case report

Paraneoplastic neuromyelitis optica spectrum disorder associated with stomach carcinoid tumor

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Hematol Oncol Stem Cell Ther 2014; 7(3): 116–119

DOI: http://dx.doi.org/10.1016/j.hemonc.2014.06.001

Neuromyelitis optica (NMO), or Devic's syndrome, is an autoimmune central nervous system demyelinating disorder primarily affecting the spinal cord and the optic nerves. It is characterized by the presence of NMO antibodies, alongside clinical and radiological findings. NMO and NMO-spectrum disorders (NMO-SD) have been reported in autoimmune disorders, and are infrequently described as a paraneoplastic syndrome with cancers of lung, breast, and carcinoid tumors of the thyroid. We report a patient who presented with severe vomiting, blurring of vision, vertigo, diplopia, left hemiparesis and hemisensory loss and ataxia. She was found to have a longitudinally-extensive demyelinating lesion extending from the medulla to the upper cervical spinal cord on MRI. Her gastric endoscopy revealed carcinoid tumor of the stomach, and classic paraneoplastic antibodies in the serum were negative. She had extremely high serum gastrin level and high titer of NMO IgG autoantibody. The patient made an excellent recovery with tumor resection and immunotherapy, with both clinical and radiological improvement. On rare instances, NMO or NMO-SD may present as a paraneoplastic neurological syndrome associated with carcinoid tumor of the stomach.

KEYWORDS: Demyelinating disease (CNS); Devic's syndrome; Autoimmune diseases; Paraneoplastic syndrome; Carcinoid tumor associated with paraneoplastic

Neuromyelitis optica (NMO), or Devic's disease, is an autoimmune, inflammatory central nervous system (CNS) syndrome, characterized by longitudinally extensive transverse myelitis, optic neuritis, and the presence of NMO-IgG autoantibodies.[1] The term NMO-spectrum disorder (NMO-SD) is used to include limited forms of NMO. (1) NMO could coexist with other autoimmune disorders,[2–4] and, rarely, may represent a paraneoplastic phenomenon.[5] We present a case of possible paraneoplastic NMO-SD in the setting of gastric carcinoid tumor. To our knowledge, the association of gastric carcinoid tumors with NMO or NMO-SD has not previously been reported.

CASE REPORT

A 38-year-old woman presented with severe vomiting, vertigo, blurred vision, diplopia, ataxic gait and left-sided numbness of two months' duration. Neurological examination demonstrated bilateral paleness of optic discs, horizontal nystagmus to left, left hemiparesis and hemisensory loss, left Babinski's sign, and gait ataxia.

MRI brain and spine revealed an enhancing hyperintense lesion extending from the medulla to the C2 cord segment (Figure 1A). Visual evoked potentials displayed bilaterally prolonged P-100. Routine blood investigations, ESR, autoimmune work up (ANA, Anti-DNA, SSA, SSB, ANCA, anti-phospholipid antibodies), viral serologies (HIV, HCV, HBV,

CMV, HSV 1 and 2), and VDRL were normal or negative. CSF analysis (cells, protein, sugar, AFB stain, bacterial cultures), and serum paraneoplastic antibodies (Hu, CV2, Ri, Ma2, amphiphysin), tested at Mayo Medical Laboratories, were negative. Serum B12 was low (83 pmol/L), and NMO-IgG was positive with high titer.

The patient had gastric endoscopy for evaluation of persistent vomiting, which revealed five gastric polyps at the antrum, treated with gastric ablation, and biopsy showed type I gastric carcinoid. Serum gastrin level was extremely high.

The patient received a five-day course of intravenous methylprednisolone (1gm/day), followed by

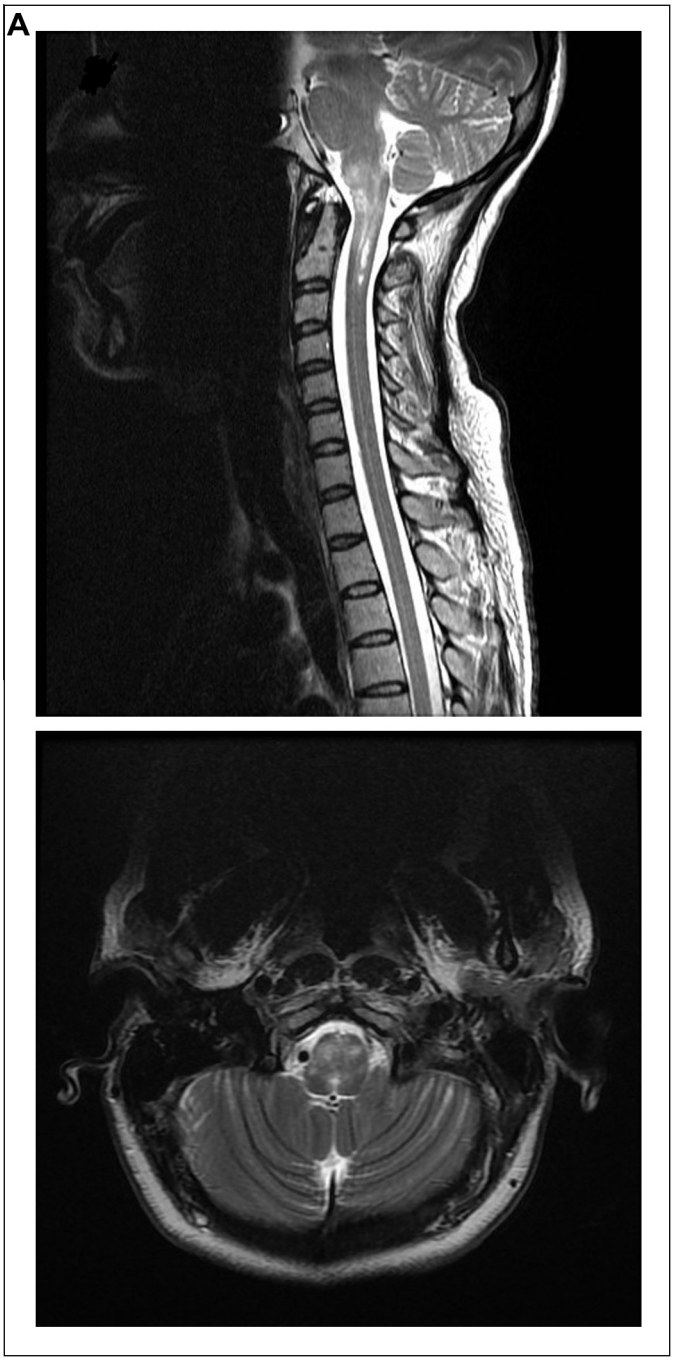

Figure 1A. Pre-treatment sagittal and axial T2-weighted MRI of medulla and cervical spine, showing diffuse, ill-defined hyperintense lesion involving the medulla oblongata and the upper cervical cord.

intravenous immunoglobulin (2 gm/kg over two days). This resulted in marked improvement in her neurological symptoms. She was discharged on prednisolone, azathioprine, and vitamin B12 replacement. Follow-up MRI showed significant regression of the previously observed lesion (Figure 1B), and several gastric endoscopies demonstrated no recurrence of the tumor. Serum gastrin returned to normal.

DISCUSSION

NMO is an autoimmune, inflammatory, demyelinating condition of the CNS, characterized by severe attacks of transverse myelitis and optic neuritis,[1] with at least two of three supportive criteria, consisting of NMO-IgG seropositivity (directed against aquaporin-4 water channels), MRI spinal cord lesions extending more than three vertebral levels, and onset MRI brain

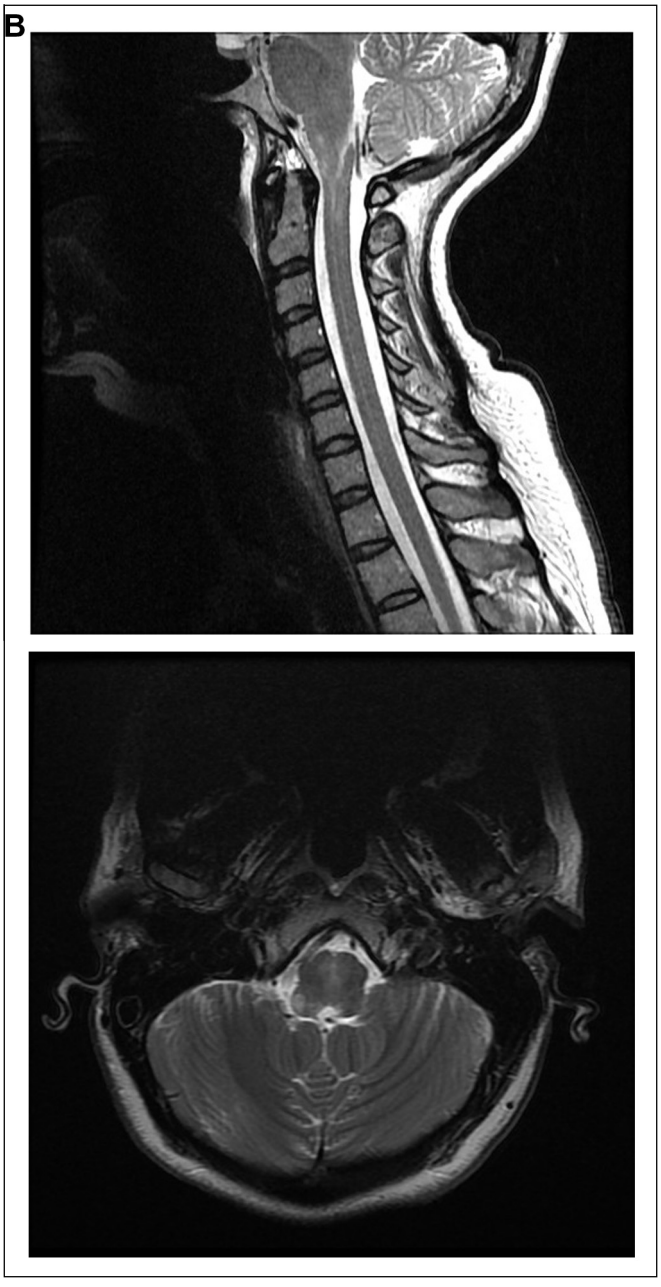

Figure 1B. Sagittal and axial T2-weighted MRI obtained after one year of therapy, showing resolving lesion at the cervicomedullary junction and upper cervical cord.

not meeting diagnostic criteria for multiple sclerosis.[6] NMO-SD is a term also used to include limited forms of NMO, such as isolated single or recurrent forms of transverse myelitis, unilateral or bilateral optic neuritis, Asian optic-spinal multiple sclerosis, and NMO associated with systemic autoimmune disorders. These include systemic lupus erythematosus,[2] Sjögren's syndrome,[3] and myasthenia gravis,[4] and signify the coexistence of two autoimmune disorders rather than a vasculitic complication related to the systemic disease.[1,7] Although rare, NMO may represent a paraneoplastic phenomenon associated with various cancers, including thymoma, breast, and thyroid tumors.[5]

Carcinoids are neuroendocrine tumors that originate from the enterochromaffin cells of the gastrointestinal tract (74%), bronchial system (25%), and other less frequent organs.[8,9] These tumors cause symptoms by local mass effect, fibrosis, metastasis, or secretion of bioactive substances, including various hormones, cytokines and growth factors. As a result, patients may present with a carcinoid syndrome, causing cutaneous flushing, diarrhea, abdominal pain, cardiopulmonary effects, and various endocrinological syndromes.[8]

Carcinoid tumors may present with neurological symptoms, which, in the majority of cases, are due to endocrine changes, such as myopathy or metastases. Carcinoid-related paraneoplastic neurological syndromes have occasionally been described in isolated case reports.[9] These include Lambert Eaton myasthenic syndrome, cerebellar degeneration, limbic encephalitis, sensory neuropathy, autonomic dysfunction, and myelopathy with brain stem encephalitis.[9,10]

Our patient was diagnosed with NMO-SD, and was found to have gastric carcinoid tumor. While this occurrence could be incidental, it may represent a possible paraneoplastic effect of the cancer. She made an excellent recovery with treatment of the neurological condition, as well as tumor ablation, with no recurrence on prolonged follow up.

Pittock et al.[5] reported several types of neoplasms in patients with NMO-SD and NMO IgG seropositivity, including breast carcinoma, thyroid Hürthle cell, carcinoid, B-cell lymphoma, and pituitary somatotropinoma. They propose that tumor cells may express onconeural antigens that can trigger an aquaporin-4 immune response. Indeed, aquaporin-4 is expressed in many tissues outside the CNS, such as skeletal muscle, lungs, and stomach parietal cells.[5]

In addition, several cytokines, especially interleukin 6 (IL-6) are secreted directly by carcinoid tumors. By enhancing the production of various acute phase proteins such as serum amyloid, C-reactive protein, and fibrinogen, IL-6 has an important role in the development of inflammation.[10] Similarly, NMO has been associated with a major activation of humoral immunity, and the CSF has shown significant increases in IL-5, IL-6, and IgM secreting cells.[11]

CONFLICT OF INTEREST

None declared.

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