CK7+/CK20– Merkel Cell Carcinoma Presenting as Inguinal Subcutaneous Nodules with Subsequent Epidermotropic Metastasis

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Merkel cell carcinoma (MCC) is an uncommon malignant neuroendocrine tumour that typically presents as indurated dermal nodules in elderly patients. MCC presenting as subcutaneous nodules is rare and the biological behaviour is not well characterized. We report here a case of MCC presenting as inguinal subcutaneous masses with subsequent epidermotropic metastasis.

CASE REPORT

A 77-year-old man presented to our clinic with bilateral painless inguinal subcutaneous masses and a pubic nodule. The patient first noticed the right inguinal lump 3 years previously, and the left groin mass developed a year later. One year previously a pubic nodule appeared with bleeding on palpation. Thus the patient sought medical advice.

On physical examination, the two inguinal subcutaneous tumours were mobile with normal overlying skin, and measured 5 and 3 cm in diameter, respectively. The pubic nodule measured $2.5 \times 1.8 \times 0.8$ cm. The base was mildly erythematous, but not indurated (Fig. 1).

The pubic tumour was excised and the histopathology revealed an exophytic tumour composed of sheets and nests of uniform cells with epidermotropism. Focal lymphatic invasion was noted without perineural involvement. The mitotic figures were high (10/10 high-power field), but no tumour necrosis was found. The tumour cells were positive for cytokeratin (CK) 7, neurone-specific enolase, chromogranin, synaptophysin, and negative for CK 20, thyroid transcription factor (TTF-1) and thrombomodulin (Fig. 2). A core biopsy from the right inguinal mass revealed tumour cells of similar cytology in a myxoid stroma.

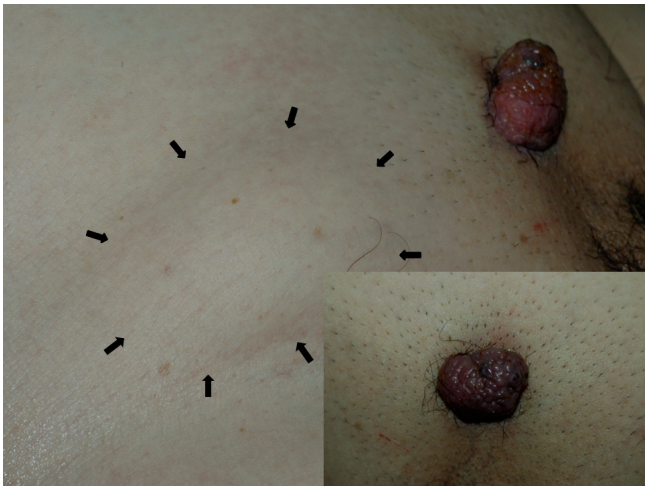

Fig. 1. A subcutaneous nodule on the right groin (arrows) and an exophytic erythematous, firm tumour with cerebroid surface and telangiectasia on the pubic area (*inset*, front view).

Whole-body computer tomography, abdominal sonography, colonoscopy, and panendoscopy showed only subcutaneous inguinal masses and gastritis. The serum biochemistry was unremarkable, except for hyperuricemia. Metastatic carcinoid of unknown primary was initially diagnosed. Because of the indolent nature of the inguino-crural tumours, he refused further treatment.

During follow-up, the tumours on the inguinal areas enlarged gradually and several thumb-tip-sized tumours appeared on the previous surgical site. After 2 years, computer tomography showed multiple nodules in both lower lung fields with pleural effusions, marked soft tissue masses encasing the bilateral external iliac vessels extending down to bilateral inguinocrural areas, and hypervascular papillary tumours at the base of the penis. A diagnosis of neuroendocrine carcinoma with cutaneous metastasis was subsequently made. Multiple spinal metastases developed one year later. He died of pneumonia 30 months after first diagnosis of this carcinoma. Throughout the history, he did not show any carcinoid symptoms and his 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) was normal.

DISCUSSION

The three main differential diagnoses of our case included MCC, carcinoid tumour, and metastatic small cell lung carcinoma (SCLC). SCLC was excluded because of the negative result of TTF-1 stain and the long-latency between the inguinal masses and the subsequent systemic metastasis. A diagnosis of metastatic carcinoid tumour was originally favoured based on the typical histology, showing sheets and nests of uniform cells with round nuclei and eosinophilic cytoplasm. Epidermotropism, however, has not been reported in carcinoid tumour, but occurs in 5–30% of MCC (1). In addition, the absence of carcinoid syndrome symptoms and a normal urinary 5-HIAA, despite systemic metastases, also failed to support the initial diagnosis of carcinoid tumour. In view of the clinico-histopathological presentation and course we favoured a diagnosis of MCC, particularly as a cutaneous polypoid lesion with telangiectasia (2) and a subcutaneous groin mass (3–7) are recognised presentations of MCC. A potential diagnostic pitfall lies in the CK20 negative immunohistochemical stain of this case. However, in a review study CK20 was expressed in only 339 of 391 (87%) of MCC cases (8), and a subset of CK7+/CK20– MCC has been recently reported (9). Another atypical feature of our case is the relatively large neoplastic cells showing round nuclei and eosinophilic cytoplasm, but this unusual cytological character has also been reported (10). Based on the above reasons, the diagnosis of MCC seems most plausible.

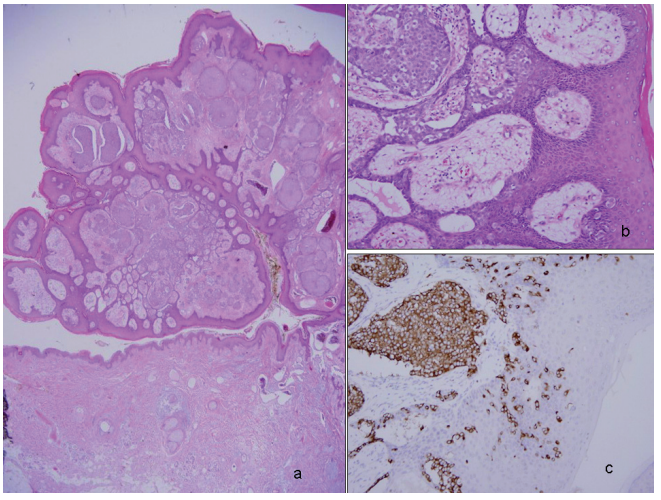

Fig. 2. Histology showing an exophytic tumour composed of sheets and nests of uniform cells with round nuclei and eosinophilic cytoplasm with epidermal connection forming a fenestrated pattern (a and b, haematoxylin & eosin ×40 and ×200, respectively) and extensive epidermotrophism consisting of both single cells and small nests (c, synaptophysin stain, ×100).

MCC usually occurs on sun-exposed areas in elderly people, presenting typically as dermal tumours that frequently extend to the epidermis and/or the subcutis. Rarely, MCC may have an initial presentation as subcutaneous nodules without surface change. Most of these cases showed close proximity with the lymphoid tissue, and they were reported either as primary nodal MCC (3–7, 11), or subcutaneous MCC (12–14). In all these MCC cases, there were no primary tumours other than the subcutaneous masses despite extensive investigations. A recent study showed that trisomy of chromosome 6 can be found in 47% of typical MCC as well as in half of the primary nodal MCC (15). This finding further supported the similarity of these two types of MCCs.

The cellular origin of MCC remains inconclusive, especially for MCC presenting as subcutaneous nodules. One hypothesis is that the nodal or subcutaneous MCCs are metastases of regressed occult primary tumours. However, the long disease-free interval in some of the cases is unusual for metastatic MCC (7). Another hypothesis is that nodal MCC arises *de novo* in the lymph node. The neoplastic cells may derive from epithelial inclusion in the lymph node, from stem cells of the lymphoreticular system, or from cells with dual features of endocrine and epithelium cells (7).

Recently, a new polyomavirus named Merkel cell polyomavirus (MCPyV) has been implicated in the pathogenesis of MCC (16), but a lower detection rate of MCPyV in MCC in Asia-Pacific subjects was reported (17, 18). In our case, nested PCR tests failed to detect MCPyV, and fluorescence *in situ* hybridization showed no evidence of trisomy 6.

The authors declare no conflict of interest.

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