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Teaching NeuroImage: Paraneoplastic Cerebellar Degeneration and Antibodies to TRIM 9 and 67 Secondary to Melanoma

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Paraneoplastic cerebellar degeneration (PCD) has been described in a few isolated patients with melanoma and different neuronal antibodies (Yo and CARPVIII).[1]

A 63-year-old woman developed a subacute severe pancerebellar syndrome. At clinical examination, she exhibited bilateral gaze-evoked nystagmus, down-beat nystagmus, left dysmetria, and gait ataxia. Brain MRI showed severe cerebellar edema (Figure1). Antibodies to tripartite motif proteins (TRIM) 9 and 67 were detected in both serum and cerebrospinal fluid by rat brain immunohistochemistry and immunoblot (Euroimmun, Germany). These antibodies have previously been described in two patients with PCD[2]. Cancer work-up identified a BRAF-mutated metastatic melanoma without brain involvement. Immunohistochemistry of paraffin-embedded melanoma section with a polyclonal rabbit antibody against TRIM9 (RRID AB_2815650; Thermo-Fisher-Scientific, USA) was positive in the tumor cells suggesting TRIM9 expression by the tumor (Figure2). Patient deteriorated despite treatment with corticosteroids, immunoglobulins, and rituximab, remaining unable to walk independently 18 months later. Anti-BRAF treatment yielded partial oncological response.

References

1. Joubert B, Rostasy K, Honnorat J. Immune-mediated ataxias. Handbook of clinical neurology 2018;155:313-332.

2. Do LD, Gupton SL, Tanji K, et al. TRIM9 and TRIM67 Are New Targets in Paraneoplastic Cerebellar Degeneration. Cerebellum 2018.

Legend of figures

Figure1. Baseline and follow up MRI images.

Baseline MRI (A, B) disclosed hyperintense T2 lesions in both cerebellar hemispheres (arrows) and effacement of the sulci. The follow-up MRI (C, D) 18 months later showed cerebellar atrophy.

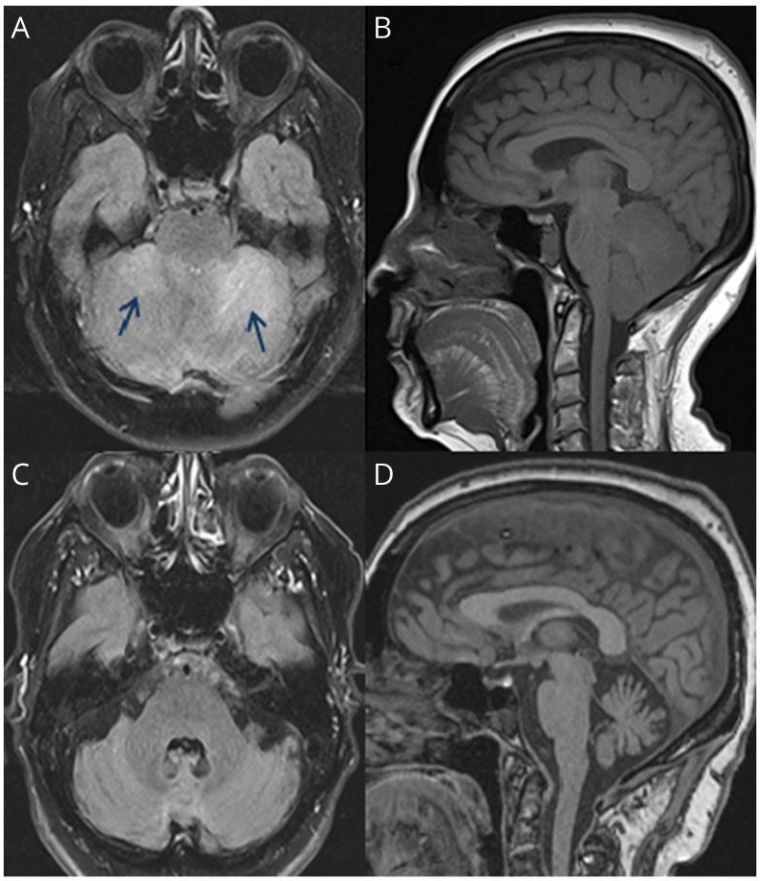
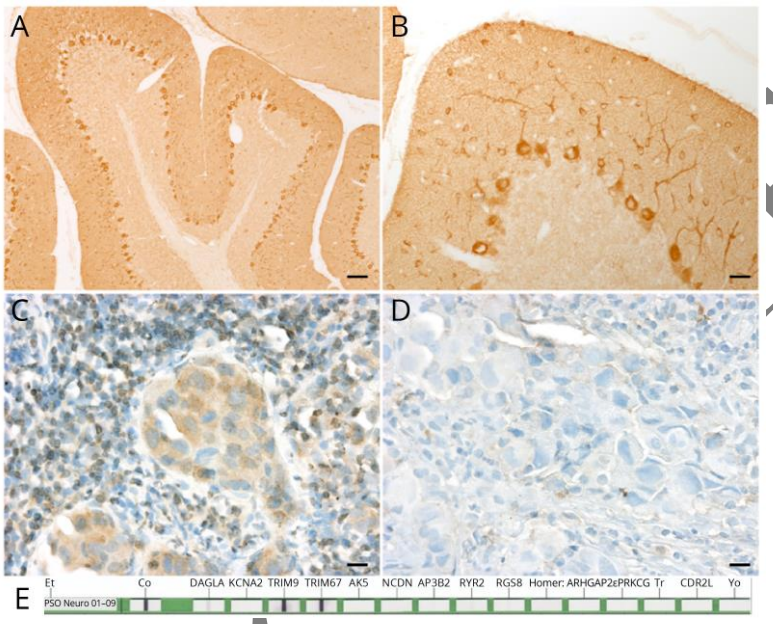


Figure 2. TRIM9-67 antibody detection and expression in patient's tumor.

Immunoreactivity of the patient's serum on the Purkinje cells of rat cerebellum (A-B). Lymph node section invaded by melanoma. Tumor cells are immunostained with TRIM9 (C) but not with control IgG polyclonal antibodies (D). Commercial line blot tested with patient's serum shows positive TRIM9 and TRIM67 bands (E). Scale bars represent: A 200 µm, B-C-D 20 µm.



Multiple-choice question -> Correct answer C

In light of the updated diagnostic criteria for Paraneoplastic Neurologic Syndromes (PNS) published in Neurology: Neuroimmunology & Neuroinflammation in 2021; 8:e1014. how would you classify this case report?

a) PNS-Care score of 3 points: non-PNS. The patient's rapidly progressive cerebellar syndrome indicates a high-risk phenotype, but because the antibody is not high or intermediate risk for cancer, an oncologic relationship cannot be scored.

b) PNS-Care score of 5 points: Possible PNS. The patient's high-risk phenotype, combined with an intermediate-risk antibody, suggests a possible relationship with the tumor.

c) PNS-Care score of 7 points: Probable PNS. The patient's high-risk phenotype, combined with an antibody against an antigen expressed in the tumor, suggests a probable relationship with the tumor.

d) Not applicable. Since melanoma is not typically associated with Paraneoplastic Neurologic Syndromes, the diagnostic criteria are not useful in this case.

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