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Case report

Paraneoplastic neuromyelitis optica associated with fever of unknown origin as an early manifestation: A case report

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ABSTRACT

Tumors have been frequently reported to be associated with neuromyelitis optica (NMO). Here we review a case of a 34-year-old woman who presented with complaint of one-sided visual loss. All Lab tests exhibited negative results which decreased the possibility of Auto-immune or neuro-inflammatory disorders. Magnetic resonance imaging (MRI) of the brain and spinal cord was done as a part of work up, which showed Meningioma in anterior fossa without any other findings supporting neuro-demyelinating disorders. After complete surgical removal of the meningioma, patient's visual loss was completely resolved. 4 weeks later, she was admitted to the hospital for the second time with fever fulfilling the Fever of Unknown Origin (FUO) criteria. One week after she was discharged, she came back with paraplegia. MRI with Gadolinium showed an enhancing lesion involving T6-T9 segments of the thoracic spine. In order to rule in NMO, we checked for antibody to aquaporin-4 (AQP4-Ab) and the result was positive. This is the first report showing a probable association between FUO and NMO. Our case also demonstrates how variable the clinical presentations of NMO can be. We suggest that the diagnosis of NMO should be considered in the appropriate clinical setting despite of the presence of unconventional manifestations.

1. Introduction

Neuromyelitis optica (NMO or Devic's disease) is an autoantibody-mediated demyelinating disorder characterized by serum IgG auto-antibodies (NMO-IgG) that react with aquaporin-4 antigens (AQP4) (Wingerchuk et al., 2015). Although NMO commonly involves optic nerve and spinal cord, it is acknowledged that brain involvement is not rare in this disorder (Pittock et al., 2006). Here, we present a case of a paraneoplastic NMO patient with unique early manifestations.

2. Case presentation

A 34-year-old right-handed white female was admitted to Alzahra general hospital, Isfahan, Iran with two-day history of unilateral visual loss. She suffered a sudden onset of severe unilateral periorbital pain. Her vital signs were within normal range. She reported no previous episode of the same complaint. The patient was initially referred to a neuro-ophthalmology clinic by an ophthalmologist for evaluation of visual loss. Initial examination revealed a severe visual deficit. Her visual acuity had dropped to 5/10 on the left (OS) and 10/10 on the right (OD). There was also a relative afferent pupillary defect (RAPD) on the left side. Other fundoscopic findings were normal. The patient exhibited negative for neuromyelitis (NM0) antibody (AQP-4 IgG), Myelin oligodendrocyte glycoprotein (MOG) antibody, Anti double-stranded DNA antibody (anti-dsDNA), antinuclear antibody (ANA), anticardiolipin (aCL) antibody, and antiphospholipid (aPL) antibody.

Brain magnetic resonance imaging (MRI) showed a meningioma of anterior cranial fossa that was enhanced on T1 weighted image and appeared to be a mass lesion in axial MRI (Fig. 1). No other lesions were noted on MRI of the brain and spine. She was seen by a neurosurgeon and was subsequently admitted to the Neurosurgery department of Alzahra Hospital in Isfahan. Removal of the brain tumor was performed 2 weeks later and there were no complications during the entire surgical procedure. Her visual acuity was completely corrected in the left eye after the surgery. Although the visual loss was corrected after the surgical removal of the tumor, other features of her complaint were consistent with optic neuritis, especially the unilateral involvement of the optic nerve.

Approximately 4 weeks later, the patient presented with fluctuant fever, chills, malaise and sweating. Her temperature ranged from

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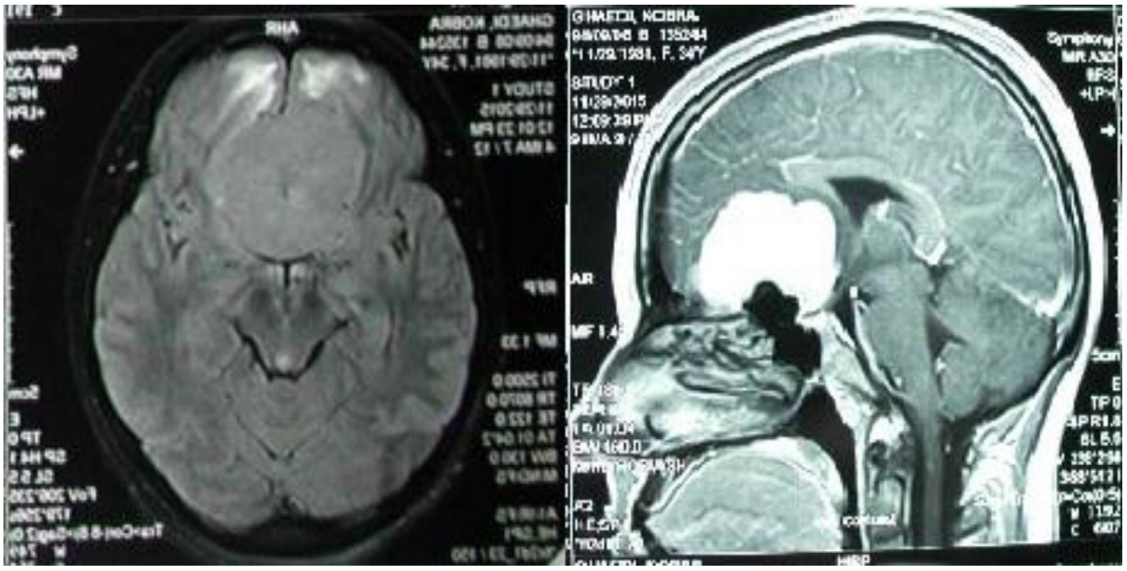

Fig. 1. . **Tumor lesion in brain MRI** Axial and Sagittal MRI show large extension of the mass lesion in supracellar region. Right side is axial FLAIR MRI and left side is T1-weighted post contrast MRI.

101.2°F to 104°F. She was admitted to the hospital and the workup was focused on ruling out infectious and neoplastic etiologies. On admission, she had a 102.7°F fever and her heart rate was 124 bpm. There were also no chest, abdomen, or joint symptoms. We found normal white blood cell (WBC) and platelet series, normocytic-normochromic mild anemia, Erythrocyte Sedimentation Rate (ESR) of 39 mm/h and normal C-Reactive protein (CRP). Glucose, calcium, phosphate, magnesium, liver profile and albumin were also normal. Kidney function tests and urinalysis showed negative microalbuminuria with normal renal function. Serum transaminases and alkaline phosphatase were within normal range. Repeated blood cultures were all negative with no signs of bacterial or fungal infections. Tumor marker levels were within normal limits and immunologic tests were negative. The cerebrospinal fluid (CSF) examination revealed normal protein levels and WBC count, also oligoclonal band were not detected. CSF cytological and microbiological examinations were negative. Her chest X-Ray was normal. No obvious abnormalities were found in the brain and cervical MRI. The patient was observed closely for 4 weeks. She was diagnosed with Fever of Unknown Origin (FUO) and was discharged with a prescription of oral antipyretics. After five days patient's fever was completely resolved.

One week later, the patient attended the clinic complaining of paraplegia. AQP4 antibody was checked again and it was positive. Repeated brain and cervical MRI were normal. However, thoracic MRI revealed demyelinating plaques involving T6 – T9 segments (Fig. 2).

The diagnosis of NMO was confirmed and the patient underwent a course of high dose methylprednisolone (IVMP) for five days (1 g/day). After prednisone tapering, rituximab was given as maintenance therapy. She showed considerable improvement, and shortly thereafter she was discharged to outpatient rehabilitation. We followed the patient for 2 years and no relapses were reported.

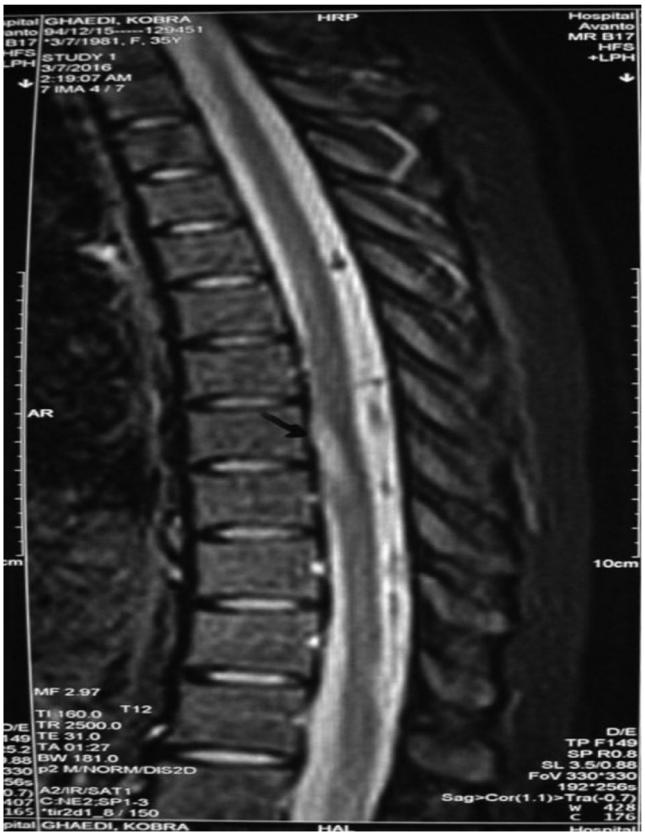

Fig. 2. Magnetic resonance imaging (MRI) of the thoracic spine A sagittal section demonstrate longitudinally hypersignal changes on T2-weighted image.

3. Discussion

By adding initial Optic Neuritis to the whole picture, our patient showed typical features of NMO based on 2006 criteria, which defines NMO as having: Optic neuritis, acute myelitis and at least two out of three supportive criteria: Contiguous lesion on MRI of the spinal cord extending over three or more segments; brain MRI does not meeting multiple sclerosis (MS) diagnostic criteria; and seropositivity for AQP-4 IgG (Wingerchuk et al., 2006). Coexistence of meningioma and typical features of NMO helped us confirm the diagnosis of Paraneoplastic NMO. Paraneoplastic autoimmune neurological disorders are manifestations of body's immune response initiated by the production of antibody against the neuronal antigens expressed on the surface of neoplastic cells. Innate and adaptive immune systems are the underlying autoimmune processes which are thought to be involved (Dalmau and Rosenfeld, 2008).

AQP-4 antigen, which is expressed on the surface of tumor cells, is identified as a target antigen of an autoantibody biomarker and

therefore reacts with highly specific serum IgG autoantibody (anti-AQP-4) in the periphery. Anti-AQP-4 antibody can access the Central Nervous System (CNS) through the circumventricular organs. Once in the CNS, anti-AQP-4 binds to AQP-4 water channel protein on astrocyte foot processes to form an antigen-antibody complex. This leads to modification of target function, target internalization, reduction in surface expression and complement activation, causing cell death (complement-dependent cytotoxicity) and activation of effector cells, such as natural killer cells. These findings explain the pathologic correlation between AQP-4 expression and CNS lesions of NMO patients. The antigen- antibody complex causes activation of the complement cascades and Fc receptors, leading to antibody-dependent cellular cytotoxicity (ADCC) mediated by granulocytes and natural killer cells. Binding of complement proteins to the IgG Fc region results in the formation of membrane attack complex and thus complement dependent cytotoxicity (CDC) and consequent recruitment of more inflammatory cells. Leukocytes degranulation augments inflammation in the CNS, leading to blood–brain barrier disruption and entrance of more AQP-4 auto- antibodies to CNS. Both CDC and ADCC are involved in astrocyte cell death, which are believed to be a secondary inflammatory response causing oligodendrocyte and neuronal damage and demyelination (Papadopoulos and Verkman, 2012; Ratelade and Verkman, 2012). Para-neoplastic NMO is formulated as coexistence of NMO and cancer, which is increasingly being reported. Some related types of cancer are as follows: Tumors of breast, lung, thyroid, thymus, uterus, prostate, pituitary. Our report demonstrates an association between Meningioma and NMO, which has never been reported in previous studies.

The fundamental point we intend to indicate in our study is the probable association between NMO and FUO. FUO was defined as a disease condition of temperature exceeding 100.9°F on at least three occasions over a period of at least three weeks, with no diagnosis made despite one week of inpatient investigation. Although FUO has been reported to be associated with many types of disorders including cancers in general, the sequence of events in our case does not explain the fever as a possible sign of meningioma. Our patient developed FUO four weeks after a successful removal of her tumor and fever work-up showed no neoplastic origin of the high temperature after 4 weeks of close observation. In NMO, the area postrema and hypothalamus can be unusually affected, causing symptoms including: nausea, hiccups, vomiting and diencephalic syndrome (Gao et al., 2016).

One of the basic functions of hypothalamus is regulation of body temperature. Damage to this brain structure can cause hyperthermia or hypothermia. Considering the fact that NMO may involve the main regulator of body temperature, FUO can be explained as a manifestation of the disease.

According to our findings, physicians should consider NMO in patients with long lasting fever who present with optic neuritis and other possible neurological symptoms of NMO, even when initial MRI or Aquaporin-4 antibody (AQP4-IgG) levels are not significant. As in this case, fever can be present as an early manifestation of NMO; Thus checking for the anti-AQP4 antibody may be helpful for establishing the diagnosis and proper treatment strategy.

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Conflict of interest

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Reference

Dalmau, J., Rosenfeld, M.R., 2008 1Apr. Paraneoplastic syndromes of the CNS. Lancet Neurol. 7 (il (4)), 327–340.

Gao, C., Wu, L., Chen, X., Long, Y., Zhong, R., Yang, N., Chen, Y., 2016 1Nov. Hypothalamic abnormality in patients with inflammatory demyelinating disorders. Int. J. Neurosci. 126 (ember (11)), 1036–1043.

Papadopoulos, M.C., Verkman, A.S., 2012. Aquaporin 4 and neuromyelitis optica. Lancet Neurol. 11 (June (6)), 535–544.

Pittock, S.J., Lennon, V.A., Krecke, K., Wingerchuk, D.M., Lucchinetti, C.F., Weinshenker, B.G., 2006 1Mar. Brain abnormalities in neuromyelitis optica. Arch. Neurol. 63 (3), 390–396 ch.

Ratelade, J., Verkman, A.S., 2012. Neuromyelitis optica: aquaporin-4 based pathogenesis mechanisms and new therapies. Int. J. Biochem. Cell Biol. 44 (September (9)), 1519–1530.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., De Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (July (2)), 177–189.

Wingerchuk, D.M., Lennon, V.A., Pittock, S.J., Lucchinetti, C.F., Weinshenker, B.G., 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology 66 (May (10)), 1485–1489.