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CASE REPORT

An index case of primary osseous PEComa in a paediatric craniofacial skeleton

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Abstract
Perivascular epithelioid cell tumours, known as PEComas, are a family of tumours with immunoreactive melanocytic and smooth muscle markers. They are a rare heterogeneous group in adulthood and childhood with primary osseous PEComas representing an even rarer subgroup. The clinical behaviour is not well understood and the treatment options vary. We present an index case of a primary osseous PEComa of the craniofacial skeleton in a 3-year-old girl.
Level of evidence: Level V, diagnostic; therapeutic; risk/prognostic study.

Keywords Craniofacial · Neoplasms · PEComa

Clinical case

A 3-year-old girl presented to her family doctor with a slowly enlarging glabella mass over the past 3 months. She had no significant past medical history, recent trauma, or symptoms. An obvious lump centrally located in the glabella was non-tender and firm (Fig. 1). She was referred to a tertiary centre unit for evaluation and assessment. An incisional biopsy to determine its benign or malignant nature was taken showing pigmented perivascular epithelioid cell tumour, known as PEComa, with a positive HMB-45 marker and TFE3 rearrangement. Histological analysis showed cytoplasmic staining for desmin and focal staining for SOX10 and CD99. AE1/3, CD56, and EMA showed no significant staining. The renal cell carcinoma maker RCC was negative, but CD10 was positive. S100 and Melan-A (Mart-1) were negative making melanoma unlikely. The abnormal cells appeared predominately in a perivascular location with mitotic figures. The cells were highly cellular with perivascular invasion. The specimen compromised a connective tissue, bony and fibro-fatty tissue. It showed melanocytic features loosely arranged in an alveolar pattern with thin fibrous septa. A CT and MRI scan was performed showing a subgaleal transcranial mass measuring 20 × 36 × 32 mm with epidural extension (Fig. 2a, b).

A multidisciplinary team assessment was carried out and the decision was made for surgical management of the tumour. She had a frontal craniotomy (coronal approach) with en bloc resection and reconstruction using rib and calvarial bone (Fig. 3). Histology of the specimen showed involved margins of the lateral aspects of the frontal bone resection as well as the inferior margin of the nasal bone segment. The tumour was bony in origin with no overt signs of malignancy. A wider resection of frontal and nasal bone margins bilaterally and inferiorly was taken with reconstruction of nasal defects from rib grafts and calvarial bone fashioned from Alice band craniotomy. Follow-up imaging 6 months later confirmed the development of a new lesion adjacent to the roof of the right orbit extending into the sphenoid sinus with a small intracranial component. Stereotactic endonasal transsphenoidal endoscopic surgery was performed to remove the recurrent skull base PEComa with extension into the dura.

She remained well until further 6-month follow-up imaging confirmed further enhancement and recurrence. A complete chest and abdomen CT PET scan showed no enhancing lesions. Haemoncologists advised for sirolimus treatment after her endonasal transsphenoid endoscopic surgery to control the disease and the potential of recurrence. A repeat imaging

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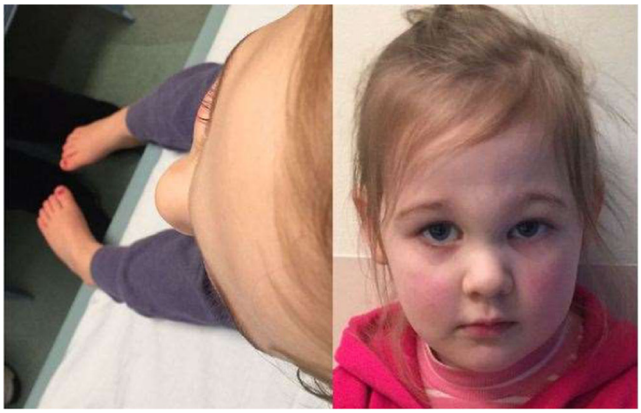

Fig. 1 Clinical photos of patient aged 3 years presenting with glabella lump

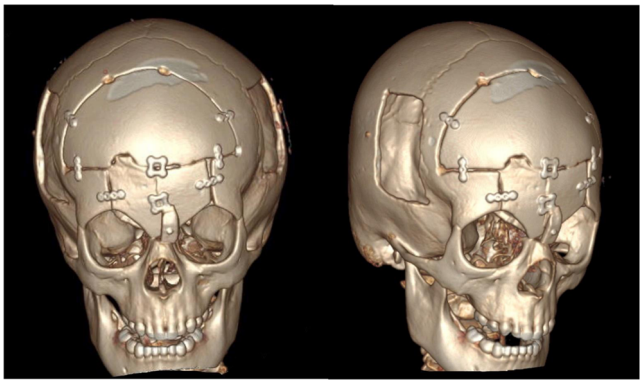

Fig. 3 Post-operative CT scan demonstrating 3D reconstruction using rib and calvarial bone grafts

showed a second new set of recurrences measuring 19 × 12 × 17 mm with minimal extension towards the inferior right frontal lobe superiorly and into the orbit, making some contact with the right superior rectus inferiorly. Another lesion was also present in the left orbital roof, measuring 10 × 5 × 8 mm, which also extended into the orbit inferiorly (Fig. 4). A PET scan showed no FDG enhancement in this region. The sirolimus treatment was ceased in light of this recurrence and discussion about sarcoma-type chemotherapy and proton beam radiation was considered. She underwent further resection from the previous coronal scalp incision with a bifrontal craniotomy and exposure of the orbital roof on both sides. The tumour was resected, and the orbital roof was then resected back to normal-appearing bone and reconstructed using MEDPOR implants. Post-operatively, she had a repeat imaging with no change in clinical disease status and ongoing monitoring that has since shown no further growth.

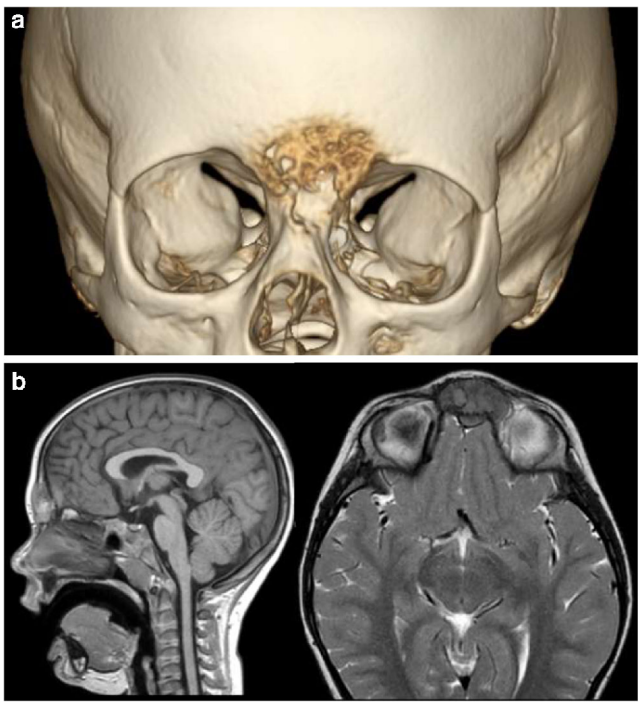

Fig. 2 **a** 3D CT scan demonstrating PEComa located at the glabella measuring 20 × 36 × 32 mm. **b** MRI scan showing T1 sagittal and T2 axial attenuation of the PEComa in the glabella region

Discussion

PEComas are a heterogeneous group of tumours of characteristic perivascular epithelioid cells with immunoreactive smooth muscle and melanocytic markers. They can arise at any location and fall under the family of PEComa with presentations including lymphangioleiomyomatosis (LAM), primary extra-pulmonary sugar tumour, clear cell myomelanocytic tumour of the falciform ligament/ligamentum teres (CCMMT), and abdominopelvic sarcoma of PECs [1]. There are genetic associations with TSC1 (hamartin) and TSC2 (tuberin) genes that are involved in melanin formation and cell proliferation via mTOR pathway. The TFE3 gene is also accounted for in other subsets where some cases lack the TSC2 arrangement affecting treatment

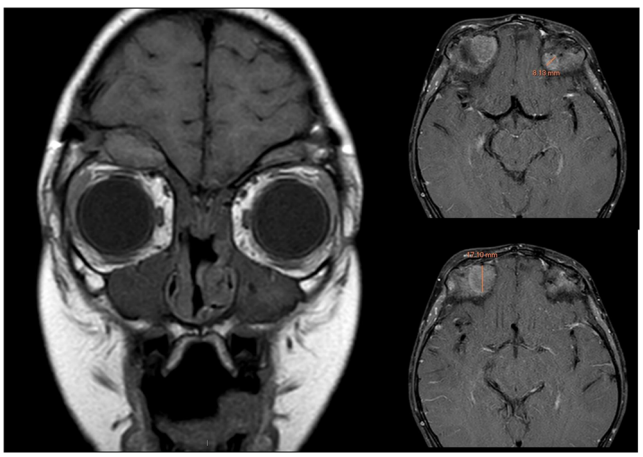

Fig. 4 MRI scan showing T1 attenuation in the right orbital roof measuring 19 × 12 × 17 mm and the left orbital roof measuring 10 × 5 × 8 mm with minimal extension into the orbit

responsivity [2]. The majority of the tumours can be distinguished nonetheless by immunophenotype and biological markers. The most sensitive melanocytic markers are HMB45, Melan-A, and microphthalmia transcription factor (MiTF) [3]; other smooth muscle markers include SMA, actin, and muscle myosin. The main differential diagnosis ranges from soft tissue sarcomas, adipocytic tumours, smooth muscle cell tumours, and other clear cell tumours. Although most act in a benign fashion, there are subsets that have a malignant potential and pose challenges in both diagnosis and management. These tumours tend to occur in adulthood with a female predilection (median 38 years) with a great variability of presentation ranging from intra-abdominal, gynaecological region, soft tissues, and bones. In children these tumours are rare and can pose a diagnostic challenge in its initial presentation. They tend to have a more equal distribution in infancy, and as adolescence and puberty begin, the female predominance is more recognised suggesting the role of hormonal factors. A histological diagnosis criteria, known as Folpe's criteria [4], provides the clinician with a tool to assess the degree of malignancy based on least two unfavourable morphological markers: size > 5 cm, infiltrative pattern, high nuclear grade and cellularity, mitotic rate bigger than 1/50 high-power field, necrosis, and vascular invasion.

Whilst PEComas of the head and neck have been reported in adults, it is be highlighted that primary bone involvement is exceedingly rare overall. Of the documented twelve primary osseous PEComas to date in adults, to the best of our knowledge, this is the first reported case of a PEComa in the paediatric craniofacial skeleton. Yamashita series of 6 primary osseous PEComa showed a tendency for long bones of the extremities although the average age was 51.5 years [5]. There has also been a case of an elderly women with primary osseous PEComa of the mandible. However, there is a little documentation on the recurrence of osseous PEComas in adults or children, but a risk stratification analysis suggests that a primary tumour size > 5 cm and high mitotic rate are significantly associated with recurrence after primary resection [6].

The past decade has seen much advancement on the role of biological and immunotype markers in the diagnosis and treatment of these tumours. Our histological analysis in accordance with Folpe's criteria showed a size > 5 cm, infiltrative growth pattern, and a mitotic rate > 1/50, defining the condition as malignant. Melanoma was excluded by lack of staining for S100, and undifferentiated clear cell sarcoma was ruled out by normal cytogenetic studies.

There is no clear consensus on treatment albeit surgical resection remains the primary treatment for these tumours with consideration for neoadjuvant treatment in unresectable cases. Our case represents a malignant PEComa in a child with a prolonged indolent course. Although the patient had three surgical resections and sirolimus treatment, the clinical behaviour of the disease appears more malignant than initially anticipated. The role of sirolimus as an mTOR inhibitor has received favourable attention for unresectable disease. Unfortunately, in our case, after the second resection, sirolimus was ceased since it was not efficacious in preventing disease progression particularly with her TF3E gene translocation. It is considered a good drug with a mild toxic profile and manageable treatment regime; however, there is overall paucity of data for adults and children in understanding treatment efficacy for osseous disease progression and drug resistance [7]. There is a discussion in the literature of systemic treatment with chemotherapeutic agents that has been reported in a similar case with slight regression [8]. We believe this may be considered in specific individuals whom display unresectable disease and unfavourable sirolimus outcomes with consideration of the cytotoxic profile. In our case, after 12 months of sirolimus treatment, the patient's recurrence occurred on the opposite side of the initial site of the operation and displayed dural invasion. At the time after multidisciplinary discussion with family and teams, a decision for surgical resection was agreed upon to resect the tumour. The option for sarcoma-type systemic chemotherapy and proton beam radiation was discussed at a multidisciplinary form; however, a collaborative decision to further resect amenable disease was considered first before second-line neoadjuvant chemotherapeutic agents. Since the third resection and 6-month repeat imaging, there has been no noticeable recurrence or change in the disease status of the patient.

Conclusion

This case can be considered a growing subset of PEComas identified where TFE3 gene rearrangements lack the TSC2 alterations characteristic of conventional PEComas [2]. Their biological behaviour is yet to be fully understood and remains an area of research and potential targeted therapies. In a growing facial skeleton, albeit exceedingly rare, the recognition of this condition should be added to the differentials with implications for treatment and management options. The importance of long-term follow-up and establishment of a multidisciplinary team are fundamental to the growing child's face particularly with the biological behaviour of the disease.

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Compliance with ethical standards

Funding There was no funding for this research publication.

Conflict of interest Jason Diab, Tomas O'Neill, Lynette Moore, Stephen Santoreneos, and Walter Flapper declare that they have no conflict of interest.

Ethical approval The human research and ethics committee has approved this research publication with no restrictions.

Informed consent Informed consent has been obtained for this research publication.

Patient consent The patient provided written consent for the use of her image.

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