

Importance of Genetic Studies in Patients with Multiple Merkel Cell Carcinomas

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Sir,

Kamiyama et al. (1) recently reported a case of a 79-year-old woman with a history of a Merkel cell carcinoma (MCC) on her right cheek who underwent wide excision followed by adjuvant chemoradiation, and remained disease-free for 10 years, before presenting with a MCC on the left cheek. The tumour type was confirmed via histology and immunostaining, and both tumours were positive for Merkel cell polyomavirus (MCPyV) DNA by real-time polymerase chain reaction (RT-PCR) as well as immunostaining for the MCPyV large T antigen. The authors state that the two MCCs represent distinct primary tumours, and that their report is the first case of two primary MCCs of the skin with documented MCPyV infection. They reject the possibility that the second tumour could be a metastasis, based on the facts that: (i) there was no local or lymph node recurrence or metastasis during the 10-year follow-up period after the first tumour was removed; and (ii) MCC usually exhibits rapid growth, with both nodal and recurrent metastases tending to occur soon after the initial tumour is detected. Both of these facts, as well as the contralateral location of the second tumour, support their contention that the two tumours may represent distinct primaries. However, there is growing evidence that clinical presentation alone may give a misleading impression of the relationship between multiple MCC tumours in the same patient.

In the English literature, there have been 6 other reports of multiple cutaneous MCCs that have been claimed as distinct primaries (2–7). However, only 2 of these have made use of genetic analysis to prove the relationship between the tumours. Nagy et al. (4) used array comparative genomic hybridization (aCGH) to demonstrate that an MCC of the lip and a subsequent MCC of the palatine tonsil, separated by 7 years, were non-identical, based on significant differences in copy number at 31 chromosomal locations. As these tumours also shared 45 chromosomal regions with identical copy number alterations, the second tumour clearly did not arise entirely independently from the first, and may represent a metastasis that underwent significant changes during the intervening 7 years. Schrama et al. (7) reported a case of a woman with MCCs of the contralateral arms, separated in time by 6 years. They proved that the tumours arose as independent primaries by directly sequencing the large T antigen DNA that had been integrated into the patient's tumour cell genome, demonstrating multiple base-pair differences between the two samples.

We recently reported a case of a woman who presented to our institution with an MCC of the right cheek followed by a second MCC lesion of the left ankle 4 months later. Given the distant and contralateral cutaneous locations of these lesions and the absence of evidence for metastasis to any other sites based on sentinel lymph node biopsy and positron emission tomography/computed tomography (PET/CT) scan, the possibility of a second primary lesion was considered (8). However, aCGH of tumour tissue samples demonstrated identical copy number variation profiles in the 2 tumours, proving that the second tumour, despite its distant location, represented a rapid, isolated cutaneous metastasis of the first. Although it is true that MCC typically exhibits local recurrence and lymph node metastasis prior to distant metastasis, our reported case, as well as similar additional cases in our experience, illustrate that haematogenous spread of MCC between distant cutaneous sites can occur in the absence of evidence for lymphatic spread.

It is important to use currently available genetic assays, such as aCGH and direct virus genome sequencing (perhaps readily applicable in this case in which both lesions were MCPyV-positive), to elucidate the relationships between multiple MCC tumours, given that these findings have important implications for staging and management of this highly aggressive cancer. As illustrated by our experience, the clinical finding of a second lesion at a distant anatomical location with no clinical evidence of any lymph node or distant organ involvement does not in itself confirm the diagnosis of a second primary MCC. To make a definitive diagnosis of a second primary MCC, additional confirmatory molecular studies are needed.

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Response to: Importance of Genetic Studies in Patients with Multiple Merkel Cell Carcinomas

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Sir,

We thank Drs Ahronowitz et al. for their valuable comment on our case report, and offer the following reply.

We fully understand that genetic assays, such as aCGH and direct virus genome sequencing, are necessary to distinguish a second primary Merkel cell carcinoma (MCC) from metastasis of the first MCC. However, both Merkel cell polyomavirus genome sequencing and virus-integration-site analysis were difficult in this

case, because only formalin-fixed paraffin-embedded specimens that had been stored for a long time were available for such analyses of the first MCC. We had difficulty sequencing the large T antigen, and concluded that it was impossible to obtain reliable results from those samples. We intend, however, to continue to try to complete an aCGH analysis and will publish an additional reply if we are successful in drawing reliable conclusions by this method.