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Case Report

Paraneoplastic striatal encephalitis and myelitis associated with anti-CV2/CRMP-5 antibodies in a patient with small cell lung cancer

Nese Dericioglu[a,*], Rahsan Gocmen[b], Ersin Tan[a]

[a] Hacettepe University, Department of Neurology, Ankara, Turkey
[b] Hacettepe University, Department of Radiology, Ankara, Turkey

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1. Introduction

Paraneoplastic neurological syndromes (PNS) affecting the central nervous system are infrequent, presenting in < 1% of all those with cancer. The relevant auto-antibodies, that are detected in serum or cerebrospinal fluid, can target either neuronal cytoplasmic/nuclear proteins or neuronal cell surface proteins such as ion channels. The type of antibodies detected may determine the underlying malignancy and also response to immunotherapy.

Anti-CV2/CRMP-5 is a 62-kDa neuronal cytoplasmic protein of the collapsin response-mediator family that is usually correlated with thymoma or small cell lung cancer (SCLC). The PNS associated with anti-CV2/CRMP-5 is generally characterized by encephalomyelitis, paraneoplastic sensory neuronopathy, uveitis or chorea [1]. We have recently encountered a patient with prominent motor weakness and behavioral changes whose cranial MR investigation was compatible with striatal encephalitis and spinal MR imaging revealed longitudinal myelitis. Paraneoplastic antibody screening was positive for anti-CV2/CRMP-5 antibodies. Meticulous workup disclosed small cell lung cancer (SCLC) as the underlying pathology.

2. Case report

A 54-year-old female patient was admitted due to weakness in the left arm and both legs. Her complaints began a year ago with left leg weakness and accompanying pain below the knee. Three weeks prior to admission she developed severe weakness in both legs and left arm. Her family also noticed abnormal movements in both arms. Meanwhile she also displayed altered behavior, and seemed to be more nervous than ever. She spoke too much, tended to repeat the same sentences, and could only sleep two hours at night. The patient had lost weight within the last 3 months. Besides, she complained of shortness of breath. Her past medical history revealed hypertension, total abdominal hysterectomy for uterine leiomyoma and cigarette smoking (one package per day for 30 years). Family history disclosed lung cancer in her mother. On neurologic examination she was conscious, however had difficulty in obeying commands. She had paraparesis and left upper extremity weakness, with corresponding hyperactive deep tendon reflexes. Cranial nerve functions and sensory exam were normal. Choreiform movements were not evident upon admission.

Her complete blood count, biochemistry and blood tumor markers (alpha-fetoprotein, CA-125, CA15-3, CA19-9, carcinoembryonic antigen) were within normal limits. ESR was 24 mm/h. CSF protein was 51.2 mg/dL, glucose was 86 mg/dL. There were no neoplastic cells on cytologic examination. IgG index was 3.8 and oligoclonal band studies were compatible with intrathecal synthesis. Electrophysiologic studies suggested anterior horn motor neuron or multiple radicular involvement in the cervical and lumbar regions (supplementary Tables 1 and 2). Cranial MR imaging was impressive for bilateral symmetrical hyperintensity in basal ganglia, especially corpus striatum (Fig. 1A–C). MR perfusion showed mildly decreased blood volume (Fig. 1E), and MR spectroscopy indicated mildly decreased NAA peak (Fig. 1F). Spinal MR in cervical and thoracic segments revealed longitudinally extensive abnormal T2W signal (Fig. 1D). Due to the possibility of paraneoplastic striatal encephalitis and myelitis the patient underwent computed tomography of the chest, which was reported as two separate mass lesions

* Corresponding author at: Hacettepe University, Faculty of Medicine, Department of Neurology, Sihhiye, 06100, Ankara, Turkey.
E-mail address: nesedr@hacettepe.edu.tr (N. Dericioglu).

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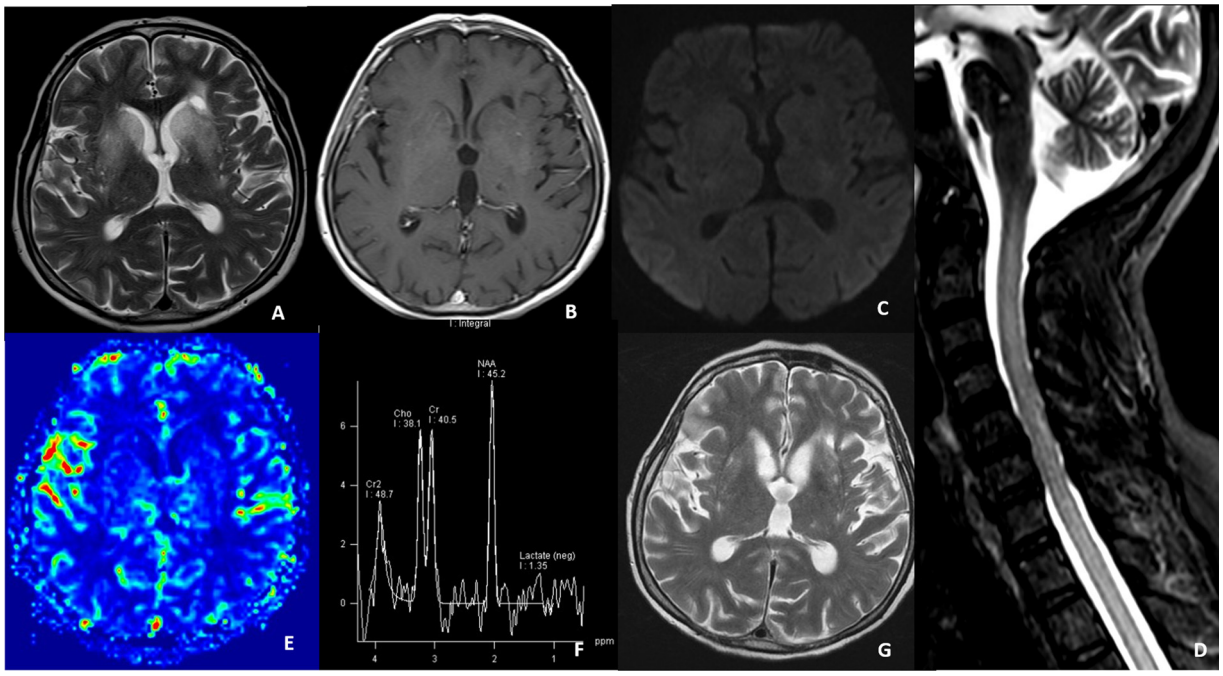

Fig. 1. (A–G): MRI findings at the time of the neurologic event (A–F) and at follow-up one month later (G). Axial T2W image (A) shows symmetrical hyperintensity in the bilateral caudate nuclei and putamina. There is no contrast enhancement (B), diffusion restriction (C), hemorrhage, or expansion. Sagittal cervical spine T2W MRI image (D) shows longitudinally extensive T2 signal abnormality extending over 10 spinal segments. T2* MR perfusion -cerebral blood volume color map- (E) demonstrates mildly decreased blood volume. ^{1}H MR spectroscopy (TE = 135 msec) (F) shows mildly decreased NAA peak; no abnormal lactate peak is observed. Follow-up axial T2W image (G) reveals substantial resolution in previously affected regions.

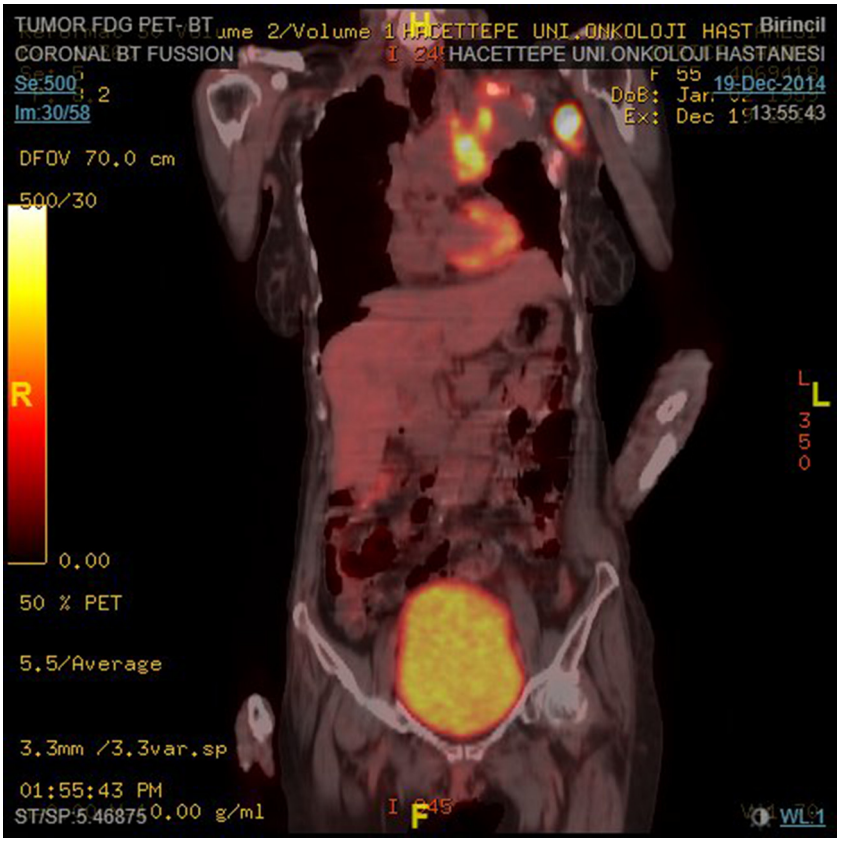

Fig. 2. Coronal PET image of the body demonstrates increased FDG uptake in two separate lesions located in the upper lobe of the left lung (roughly 4 cm and 3 cm in diameter; SUV: 12.9 and 14.4) and also left axillary lymph nodes (about 2 cm in diameter; SUV: 18.2).

(44 × 34 mm and 35 × 36 mm) in the upper lobe of the left lung with left axillary lymphadenopathy. FDG-PET displayed pathological FDG uptake in the two previously mentioned pulmonary lesions and left axillary lymph nodes (Fig. 2). FDG uptake of the brain was normal. Bronchoscopic biopsy of the pulmonary lesions was consistent with SCLC. Her paraneoplastic antibody workup (including anti-CV2/CRMP-5, anti-amphiphysin, anti-Ma2, anti-Ri, anti-Yo, anti-Hu and anti-Recoverin) was positive for anti-CV2/CRMP-5. These antibodies were detected by a semi-quantitative immunofluorescence antibody assay and demonstrated the highest possible level. The patient received 1000 mg/day of methyl prednisolone for 5 days. Control cranial MR imaging displayed substantial resolution in previously affected regions (Fig. 1G). Her neurologic symptoms did not improve after steroid therapy, and she was discharged 25 days later. Shortly she was admitted to the oncological intensive care unit because of shortness of breath. Her general medical condition deteriorated rapidly, therefore chemotherapy was not initiated. She died 4 months after discharge from the neurology department.

3. Discussion

We presented a rare case of PNS with striatal encephalitis and longitudinal myelitis due to anti-CV2/CRMP-5 related autoimmunity in a patient with SCLC. Consistent with the MR imaging findings, her history suggested the presence of chorea although we did not observe it upon admission. There are very few cases of paraneoplastic striatal encephalitis (PSE) in the literature [1–3]. All the patients are middle age or elderly, with no gender preference. In most instances the underlying malignancy is SCLC. Autoantibodies are either anti-Hu or anti-CV2/CRMP-5, with some patients having more than one type of antibody [1]. Clinical findings usually consist of choreiform movements, ataxia, vertigo, peripheral neuropathy or dementia. Weakness and emotional lability, as were prominent in our patient, were other less common symptoms. Cranial MR imaging investigations in most previous patients with PSE demonstrated T2W hyperintense signals in the basal ganglia [1–3]. Differential diagnosis of cranial MR imaging findings includes toxic/metabolic disorders, viral encephalitis and autoimmune encephalitis. On the other hand, spinal MR imaging demonstrated longitudinal myelitis. Myelopathy in a paraneoplastic context is most commonly correlated with SCLC. Autoimmune myelopathy associated with CRMP-5 IgG was reported to cause longitudinally extensive lesions in 25% of the patients. Cervical cord biopsy in one patient with thymoma and anti-CRMP5 antibodies revealed reactive gliosis, foci of edema and necrosis, with numerous macrophages and some perivascular lymphocytes [4]. The clinical symptoms and electrophysiological investigations in our patient suggested paraneoplastic anterior horn motor neuron involvement or motor neuropathy without sensory involvement, although radiological findings were more extensive. FDG-PET findings of the brain in PSE are not well known. Contrary to our patient, striatal hypermetabolism was reported in three patients with limbic encephalitis correlated with anti-voltage gated potassium channel antibodies [5]. In another case with anti-CRMP5 antibody associated paraneoplastic chorea, PET was consistent with bilateral caudate hypometabolism [1]. However cerebral PET imaging studies were normal in our patient. Different results may be due to different stages of the disease process in these patients or due to different characteristics of the autoimmune antibodies (i.e. attacking cell surface vs intracellular antigens).

Treatment modalities and response to therapy vary among patients. Chemotherapy was tried in a few patients [1,2], and so far seems to be the best choice of management. Neurologic deficits improved in some cases [1,2]. Corticosteroids, intravenous immunoglobulin or plasmapheresis were not usually helpful. Most patients died within several months of presentation. This finding is not surprising in patients with antibodies directed at intracellular antigen targets (i.e., onconeural antibodies). In these patients the neuronal dysfunction is mediated by cytotoxic T cells and usually results in irreversible neuronal damage. Autopsy studies in a few patients with PSE have shown diffuse perivascular lymphocytic infiltrates, microglial activation and neuronophagia in the striatum or throughout the neuraxis [1,3].

4. Conclusion

Our findings are in line with those of previous cases with PSE. Acute onset of chorea, muscle weakness, behavioral abnormalities in an elderly patient with hyperintense appearance of basal ganglia in cranial MR and spinal imaging should raise the possibility of PNS and prompt the investigation of onconeuronal antibodies (especially anti-Hu and anti-CV2/CRMP-5), especially in patients with high risk for malignancy. Rapid and aggressive tumor treatment may improve outcome in some patients.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.clineuro.2018.05.010

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