Case Report

Paraneoplastic myasthenia gravis associated with Merkel cell carcinoma

與麥克氏細胞癌相關的腫瘤附屬重症肌無力

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Background: Merkel cell carcinoma (MCC) is an unusual primary neuroendocrine cutaneous carcinoma which may rarely be associated with neurological paraneoplastic syndromes. Nevertheless, the coexistence of myasthenia gravis (MG) with MCC has not been previously reported. History: A 74-year-old man presented with dysphagia, tetraparesis, horizontal diplopia and right palpebral ptosis. MG was diagnosed and treatment with piridostigmine and IV immunoglobulin was given, leading to a partial response. Two weeks later, there was rapid growth of a painless left suprapatellar nodule which was compatible with MCC. Conclusion: Merkel cell carcinoma may rarely present as refractory MG. Tumour excision may be necessary for resolution of the syndrome.

Keywords: Merkel cell carcinoma, myasthenia gravis, paraneoplastic neurological syndrome

Introduction

Merkel cell carcinoma (MCC) is a malignant and aggressive skin tumour of neuroendocrine origin. Its worldwide incidence is 0.6 per 100,000 people, presenting mainly in immunosuppressed elderly men, solid-organ transplant recipients and HIV-infected patients. Its association with paraneoplastic syndromes is rare and of these, neurological syndromes are the least common. To the best of our knowledge, this is the first case of MCC associated with myasthenia gravis (MG).
Case history

A 74-year-old man presented with dysphagia. There was a history of prostate cancer treated with radiotherapy, which was in remission. Over the past few weeks, there was an onset of dysphonia, tetraparesis and progressive horizontal diplopia. Physical examination showed right palpebral ptosis, diminished muscle strength of all the extremities and flexion/extension weakness of the neck muscles. Routine blood investigations revealed no abnormalities. As MG was suspected, a computed axial tomography of the chest with IV contrast dye was performed, excluding a mediastinal mass. The edrophonium (Tensilon) test was positive and circulating acetylcholine receptor antibodies were detected (41% (negative: <15%), 78% (negative: <32%) and 14.2 nmol/L (positive: >0.05) for binding, blocking, and modulating antibodies respectively). The diagnosis of MG was confirmed with a repetitive nerve stimulation, in which an impaired myoneural post-synaptic response was observed. The patient received pyridostigmine bromide at a dosage of 30 mg qid, with no improvement. He was then treated with plasma exchange and IV human immunoglobulin (Octogam®) was administered for five doses, with a partial clinical response. Two weeks later, he presented with a 2x3 cm soft-tissue nodule on the left suprapatellar region. An excisional biopsy of the lesion was performed (Figure 1). Macroscopic examination of the biopsy specimen revealed two violaceous nodules 1.7 cm and 1.5 cm in size. Histopathological examination showed that there was involvement of both dermis and subcutis with small, rounded and blue cells in the papillary dermis and infiltration of the reticular dermis and subcutis (Figure 2). There was no involvement of the epidermis (Figure 3). On immunohistochemical staining, there was intense and diffuse expression of CD56+ (both nucleus and cytoplasm); cells also showed intense and diffuse staining for cytokeratin 20; and >50% of cells show cytoplasmic staining for synaptophysin and chromogranin A (Figure 4). The patient was therefore diagnosed as having MCC associated with MG as a paraneoplastic syndrome. There was resolution of symptoms after excision of the tumour.

Discussion

MCC is an aggressive neuroendocrine skin cancer. Merkel cells, also named slowly adapting type one (SA1) mechanoreceptors, are located in the basal stratum of the epidermis, have long been described as being the precursors of the tumour. Nevertheless, there is new evidence to suggest that the dermo-epidermal junction stem cells and B cells are the real precursors.

This oncological disorder occurs predominantly in elderly people, with a mean of age of 69 years at diagnosis with males being affected more commonly than women. It has been strongly associated with immunocompromised states, such as solid organ transplant recipients, chronic lymphocytic leukaemia and HIV-infected patients. Due to its predilection for sun-exposed areas, it may be identified in an early stage, although it tends to be indolent at presentation.

The increasing incidence of MCC in immunocompromised patients and the associated spontaneous tumoural regression recently reported in literature, suggests the key involvement of the immune system against tumoural cells. We report this condition in an immunocompetent patient, which is not a common presentation. A study conducted by Vandeven et al demonstrated that immunosuppressed patients usually presented with a primary cutaneous lesion. Otherwise, an immunocompetent state was associated with the lack of a cutaneous lesion and a higher antibody titre against oncoproteins expressed in Merkel polyoma infected cells (median 26,229 U/mL vs 3,492, p<0.001). This could explain its association with neurological paraneoplastic syndromes of autoimmune origin, in this case being MG.
In this patient, an immunocompetent state induces the excessive production of auto-antibodies, causing disabling neurological symptoms at an early tumoural stage of the tumour (T2N0M0), unlike other reported cases in which paraneoplastic syndromes are often diagnosed at an advanced stage.4,11

There are tumours that share similar histological characteristics with MCC, such as small cell lung carcinoma. This tumour has been associated with similar paraneoplastic syndromes. Jia et al in 2018 reported the co-existence of MG and Eaton-Lambert syndrome associated with small cell lung carcinoma.12

**Figure 1.** Macroscopic characteristics of the lesion. Excision biopsy of skin lesion. There are two violaceous nodules of 1.7 cm and 1.5 cm in size (largest diameter) which involve both the dermis and subcutis.

**Figure 2.** Histological findings: Haematoxylin and eosin (H&E) staining of the tissue, view at 10x. There are small, rounded and blue cells in the papillary dermis which infiltrate the reticular dermis and subcutis. The epidermis is not involved.

**Figure 3.** Histological findings: Haematoxylin and eosin staining of the tissue, view at 40x. There are small, blue, rounded cells in the papillary dermis of about 12-15 microns, with voluminous and hyperchromatic nuclei, scanty cytoplasm and multiple mitoses, some of which have atypical features.
Figure 4. Immunohistochemical staining. (A) Cells show intense and diffuse expression of CD56+, in both nucleus and cytoplasm. (B) Cells show intense and diffuse positivity for cytokeratin 20. (C) More than 50% of cells show cytoplasmic positivity for synaptophysin. (D) Cytoplasmic positivity for chromogranin A.
Although paraneoplastic syndromes associated with MCC can manifest as myasthenia-like syndromes, there are only published cases linked to Eaton-Lambert, and MG has not been previously reported.4,5

Unlike seronegative MG, a seropositive state is associated with a lower treatment failure rate. In this case, the lack of therapeutic response, even though it was a seropositive myasthenic syndrome, could be explained because of the continuous immunoneurological stimulation by the tumour and the exaggerated response by the host. Altogether, this can explain the improvement in neurological symptoms after the tumour was excised.5

In conclusion, for cases of MG which are not associated with thymus neoplasia, which are of idiopathic nature or which are refractory to treatment, the coexistence of a MCC should be considered. In such cases, the excision of the lesion can drastically improve the patient’s prognosis.

References