CLINICAL CASE

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

A.P. Singh¹, K. Patel¹, Y. Sergides¹, K. Love², A.D. Purushotham¹
¹Cambridge Breast Unit and ²Department 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).
The 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 Friedrich 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 occurrence 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 Bel-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