Merkel cell carcinoma in a patient with relapsing-remitting multiple sclerosis treated with Fingolimod

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Introduction

MCC is a rare and very aggressive carcinoma of the skin, usually affecting the elderly or immunosuppresed patients, frequently associated with integration of genomic sequences of Merkel cell polyomavirus (MCPyV) [1]. Fingolimod is a sphingosine 1 recpetor (S1P) modulator, used in relapsing–remitting multiple sclerosis (MS) not responding to first-line therapies.

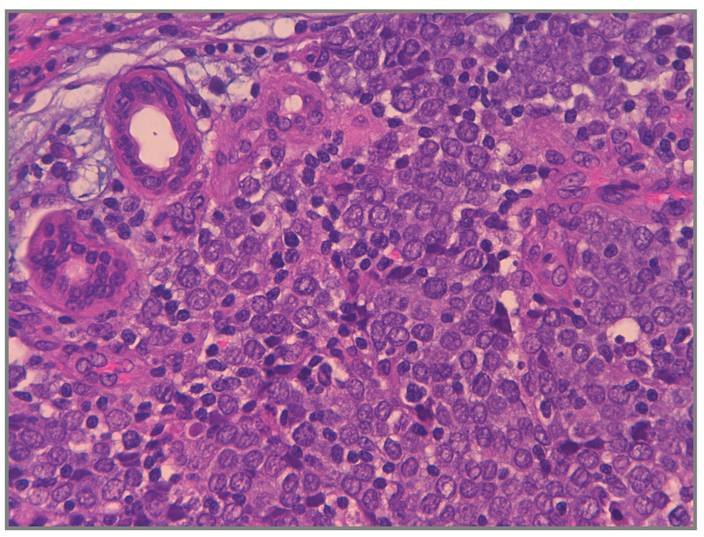
Case report

A 54-year-old woman, affected by MS since 1997, has been initially treated with interferon beta1b every other day for 13 years with clinical stability, than in 2010 a follow-up brain MRI showed an increase in lesion load requiring a shift to Fingolimod. After initiation low-grade lymphopenia (WHO grade 3 < 500 cells/mm^3) was observed and an episode of herpes zoster reactivation in the lumbar-sacral left area. Comorbidities were autoimmune tiroiditis, dyslipidaemia and slight increase in hepatic transaminases.
In October 2015 Merkel cell carcinoma in the left arm was diagnosed, and the patient followed a surgical excision including satellite lymph nodes, the latter negative for microsatellite infiltration. Skin biopsy proved Merkel cell polyomavirus (MCPyV) positivity. A relapse of the tumour was surgically removed after 3 months, Fingolimod was stopped and the patient started radiotherapy. 6 months later, the patient was admitted for a secondary relapse, with the finding of metastatic disease at axillary lymph nodes.

Discussion and conclusion

Typical Fingolimod adverse events (AEs) associated with the mechanism of action are bradycardia and macular oedema. Other AEs could be associated with immunomodulation and modification of immune surveillance, such as varicella zoster virus (VZV) infections, progressive multifocal leukoencephalopathies (PML) and a few skin tumours such melanomas. Merkel carcinoma might be included in the group of skin tumours.
SP1 receptor down regulation during Fingolimod treatment generates a sequestration in the lymphoid organs of a proportion of CCR7 expressing lymphocytes (CD4 naïve T cells and central memory T cells), without affecting many of the functional properties of the cells [2].
However, the effect induced by Fingolimod could modify and lower specific immunity to certain viral infections, such as VZV [3]. A similar mechanism toward other viral families, may be argued (i.e. MCPyV).

In conclusion, there is growing attention to the effects on immune surveillance by therapies used in MS, such as Fingolimod, in terms of possible reactivation of latent infections, which in turn might contribute to the pathogenesis of some rare neoplastic complications, possibly including Merkel cell carcinoma.



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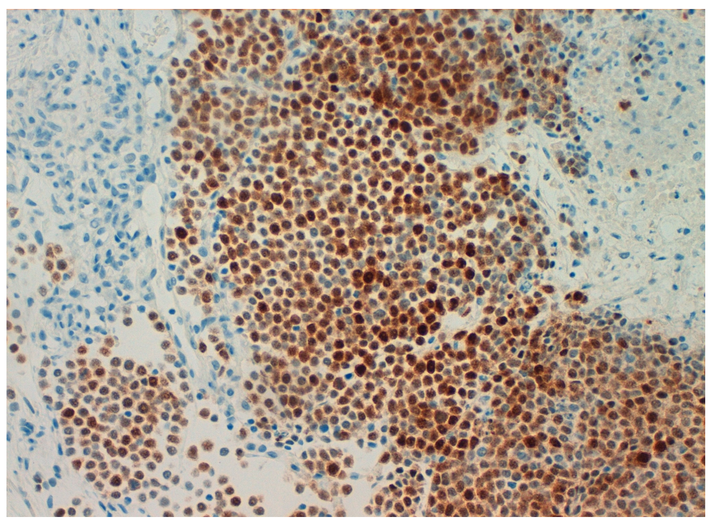

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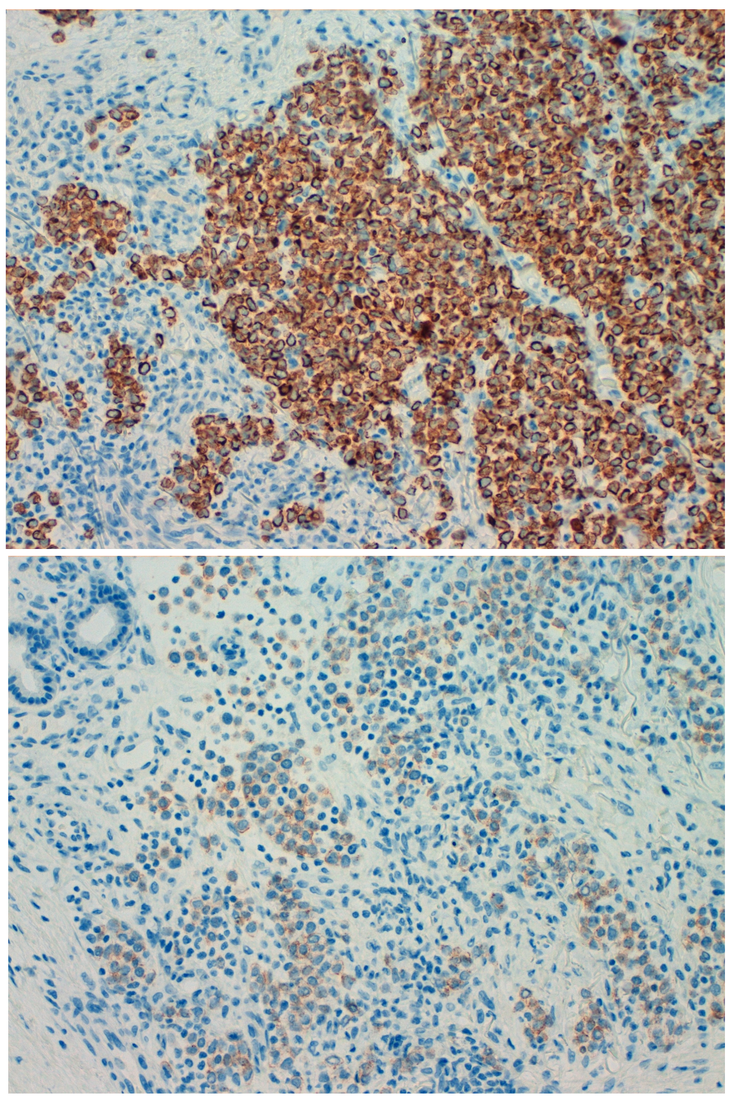

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Figure Legends

1. H&E stain (40X): (40X): small cell neoplasia, scant cytoplasm, nuclear cromathin pattern, solid growth infiltrating adnexal structures (up right).
2. IHC (20X): intense nuclear MCPyV positivity.
3. IHC (20X): typical dot-like CK-20 positivity (up); weak chromogranin A positivity (down).

Bibliography

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