Human Pathology (2014) 45, 1978–1981

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Case study

Transformation of Merkel cell carcinoma to ganglioneuroblastoma in intracranial metastasis☆

Boleslaw Lach MD, PhD, FRCPC[a,*], Sangeeta S. Joshi MD, FRCPC[b], Naresh Murty MD, FRCSC[c], Nasimul Huq MD, FRCSC[b,d]

[a]*Department of Pathology & Molecular Medicine, Hamilton General Hospital and McMaster University, Hamilton, Ontario, Canada, L8L 2X2*
[b]*Greater Niagara General Hospital, Niagara Health System, Niagara Falls L2E 6X2, McMaster University, Hamilton, Ontario, Canada*
[c]*Department of Neurosurgery, Hamilton General Hospital and McMaster University, Hamilton, Ontario, Canada, L8L SG8*
[d]*Clinical Surgery, McMaster University, Hamilton, Ontario, Canada, L2G S24*

Received 26 August 2013; revised 15 January 2014; accepted 17 March 2014

Keywords:
Merkel cell carcinoma;
Ganglioneuroblastoma;
Neuroendocrine tumors;
Brain metastases;
Dural metastases

Summary Merkel cell carcinoma is an aggressive neuroendocrine tumor occasionally demonstrating aberrant differentiation to other epithelial and nonepithelial cell lines. We describe a case of Merkel cell carcinoma displaying unique patterns of differentiation in the primary focus and brain metastasis. The skin primary was almost uniformly small cell carcinoma positive for epithelial and neuroendocrine markers, with a few glial fibrillary acidic protein– and cytokeratin 20–positive cells. The neoplasm contained giant cells immunoreactive for neurofilament and negative for epithelial markers. The neck lymph node metastasis was a typical neuroendocrine Merkel cell carcinoma positive for cytokeratin 20. A solitary dural intracranial metastasis displayed features of aggressive ganglioneuroblastoma, expressing many neuronal antigens with no evidence of glial or epithelial differentiation. After total gross resection, the tumor recurred within 3 months, and the patient developed skeletal metastases and died 6 months after craniotomy.

1. Introduction

Merkel cell carcinoma (MCC) is an uncommon neuroendocrine skin tumor developing usually in sun-exposed areas of the elderly or immunosuppressed, predominantly white individuals [1]. The tumor is aggressive, with a high local recurrence rate, early metastases to regional lymph nodes and distant locations, and a disease-related mortality rate of 25% to 30% in 5 years [2]. The tumors may show an additional intrinsic component of basal and squamous cell carcinoma (SCC) [1,3–6]. Much less common is nonepithelial divergent differentiation in the primary or metastatic MCC [3–6]. Although neuroblastic patterns occasionally are observed in MCC [4,6], ganglioneuroblastic differentiation in the primary tumor has been reported only once [6]. We describe an elderly patient with MCC of the scalp who developed metastases to a cervical lymph node and the dura mater overlying the left cerebral hemisphere. The skin tumor and the intracranial focus displayed variably expressed histologic and immunohistochemical patterns of neuroendocrine and ganglionic differentiation.

☆ The authors have no conflicts of interest to disclose.

* Corresponding author. Department of Pathology & Molecular Medicine, HHS, Hamilton General Site, 237 Barton St East, Hamilton, Ontario, Canada L8L 2X2.
E-mail address: lach@hhsc.ca (B. Lach).

http://dx.doi.org/10.1016/j.humpath.2014.03.021
0046-8177/

2. Clinical history and methods

A 77-year-old man was admitted to the hospital because of progressive memory deterioration, difficulties in expressing himself, and frequent loss of balance. He had a history of 5 resections of separate SCCs of the head over a period of approximately 14 years. Two years before the present admission, he underwent removal of an MCC of the cranial vertex measuring approximately 3.2 × 2.0 × 2.0 cm. The resection edges of the MCC, as well as the margins of all SCCs, were free of tumor. The slides of the previously resected SCCs were reviewed, and the possibility of an overlooked MCC component was excluded.

Emergency computed tomographic and magnetic resonance imaging (MRI) scans revealed a large extra-axial tumor in the left frontotemporal area, suggestive of a malignant meningioma (Fig. 1). At the time of these radiologic studies, an enlarged cervical node (approximately 2.0 × 3.0 × 3.0 cm) was discovered on the right side and was biopsied. At craniotomy, the tumor was well demarcated, extra-axial, dura based, and invading the underlying brain. There was no sign of bone involvement on radiologic studies or during the operation. Four days after gross total resection, the patient was discharged home.

An MRI scan performed 3 months after surgery revealed a recurrent tumor. A bone scan demonstrated multiple metastases to the ribs, pelvis, and lower thoracic vertebrae. He died 6 months after craniotomy.

Multiple sections of the skin tumor, lymph node biopsy, and brain metastasis were processed to paraffin embedding and stained with hematoxylin and eosin. Selected sections were immunostained routinely for some or all of the tissue antigens listed in the Table using commercially available primary antibodies and following the recommended dilutions and tissue preparations, as previously reported [7].

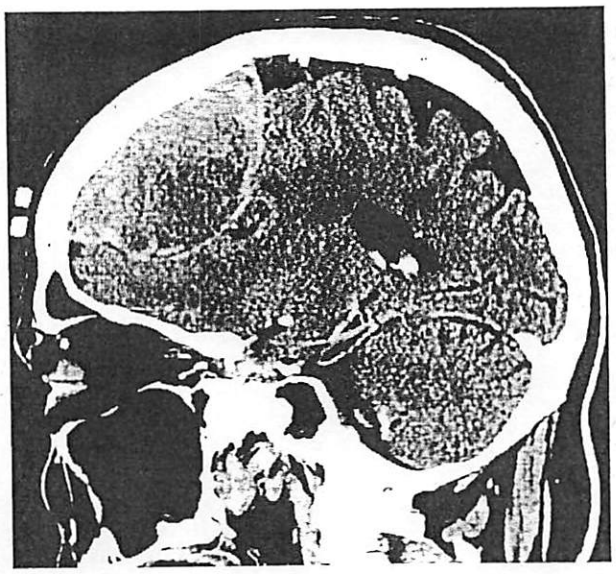

Fig. 1 Enhanced MRI showing large parasagittal tumor seemingly arising from dura mater and mimicking meningioma. Skull bones appear intact.

3. Results

The primary tumor of the skin displayed tightly packed, uniformly small cells with scant cytoplasm, hyperchromatic nuclei with nucleoli, and frequent mitoses. Neuroblastic Homer-Wright rosettes were easily identifiable (Fig. 2A). All cells were immunoreactive for cytokeratin (CK) with AE1/3 antibodies, as well as for synuclein (SYN), β-tubulin, tau, and neural cell adhesion molecule (NCAM; Table). The CD99, neuron-specific enolase (NSE), and Bcl-2 reactions were present focally, whereas less than 1% of the cells displayed dot-like or perinuclear presence of CK20, neurofilament (NF), cytoplasmic chromogranin (CHRG), and calretinin (CAL). The tumor was sprinkled with multinucleated giant cells immunoreactive for NF and vimentin (VIM; Fig. 2B). A small group of fusiform glial fibrillary acidic protein (GFAP)–positive cells indicated focal glial differentiation. The nodal metastasis displayed exclusively small cells immunoreactive for CKAE1/3, CK20, CHRG, and SYN. Because of the paucity of specimen tissue, only a small number of immunohistochemical stains could be performed (Table).

Microscopic examination of the brain metastasis revealed a pleomorphic tumor with extensive necrosis. The neoplastic cells ranged from small ones reminiscent of those in the skin primary to large ones with highly atypical hyperchromatic nuclei (Fig. 2C). Homer-Wright rosettes, as well as atypical mitoses and apoptotic nuclei, were numerous. Almost all cells displayed positive immunostaining for SYN, NCAM, tau protein, β-tubulin, and Ki-67 (Fig. 2D-F). The tumor was entirely negative for NF, CHRG, NSE, GFAP, and all the keratins, including CK20 (Table). Electron microscopic examination of the dural metastasis revealed small cells with scant cytoplasm and short dendritic-like processes that contained microtubules and dense-core 100- to 150-nm neurosecretory granules and formed poorly developed synaptic-like junctions.

4. Discussion

The histologic appearance and immunophenotype of the skin tumor were consistent with the diagnosis of MCC. However, the presence of Homer-Wright rosettes, a distinct population of NF^+ giant cells, and focal GFAP immunoreactivity indicated a component with neuroblastic/ganglionic and glial differentiation. The most frequent divergent differentiation in MCCs is [9] to SCC [3–5]. Only exceptional cases show nonepithelial tissue such as neuroblastic, sarcomatous, or melanotic [3–6].

Table Antibodies used for immunohistochemistry staining

Antibody	Distributor	Abbreviation, dilution	Immunoreactivity		
			Brain	Skin	Lymph node
Neurofilament Mab	Dako	NF, 1:400	−	+, GC+	ND
NCAM	Dako	CD56, undiluted	+++	+++, GC−	ND
β-Tubulin	Sigma	βTUB, 1:5000	++ (+)	+++, GC−	ND
Synaptophysin Mab	Dako	SYN, 1:25	+++	+++, GC−	++
Chromogranin A Mab	Dako	CHRG, 1:100	−	±F, GC−	+
Calretinin poly Ab	Invitrogen	CAL, 1:200	+	±F, GC−	ND
Neuron-specific enolase	Dako	NSE, undiluted	−	+, GC−	ND
Tau protein poly Ab	Dako	Tau	+++	++, GC−	ND
S100 protein	Dako	S100, 1: 4000	−	−	−
Epithelial membrane antigen Mab	Dako	EMA, 1:100	−	−	ND
CK20	Dako	CK 20, 1:100	−	±	+++
Keratins [a]	Dako	CAM5.2, CK5/6, AE1/AE3, CK7, undiluted	All −	+++, GC− AE1/AE3	+++ AE1/AE3
Glial fibrillary acidic protein poly Ab	Dako	GFAP, 1:3000	−	±, GC−	ND
Antihuman melanosome	Dako	HMB 45, undiluted	−	−	−
Bcl-2 oncoprotein	Dako	BCL2, undiluted	−	++F, GC−	ND
CD99	Dako	CD99, undiluted	−	++	ND
Desmin	Dako	DSM, undiluted	−	−	ND
Vimentin	Dako	VIM, 1:200	−	−, GC+++	ND
p53	Dako	p53, 1:200	−	+F, GC−	ND
Ki-67 MAb	Dako	Ki-67, 1:1000	+++	+++	ND
β-Catenin	Dako	BCAT, undiluted	+	++, GC−	ND
TTF-1	Dako	TTF-1, undiluted	−	−	−
Leucocyte common antigen	Dako	LCA, undiluted	ND	−	−

NOTE. Grading of immunoreactions: −, entirely negative; ±, very weak or few scattered positive cells; +, weak staining in many cells; ++, intermediate reactivity; +++, strong staining in most of or all cells.

Abbreviations: Ab, antibody; F, focal; GC, giant cells; Mab, monoclonal antibody; ND, not done; poly, polyclonal.

[a] Primary tumor and lymph node metastasis were immunostained with AE1/3 and CK 20 antibodies. The brain metastasis was also immunostained and showed no reactions for SYN, serotonin, CAL, somatostatin, adrenocorticotropic hormone, ubiquitin, CD34, c-Kit, and SV40 T antigen.

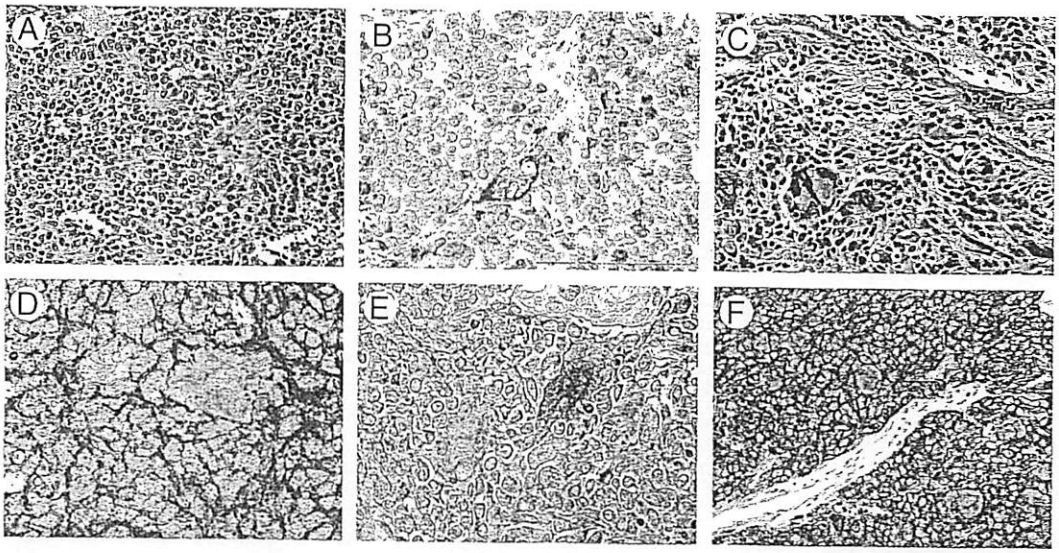

Fig. 2 Primary MCC of skin. A, Uniformly small cell tumor with several Homer-Wright rosettes. B, Ganglionic cell immunoreactive for neurofilament. Only occasional small cells show dot or perinuclear NF reaction. Brain metastasis (C–F). C, Pleomorphic tumor with poorly developed focal areas of fibrillary neuropil. D, Strong reaction for SYN in small cell population and borderline immunoreactivity in large ganglionic cell. E, Immunoreactivity for β-tubulin. F, Tau expression in all tumor cells.

However, this phenomenon may be more common than reported because in the selected series of MCC cases with SCC differentiation, a sarcomatous component was demonstrated in one-third of tumors [5]. In one case, glial cell differentiation was suspected morphologically but not proved by immunohistochemistry [5].

A unique example of MCC with an SCC and component of CK20-positive ganglionic cells has been reported by Vanchinathan and associates [6]. The ganglionic cells in our case were immunoreactive for NF and VIM and entirely negative for CK20 and for all the remaining cell markers. Ganglionic differentiation in primary malignant dermal tumors is exceedingly rare, and, except for the above-mentioned single case of MCC, it has been reported only in melanomas [8].

The lymph node metastasis displayed all the morphologic and immunohistochemical features of a typical MCC. The absence of ganglionic cells in the nodal metastasis could be a sampling error, given the small biopsy specimen. The dural metastasis had lost reactivity for all the keratins, as well as for NF, GFAP, CHGR, and NSE, but retained limited ganglioneuroblastic differentiation, having a SYN^+, β-$tubulin^+$, and tau^+ immunophenotype. Furthermore, the ultrastructural features were clearly neuroblastic, without a trace of epithelial or glial differentiation [9].

Reactivity for tau has not been examined in MCC. Interestingly, unlike the diffuse immunoreactivity in this case, the previously reported tau^+ brain gangliogliomas contained identifiable neurofibrillary tangles [10]. However, the presence of tau in a variety of astrocytic tumors [11] qualifies tau as a relatively nonspecific neuroectodermal tissue marker, rather than a selective ganglionic cell marker.

Involvement of the central nervous system in MCC has not been addressed in the most recent large clinical studies of MCC [2]. In a comprehensive review of the literature specifically focused on this issue, Bailey and colleagues [12] were able to find 33 cases of MCC with intracranial metastases. One of their patients and only 3 of the previously reported individuals had isolated dural tumors. As in our patient, intracranial extension of MCC in some of these cases took place through radiologically intact skull bones and was attributed to invasion of the emissary and diploic veins.

In summary, this is an unusual case of MCC of the scalp with divergent ganglionic and focal glial differentiation in the primary skin lesion. Metastases of this tumor displayed 2 distinct immunophenotypes: a typical MMC in the cervical lymph node and a highly anaplastic ganglioneuroblastoma in the dura overlying the frontal lobe. This unusual pattern of divergent differentiation of neuroendocrine neoplasms is not limited to MCC. In a personal observation by one of the authors (B. L., unpublished), ganglioneuroblastic and glial differentiation may have occurred in brain metastases of small cell carcinomas of the lung. Distinguishing between these 2 tumors is often possible on the basis of frequent TTF-1 immunoreactivity in lung carcinomas and uncommon or absent expression of this antigen in MCCs [5,13].

Acknowledgments

The authors are grateful to Ms Anna Lach, MSc, for editing and Ms Capreta Bruna for secretarial help in the preparation of the manuscript.

References

[1] Kuwamoto S. Recent advances in the biology of Merkel cell carcinoma. HUM PATHOL 2011;42:1063-77.
[2] Fields RC, Busam KJ, Chou JF, et al. Five hundred patients with Merkel cell carcinoma evaluated at a single institution. Ann Surg 2011;254:465-75.
[3] Walsh NMG. Primary neuroendocrine (Merkel cell) carcinoma of the skin: morphologic diversity and implications thereof. HUM PATHOL 2001;32:680-9.
[4] Skelton HG, Smith KJ, Hitchcock CL, McCarthy WF, Lupton GP, Graham JH. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. J Am Acad Dermatol 1997;37:734-9.
[5] Martin B, Poblet E, Rios JJ, et al. Merkel cell carcinoma with divergent differentiation: histopathological and immunohistochemical study of 15 cases with PCR analysis for Merkel cell polyomavirus. Histopathology 2013;62:711-22.
[6] Vanchinathan V, Marinelli EC, Kartha RV, Uzieblo A, Ranchod M, Sundram UN. A malignant cutaneous neuroendocrine tumor with features of Merkel cell carcinoma and differentiating neuroblastoma. Am J Dermatopathol 2009;31:193-6.
[7] Lach B, Arredondo J. Cobblestone lissencephaly in Schinzel-Giedion syndrome. J Child Neurol 2013;28:259-63.
[8] Banerjee SS, Menasce LP, Eyden BP, Brain AN. Malignant melanoma showing ganglioneuroblastic differentiation: report of a unique case. Am J Surg Pathol 1999;23:582-8.
[9] Hirose T, Scheithauer BW, Lopes MBS, et al. Ganglioglioma: an ultrastructural and immunohistochemical study. Cancer 1997;79:989-1003.
[10] Brat DJ, Gearing M, Goldthwaite PT, Wainer BH, Burger PC. Tau-associated neuropathology in ganglion cell tumours increases with patient age but appears unrelated to ApoE genotype. Neuropathol Appl Neurobiol 2001;27:197-205.
[11] Miyazono M, Iwaki T, Kitamoto T, Shin R-W, Fukui M, Tateishi J. Widespread distribution of tau in the astrocytic elements of glial tumours. Acta Neuropathol 1993;86:236-41.
[12] Bailey TL, Fung MA, Gandour-Edwards R, Ellis WG, Schrot RJ. Clinical emergence of neurometastatic Merkel cell carcinoma: a surgical case series and literature review. J Neurooncol 2011;102:147-55.
[13] Llombart B, Monteagudo C, Lopez-Guerrero JA, et al. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma: in search of prognostic markers. Histopathology 2005;46:622-34.