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PARANEOPLASTIC CEREBELLAR DEGENERATION ASSOCIATED WITH ANTI-ITPR1 ANTIBODIES

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In recent years, the spectrum of anti-Purkinje cell autoimmunity has widened to include novel clinico-immunologic entities, a number of which have been associated with antibodies targeting intracellular antigens (protein kinase C gamma (PKC γ), carbonic anhydrase-related protein (CARP VIII), Ca/Rho GTPase activating protein 26 (ARHGAP26), inositol 1,4,5-trisphosphate receptor 1 (ITPR1), and HOMER3).^{1–3} Anti-ITPR1 belong to this group of newly discovered anticerebellar autoantibodies,⁴ but little is known regarding the exact clinical and paraclinical phenotypes associated with these antibodies and their potential association with cancer.

Here, we report a young woman, carrier of a detrimental germline mutation in the *BRCA1* gene, who at the age of 28 years developed autoimmune cerebellar ataxia associated with anti-ITPR1 antibodies with no associated malignancy, but 11 years later was diagnosed with a breast cancer with ITPR1 expression detected on the tumor.

Case report. A 31-year-old Martinican woman was investigated in view of a 3-year history of subtly progressive ataxia. Neurologic examination revealed a static-kinetic cerebellar syndrome characterized by moderate gait ataxia and mild dysarthria. In addition, she was obese and had arterial hypertension. There was no history of excess alcohol intake. She had no family history of neurologic disease but a history of breast cancer in her maternal side. Brain MRI revealed pontocerebellar atrophy with hot cross bun sign, without any other supratentorial or infratentorial abnormalities (figure 1, A–B). There was no evidence of peripheral neuropathy on electroneuromyography. The CSF was acellular with normal glucose and protein levels and no oligoclonal bands. Extensive investigation for underlying infective, autoimmune, and metabolic etiologies was negative with the exception of high-titer anti-Purkinje cell autoantibodies detected by indirect immunohistochemistry⁴ in both the serum (titer 1/32,000) and the CSF (titer 1/1,000). All specific testing for known CNS autoantibodies were

negative.⁴ Comprehensive tumor screening by total-body 18-fluoro-deoxyglucose PET (¹⁸FDG-PET), bone marrow biopsy, and dermatologic and gynecologic explorations revealed no occult malignancy. She received 6 cycles of high-dose IV methylprednisolone (1 g/d for 3 days), followed by 10 sessions of plasma exchange, without clinical improvement. She continued to have regular tumor screening with total-body ¹⁸FDG-PET.

Over the following 2 years, her neurologic status worsened, and she became unable to walk unassisted. CSF analysis and neuroimaging were unchanged. Three cycles of IV immunoglobulin (2 g/kg) were attempted, without clinical benefit. Thereafter, she stabilized but remained severely disabled. Anti-Purkinje cell autoantibodies were persistently positive in the serum and were later characterized as anti-ITPR1 antibodies.⁴

Following familial genetic counseling, she was tested positive for a detrimental germline mutation in the *BRCA1* gene that was first identified in a relative affected with breast cancer (figure e-1 at Neurology.org/nn), and she thus entered a dedicated screening program for breast and ovarian cancers.

Six years later, a suspicious lymph node was detected on mammography. She underwent radical right mastectomy, revealing a bifocal ductal carcinoma (grade I; estrogen-receptor-positive (ER+) 100%, progesterone-receptor-positive (PR+) 90%, Her2/neu–), with 2 intramammary and 1 axillary metastatic lymph nodes. Immunopathology revealed substantial ITPR1 expression in both the breast tumor and the metastatic lymph nodes (figure 1, C–F). Local radiotherapy was considered unfeasible because of her comorbidities, and adjuvant tamoxifen was introduced. At 6-month follow-up, she was considered in tumor remission; her neurologic status was unchanged.

Discussion. Here, we report the case of a young woman presenting with autoimmune cerebellar ataxia and anti-ITPR1 antibodies, who 11 years after onset was diagnosed with breast cancer. Both the breast tumor and metastatic lymph nodes expressed ITPR1, suggesting that the long-standing cerebellar autoimmunity was in fact paraneoplastic.

So far, only 4 cases of cerebellar ataxia related to anti-ITPR1 autoimmunity have been published,⁴

Supplemental data
at Neurology.org/nn

Figure 1 MRI features and immunopathology

MRI features (A, B). Brain MRI obtained in 2007 showed an already severe pontocerebellar atrophy in sagittal T1- (A) and axial T2- (B) weighted images. Hot cross bun sign, marked enlargement of cerebellar sulci, fourth ventricle, and basal cisternae are evident in T2-weighted images (B). Immunopathology (C-F). Patient's breast cancer specimen (C, E) incubated with anti-inositol 1,4,5-trisphosphate receptor 1 (ITPR1) rabbit commercial antibody 1:1,000 (C) and control rabbit serum (E). The lymph node metastasis specimen (D, F) incubated with anti-ITPR1 rabbit commercial antibody 1:1,000 (D) and control rabbit serum (F). Magnification $\times 200$.

and tumor association is limited to the present case. To date, it is thus impossible to draw any conclusion regarding the possible association of anti-ITPR1 antibodies to cancer. Still, ITPR1 is expressed in a number of tumors such as breast and liver cancers, melanomas, and lymphomas,⁵ and we thus expect anti-ITPR1 autoimmunity to potentially associate with these tumor types.

Our patient was diagnosed with breast cancer 11 years after the onset of the cerebellar syndrome, far longer than ever reported.⁶ Cancer was diagnosed while still subclinical, during scheduled assessments, within a BRCA1 tumor surveillance program that was established by oncologists. Our case underlines the importance for neurologists to carefully evaluate individual cancer risk in all patients with autoimmunity to intracellular antigens.

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