CRMP-5-Autoantibodies in Testicular Cancer Associated with Limbic Encephalitis and Choreiform Dyskinesias

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Dear Sir,

In addition to the well-known paraneoplastic-syndrome-associated antineuronal autoantibodies anti-Hu, anti-Yo and anti-Ri, a variety of different autoantibodies has been described in paraneoplastic neurological syndromes (PNS). One of these antibodies is an autoantibody binding to collapsin-response-mediating protein 5 (anti-CRMP-5) [1], a phosphoprotein belonging to a group of proteins being important for axonal growth and also expressed in oligodendrocytes [2]. This antibody is most likely identical with the antibody labeled anti-CV-2 some years earlier [3, 4]. There is no distinguishable neurological syndrome related to the presence of anti-CRMP-5, but most patients suffer from peripheral neuropathy, including optic neuropathy or movement disorders [5]. Most cases are associated with small-cell lung cancer, but association with other tumors like thymoma has been reported as well [1] (table 1). An association with germinal cell tumors has not been reported so far. These patients may have anti-Ma autoantibodies, a group of antineuronal nuclear autoantibodies. We here describe a patient presenting with symptoms of a limbic encephalitis and choreiform dyskinesias associated with anti-CRMP-5 due to a testicular tumor.

Case Report

A 40-year-old man presented with agitation, disorientation and optical hallucinations. He had a history of a malignant seminoma that had been treated with orchiectomy 7 years previously. He was admitted to a psychiatric ward of an outside general hospital but was transferred to our neurology service after he had had an epileptic seizure on admission day. At admission in our department, he was mildly disoriented. He also showed moderate amnesic symptoms and mild dysarthria, but neurological examination revealed no other abnormalities. A cranial magnetic resonance imaging study including contrast enhancement with gadolinium and a routine electroencephalogram were both normal. Cerebrospinal fluid (CSF) analysis showed 18 lymphocytes with no other abnormalities. He was treated with aciclovir until herpes simplex virus polymerase chain reaction proved to be negative, and additionally with ampicillin and ceftriaxone. Within 2 days he became increasingly agitated and suffered 2 more epileptic seizures necessitating anticonvulsive therapy with carbamazepine. Within the next few days, he became somnolent and developed severe swallowing and breathing difficulties. In addition, the patient developed

orofacial and manual choreiform dyskinesias. An electroencephalogram at that time showed diffuse generalized slowing without any epileptiform discharges. Cranial magnetic resonance imaging including arterial and venous angiography was again completely normal. Due to respiratory failure the patient was sedated, intubated and put on mechanical ventilation 8 days after symptom onset, and subsequently transferred to our hospital's neurological intensive-care unit. In spite of discontinuation of the sedation, the patient remained comatose but showed persistent and severe choreiform dyskinesias that did not respond to tiapride, benzodiazepines or baclofen. CSF analysis showed 14 lymphocytes, a total protein content of 343 mg/l and oligoclonal bands. Antibodies against neurotropic viruses, *Borrelia* and *Treponema* were negative in CSF and serum, as was a screening for the most frequent paraneoplastic antineuronal antibodies (anti-Hu, -Yo and -Ri). A whole-body fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed a contrast-enhancing and FDG-positive structure (4 × 3.5 × 7 cm) near the right iliac artery, most likely corresponding to 2 neighboring lymphatic nodes. No other abnormality was ob-

Table 1. Cases with paraneoplastic neurological symptoms and anti-CRMP-5

Author	n	Age years	Gender	Neurological symptoms	MRI	Tumor	Other antibodies	CRMP titer	Outcome
This case	1	40	m	agitation, seizure, cognitive deficits, cranial nerve deficits, limbic encephalitis, choreiform dyskinesia	normal	testicular cancer	negative	1:64,000	improvement after tumor resection and chemotherapy
Kinirons et al. [9], 2003	1	62	m	confusion, choreiform movements, nystagmus, ataxia	bilateral striatal hyperintensity	SCLC	no detailed data	1:64,000	died from sepsis
Cross et al. [6], 2003	16	52–74	9 f 7 m	optic neuritis 16, cognitive 4, Sz 1, cranial nerves 5, peripheral nerves 5, myoclonus 1, chorea 1, dyskinesia 1, cerebellar 5	abnormal signal changes in 10/10	SCLC	10 with additional antibodies: Ca channel, amphiphysin, ANNA-1	from 1:1,000 to 1:500,000	5 improved after tumor therapy, prednisone, plasmapheresis
Yu et al. [1], 2001	121	44–88	no detailed data	seizures 11, psychosis 4, dementia 29, chorea 12, athetosis 1, cerebellar 26, opsoclonus/myoclonus 6, spinal 19, neuromuscular 14	no detailed data	lung 89 (SCLC 69), thymoma 7, colon 2, skin 2, breast 1, prostate 1, ureter 1, B lymphoma 1, brain 1	no detailed data	u.k.	u.k.
Vernino et al. [5], 2001	16	69 mean	10 f 6 m	chorea 16, dystonia 4, limbic encephalitis 5, cerebellar 3, taste/smell 4, polyneuropathy 5, vision loss 5	no detailed data	SCLC 12, renal 1, NHL 1, lung mass 2	positive: ANNA-1 6, Ca channel 5, K channel 1	from 1:256 to 1:61,000	9 alive after 17–38 months
Medrano et al. [10], 2003	1	73	m	ataxia, nystagmus	no detailed data	adenocarcinoma lung	ANNA-1 negative	u.k.	dead
Shams'ili et al. [11], 2003	5	no detailed data	no detailed data	sensory neuropathy 3, limbic encephalitis 1, encephalomyelitis 1	no detailed data	no detailed data	no detailed data	u.k.	u.k.
Samii et al. [12], 2003	1	49	f	chorea, oropharyngeal dysmotility	MRI negative	NHL	negative	not given	no change despite chemotherapy
Joshi et al. [13], 2003	1	17	f	aseptic meningitis	no detailed data	chondroblastoma	AChR antibody, PCA-2 positive	u.k.	u.k.
Honnorat et al. [14], 1996/ Rogemond and Honnorat [15], 2000	23	45–77	8 f 15 m	cerebellar 9, limbic encephalitis 3, polyneuropathy 6, encephalomyelitis 6, optic neuropathy/uveitis/retinitis 3, myasthenia 2	u.k.	SCLC 13, thymoma 3, uterine sarcoma 2, neuroendocrine 1, undetermined 3, prostate 1	ANNA-1, PCA, ANNA-2, AChR in 8 patients positive	from 1:1,000 to 1:100,000	u.k.
Antoine et al. [16], 1999	1	62	f	polyneuropathy, cerebellar	u.k.	mediastinal carcinoma	no detailed data	u.k.	u.k.
de la Sayette et al. [8], 1998	1	62	m	cerebellar, optic neuritis bilateral	u.k.	SCLC	no detailed data	u.k.	improved after resection

f = Female; m = male; u.k. = unknown; Sz = seizure; SCLC = small-cell lung cancer; NHL = non-Hodgkin lymphoma; ANNA = antineuronal nuclear antibodies; PCA = Purkinje cell antibodies; AChR = acetylcholine receptor.

served. α -Fetoprotein concentration was 28 ng/ml (normal <7), but human chorionic β -gonadotropin and β_2 -microglobulin were normal. The patient underwent laparotomy for removal of the suspect structures. Histology showed a malignant mixed tissue germinal tumor. In addition, serum samples were sent to another laboratory to look for other antineuronal autoantibodies. Anti-CRMP-5 could be detected in a Western blot using recombinant CRMP-5 (titer 1/64,000). All other antineuronal autoantibodies tested (anti-amphiphysin, anti-Tr, antineuronal nuclear antibody 3, Purkinje cell antibody 2, anti-Ma) were negative. The patient underwent 5 cycles of plasmapheresis and afterwards chemotherapy (cisplatin, etoposide, bleomycin). His cognitive and neurological functions gradually improved over the next 2 weeks. He was weaned from the respirator and was discharged awake and communicating.

Discussion

Anti-CRMP-5 antibodies have been found predominantly in patients with peripheral and optic neuropathy and small-cell lung cancer or thymoma (table 1). In our patient, however, extensive investigations including high-resolution thoracic CT scan and whole-body combined FDG-PET/CT did not show any sign of lung tumor. However, a germ cell tumor could be found, and the patient's symptoms improved remarkably after resection of the tumor.

Whether anti-CRMP-5 itself has pathogenic effects on the nervous system structure or is only the diagnostic hallmark of a T-cell-driven autoimmune process remains to be elucidated. Most PNS are obviously T cell mediated and therefore their effective treatment is still a major problem. Plasmapheresis, intravenous immunoglobulin therapy and corticosteroids were helpful in some cases [6]. However, most patients do not respond to immunosuppressants or immunomodulators. Treatment of the underlying tumor itself has

been shown to be the only significant factor for stabilization of the PNS in anti-Hu-positive patients [7] and seems to be beneficial in anti-CRMP-5-positive patients [5, 6, 8]. As this case report illustrates, unexplained neurological symptoms, suspect for a paraneoplastic disease, may require an intensive tumor screening including combined PET-CT.

Although chorea or other movement disorders can be found in a high proportion of anti-CRMP-5-positive patients, other neurological symptoms are more frequent (table 1). Typically, the clinical presentation of the PNS does not correlate with a distinct antineuronal antibody. Therefore, a careful screening for all antineuronal antibodies such as the subtypes of antineuronal nuclear antibodies, Purkinje cell antibodies, anti-amphiphysin and anti-CRMP-5 should be performed.

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