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Clinicopathological spectrum of a series of Merkel cell carcinomas diagnosed at a tertiary cancer referral center in India, with current concepts

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare, clinically aggressive primary cutaneous neuroendocrine carcinoma. The present series describes clinicopathological features of 16 MCCs diagnosed at a tertiary cancer referral center. Sixteen MCCs occurred in 10 men and 6 women (M/F = 1.6:1), between the ages 37 and 74 years (mean, 58.3; median, 58.6), commonly in lower extremities (7) (43.7%) and head and neck sites (5) (31.2%), followed by upper extremities (3) (18.7%) and abdominal wall (1). Tumor size varied from 0.5 to 9.9 cm. Histopathologically, most tumors were composed of round to oval cells, mostly arranged diffusely with hyperchromatic nuclei, including "sudden" pleomorphism in some tumors. Variable features included coexisting Bowen disease (2/16), along with squamous, pseudoglandular, and rhabdomyoblastic dedifferentiation, all in a single tumor. Immunohistochemically, tumor cells were positive for at least a single epithelial marker in all 16 cases (100%) cases, including CK20, mostly paranuclear "dot-like" (12/13, 92.3%); CK (8/9, 88.8%), AE1/AE3 (3/3, 100%), and CK7 (1/6, 16.6%), along with neuroendocrine markers (16/16, 100%), including synaptophysin (11/13, 84.6%), chromogranin (12/15, 80%), and CD56 (4/4, 100%). Among other immunohistochemical markers, positive CKIT/CD117 was positive in 3 of 3 tumors. Surgical resection was performed in 11 (100%) of 11 cases, with adjuvant chemotherapy offered in a single case. Two cases with large-sized tumors, along with another case developed lymph node metastasis, including 1 who later developed pulmonary metastasis. Two patients were free of disease and 2 were alive with disease. Merkel cell carcinomas exhibit a diverse histopathological spectrum, including coexisting Bowen disease and, rarely, rhabdomyoblastic dedifferentiation, in some cases. Optimal immunohistochemical markers include CK20, synaptophysin, chromogranin, and CD56 for a timely diagnosis. Surgical resection is the treatment mainstay. Large-sized tumors and MCCs showing dedifferentiation portend a relatively more aggressive clinical course. Other recent developments in this tumor are discussed herewith.

1. Introduction

Merkel cell carcinoma (MCC) is a rare, aggressive primary neuroendocrine carcinoma of the skin, mostly known to occur on sun-exposed areas, including the face and other head and neck sites, with propensity for metastasis. It is also known as cutaneous APUDoma, primary cutaneous small cell carcinoma, primary cutaneous trabecular carcinoma/Toker tumor, and anaplastic carcinoma of skin [1].

Merkel cell carcinoma has a diverse clinicopathological spectrum, including its uncommon association with Bowen disease and squamous cell carcinoma [2–4]. Histopathologically, it is mostly characterized by malignant round cells, but is rarely known to display heterologous dedifferentiation [5].

Merkel cell carcinoma was previously thought to be derived from Merkel cell, a specialized, nonkeratinizing epithelial cell found in the basal cell layer of the epidermis and dermis and around hair follicles. Lately, it has been found to be caused by Merkel cell polyomavirus in most cases [6].

This study constitutes as the first largest series on clinicopathological spectrum of MCCs, diagnosed at a single institution in India, including current concepts.

2. Materials and methods

After computerized search of medical records from January 1, 2000, to December 31, 2014, 23 cases were retrieved with MCC as a diagnosis or as one of the differential diagnoses. Finally, 16 cases were included. Conventional hematoxylin and eosin–stained slides along with immunohistochemical (IHC) stained microsections were reviewed by a single author (BR).

The specimens were in the form of tumor resections (8 cases), biopsies (4 cases), and paraffin blocks, with or without stained slides (4 cases), the latter from referring laboratories or other hospitals.

Tumor staging was done as per 3-tier system, including stage I (localized lesion), stage II (nodal metastasis), and stage III (distant metastasis) [7,8].

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Table 1
Various antibody markers used in the present study

IHC marker	Clonality, clone	Dilution	Antigen retrieval	Manufacturer
CK20	Monoclonal, Ks20.8	1:50	Heat (tris-EDTA) Microwave	Dako, Produkionsveg, Glostrup, Denmark
CK	Monoclonal, MNF116	1:200	Pronase (enzymatic)	Dako
CK7	Monoclonal, OV-TL-12/30	1:100	Heat (tris-EDTA) microwave	Dako
EMA	Monoclonal, E29	1:1200	Pepsin(Enzymatic)	Dako
Synaptophysin	Polyclonal	1:100	Heat (tris-EDTA) Pascal	Thermo scientific PA, USA
Chromogranin	Polyclonal	1:250	Heat (tris-EDTA) Pascal	Dako
CD56 (NCAM)	Monoclonal, Bc56CO4	1:50	Heat (tris-EDTA) Pascal	Dako
c-KIT/CD117	Polyclonal	1:300	Heat (sodium citrate) microwave	Dako
Ki-67	Monoclonal, MIB1	1:200	Heat (tris-EDTA) Pascal	Dako
MIC2	Monoclonal, 12E7	1:50	Heat (tris-EDTA) Pascal	Dako
NSE	Monoclonal, BsNcHI4	1:50	Heat (tris-EDTA) Pascal	Dako

Immunohistochemical (IHC) staining was performed using the polymer technique (Dako REAL Envision detection system, Glostrup, Denmark) including peroxidase/3-3-diaminobenzidine tetrahydrochloride (DAB). Details of various antibody markers have been enlisted (Table 1).

3. Results

Sixteen primary MCCs occurred in 10 men and 6 women (M/F = 1.6:1), between the ages 37 and 74 years (mean, 58.3; median, 58.6). Clinically, the most common complaint, known in 12 cases, was swelling/mass with/without skin ulceration; mostly over few days and months (6 cases), to as long as 3 to 4 years (2 cases). Site-wise, tumor commonly occurred in the lower extremities (7) (43.7%) and head and neck sites (5) (31.2%), followed by the upper extremities (3) (18.7%) and abdominal wall (1). Tumor size, known in 5 cases, varied from 0.5 to 9.9 cm. Stage-wise, most cases (10) (62.5%) presented with stage I, followed by 6 (37.5%) cases, who presented with stage II disease. A single patient developed metastasis after stage II disease.

Histopathologically, almost all tumors were composed of malignant round to oval cells, mostly arranged in a diffuse pattern, followed by trabecular, cord-like, nesting, and occasionally pseudoglandular patterns. Individual tumor cells were composed of hyperchromatic nuclei with "salt and pepper" chromatin, inconspicuous nucleoli, and scanty cytoplasm, along with prominent apoptosis, mitoses, and variable amount of necrosis. "Sudden" anisokaryosis/nuclear pleomorphism was additionally noted in some tumors, as well as "streak" artefact in a few tumors. Overlying skin was ulcerated in 4 tumors. Lymphovascular emboli were noted in 2 tumors.

Coexisting Bowen disease was noted in 2 out of 16 (12.5%) tumors. A single tumor exhibited squamous and rhabdomyoblastic dedifferentiation.

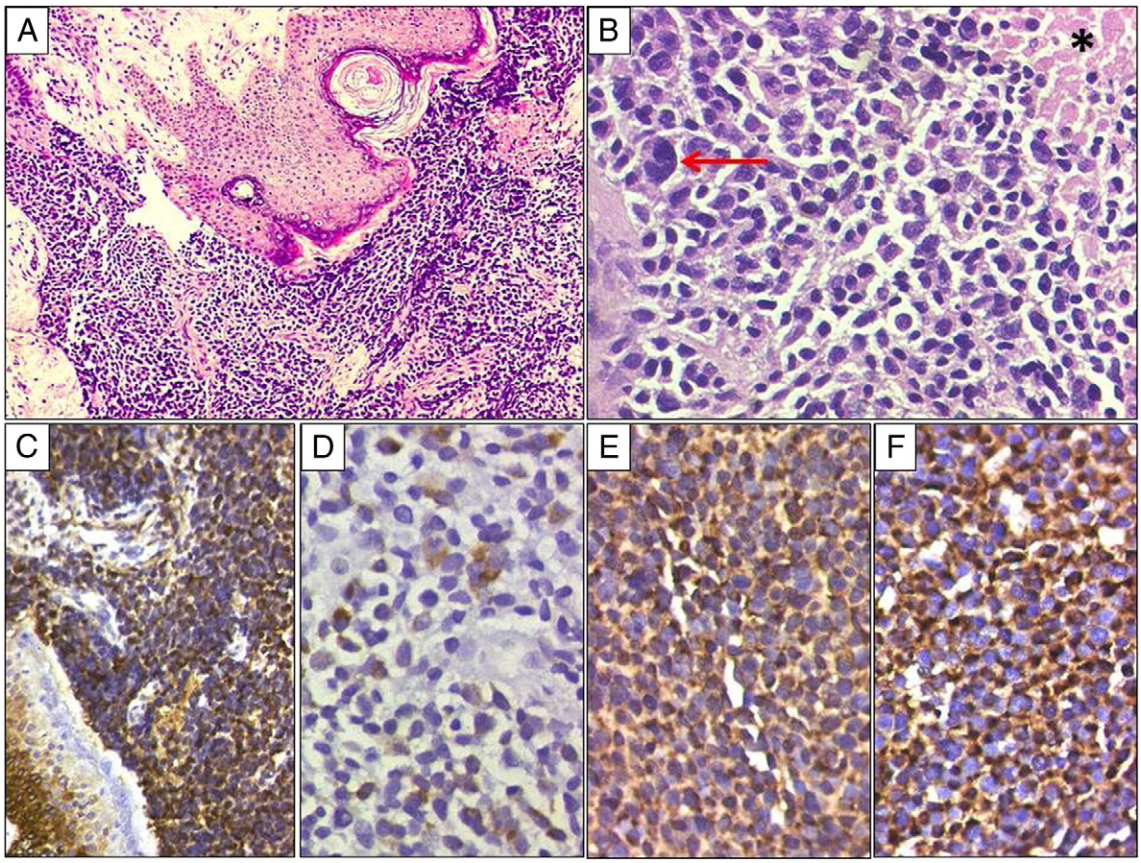

Fig. 1. Merkel cell carcinoma. Histopathological features. (A) Epidermis with a tumor below composed of malignant round cells, medium power. (B) Malignant round to oval cells with hyperchromatic nuclei, scanty to moderate cytoplasm, exhibiting "sudden" nucleomegaly (arrow). Focal necrosis also seen (asterisks), high power. (C) Immunohistochemistry (C-F). (C) Tumor cells displaying cytokeratin (CK) positivity, DAB, medium power. (D) Distinct paranuclear dot-like CK20 positivity, DAB, high power. (E) Tumor cells displaying CK7 positivity, DAB, high power. (F) Tumor cells displaying diffuse synaptophysin positivity, DAB, high power.