

Paraneoplastic Cerebellar Syndrome and Optic Neuritis With Anti-CV2 Antibodies

Clinical Response to Excision of the Primary Tumor

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Objective: To describe a patient with a paraneoplastic cerebellar syndrome and optic neuritis with circulating anti-CV2 antibodies and clinical improvement after excision of a small cell lung carcinoma.

Design: Report of a case.

Setting: A 62-year-old man simultaneously developed a severe cerebellar syndrome and a bilateral optic neuritis predominantly in the left eye (visual acuity, 20/25 in the right eye; <20/400 in the left eye; and bilateral swelling of the optic discs).

Main Outcome and Results: Anti-CV2 antibodies, recently described as associated with paraneoplastic neurological syndrome, were detected in the patient's serum sample. These antibodies were demonstrated to react with the cytoplasm of a subpopulation of oligodendro-

cytes in the white matter of rat brain in the cerebellum, brainstem, spinal cord, and optic chiasm. The patient was found to have a small cell lung carcinoma, which was removed. After excision of the tumor, the cerebellar syndrome improved dramatically and the papilledema disappeared despite aftereffects of the optic neuritis.

Conclusions: These findings were consistent with the diagnosis of a paraneoplastic neurological syndrome, although both optic neuritis and remission of the cerebellar syndrome are uncommon patterns of paraneoplastic syndromes. CV2 antigen expression by the oligodendrocytes of the cerebellum, brainstem, spinal cord, and optic chiasm correlated with the clinical syndrome observed in our patient. However, the precise pathophysiological role of anti-CV2 antibodies is still unknown.

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PARANEOPLASTIC neurological syndromes are rare inflammatory disorders involving single or multiple levels of the central or peripheral nervous systems.¹ They have been attributed to a remote effect of cancer, which is often a small cell lung carcinoma. The illness possibly depends on autoimmune processes directed against antigens shared between the tumor and the nervous system.² Among diverse clinical manifestations, one of the best defined syndromes is paraneoplastic cerebellar degeneration (PCD), either isolated or in association with a more diffuse encephalomyelitis. Its pathological hallmark is a diffuse loss of cerebellar Purkinje cells.¹ Isolated cases of PCD could be associated with anti-Yo antibodies, whereas anti-Hu antibodies have been demonstrated in cases of PCD with encephalomyelitis.^{3,4} Optic neuritis, however, is a particularly rare paraneoplastic syndrome.⁵⁻⁸ Indeed, according to published reports, most paraneoplastic disorders of the visual pathway involve the pho-

toceptors of the retina.⁹⁻¹¹ We describe a patient who suffered a cerebellar ataxia and a bilateral, although asymmetrical, optic neuritis that led us to discover a small cell lung carcinoma. Anti-CV2, a recently described antibody associated with paraneoplastic neurological syndromes,¹² was detected in the patient's serum sample.

REPORT OF A CASE

On August 25, 1995, a 62-year-old man who was a heavy smoker presented with vertigo, sweat, vomiting, and vertical diplopia of abrupt onset. Examination revealed a deviation to the right and a vertical nystagmus, without other neurological signs. On September 7, his state worsened suddenly. He simultaneously developed a painless loss of vision in the left eye and a cerebellar syndrome, characterized by dysarthria, severe gait ataxia, and slight dysmetria and hypermetria of the left limbs. Otherwise, there was no evidence of muscular weakness, pyramidal signs,

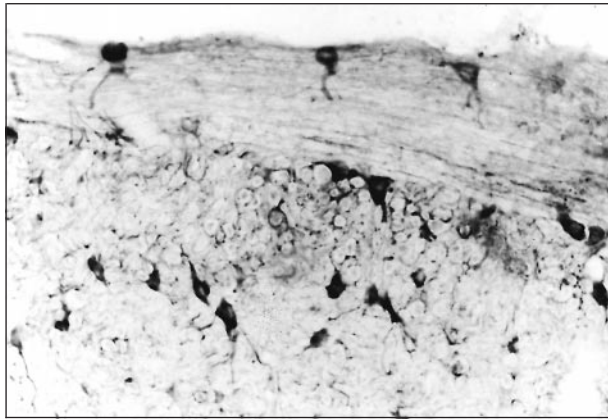


Figure 1. Indirect immunoperoxidase stain of a section of a 6-week-old rat brainstem (ventral spinocerebellar tract and spinal trigeminal nerve tract) incubated with the patient's serum at a dilution of 1:1000. An oligodendroglial staining typical of anti-CV2 antibodies is observed (original magnification $\times 200$).

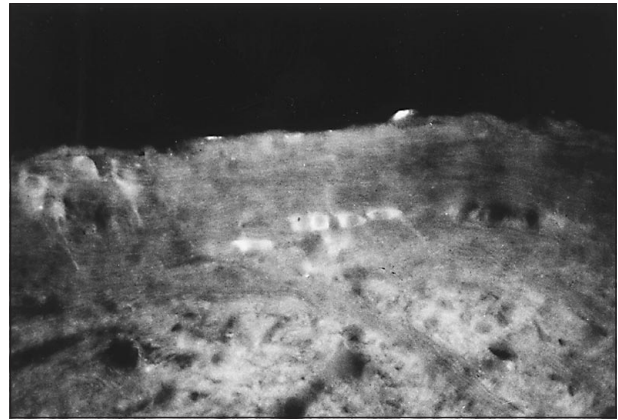


Figure 2. Indirect immunofluorescence of a section of a 6-week-old rat optic chiasm incubated with the patient's serum at a dilution of 1:1000. Labeled interfascicular cells with a clusteringlike string of beads suggestive of oligodendrocytes are observed (original magnification $\times 200$).

sensory loss, cranial nerve palsy, or loss of deep tendon reflexes. The visual acuity was 20/25 in the right eye and less than 20/400 in the left eye. The pupillary functions were normal. Funduscopic examination revealed bilateral swelling of the optic discs, which was more prominent in the right eye. Fluorescein angiography showed marked leakage in the area of the optic discs, also prominent in the right eye, and a slight impregnation of the walls of the retinal veins in the left eye. Visual field and visual-evoked potentials could not be studied at that time. The static cerebellar syndrome worsened progressively, and 1 month later, the patient could no longer stand or sit and his speech was unintelligible.

The findings of computed tomography and magnetic resonance imaging of the brain were unremarkable. The results of the following laboratory investigations were normal: a routine blood chemistry profile, blood cell counts, erythrocyte sedimentation rate, protein electrophoresis, and determinations of C reactive protein, angiotensin-converting enzyme, and antinuclear, anticardiolipine, and anticytoplasmic antibody levels. Because a disseminated coagulopathy was suspected, coagulation testing was performed and revealed no abnormalities. Electroencephalography showed some bilateral anterior slow waves. Cerebrospinal fluid analysis revealed the following values: glucose, 3.8 mmol/L (68 mg/dL); chloride, 109 mmol/L; protein, 0.86 g/L; IgG index, 1.18 (normal, <0.50); and leukocytes, 2×10^6 , some with a plasmacytic differentiation. There were no abnormal cells.

A paraneoplastic syndrome was suspected. Three months previously, in May 1995, a chest x-ray film and a thoracic computed tomographic scan had revealed a left hilar opacity suspected to be an adenopathy. The results of bronchofibroscopy and cytologic and histologic analysis were unremarkable. In September 1995, a second thoracic computed tomographic and magnetic resonance imaging scan failed to show an increase in the size of this isolated adenopathy; bronchofibroscopy again revealed no abnormalities; and tumoral markers (carcinoembryonic antigen, α -fetoprotein, carbohydrate 19.9, prostate-specific antigen, neuron-specific enolase, and CYFRA 21-1) were

absent. Serum and cerebrospinal fluid samples were negative for the usual paraneoplastic antineuronal antibodies (anti-Hu, anti-Yo, and anti-Ri) detected by immunohistochemical and Western-blot techniques, as previously reported.¹³ However, indirect immunohistochemical studies with adult rat brain demonstrated the presence of antibodies that reacted with the cytoplasm of a subpopulation of oligodendrocytes in the white matter of the cerebellum, brainstem, and spinal cord (**Figure 1**), as observed in patients with anti-CV2 antibodies.¹² Using Western blots of a soluble fraction of newborn rat brain proteins, a characteristic 66-kd band was identified in the serum sample. The identity of the antibody was confirmed by immunoprecipitation of the CV2 protein¹² and by an immunohistochemical competition assay in which preincubation of a section of rat brain with the patient's serum sample blocked the reactivity of a previously characterized biotinylated anti-CV2 antibody (data not shown). By indirect immunofluorescence, the anti-CV2 antibody titer was 1:10 000. Using adult rat optic chiasm sections (**Figure 2**), we confirmed, by indirect immunofluorescence, the presence of oligodendroglial cells expressing CV2 antigen in this structure.

Explorative thoracotomy was performed on November 2, and the results of the operative examination confirmed the existence of a small cell lung neuroendocrine carcinoma. Therefore, an intrapericardic pneumectomy with ganglionic curettage was performed. The primary lung tumor was small and peripheral, without pleural invasion. There was a single massive lymph node metastasis but with an intact capsule. Treatment was completed with chemotherapy (cisplatin [total dose, 1200 mg] and etoposide [total dose, 3600 mg]), which was initiated December 20, 1995, and mediastinal and subclavicular radiation therapy, which was initiated January 17, 1996.

As soon as the patient was extubated, his speech seemed better. The static cerebellar syndrome improved dramatically over the following month. On December 4, 1995, the patient's speech was absolutely normal, as was his capacity to sit. He could stand up and walk with help. The vertical nystagmus had improved. The slight hypermetria and dysmetria of the left limbs was

still present. A bilateral Babinski sign had appeared. The left and right fundi became normal, but the visual acuity had not improved much (20/20 in the right eye, 20/200 in the left eye). A visual field study revealed a central scotoma of the left eye. Pattern-reversal visual-evoked potentials were severely affected in the left eye and had a delayed latency in the right eye (P100 wave, 127 milliseconds). The findings of retinal fluorescein angiography were normal except for a small scar on the left macula. Anti-CV2 antibodies were still detected in the serum sample at a titer of 1:5000. In June 1997, the patient's disability was slightly improved in comparison with the postsurgical period in December 1995, as the patient could walk without assistance for a short distance. There was no known tumor recurrence.

COMMENT

Our patient presented with an acute cerebellar syndrome associated with a loss of vision in the left eye and bilateral optic disc swelling. These symptoms occurred without evidence of vascular disease, and the presence of a circulating anti-CV2 antibody suggested a paraneoplastic disorder and led us to suspect, diagnose, and treat a small cell lung neuroendocrine carcinoma. The occurrence of a mild pyramidal syndrome suggested an encephalomyelitis with a predominant cerebellar syndrome rather than a pure cerebellar degeneration. Surprisingly, a dramatic improvement of the cerebellar syndrome occurred after the surgical excision of the tumor; the papilledema also disappeared. The 3 particular points of this case are (1) the presence of anti-CV2 antibodies; (2) the optic neuritis, which is an unusual paraneoplastic syndrome; and (3) the remission of the cerebellar syndrome, which is uncommon.

Anti-CV2 autoantibodies have been reported in 11 patients with paraneoplastic neurological syndromes.¹² These antibodies recognized a 66-kd soluble protein developmentally regulated and specifically expressed in the adult brain by a subpopulation of oligodendrocytes in the white matter of the brainstem, spinal cord, and cerebellum.¹² There are no specific related tumors or specific neurological syndromes, although small cell lung carcinoma and cerebellar degeneration are the most frequent of both tumors and symptoms. The exact pathophysiological role of anti-CV2 antibodies is as yet unknown. Although anti-CV2 antibodies recognize an oligodendrocytic antigen in the adult brain, no demyelination was observed in the brains in 3 reported autopsy cases in which the patients had circulating anti-CV2 antibodies.^{12,14} Nonetheless, the detection of these autoantibodies in patients with neurological disorders is a useful tool to indicate the presence of an occult tumor when tests are negative for anti-Hu, anti-Ri, and anti-Yo antibodies.

Paraneoplastic ophthalmologic syndromes are usually retinopathies and rarely optic neuritis.^{9-11,15} None of the patients with retinopathy described in the literature simultaneously developed a neurological syndrome, with the exception of the atypical case reported by Antoine et al.¹⁴ Clinically, paraneoplastic retinopathy is characterized by a triad associating photosensitivity, ring scotoma, and narrowing of the caliber of the retinal arteri-

ole.¹¹ Although our patient had slight changes in the left retinal veins and, thereafter, a small macular scar, a retinopathy is unlikely, as none of the characteristic symptoms were observed. On the contrary, the sudden onset and painless loss of vision concomitant with bilateral swelling of the optic discs, left central scotoma, and altered visual-evoked potentials point to a bilateral, asymmetrical optic neuritis. The coexistence of the optic neuritis with the cerebellar syndrome, the absence of vascular or general inflammatory disease, and the remission of papilledema after the excision of the tumor strongly suggest a paraneoplastic syndrome, even if paraneoplastic optic neuritis is a very rare entity. Indeed, to our knowledge, only 4 convincing cases have been reported.⁵⁻⁸ Some have occurred in association with encephalomyelitis^{6,7}; others, with concomitant damage of the retina.^{10,15} One of the cases reported by Malik et al⁸ is clinically the most similar to ours, as it includes small cell lung carcinoma, a cerebellar syndrome, and optic neuritis. Furthermore, these authors reported autoantibodies in the patient's serum sample that were directed against neuronal and glial cells of the cortex, cerebellum, and optic nerve and that could contain an anti-CV2 antibody. In the reported cases of paraneoplastic optic neuritis, anatomical data have emphasized marked and specific demyelinating lesions of the optic nerve,⁵⁻⁸ rather than nonspecific perivascular inflammation^{6,7} and axonal loss. However, although our study has demonstrated that the CV2 antigen is expressed by oligodendrocytes in the chiasm, which would suggest a possible immune involvement of this structure, without a pathological examination we are unable to conclude that there is demyelination.

Interestingly, visual abnormalities seem more frequent in patients with paraneoplastic neurological syndromes that are associated with anti-CV2 antibodies rather than with other autoantibodies. Indeed, although Yo, Hu, and Ri antigens are also expressed by the retina,^{16,17} to our knowledge visual loss has not been reported in patients with anti-Hu or anti-Ri antibodies, and only 2 of 55 patients with anti-Yo antibodies and PCD have been described as having progressive visual loss, although with few details.⁴ On the contrary, 2 of 11 patients with anti-CV2 antibodies have been described as having visual impairment. One patient developed cerebellar ataxia, sensory neuropathy, and a loss of vision of unknown cause.¹² The second patient demonstrated cerebellar ataxia, sensorimotor neuropathy, and retinopathy with posterior uveitis and expression of CV2 antigen by the retina.¹⁴

Also of note is the dramatic improvement in the cerebellar syndrome in our patient. Although clinical improvement after treatment of the neoplasm is commonly emphasized as characteristic of paraneoplastic syndromes,¹ it is in fact rarely observed in the central nervous system. Obviously, in this instance, the remission of the neurological state after surgical therapy is a very uncommon feature of PCD. In the literature, we found 9 other cases of remission of PCD.¹⁸⁻²⁴ Successful treatments have been various: surgical excision of the tumor,^{18,19} immunosuppressive therapy with cyclophosphamide,^{21,24} intravenous immunoglobulin therapy,^{22,23} and plasmapheresis.²⁰ Rapid therapeutic response is usually observed, and a complete recovery from neurologi-

cal deficit has been documented. The importance of early diagnosis and treatment, after the onset of the neurological disease, is stressed by all authors. Unresponsiveness to treatment might therefore be explained by delayed therapy and then by irreversible neuronal damage. Nonetheless, even early treatment is believed to be of little value.^{3,4,25} As none of the cases with remission includes histopathological data, the question arises as to the nature of the cerebellar lesions that were observed. Namely, is the illness at a stage where Purkinje cell damage is reversible, or could a lesion other than loss of the Purkinje cell, which characterizes PCD, explain the ataxia?

CV2 antigen expression by the oligodendrocytes of the cerebellum, brainstem, spinal cord, and optic chiasm, but not by the oligodendrocytes of the cerebral hemispheres, is correlated with the occurrence of the cerebellar syndrome and optic neuritis observed in our patient. However, demyelination is unlikely to explain these neurological symptoms, because this lesion was not observed in the 3 autopsy cases involving patients with circulating antibodies.^{12,14} Therefore, other mechanisms should be hypothesized to explain the neurological dysfunction, such as an immune-mediated secretion or a toxic secretion of cytokines. However, more data are necessary before a conclusion can be reached regarding the etiological significance of circulating anti-CV2 antibodies in patients with paraneoplastic neurological syndromes.

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