Malignant perivascular epithelioid cell tumor of the orbit: Report of a case and review of literature

Md. Shahid Alam, Bipasha Mukherjee, S Krishnakumar[1], Jyotirmay Biswas[1]

Perivascular epithelioid cell tumor (PEComa) is a rare neoplasm considered to arise from myomelanocytic cell lineage. The uterus is reportedly the most common site to be involved. Orbital PEComa is extremely rare with only two cases reported till date. A 5-year-old male presented with a right medial orbital mass for the last 6 months. The patient was diagnosed with alveolar soft part sarcoma elsewhere. Magnetic resonance imaging features were suggestive of lymphangioma with bleeding. The excision biopsy revealed multiple tumor cells comprising epithelioid cells with clear cytoplasm, along with nuclear atypia and mitosis. Immunohistochemistry was positive for HMB-45, smooth muscle actin, vimentin, and CD-34. It was negative for cytokeratin, S-100, and synaptophysin, which clinched the diagnosis of malignant orbital PEComa. Neoadjuvant chemotherapy was administered. There was no recurrence at 24 months of follow-up. At present, there is no consensus on management protocol for malignant PEComa. Complete surgical excision with chemotherapy appears to offer the best prognosis.

Keywords: Malignant, myomelanocytic, orbit, perivascular epithelioid cell tumor

Perivascular epithelioid cell tumors (PEComa) are a family of rare neoplasms defined by the World Health Organization classification of tumors as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells (PECs)."[1] They presumably originate from myomelanocytic cell lineage, being generally positive for both melanin (HMB-45, Melan-A) and smooth muscle cell markers (Actin, Desmin).[2] The concept of "PEC" as a distinct entity was first proposed by Bonetti in 1992, but the term "PEComa" was later coined by Zamboni.[3] The uterus is the most commonly affected site; other anatomical sites involved are the liver, rectum, heart, breast, bone, urinary bladder, abdominal wall, and pancreas.[2,3] To the best of the authors' knowledge, two cases of benign orbital PEComa have been reported till date.[4,5] We herewith report the first documented case of malignant orbital PEComa and review the published literature.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_331_17

Departments of Orbit, Oculoplasty, Reconstructive and Aesthetic Services and [1]Ocular Pathology, Sankara Nethralaya, Medical Research Foundation, Chennai, Tamil Nadu, India

Correspondence to: Dr. Bipasha Mukherjee, Department of Orbit, Oculoplasty, Reconstructive and Aesthetic Services, Sankara Nethralaya, Medical Research Foundation, 18, College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: mshahidalam@gmail.com

Manuscript received: 29.04.17; Revision accepted: 17.06.17

Case Report

A 5-year-old male child presented to our clinic with complaints of gradually increasing prominence of the right eye for the past 6 months. There was no other significant systemic history. The patient had undergone incisional biopsy elsewhere and been diagnosed as alveolar soft part sarcoma. He had received three cycles of chemotherapy, details of which were not available. On examination, the general condition of the child was stable. The patient was not cooperative for Snellen's visual acuity but was following light and maintained central, steady fixation with both eyes. Relative afferent pupillary defect was present and retrobulbar resistance was raised in the right eye, and 15 mm of nonaxial proptosis was present. The globe was laterally displaced [Fig. 1]. There was no thrill on palpation or any bruit on auscultation. Extraocular motility was restricted in all directions of gaze. A firm, nontender mass was palpable along the right medial orbital wall. Right eye optic disc edema was present. Anterior and posterior segment examination of the left eye was unremarkable.

Computerized tomography scan obtained 4 months back showed a brilliantly enhancing well-defined solid mass lesion with central necrosis in the right medial orbit with smooth remodeling of the surrounding bone [Fig. 2a]. Magnetic resonance imaging (MRI) of the orbit showed a large lobulated mixed-intensity lesion in the medial orbit pushing the optic

Cite this article as: Alam MS, Mukherjee B, Krishnakumar S, Biswas J. Malignant perivascular epithelioid cell tumor of the orbit: Report of a case and review of literature. Indian J Ophthalmol 2017;65:889-91.

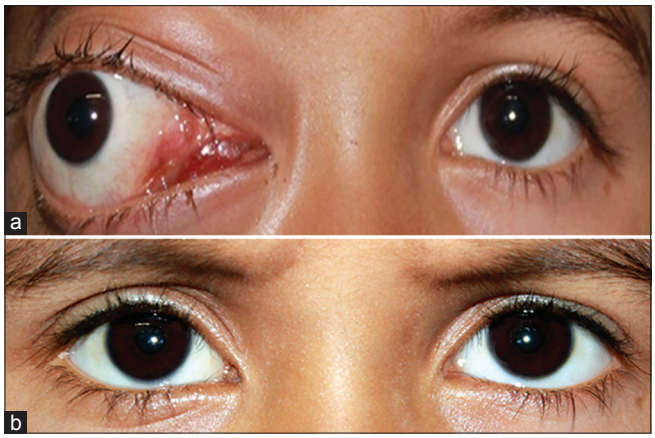

Figure 1: (a) Clinical photograph showing grossly dystopia right globe, pushed out by the medial orbital mass lesion. (b) Clinical picture was taken at follow-up showing resolution of proptosis

nerve laterally, with fluid-fluid level [Fig. 2b]. Based on neuroimaging, a diagnosis of orbital lymphangioma with intralesional hemorrhage was suspected.

Considering the earlier diagnosis of alveolar soft part sarcoma, the patient was taken for surgery under frozen section. Frozen section showed multiple atypical cells suggestive of malignancy. There was profuse bleeding from the lesion intraoperatively. Permanent section showed tumor cells arranged in lobules separated by fibrous septa with multiple tiny blood vessels in between. Multiple epithelioid cells with clear cytoplasm were seen. Nuclear atypia and mitotic activity were present [Fig. 3a]. Immunohistochemistry (IHC) was positive for HMB-45, vimentin, smooth muscle actin (SMA), and CD-34 [Fig. 3b-d]. It was negative for CK (AE1/AE3), S-100, and synaptophysin. Correlating the histopathological and immunohistochemical features the diagnosis of malignant orbital PEComa was made. Systemic evaluation revealed no metastasis. The patient was administered five cycles of adjuvant chemotherapy (vincristine, Adriamycin, and cyclophosphamide) under supervision of a pediatric oncologist.

MRI was repeated after five cycles which revealed residual lesion. Complete excision of the tumor was attempted. The patient received one more cycle of adjuvant chemotherapy. MRI repeated after 6 months' interval did not demonstrate recurrence, or any residual lesion [Fig. 2c]. Patient has currently completed 2 years of follow-up and is free from recurrence. During his last follow-up, best corrected visual acuity was noted to be 6/36; N24 in the right and 6/6; N6 in left eye. Hertel exophthalmometer reading was 16 mm in both eyes. Optic disc edema had resolved, but optic disc pallor was noted in the right eye.

Discussion

The controversy regarding the significance of PECs[6] persists as there is no normal counterpart to these ubiquitous cells.[2] Recently, PEComas have shown characteristic chromosomal aberrations, thereby suggesting PECs as distinct tumor cells.[7]

The PEComa family of tumors currently comprises angiomyolipoma, clear cell sugar tumor, lymphangioleiomyomatosis, and less differentiated PEComas of other anatomical sites described as "PEComa not otherwise specified (PEComa NOS)."[8] A recent review identified a total of 234 cases of PEComa NOS including one case of orbital PEComa,[2] which has already been reported by Iyengar *et al*.[5] The median age of presentation in this cohort was 43 years and 73% of cases occurred in females. Uterus was the most common site of origin followed by skin, liver/falciform ligament, retro peritoneum, and colon/rectum.[2] Clinical and radiological features in these locations are quite similar to soft tissue sarcoma or malignant melanoma.[2] Bleeker *et al*. in their review on the management of PEComa have stressed on the lack of consensus on treatment strategies for PEComa, but this may be partially due to the rarity of the disease and lack of randomized controlled trials. However, the review does mention complete surgical resection as an effective management option along with chemotherapy, which can be neoadjuvant, adjuvant or both. The regimes utilized are similar to those used in soft tissue sarcoma with an anthracycline backbone.[2] One of the two reported cases of orbital PEComas was a 9-year-old female, while the other was a 54-year-old male.[4,5]

There are no definite imaging characteristics to diagnose PEComa. Histopathologically, they are composed exclusively of epithelioid or spindle cells, or a mixture of both, with clear to granular eosinophilic cytoplasm.[9] Immunohistochemical features of PEComa are quite characteristic and form the basis of diagnosis. They are positive for melanocytic (HMB-45, Melan-A) and smooth muscle cell markers (Actin, Desmin) and negative for cytokeratin and S-100.[9] Alveolar soft part sarcoma, which was the initial diagnosis in the present case, is negative for melanocytic marker (HMB-45), unlike PEComa.

The differential diagnoses of orbital PEComa include malignant melanoma, pigmented paraganglioma and smooth muscle neoplasms. All these entities can be distinguished from PEComa on the basis of IHC. A malignant melanoma is positive for HMB-45 and S-100, and paraganglioma shows positivity to chromogranin and S-100. Although PEComas, like malignant melanomas, are positive for HMB-45 and their epithelioid morphology with positive melanocytic markers might mimic a pigmented paraganglioma, they are mostly negative for S-100.[9] Both PEComas and smooth muscle neoplasms can show positivity to SMA, but the latter do not stain positive for melanocytic markers.[9] Co-expression of melanocytic markers and SMA is thought to be the hallmark of PEComa and was seen in over 80% of cases in the review by Folpe *et al*.[9] MRI features of fluid-fluid level and histopathological appearance of tumor cells with clear cytoplasm arranged in a lobular pattern prompted us to also consider orbital lymphangioma with bleeding and alveolar soft part sarcoma, respectively.

Folpe *et al*. proposed a few high-risk features based on which PEComas can be classified as benign, of uncertain malignant potential, and malignant.[9] These features include size >5 cm, infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate >1/HPF, necrosis, and vascular invasion. The presence of fewer than two of the above features and a size less than 5 cm was classified as benign, size more than 5 cm with no other high-risk features as uncertain malignant potential and more than two high-risk features as malignant.[9] Our patient presented with tumor size >5 cm, showed mitotic activity and nuclear atypia, and hence was classified as malignant

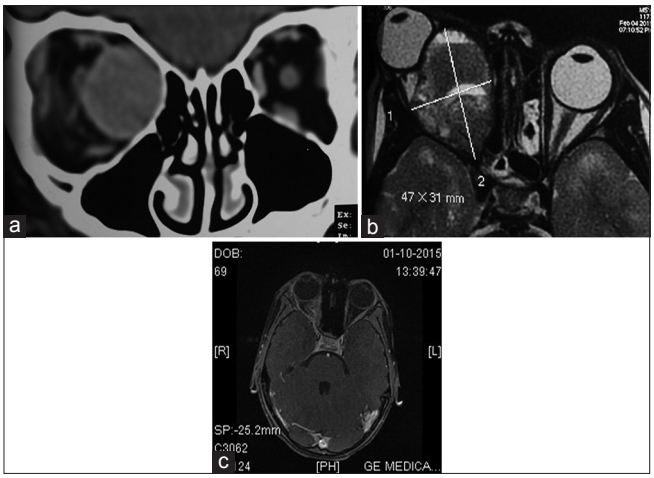

Figure 2: (a) Computerized tomography scan coronal cut showing a well-defined medial orbital isodense mass lesion pushing the optic nerve laterally. (b) Magnetic resonance imaging axial cut, T2 sequence, showing mixed intensity, medial orbital mass lesion with fluid-fluid level. (c) Axial magnetic resonance imaging showing postoperative soft tissue changes at the orbital apex

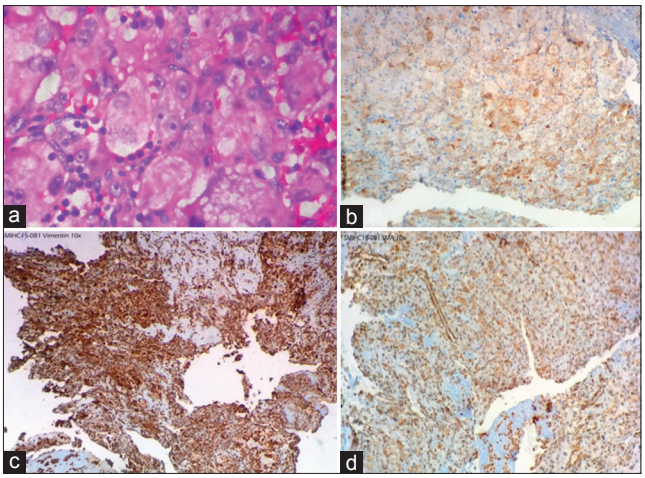

Figure 3: (a) Photomicrograph showing tumor cells arranged in lobules with epithelioid cells, surrounding blood vessels, nuclear atypia and mitosis (H and E; ×20). (b) Immunohistochemical image is showing HMB-45 positive staining. (c) Immunohistochemical image is showing vimentin positive staining. (d) Immunohistochemical image showing smooth muscle actin positive staining

orbital PEComa. Both the previously reported cases of orbital PEComas were benign.

Till date, there has been no consensus on management protocol of PEComa. Complete resection of the mass appears to offer the best prognosis. Both adjuvant and neoadjuvant chemo and radiotherapy have been tried with variable results.[9,10]

Conclusion

PEComa is an extremely rare orbital tumor. IHC is crucial for diagnosis. Complete surgical excision should be carried out whenever possible, and the patient's progress should be followed closely.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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