Journal of BUON **8:** 393-395, 2003

CLINICAL CASE

Merkel cell carcinoma associated with lobular carcinoma of the breast presenting synchronously within the same lymph node

A.P. Singh[1], K. Patel[1], Y. Sergides[1], K. Love[2], A.D. Purushotham[1]

[1]*Cambridge Breast Unit and* [2]*Department of Pathology, Addenbrookes Hospital, Cambridge, United Kingdom*

Key words: lobular breast carcinoma, Merkel cell carcinoma, synchronous lymph node metastases

Introduction

The clinical management of Merkel cell carcinoma is controversial. We present the first case of Merkel cell carcinoma co-existing with lobular breast carcinoma and the extremely rare clinical presentation of synchronous metastases from two separate tumours within the same lymph node.

Case presentation

An 81-year-old lady presented with a 4.5×3.0 cm pedunculated mass on her right forearm and a history of weight loss. A large palpable lymph node was present in the right axilla. Relevant past medical history included a locally-confined squamous cell carcinoma of the left mandible that had been completely excised 4 years earlier. Diagnostic excision biopsy of the forearm mass revealed an undifferentiated neuroendocrine carcinoma, possibly a Merkel cell carcinoma. Right axillary dissection was subsequently undertaken and 5 of the 11 nodes examined demonstrated cells of Merkel cell origin.

At follow-up 2 weeks later, a 7×5 cm left breast lump was discovered with associated skin tethering and nipple retraction. A large, firm lymph node was palpable in the left axilla. Core biopsy confirmed an oestrogen receptor positive, grade II, invasive lobular carcinoma. A further review of the right axillary nodal tissue demonstrated the presence of lobular carcinoma of breast (Figure 1) in addition to the earlier reported Merkel cell carcinoma (Figure 2) within the same lymph node.

As the history of metastatic carcinoma precluded surgical intervention, the patient was treated by primary endocrine therapy with oral aromatase inhibitors (tamoxifen was contraindicated due to the high risk of deep vein thrombosis secondary to the patient's restricted mobility). Shortly afterwards the

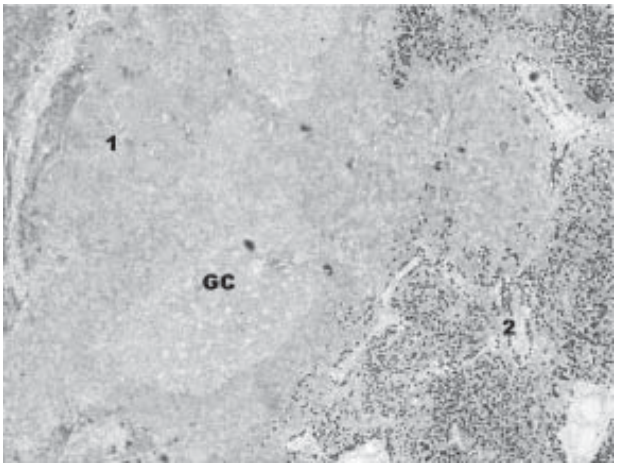

Figure 1. Axillary lymph node showing concurrent metastatic infiltrates of Merkel cell carcinoma (1) and lobular carcinoma of breast (2). Metastatic lobular carcinoma cells show strong positivity for the oestrogen receptor whilst the Merkel cell carcinoma cells remain negative. GC: Germinal centre (6F11 ×40).

Received 13-08-2003; Accepted 08-09-2003

Author and address for correspondence:

A.D. Purushotham, MD
Cambridge Breast Unit
Box 97
Addenbrookes Hospital
Hills Road
Cambridge CB2 2QQ
United Kingdom
Tel: +44 01223 586627
Fax:+44 01223 257219
E-mail: amy.byrtus@addenbrookes.nhs.uk

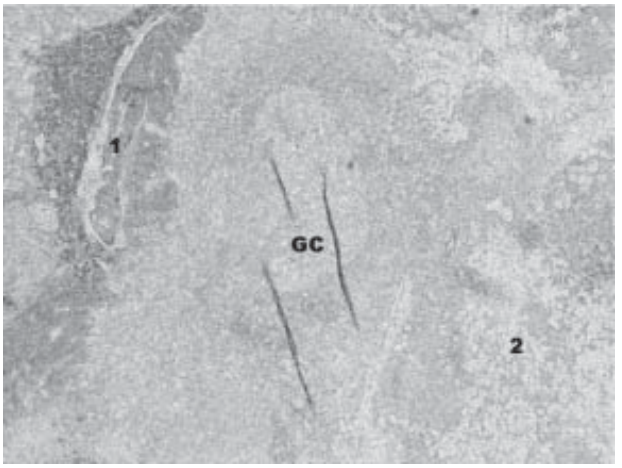

Figure 2. Same field as Figure 1 stained with immunohistochemistry for the neuroendocrine marker PGP9.5. Metastatic Merkel cell carcinoma cells show strong positivity (1) whilst the lobular breast carcinoma cells are negative (2). GC: Germinal centre (PGP9.5 ×40).

patient was admitted to hospital following collapse. An upper gastrointestinal bleed was suspected and endoscopy demonstrated a gastric ulcer which was biopsied. Histology confirmed metastatic lobular carcinoma of the breast. The patient was managed conservatively and discharged on high-dose proton pump inhibitors.

Discussion

Though the link of Merkel cell carcinoma to cutaneous and non-cutaneous solid tumours is described in the literature [1], this is the first reported case of metastatic Merkel cell carcinoma co-existing within the same lymph node as metastatic lobular carcinoma of the breast.

The Merkel cell is a cutaneous cell first described by Freidrich Sigmund Merkel in geese and duck tissue in 1875 [2] and probably involved with mechanoreception [3] amongst other functions. Primary neuroendocrine carcinoma of the skin (NECS) is a rare, high-grade neoplasm that was described by Toker in 1972 [4]. Recent immunohistochemical profiling [5] suggests that it is derived from the Merkel cell - hence its alternative designation as the Merkel cell carcinoma. An alternative hypothesis is that NECS is derived from immature totipotent epidermal stem cells or an epidermal equivalent of the Merkel cell [6].

NECS is almost exclusively a disease of elderly Caucasians with equal sex incidence [6]. The propensity of NECS to occur at sites of maximal cumulative ultraviolet light (UVL) exposure and its concurrence with UVL-related malignancies, such as squamous cell carcinoma and malignant melanoma [7], have implicated such exposure as a major aetiological factor [8]. Genetic abnormalities include a loss of heterozygosity at the chromosomal 1p36 region seen in up to one third of cases whilst other factors implicated include immunosuppression and congenital ectodermal dysplasia.

NECS presents primarily as a solitary, red or purple nodule in sun-exposed areas of the skin, most commonly in the periorbital region. It is typically non-tender, firm and rapidly growing with smooth, shiny overlying skin. Less commonly, it may also present as firm, enlarged lymph nodes or as metastatic masses in skin, lung, liver, bone or other solid organs. Diagnosis requires immunohistochemical testing with the key markers being CK20 and low molecular weight cytokeratins expressed in a dot-like paranuclear or crescentic pattern [9].

The staging of NECS, achieved using CT or MR imaging, is a simple numerical classification from 0 *(in situ)*, through stages I and II (locally confined), to stage III (local invasion or regional metastases) and stage IV (distant metastases).

Due to its propensity for local recurrence and early regional and systemic metastases, treatment has to be aggressive. However, the rarity of the malignancy and lack of long-term follow-up has precluded the identification of prognostic markers and an optimal management algorithm [10-12]. Current consensus is that locally-confined tumours require wide local excision with margins of 1-3 cm [11] and adjuvant radiotherapy in light of the high local recurrence rate (26–44%) [12]. Because early nodal spread occurs in up to 60% of the patients [11], some form of nodal dissection is recommended. More recent techniques involve lymphatic mapping and sentinel lymph node biopsy using a combined approach of radioisotope and blue dye [12]. Initial results of studies using this technique have demonstrated its suitability in NECS [10] and show encouraging results [13,14], paralleling those of malignant melanoma in which only 2% of sentinel negative patients develop loco-regional failure [15]. Approximately 12-31% of the patients present with regional metastases [16] and require resection of the primary site, complete lymphadenectomy and radiotherapy to both sites. Despite this aggressive loco-regional treatment, recurrence still occurs in 50% of patients within 2 years.

Stage IV tumours are rare and are usually treated with systemic chemotherapy, or more recently, with synchronous chemo-radiotherapy [16]. Because of its neuroendocrine profile the drugs used are cispl-

atin and etoposide or 5-fluorouracil [15,17]. More recently responses to paclitaxel have been reported and interest in novel regimens including Bcl-2 antisense therapy [18] is growing. Unfortunately the high initial response rate achieved is typically short-lived [15] and paucity of data has not yet allowed discrimination between the various regimens.

The prognosis of NECS is poor with a 50-70% survival rate at 2 years [19]. About half of all cases will develop systemic metastases within 2 years, at which stage the mean survival falls to 7 months. Cases of spontaneous regression of the primary site and even regression of metastases after resection of the primary have been reported.

The presence of synchronous metastasis from two separate primaries is extremely rare [20,21] and is further evidence for the importance of the "soil" in metastasis - a fact that is often neglected in cancer research but recognized and elegantly described by Sir Stephen Paget in 1889 - the "seed and soil" hypothesis [22].

References

1. Brenner B, Sulkes A, Rakowsky E et al. Second neoplasms in patients with Merkel cell carcinoma. Cancer 2001; 91: 1358-1362.
2. Camisa C, Weissmann A. Friedrich Sigmund Merkel. Part I. The man. Am J Dermatopathol 1982; 4: 521-526.
3. Wiessmann A, Camisa C. Friedrich Sigmund Merkel. Part II. The cell. Am J Dermatopathol 1982; 4: 527-535.
4. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972; 105: 107-110.
5. Gu J, Polak JM, Tapia FJ, Marangos PJ, Pearse AG. Neuron-specific enolase in the Merkel cells of mammalian skin. The use of specific antibody as a simple and reliable histologic marker. Am J Pathol 1981; 104: 63-68.
6. Shaw JH, Rumball E. Merkel cell tumour: clinical behaviour and treatment. Br J Surg 1991; 78: 138-142.
7. Rocamora A, Badia N, Vives R, Carrillo R, Ulloa J, Ledo A. Epidermotropic primary neuroendocrine (Merkel cell) carcinoma of the skin with Pautrier-like microabscesses. Report of three cases and review of the literature. J Am Acad Dermatol 1987; 16: 1163-1168.
8. Goepfert H, Remmler D, Silva E, Wheeler B. Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. Arch Otolaryngol 1984; 110: 707-712.
9. Sibley RK, Dehner LP, Rosai J. Primary neuroendocrine (Merkel cell?) carcinoma of the skin. I. A clinicopathologic and ultrastructural study of 43 cases. Am J Surg Pathol 1985; 9: 95-108.
10. Wasserberg N, Schachter J, Fenig E, Feinmesser M, Gutman H. Applicability of the sentinel node technique to Merkel cell carcinoma. Dermatol Surg 2000; 26: 138-141.
11. Marenda SA, Otto RA. Adnexal carcinomas of the skin. Otolaryngol Clin North Am 1993; 26: 87-116.
12. Ross MI, Reintgen D, Balch CM. Selective lymphadenectomy: emerging role for lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. Semin Surg Oncol 1993; 9: 219-223.
13. Ames SE, Krag DN, Brady MS. Radiolocalization of the sentinel lymph node in Merkel cell carcinoma: a clinical analysis of seven cases. J Surg Oncol 1998; 67: 251-254.
14. Smith DF, Messina JL, Perrott R et al. Clinical approach to neuroendocrine carcinoma of the skin (Merkel cell carcinoma). Cancer Control 2000; 7: 72-83.
15. Fenig E, Lurie H, Klein B, Sulkes A. The treatment of advanced Merkel cell carcinoma. A multimodality chemotherapy and radiation therapy treatment approach. J Dermatol Surg Oncol 1993; 19: 860-864.
16. Poulsen M, Harvey J. Is there a diminishing role for surgery for Merkel cell carcinoma of the skin? a review of current management. ANZ J Surg 2002; 72: 142-146.
17. Coit DG. Merkel cell carcinoma. Ann Surg Oncol 2001; 8 (Suppl): 99S-102S.
18. Klasa RJ, Gillum AM, Klem RE, Frankel SR. Oblimersen Bcl-2 antisense: facilitating apoptosis in anticancer treatment. Antisense Nucleic Acid Drug Dev 2000; 12: 193-213.
19. Savage P, Constenla D, Fisher C. The natural history and management of Merkel cell carcinoma of the skin: a review of 22 patients treated at the Royal Marsden Hospital. Clin Oncol (R Coll Radiol) 1997; 9: 164-167.
20. Matsumoto H, Nakane H, Aoki A et al. A case of synchronous cervical lymph node metastases from testicular and thyroid cancers showing mixed response to chemotherapy. Hinyokika Kiyo 2000; 46: 505-508.
21. Caraway NP, Wojcik EM, Saboorian HM, Katz RL. Concomitant lymphoma and metastatic carcinoma in a lymph node: diagnosis by fine-needle aspiration biopsy in two cases. Diagn Cytopathol 1997; 17: 287-291.
22. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889; 1: 571-573.