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Paraneoplastic Limbic Encephalitis Associated with Anti-CV2/CRMP5 Antibodies Secondary to Thymoma in an Adolescent

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Abstract
Paraneoplastic neurological syndromes (PNS) associated with anti-CV2/CRMP5 antibodies are rare in the literature. Various clinical manifestations can occur including paraneoplastic limbic encephalitis (PLE). Thymoma is one of the rare causes that can be associated with this syndrome. It has not been reported in the literature in children or adolescents to the best of our knowledge. We report a case of PLE in a 19-year-old male patient secondary to thymoma that was diagnosed after 5 years of onset. Anti-CV2/CRMP5 antibodies were positive in the serum and became negative after thymectomy. Diagnosis of PNS should be evoked in cases with atypical neurological manifestation and can be confirmed by the presence of onconeuronal antibodies. We report the first pediatric PLE secondary to thymoma associated with anti-CV2/CRMP5 antibodies.

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Introduction

Paraneoplastic neurological syndromes (PNS) associated with anti-CV2/collapsin response mediator protein (CRMP) 5 antibodies are rare and often precede the cancer itself. They can present with different neurological manifestations and must be kept in mind, especially in patients with atypical clinical manifestations.

Paraneoplastic limbic encephalitis (PLE) is a form of autoimmune encephalitis affecting the central nervous system secondary to autoantibodies against neuronal intracellular antigens, typically manifesting with seizures, mental and behavioral changes.

Herein, we present the clinical characteristics, diagnosis, treatment, and follow-up of one patient with PLE secondary to anti-CV2/CRMP5 antibodies in an adolescent secondary to thymoma. His imaging showed bilateral hippocampal sclerosis and atrophy.

Case Report

We report the case of a remote PLE in a 19-year-old male patient secondary to a thymoma. He is the only son of non-consanguineous parents, with a normal peri-natal history and normal developmental milestones.

His symptoms started 5 years prior, at the age of 14, with a subacute onset of personality changes, aggression, irritability, hyperactivity, memory changes, and sleep disturbance. He became distractible with poor attention and concentration, started beating his colleagues, missing his classes with constant truancy, fidgeting all the time and was involved in several impulsive acts that led to his arrest by the police a few times.

A local psychiatric hospital diagnosed him with attention-deficit/hyperactivity disorder, and he was treated with methylphenidate (Ritalin) 10 mg orally twice daily and risperidone 1 mg twice daily. His intelligence quotient (IQ) testing at that time showed lower scores in both verbal and performance aspects (70 and 56, respectively). He showed poor response to treatment and the dosage was increased to the maximum tolerable doses of both drugs, but the symptoms persisted. Atomoxetine (Strattera) was added with no superadded benefit. Clonazepam (Rivotril) was given at a dose of 2 mg twice daily and the patient started to be less hyperactive and sleep improved. Sodium valproate (Depakine) was added because his EEG showed bitemporal epileptiform discharges despite not having seizures. His cognitive and behavioral symptoms persisted with poor scholastic achievements and multiple social and legal problems. The family sought a second opinion in our Neurology Department 5 years after the onset of symptoms.

He was alert and oriented but showed poor attention and concentration, short-term memory loss with intact long-term memory, visuospatial orientation and language. His MMSE was 23/30 and the MoCA test was 22/30.

He had elated mood but with no active psychotic features. He had normal speech, cranial nerves, motor, sensory and cerebellar functions, but was hyperactive with continuous fidgeting and distractibility throughout the examination.

MRI of the brain showed bilateral T2/FLAIR hyperintensity involving the medial temporal lobes with hippocampal sclerosis and atrophy (Fig. 1). No brain imaging had previously been done for comparison.

A comprehensive laboratory workup was done to rule out a paraneoplastic and a non-paraneoplastic origin of limbic encephalitis including anti-Hu, Yo, CV2/CRMP5, Ri, Ma2,

amphiphysin, NMDA, GAD, and VGKC antibodies as well as auto-immune antibodies (ANA, dsDNA, ENA, ANCA). Only anti-CV2/CRMP5 antibodies were positive in the serum.

Lumbar puncture was performed and cerebrospinal fluid (CSF) analysis showed normal glucose, mildly elevated protein and no pleocytosis or oligoclonal bands. Electroencephalography (EEG) showed bitemporal slow waves.

Given the initial subacute onset of memory and behavioral changes with positive anti-CV2/CRMP5, a PLE was suspected despite the unusual delayed presentation. Computed tomography (CT) of the chest showed anterior mediastinal mass (Fig. 2). It was surgically resected and histopathological analysis showed thymoma stage IIa.

Repeat serum anti-CV2/CRMP5 antibodies 6 months postoperatively at the same laboratory was negative. The clinical condition of the patient has not shown much improvement though.

Discussion

PNS result from immune cross-reactivity between tumor cells and components of the nervous system by formation of "onconeural antibodies" and associated onconeural antigen-specific T lymphocytes. They affect less than 1/10,000 patients of all cancer patients and they can usually precede clinically detectable malignancy by up to 5 years in 70–80% of the cases. Less than half of the patients with PNS have paraneoplastic antibodies and their absence should not rule out the diagnosis of PNS [1].

Onconeural antibodies are classified into 3 main categories: (a) well-characterized antibodies with a strong cancer association (anti-amphiphysin, anti-CV2 [CRMP5], anti-Hu [ANNA-1], anti-Ma2, anti-recoverin, anti-Ri [ANNA-2], and anti-Yo [PCA-1]), (b) partially characterized antibodies (ANNA-3, anti-mGluR1, anti-Tr, anti-Zic4, PCA-2), and (c) antibodies occurring in both cancer- and non-cancer-associated syndromes (anti-acetylcholine receptor [AchR], anti-nicotinic AchR, anti-VGCC, anti-VGKC) [2]. These antibodies are directed against 2 categories of antigens: (a) intracellular or classic paraneoplastic antigens, including anti-Hu, Ma2, CV2/CRMP5, and amphiphysin among others, and (b) cell membrane antigens, including voltage-gated potassium channels, N-methyl-D-aspartate (NMDA) receptor and others [3].

Diagnostic criteria for a "definite" PNS require a neurological syndrome (classical or not) with well-characterized onconeural antibodies (e.g., CV2/CRMP5) and no cancer, which was fulfilled in our patient. However, the maximal interval period between neurologic symptom presentation and diagnosis of a tumor, which has been suggested to be 5 years in adults, should apparently be tailored in a pediatric age group as it can be shorter in aggressive tumors or longer leading to diagnosis delay [4].

Limbic encephalitis was initially described in the 1960s as a clinicopathological syndrome in adults. It is an inflammatory process that is usually highly confined to structures of the limbic system manifesting with subacute onset and rapidly progressive short-term memory deficit, which is the hallmark of the disease followed by mood changes, hallucinations, sleep disturbance and seizures. In 70–80% of patients, MRI fluid-attenuated inversion recovery (FLAIR) or T2 sequences show hyperintense signals in the medial portion of one or both temporal lobes [5].

Diagnosis is suggested by a classical clinical picture combined with findings on EEG, MRI, inflammatory CSF changes and well-characterized onconeuronal antibodies.

Limbic encephalitis has both a paraneoplastic and non-paraneoplastic etiology with a similar clinical picture. Identification of the paraneoplastic cause depends on finding the

tumor, the paraneoplastic antibodies, or both. The tumors more frequently involved are small-cell lung cancer (SCLC) (40–50%), testicular germ cell neoplasms (20%), breast (8%) and less commonly Hodgkin's lymphoma, teratoma and thymoma. Antibodies associated with limbic encephalitis are anti-Hu, anti-Ma2, anti-amphiphysin and anti-CV2/CRMP5 [1].

PNS associated with anti-CV2/CRMP5 antibodies are rare. They can present with limbic encephalitis, chorea, sensorimotor neuropathy, cerebellar ataxia, uveitis, and optic neuritis. Anti-CV2/CRMP5-associated limbic encephalitis is, however, a rarer disease that equally involves males and females of median age [6].

Most cases are associated with SCLC, but association with other tumors like thymoma has been reported and considered characteristic for this antibody. Other associated tumors include colon, renal and breast cancer [6].

Anti-CV2/CRMP5 antibodies were named after the index patient (initials CV with confirmatory second sample), and they were later found to target an intracellular protein called "collapsin response mediator protein 5" (CRMP5) [7].

They occur in 5% of people with SCLC, in 12% of people with myasthenia gravis with thymoma, and in 0.6% of the general population. Patients with thymoma and CV2/CRMP5-Ab were found to be younger than those with SCLC and usually developed myasthenia gravis more often. They were correlated with the presence of thymoma, but not with disease severity. Titer was found to be higher in patients with thymoma compared to those with SCLC. It could be detectable for years thus it has poor clinical correlation [8].

Thymomas are rare in children and adolescents and represent 4% of anterior mediastinal masses compared to 36% in adults. Around 70% of PNS with thymoma are myasthenia gravis and PLE was not reported in the literature in the pediatric age group [9]. Retrospective studies indicate that PLE may represent approximately 10% of pediatric limbic encephalitis cases [10, 11].

MRI in anti-CV2/CRMP5 limbic encephalitis may be normal or may show bilateral symmetrical medial temporal lobe T2/FLAIR hyperintensity. Atrophic changes can ensue if untreated. FDG-PET scan shows hypermetabolism in the temporal lobe. EEG may display epileptic foci in temporal lobes with focal or generalized slow activity. CSF analysis shows elevated protein, pleocytosis, elevated IgG index and oligoclonal bands [12].

Treatment of PNS of the CNS in general is challenging, particularly for disorders associated with antibodies against intracellular antigens which probably cause neuronal damage by cytotoxic T-cell mechanisms. Randomized placebo-controlled clinical trials to guide treatment are lacking. Evidence mainly comes from expert opinion, case reports, case series or uncontrolled studies (class IV). Treatment options for limbic encephalitis in addition to discovery and removal of the culprit tumor will include several immunomodulatory options: intravenous immunoglobulins, methylprednisolone, plasma exchange, cyclophosphamide, and rituximab. Supportive treatment includes antiepileptic drugs and psychopharmacologic agents [13].

Prognosis is a complex issue and depends on several factors, but tends to be poor for patients with antibodies against intracellular neuronal antigens as in our case [14].

Our case is unusual in many aspects. PLE secondary to anti-CV2/CRMP5 antibodies is a rare entity in the literature, association with thymoma is not commonly encountered in clinical practice and it has not been reported in childhood or adolescence to the best of our knowledge. Another aspect is the delayed discovery of the tumor causing the symptoms, as his symptoms had first been attributed to a primary psychiatric disorder for 5 years till the workup yielded positive onconeuronal antibodies and thymoma.

Conclusion

PLE associated with anti-CV2/CRMP5 antibodies is a rare disorder that may rarely occur secondary to thymoma in the pediatric age group. Our case highlights the importance of a comprehensive workup for patients with subacute and progressive short-term memory loss, and behavioral changes with or without seizures. Onconeuronal antibodies are sensitive tools for pointing to underlying malignancy. Remote and delayed presentation should not be used as exclusion criteria for paraneoplastic syndromes as well as presentation during childhood or adolescence.

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Statement of Ethics

The patient provided both oral and written informed consent for the publishing of this report.

Disclosure Statement

The authors have no conflicts of interest to declare.

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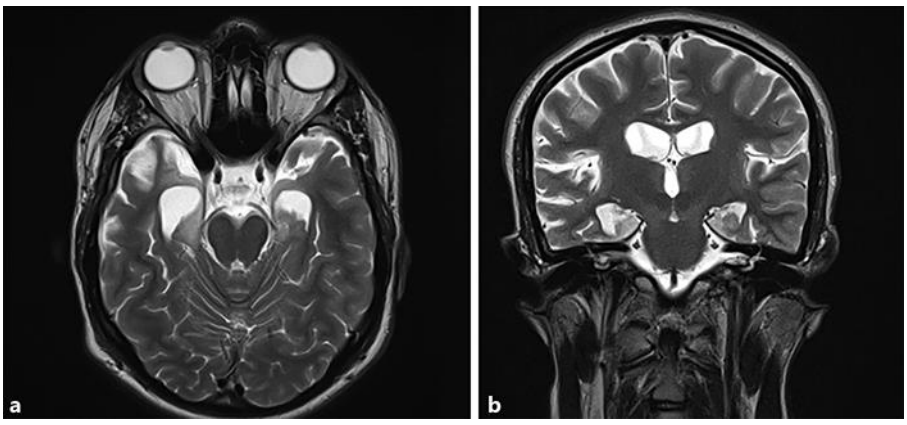

Fig. 1. MR brain. Axial (**a**) and coronal (**b**) T2 showing bilateral hyperintensity involving medial temporal lobes with hippocampal sclerosis and atrophy.

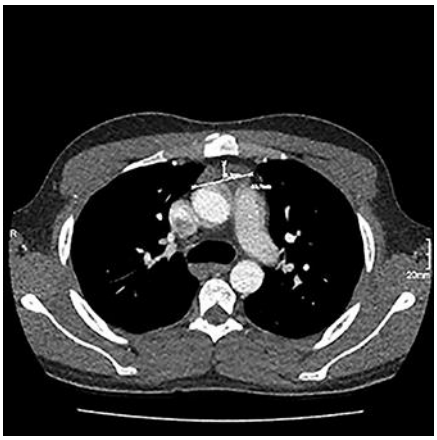

Fig. 2. CT of the chest showing anterior mediastinal mass (thymoma) measuring 40.7 × 17.2 mm.