

Journal of **Cancer Research** and **Therapeutics**

October-December 2015 Volume 11 Issue 4



Impact Factor® for 2014
0.791



Official Journal of
Association of Radiation Oncologist of India

Full Text Online at: www.cancerjournal.net



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HMB-45 negative multifocal malignant perivascular epithelioid cell tumor of the soft tissue responding to sirolimus: First case report from India

ABSTRACT

Perivascular epithelioid cell tumor (PEComa) is a group of sarcomas that exhibit a myomelanocytic phenotype and possess a unique cell type in the perivascular epithelioid cell. Traditionally HMB-45 immunoreactivity is the first criteria required to consider a tumor to be PEComa. We report a case of multifocal PEComa with negative HMB-45 marker. The patient presented with three big ulceroproliferative lesions; two over right thigh and one over the scalp in the right frontal region. The patient was prescribed with oral sirolimus to which good response was seen. To the best of our knowledge, this is the first case of HMB-45 negative multifocal malignant PEComa from India.

KEY WORDS: Immunohistochemistry, multifocal, perivascular epithelioid cell tumor, sirolimus, soft tissue

INTRODUCTION

The perivascular epithelioid cell tumor (PEComa) is a group of sarcomas with an unknown cell of origin. The spectrum of PEComa includes lymphangioliomyomatosis, angiomyolipoma, and a group of uncommon tumors that arise in gastrointestinal tract, retroperitoneum, uterus, skin, soft tissues, or lung (clear cell tumor of the lung).^[1] Usually, PEComa expresses both myogenic (HMB-45, melan A and MITF) and melanocytic markers (actin and calponin). Immunohistochemistry (IHC) has been used as a savior to clinch the diagnosis in doubtful cases; however, the results of IHC also have been variable and confusing.^[2] A very few cases of HMB-45 negative PEComas have been reported in the literature so far.^[2,3] Furthermore, multifocal PEComa (PEComatosis) is exceedingly rare, only five cases being reported so far.^[4] We report a case of multifocal PEComa of soft tissues with negative HMB-45 marker.

CASE REPORT

A 42-year-old man presented with three big ulceroproliferative lesions; one over the scalp in the right frontal region [Figure 1a] and two lesions over the right thigh [Figure 1b and c]. The patient gave a history of a small ulcero-proliferative lesion appearing at the right thigh about 6 months back. The lesion was painless, but rapidly progressed in

size along with the development of a separate new lesion at the thigh, and another one at the scalp in the right frontal region. There were no comorbidities and no history of a similar disease in the family. On clinical examination, right inguinal lymph node was grossly enlarged and firm in consistency. The size of the thigh lesions at presentation was 4 cm × 4 cm and 6.5 cm × 4 cm, while the scalp lesion was about 3 cm × 3 cm. No preauricular, postauricular or cervical nodes were palpable. There was no organomegaly. Computed tomography scans showed multiple nodular lesions in bilateral lung [Figure 2] and bilateral lobulated heterogeneously enhancing adrenal lesions; thus, suggestive of metastatic disease. Biopsy was taken separately from scalp lesion and also one of the lesions over the thigh. Microscopy and IHC patterns of both the lesions revealed similar results. Microscopy demonstrated tumor composed of plump oval to epithelioid cells in sheets with very little intervening stroma. The tumor cells had oval to irregular nuclei, finely clumped chromatin, and a prominent nucleolus. The cytoplasm was moderate in amount and eosinophilic. Mitoses were frequent [Figure 3a]. IHC studies were done using a polymer detection system with all the controls showing expected reactivity. The positive stains included vimentin, smooth muscle actin, epithelial membrane antigen, Melan A, TFE and INI1 while the tumor stained negative for HMB-45, cytokeratin, p63, CD34, CA125, S100 and desmin [Figures 3 and 4]. There was a weak positive staining for B-cell lymphoma 2

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Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.146098

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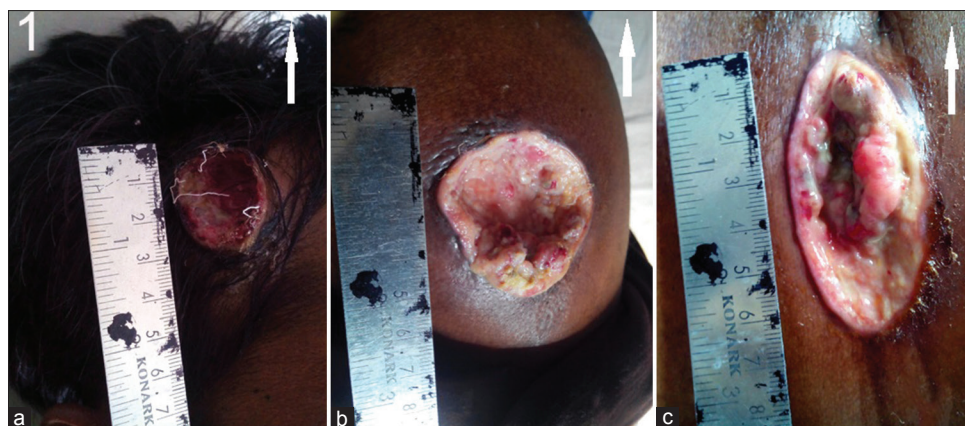


Figure 1: Clinical photograph of the patient showing large ulcerative lesions at the right frontal area of the scalp (a), and two lesions at the thigh (b and c). Arrows show the orientation of the lesions



Figure 2: Computed tomography scan showing multiple small to large (10–20 mm) lobulated nodules in bilateral lung parenchyma

and CD56 focally in tumor cells. Ki67 staining was positive in 45% of tumor cells [Figure 3b]. The overall picture supported the diagnosis of malignant multifocal HMB-45 negative PEComa. Since there is no standard therapy for malignant PEComa, and the molecular pathophysiology of the disease involves aberrant mammalian target of rapamycin (mTOR) signaling, this prompted us to use sirolimus, an oral mTOR inhibitor. Sirolimus was started at a dose of 1 mg twice a day and titrated to 2 mg twice a day over a fortnight. After 1 month, there was a subjective good response, but the reduction in size of the lesions was modest. To increase the effect of sirolimus without increasing the cost of the treatment, clarithromycin 500 mg OD was supplemented to inhibit CYP3A4; the major cytochrome enzyme metabolizing sirolimus. At 2 months follow-up, there has been a significant decrease in the size of external lesions with filling with the ulcers of the thigh [Figure 5].

DISCUSSION

The spectrum of PEComa includes related mesenchymal neoplasms that demonstrate myomelanocytic differentiation and share a characteristic cell type, the perivascular epithelioid cell.^[1] Lymphangioliomyomatosis (LAM) primarily affects

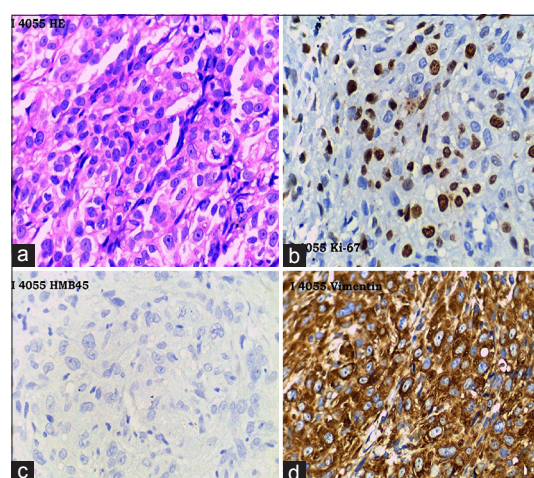


Figure 3: Photomicrograph showing tumor foci surrounded by fibrocollagenous stroma and necrotic tissue (H and E), tumor cells showing oval to irregular nuclei, finely clumped chromatin and a prominent nucleolus (a). Ki67 staining positive in about 45% of tumor cells (b), negative staining for HMB-45 (c), vimentin was stained positively throughout the tumor (d)

premenopausal women manifesting as multiple interstitial pulmonary nodules. Renal or hepatic angiomyolipoma (AML) is usually identified as an asymptomatic mass with indication of muscle, vascular and adipocytic differentiation. LAM and AML are benign and commonly encountered in patients with tuberous sclerosis complex (TSC). These entities have a very low probability of recurrence after complete surgical excision. However, a subset of rare PEComas exhibit variable malignant potential, with either local invasive recurrences or occurrence of distant metastases, usually to the lung. For metastatic PEComa, no effective therapy has been described previously.

There have been a few reports of HMB-45 negative PEComa in the recent literature. Pusiol *et al.* reported a case of cutaneous clear cell PEComa with negative HMB-45 marker in a 60-year-old male.^[2] They ascribed HMB-45 negativity to the extensive clear cell change. Yamagata *et al.* reported a case of HMB-45 negative uterine AML in a 25 years nulliparous woman.^[3] In our patient, though HMB-45 was negative, melan

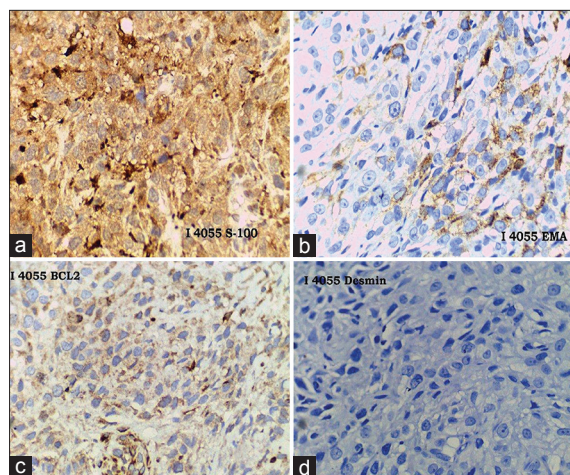


Figure 4: Photomicrograph showing weak positive staining of S-100 in few cells (a), epithelial membrane antigen and B-cell lymphoma 2 weakly positive focally in tumor cells (b and c) while there was negative staining for desmin (d)

A, another melanocytic marker, was positive.

Multifocal PEComas (PEComatosis) is extremely rare. Up to now, there have been <5 cases reported in the literature. Yang *et al.* reported a 46-year-old Chinese woman who had PEComatosis arising from the genital tract and pelvis.^[4] Froio *et al.* reported another case of PEComatosis along with endometriosis in a 39 years woman also affected by tuberous sclerosis.^[5] In our patient, there was multifocal involvement of soft tissues involving thigh and scalp simultaneously. Biopsies were taken from both the sites, and both revealed similar histopathology of PEComa confirming the diagnosis of PEComatosis.

In some reports, PEComas have been shown to share the activation of mTOR with LAM and AML.^[6] Sirolimus is a selective immunosuppressant that inhibits the activation of mTOR, a critical kinase for cell cycle progression. Thus, sirolimus is expected to have a therapeutic role in the treatment of this so far untreatable disease. Wagner *et al.* concluded that inhibition of mTORC1, pathologically activated by loss of the TSC1/TSC2 tumor suppressor complex, is a realistic mechanistic target for therapy in PEComas^[6]. Also, the activity of sirolimus in PEComa further emphasises the pathobiologic similarities linking PEComas to various tumors related to the TSC.^[7] Recently Bissler *et al.* reported 53% reduction in AML volume with sirolimus but it returned to 86% of baseline after the year of observation, which pointed to the need of continued inhibition to maintain tumor shrinkage.^[8] In our patient, we observed significant reduction in the size of external lesions of PEComatosis.

Thus, the authors would like to conclude with the note that inhibition of mTOR has resulted in a significant clinical activity in patients with PEComa and further investigation in the form of clinical trials is required to define the role of sirolimus with respect to the optimal dosing regimen. Additional studies are necessary to accept multifocal HMB-45 negative PEComa as a new variant of PEComa.



Figure 5: Clinical photograph showing regression of the lesion of the thigh with filling of the ulcer and healing with uneven pigmentation

ACKNOWLEDGMENTS

The authors would like to thank consultants in department of Oncology Dr. A Sharma, Dr. N. Sharma and Dr. S. L. Jakhar. Also, they express gratitude to PG Students of the department: Dr. Satyanarayan, Dr. Daleep Singh, Dr. Puneet Bagri, Dr. R. K. Nirban, Dr. Sitaram, Dr. Guman Singh, Dr. Murali, Dr. Tanya, Dr. Rajesh and Dr. R. Purohit.

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Cite this article as: Kapoor A, Beniwal S, Singhal MK, Kumar N, Kumar V, Kumar HS. HMB-45 negative multifocal malignant perivascular epithelioid cell tumor of the soft tissue responding to sirolimus: First case report from India. *J Can Res Ther* 2015;11:1036.

Source of Support: Nil, **Conflict of Interest:** None declared.