CASE REPORT

Metastatic Merkel-cell carcinoma: the dawn of a new era

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SUMMARY

Merkel-cell carcinoma (MCC) is a rare but aggressive cutaneous malignancy arising most often in sun-exposed Caucasians who are immunosuppressed or the elderly. Patients with metastatic disease treated with chemotherapy have a median progression-free survival of just 3 months. This report describes a 58-year-old man with a background history of psoriasis treated with immunosuppressive therapy and subsequently diagnosed with metastatic MCC. Chemotherapy produced a partial response. Then, a novel immunotherapy agent, pembrolizumab, induced a complete response maintained for at least 19 months. Quality of life was unaffected, and toxicity from immunotherapy was minimal. At the time of writing, there was no clinical or radiological evidence of recurrence and treatment is ongoing.

BACKGROUND

Historically, metastatic Merkel-cell carcinoma (MCC) has a poor prognosis. Chemotherapy can produce a significant although short-lived response before progressive and fatal disease ensues usually within 6–10 months.¹ Modern immunotherapy agents, specifically immune checkpoint inhibitor antibodies, have emerged as an effective and safe treatment for many cancers, including melanoma, renal cell carcinoma and lung cancer. Recent data have shown significant durable activity in metastatic MCC.^{2,3}

CASE PRESENTATION

A 58-year-old Caucasian man presented to his general practitioner with a fleshy, painless swelling on the dorsum of his left hand which had appeared some 3 months prior and had been steadily increasing in size (figure 1).⁴ His medical history included plaque psoriasis that was well controlled with the immunosuppressant monoclonal antibody adalimumab (Humira). This is an important element of the history as MCC is strongly associated with immunosuppression and, although rare, numerous cases with adalimumab have been reported.⁵

A clinical diagnosis of a sebaceous cyst was made by the GP and surgical excision undertaken; however, during the procedure, it became clear that this was an unusual lesion. The patient was then referred to a plastic surgeon for further treatment.

INVESTIGATIONS

Histological examination of the primary lesion described an ill-defined, raised, cream nodule measuring 15 mm in diameter and 8 mm deep, residing in the deep reticular dermis and extending into the subcutaneous fat. Immunohistochemistry confirmed the diagnosis of MCC. The oncogenic polyomavirus has been detected in 60%–80% of MCC tumours but was not tested in this case.⁶

Investigation of locoregional spread with an ultrasound examination of the left axilla revealed three suspicious, enlarged lymph nodes; however, subsequent biopsy was inconclusive due to inadequate specimen.

A staging CT scan of the thorax, abdomen and pelvis demonstrated a number of sinister, left-sided, axillary lymph nodes, the largest measuring 11 mm. In addition, multiple lesions were observed in both lobes of the liver suspicious for metastatic disease (figure 2). No other sites of metastatic disease were identified.

An ultrasound-guided biopsy of a liver lesion yielded cores of liver tissue infiltrated by high-grade malignant neoplasm. Initial immunohistochemical analysis was positive for synaptophysin and chromogranin confirming a neuroendocrine tumour subtype. Further testing demonstrated immunoreactivity for the cytokeratin CK20, thus confirming a diagnosis of Stage IV MCC.⁷

DIFFERENTIAL DIAGNOSIS

MCC is a rare cutaneous malignancy (incidence 0.6 per 100 000) and may be misdiagnosed as a benign lesion such as a lipoma, sebaceous cyst or pyogenic granuloma. Suspicion should arise with any asymptomatic intracutaneous lesion, growing rapidly over 3 months on an area of sun-exposed skin, particularly in patients who are immunosuppressed and/or over 50 years of age.⁸ The 'AEIOU' acronym can be used to remember these significant features (table 1).⁸

Despite an often delayed diagnosis at presentation, the majority of cases are local (65%) with only a minority having distant disease (8%).⁹ However, it is important to diagnose MCC early because the 5-year overall survival drops from 63% for Stage I disease to just 14% for Stage IV.⁹

TREATMENT

The patient underwent four cycles of a standard chemotherapy regimen every 3 weeks, carboplatin (AUC 5 intravenously day 1) and etoposide

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Figure 1 Merkel-cell carcinoma. No photograph of the patient's lesion was available as the General Practitioner had excised it before referral. This image was reproduced from merkelcell.org with permission.

(100 mg/m² intravenously day 1, 200 mg/m² orally, days 2 and 3). Systemic chemotherapy, despite producing a high initial response rate, is associated with a progression-free survival of just 3 months and high toxicity, thus providing the rationale for novel treatments.¹⁰

Following the completion of chemotherapy, funding was approved by the hospital's drugs and therapeutics committee for pembrolizumab (Keytruda) which was administered every 3 weeks at a dose of 2 mg/kg IV. Pembrolizumab is a humanised, monoclonal antibody against the programmed death receptor (PD-1) on T lymphocytes.¹¹ Ordinarily, this immune checkpoint pathway functions to prevent autoimmunity. However, tumour cells can overexpress PD ligand (PD-L1) leading to excess immune suppression resulting in evasion of the tumour cells from the immune system. Pembrolizumab blocks the interaction between PD-1 and PD-L1 allowing T cell-mediated destruction of tumour cells.

Figure 2 Initial staging CT scan. Multiple metastases were discovered throughout both lobes of the liver.

Table 1 Acronym to remember the significant features of Merkel-cell carcinoma when assessing a patient

A	Asymptomatic
E	Expanding rapidly over 3 months
I	Immunosuppressed
O	Older than 50
U	Ultraviolet exposure in fair skin

OUTCOME AND FOLLOW-UP

A restaging scan after completion of chemotherapy demonstrated a partial response in axillary lymph nodes and metastatic liver disease.

Given that a short duration of response was expected with chemotherapy, pembrolizumab was commenced (2 mg/kg every 3 weeks). At the time of writing, the patient had received 32 cycles of pembrolizumab over 21 months and continues to receive treatment. Clinical examination prior to each cycle has not revealed local recurrence or new lesions. Repeat imaging with CT at 4, 8, 16 and 19 months demonstrated a complete response in all sites of disease, including disappearance of hepatic metastases (figure 3).

Treatment was well tolerated with no grade 3 or 4 adverse events. Interestingly, the patient's psoriasis was reasonably well controlled, despite discontinuing adalimumab on initial diagnosis, however, he did require increased frequency of administration of topical steroids. His quality of life was excellent during immunotherapy treatment.

To date, there has been no evidence of other cutaneous and haematological malignancies, which is a risk with MCC.¹²

DISCUSSION

The increasing role of systemic immunotherapy in cancer is illustrated in this case. The rationale for immunotherapy in MCC is based on the aetiology of this disease, namely the immunosuppressive environment and the presence of the polyomavirus. Due to the rarity of this cancer, randomised controlled trials are not possible although data from recently reported phase II studies are practice changing.

Pembrolizumab has been shown to produce a 56% response rate in chemotherapy naive patients with Stage IV disease.² The same study demonstrated a progression-free survival at 6 months

Figure 3 Most recent CT. No evidence of metastases was appreciated after 19 months of immunotherapy.

of almost 70% and resulted in Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval. More recently, the JAVELIN Merkel 200 study demonstrated a 32% response rate with avelumab, a PD-L1 inhibitor, in patients with metastatic MCC previously treated with chemotherapy, resulting in FDA and EMA approval.³

In this case, a partial response was seen with conventional systemic chemotherapy and a durable, complete response with immunotherapy. The progression-free survival of at least 19 months with pembrolizumab exceeds previously published data (9.7 months).² Treatment with pembrolizumab is ongoing at the time of writing.

Further research is required to establish the optimal treatment duration of immunotherapy for metastatic MCC; however, it is likely to supersede the use of chemotherapy in the near future.

Learning points

- ▶ Immunotherapy should be considered for all patients with metastatic Merkel-cell carcinoma irrespective of aetiology and polyomavirus status.
- ▶ This case demonstrated a progression-free survival of 19 months with pembrolizumab which is ongoing at the time of writing, far exceeding historical data.
- ▶ The role of immune checkpoint inhibitor antibody therapy is increasing in cancer.
- ▶ Immunosuppressive therapies such as adalimumab pose a well-documented although small enhanced risk of malignancy.

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