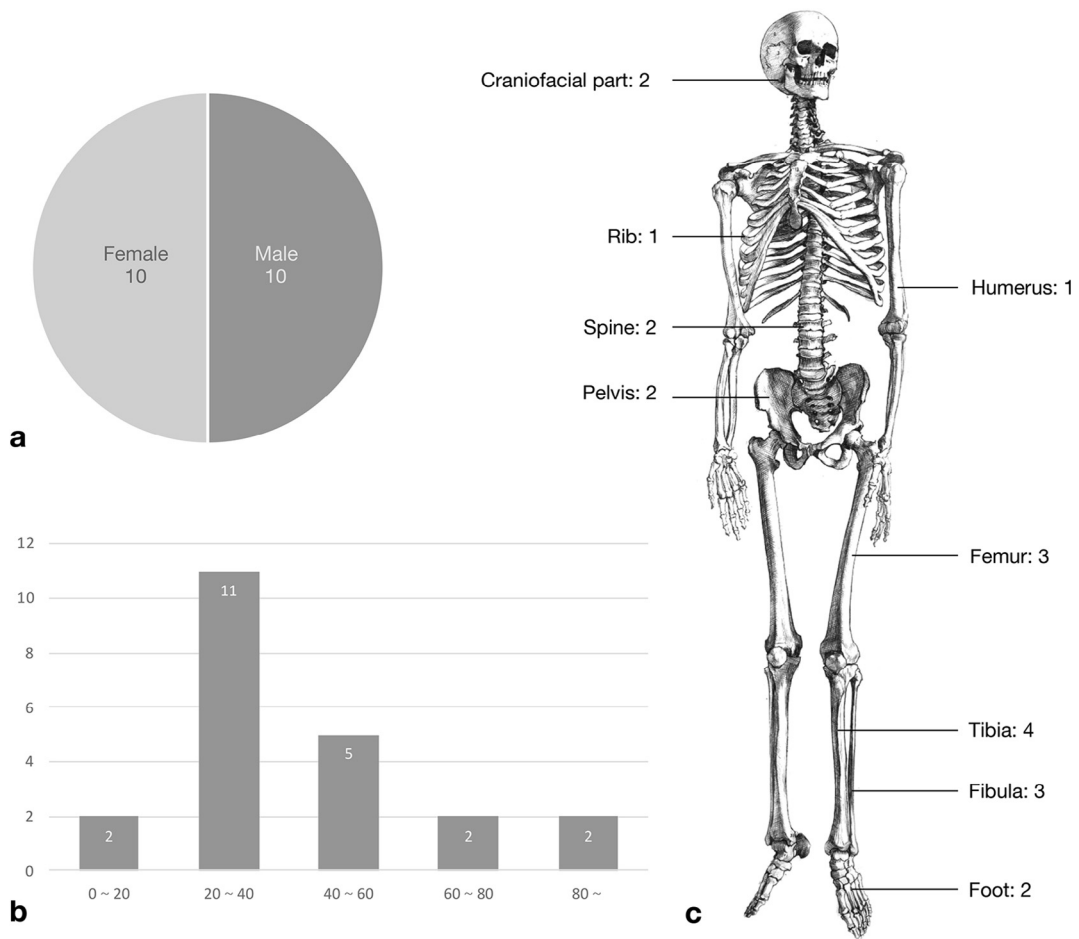
Immunohistochemically, both benign and malignant PEComas typically express positive for melanocytic markers, such as Melan-A, HMB-45 and microphthalmia-associated transcription factor (MITF), and muscle markers, such as SMA and calponin [1]. At least two main molecular subtypes of PEComas were identified. About 10% of PEComa with TFE3 rearrangement show strong nuclear staining for TFE3, and attenuated or missing expression of myogenic markers [1,3].

The differential diagnostic spectrum of PEComas varies (Table 4) [1,3]. Concerning our case, the differential diagnoses included metastatic clear-cell carcinoma (especially of renal origin), metastatic melanoma and clear-cell sarcoma. However, no evidence was found that the lesion in the humerus was a metastatic neoplasm. Furthermore, the tumor cells failed to express epithelial markers and the S100 protein, and were positive for smooth muscle markers, which ruled out the possibility of these other potential lesions [17,20]. In addition to morphological differentiation, it is necessary to further differentiate our PEComa from an alveolar soft part sarcoma (ASPS) because of the confusing partial nuclear TFE3 positivity [3]. Contrary to PEComas, ASPS lacks expression of melanocytic markers [20]. As in our case, HMB45 positivity and weak Melan-A positivity excluded the possibility of an ASPS. This finding was also supported by the molecular genetic clarification that confirmed the absence of TFE3 rearrangements.

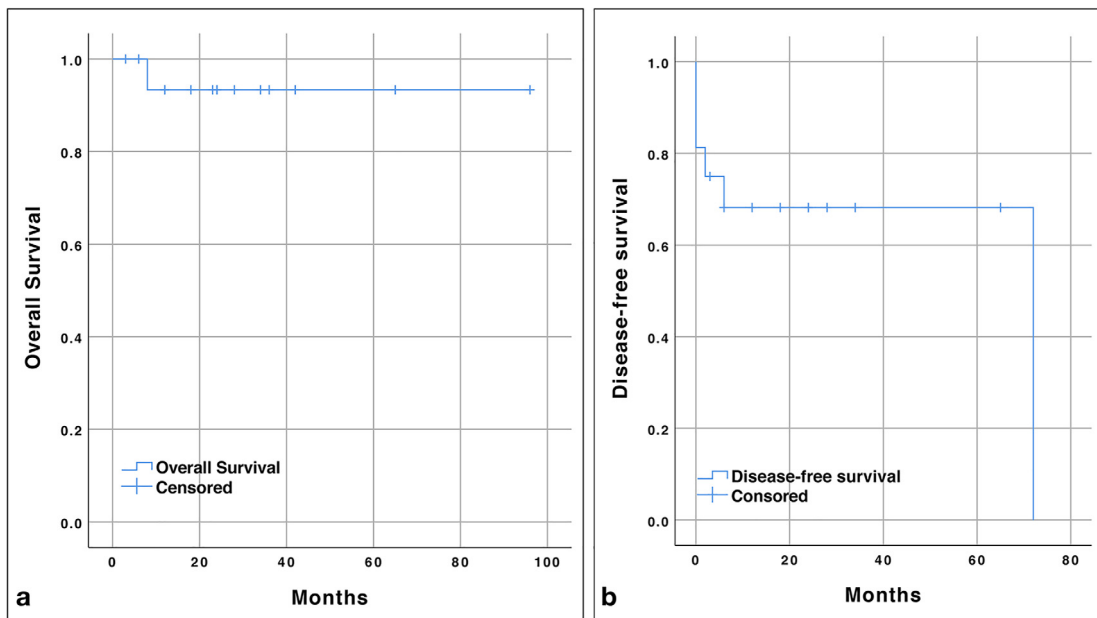
#### 4.4. Treatment and prognosis

Due to their rarity, the optimal treatment of bone PEComas is uncertain. For benign lesions, there was no recurrence or metastasis detected 12–65 months after operation. By contrast, malignant PEComas and lesions with malignant potential may pursue an aggressive clinical course including metastasis at present, repeatedly recurrence after surgery, or metastasis during follow-up,





**Fig. 6.** Patient distribution. Twenty patients with PEComa primary arising in bone distributed by (a) gender, (b) age, and (c) anatomic location, respectively.



**Fig. 7.** Survival of pooled cases. (a) Overall survival. (b) Disease-free survival. In seventeen patients with available follow-up, the overall survival ranged from 3 to 96 months. Three patients present with metastasis, and three patients experienced metastasis or recurrence 2 to 72 months after treatment.

**Table 3**  
Imaging characteristics of PEComa and features indicating malignancy.

| Modality    | PEComa arising in other sites   | Osseous PEComa   |
|-------------|---|--|
| X-ray or CT | Unenhanced: solitary or multiple mass of hypodense to isodense to the muscles with well-defined borders and of a regular shape<br>Enhanced: heterogeneous contrast uptake, significantly enhanced on arterial and venous phases, and appeared slightly hypodense on delayed phases<br>Malignancy: necrosis and calcification; metastases to lung, liver and lymph nodes | Unenhanced: osteolytic lesions, sometimes with mixed lytic and sclerotic lesions<br>Enhanced: lesion with enhancement, sometime with detectable necrosis<br>Malignancy: destruction of the bone cortex and the formation of soft tissue masses |
| MRI         | T1WI: intermediate or hypointense<br>T2WI: heterogeneous hyperintense<br>Enhanced: heterogeneous and significant enhanced on the arterial and venous phases, slightly hypointense on the delayed phase<br>Malignancy: sometimes with non-enhancing necrotic areas   | T1WI: heterogeneous hypointense or intermediate<br>T2WI: heterogeneous hyperintense<br>Enhanced: homogeneous enhancement<br>Malignancy: not reported   |
| US          | Mass with variable appearance, sometimes with internal flow   | Not reported   |
| ECT         | Not reported.   | Malignancy: lesion with abnormal bone metabolism activity  |
| PET/CT      | Malignancy: intense <sup>18</sup> F-FDG uptake.   | Malignancy: intense <sup>18</sup> F-FDG uptake   |

Note: Extracted and summarized from previous studies [24–32].  
Abbreviations: <sup>18</sup>F-FDG fluorine-18-fluorodeoxyglucose positron, CT computed tomography, ECT emission computed tomography, EUS endoscopic ultrasound, MRI magnetic resonance imaging, PEComa perivascular epithelioid cell tumor, PET/CT positron emission tomography/computed tomography, SUV<sub>max</sub>, maximum standard uptake value, US ultrasound, WI weighted imaging.

**Table 4**  
Immunohistochemical profile of PEComa and differential diagnosis.

|                     | TFE3      | S100 | Melan-A | HMB-45 | MITF | Sm-Actin | Caldesmin | Desmin | Myogenin | MyoD1 | Myoglobin | Pan-CK | INI1 | CD10 | ER  | PR  |
|---------------------|-----------|------|---------|--------|------|----------|-----------|--------|----------|-------|-----------|--------|------|------|-----|-----|
| Present Case        | partial + | -    | weak +  | ±      | n/a  | ±        | ±         | ±      | /        | -     | -         | -      | n/a  | n/a  | n/a | n/a |
| PEComa              | -         | -/+  | ±       | ±      | ±    | ±        | +/-       | +/-    | -        | -     | -         | -      | ±    | -    | -/+ | -/+ |
| TFE3-PEComa         | ±         | -/+  | ±       | ±      | ±    | -/+      | -/+       | -/+    | -        | -     | -         | -      | ±    | +/-  | -/+ | -/+ |
| Melanoma            | -         | ±    | ±       | ±      | ±    | -        | -         | -      | -        | -     | -         | -      | ±    | +/-  | -   | -   |
| ASPS                | ±         | +/-  | -       | -      | -    | -/+      | -         | +/-    | -        | -     | -         | -      | ±    | -/+  | -   | -   |
| Pleomorphic RMS     | -         | -    | -       | -      | -    | -        | -         | ±      | +/-      | +/-   | ±         | -      | ±    | -/+  | -   | -   |
| TFE3-RCC            | ±         | -    | -/+     | -/+    | -    | -        | -         | -      | -        | -     | -         | -/+    | ±    | +/-  | -   | -   |
| Low-grade ESS       | -         | -    | -       | -/+    | -    | +/-      | -         | -/+    | -        | -     | -         | -/+    | ±    | ±    | ±   | ±   |
| High-grade ESS      | -         | -    | -       | -/+    | -    | -        | -         | -      | -        | -     | -         | -      | ±    | -    | -   | -   |
| Uterine LMS         | -         | -    | -       | -/+    | -    | ±        | ±         | ±      | -        | -     | -         | -/+    | -    | +/-  | -/+ | -/+ |
| Epithelioid sarcoma | -         | -    | -       | -      | -    | -        | -         | -      | -        | -     | -         | ±      | -    | -    | -   | -   |

Note: Extracted and summarized from previous studies [1,3].  
Abbreviations: ASPS alveolar soft part sarcoma, CK cytokeratin, ER estrogen receptor, ESS endometrial stromal sarcoma, HMB 45 human melanoma black 45, INI1 integrase interactor 1, LMS leiomyosarcoma, MITF microphthalmia-associated transcription factor, PEComa perivascular epithelioid cell neoplasm, PR progesterone receptor, RMS rhabdomyosarcoma, RCC renal cell carcinoma, Sm smooth muscle, SMA smooth muscle actin, TFE3 transcription factor E3. +typically positive, +/- variable, often positive, -/+ variable, mostly negative, - typically negative, n/a not applicable.

which requires more aggressive treatments further than resection. Four previous cases were treated with chemotherapy [13,17,19,22]; radiotherapy was preformed preoperatively and palliatively in two cases [13,19], and radio-frequency ablation was performed in one case [17].

Since Kenerson et al [33] revealed that PEComas usually showed increased mTOR signaling, mTOR inhibitors were introduced to treat PEComas. The largest case series so far concluded that mTOR inhibitors are the most active agents [34]; however, some of the studies doubted the general importance of this therapy [35–38]. Molecularly, 80% of PEComas were *TFE3* rearrangement negative and thus with increased mTOR pathway activation [39,40]. On the other hand, a minority of PEComas with *TFE3* rearrangements, which hypothetically might result in them being unresponsive to targeted mTOR therapy [39–41]. Two previous cases were controlled with temsirolimus and sirolimus for several months and 6 years, respectively, without investigation of *TFE3* rearrangement [13,17]; while one case treat the patient with sirolimus who has a *TFE3* translocation, but showed recurrence [23]. In our case, the molecular test provided the rationale to start an mTOR inhibition therapy, the patient showed favorable response.

These results indicated heterogeneity of PEComas [3,37], and called more evidence for mTOR inhibitors for PEComa therapy [42], especially for the mechanisms of resistance to mTOR inhibition.

Given the absence of prospective clinical trials in this exceedingly rare disease, palliative radiotherapy, anlotinib and zoledronic acid [43,44] were given, as progression of disease was shown. For advanced or metastatic PEComas, anti-angiogenics are options in further line, thus a combination of apatinib and camrelizumab [42,45–47] was used to control the disease. These treatments have not been used in bone PEComas, and with limited evidence as a choice for malignant PEComas, which needs further studies to clarify.

Although varies treatment was introduced, surgery is still the predominant treatment approach for PEComa. The predictive value of *TFE3* for individualized therapy strategies was a possible finding instead of a confirmative viewpoint [42], but molecular test should still be regarded as the best possible approach [3]. Accordingly, mTOR inhibitors are considered for patients with multiple lesions or intolerance to surgery [42]. Anti-angiogenetic drugs, and antiestrogen drugs in female patients, can be selected in a setting where no other options are available [42,48]; while PD-1 antibody might

be also considered as a reasonable choice [46,47]. Further studies are encouraged to guide treatment selection in malignant PEComas.

The prognoses of PEComas are variable and mainly depend on the tumor size, pathological characteristics, and genetic background [2,15,22,42]. PEComas with malignant pathological features or *TFE3* fusion usually follow an aggressive clinical course, with local recurrence and distant metastasis rates [6]. That said, appropriate and timely treatment may improve the prognosis of patients suffering from a malignant bone PEComa.

#### 4.5. Limitations

There are some limitations of this study. Firstly, some of the immunohistochemical staining which might be helpful in differential diagnosis of PEComa were not available, due to decalcification process of the resected specimen. Secondly, we did not perform a further molecular test to detect *TFE3* translocation or other potential molecularly distinct rare subtype of PEComa. Thirdly, potential correlation between PET findings and molecular background were not investigated, as well as potential mechanism of development of treatment resistance. Fourthly, more robust scientific basis for our treatment selection after the resistance of mTOR inhibitor was needed. Finally, only a small number of cases were available in our literature review with heterogeneous quality and missing follow-up details, therefore it is hard to reach any robust statistical conclusion.

#### 5. Conclusion

In conclusion, we reported the detailed clinicopathological and radiological features of a primary malignant PEComa arising in the humerus with multiple metastases of an adult female, emphasizing its invasive biological behavior and difficulties in management. Clinicopathological and radiological correlation is mandatory to the correct diagnosis and to determine its malignancy. More studies are required to understand the role of molecular test in selecting suitable treatment and mechanisms of treatment resistance.

#### CRedit authorship contribution statement

**Jingyu Zhong:** Conceptualization, Methodology, Investigation, Formal analysis, Validation, Writing - original draft, Writing - Review & Editing. **Yangfan Hu:** Investigation, Formal analysis, Validation, Writing - Review & Editing. **Liping Si:** Investigation, Formal analysis, Validation, Writing - Review & Editing. **Yue Xing:** Investigation, Writing - Review & Editing. **Jia Geng:** Investigation, Writing - Review & Editing. **Qiong Jiao:** Investigation, Writing - Review & Editing. **Huizhen Zhang:** Investigation, Supervision, Writing - Review & Editing. **Weiwu Yao:** Conceptualization, Supervision, Funding acquisition, Writing - Review & Editing.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Competing interests

The authors declare that they have no competing interests.

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