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Short Communication

Immunoglobulin G4–related disease involving both cerebral parenchyma and spinal cord: A case report

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ABSTRACT

IgG4-related disease (IgG4-RD) is an immune-mediated condition that affects multiple organ systems with tumorlike swelling. Here, for the first time, we report a rare case of IgG4-RD that involves the cerebral parenchyma, intramedullary spinal cord and lymph nodes. The diagnosis of IgG4-RD was made based on histological features, multi organ involvement and high serum IgG4 levels. The patient responded well to glucocorticoid treatment. Our case broadens the phenotypic presentation for the neurological sequelae of IgG4-RD.

1. Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated condition that affects multiple organ systems with tumorlike swelling.(Stone et al., 2012) The disease mainly affects middle-aged to elderly men. The diagnosis of IgG4-RD is primarily made on the basis of histopathological findings, requiring at least 2 of the following 3 histological features: lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis.(Deshpande et al., 2012) Tissue IgG4 positive-cell counts and IgG4: IgG ratios of cells (> 40%) are secondary in importance. (Deshpande et al., 2012) However, the minimum number of IgG4 + plasma cells that are required to support the diagnosis appears to vary between tissues and sometimes between biopsy and resection material. (Deshpande et al., 2012) For example, for most tissues, the cut-off value should be at least 30 cells per high-power field, but in some tissues, including the kidney, > 10 cells per high-power field (HPF) is compatible with a diagnosis of IgG4-RD.(Deshpande et al., 2012) Generally, surgical specimens show larger numbers of IgG4 + plasma cells than do needle biopsy specimens.(Deshpande et al., 2012) The disease is also characterized by elevated IgG4 serum concentrations (> 135 mg/dL). (Deshpande et al., 2012) Most patients respond to glucocorticoid treatment.(Deshpande et al., 2012)

Although the organ-specific diagnostic criteria for the central nervous system (CNS) have not been established, it is suggested that the diagnosis of IgG4-RD of the CNS is made on the basis of clinical, radiographic, serological, and pathological evidence.(AbdelRazek et al., 2018) CNS involvement in IgG4-RD mainly includes the dura matter, the orbit and the pituitary gland and stalk.(AbdelRazek et al., 2018) To the best of our knowledge, brain parenchyma combined spinal cord involvement has never been reported in IgG4-RD.(AbdelRazek et al., 2018) Here, we first report a case of IgG4-RD that involves the cerebral parenchyma, intramedullary spinal cord and lymph nodes.

2. Case report

A 47-year-old man with no history of disease except rheumatoid

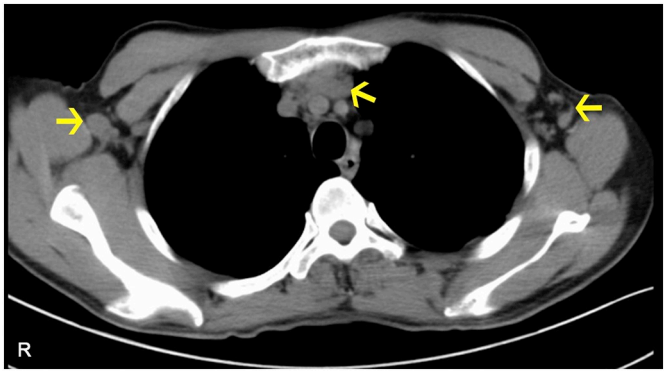

Fig. 1. CT of the chest. Enlargement of mediastinal and bilateral axillary lymph nodes (arrows).

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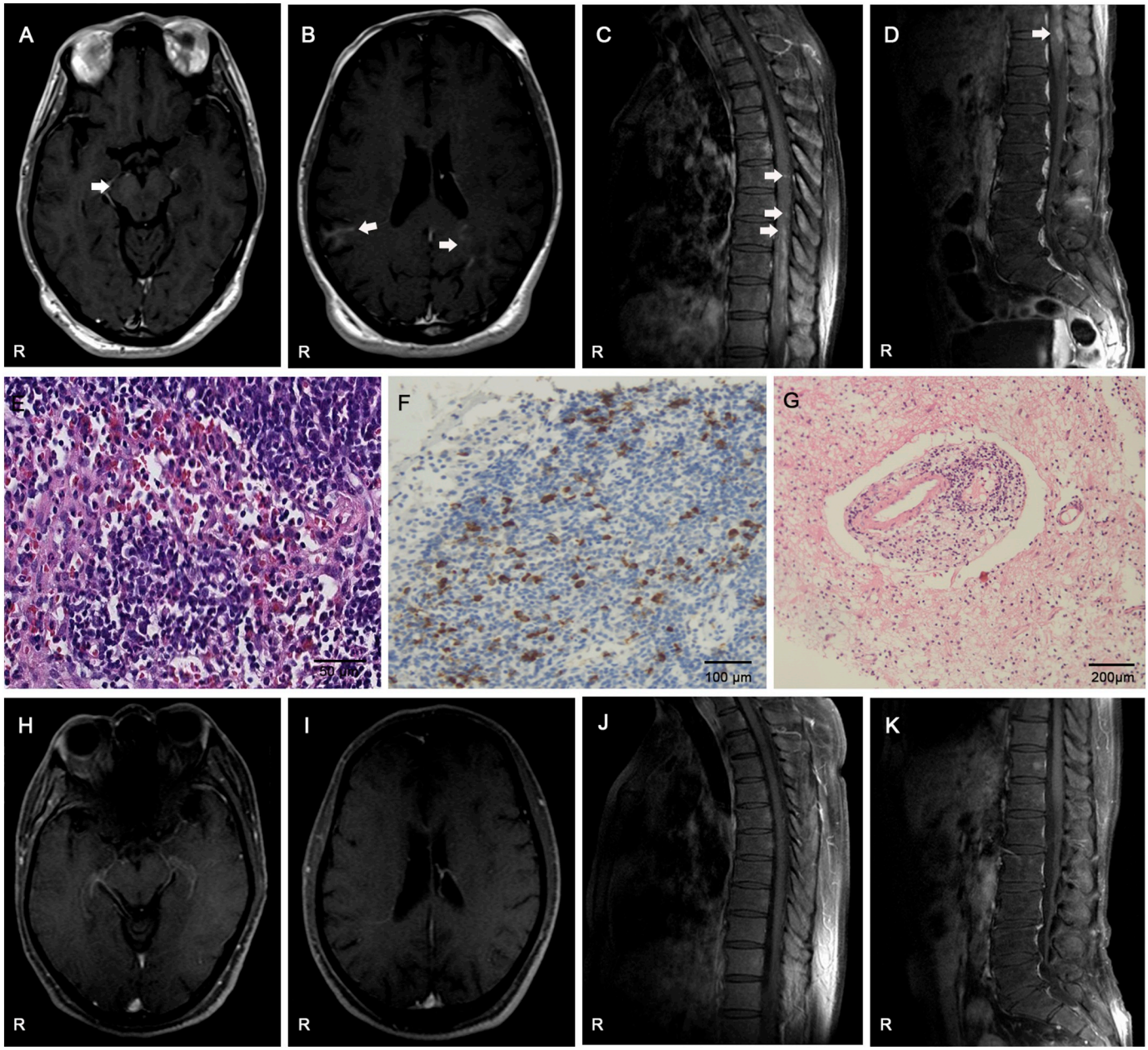

Fig. 2. Brain and spinal cord coronal T1 post-contrast MRI and pathologic findings of the biopsy.
(A–B) Initial MRI that was performed 37 days after onset showed T1-hyperintense lesions in the right brainstem, the right temporal-parietal lobe and the left periventricular white matter, and (C–D) spinal cord that extended contiguously from the thoracic spine (T6–7) to the conus medullaris (arrows). (E) The biopsy specimens from left axillary lymph node showed the infiltration of plasma cells and eosinophils (hematoxylin-eosin; bar represents 50 μm). (F) Immunohistochemical staining for IgG4 reveals focally IgG4-positive plasma cells 50–60 cells/high-power field and the ratio of IgG4 + /IgG + cells > 40% (bar represents 100 μm). (G) Biopsy samples from the brain showed lymphoplasmacytic infiltration (hematoxylin-eosin; bar represents 200 μm). (H–K) Eight months after glucocorticoid treatment, the T1-hyperintense lesions in the cerebral parenchyma and spinal cord showed significant improvement.

arthritis (RA) suffered from progressive numbness in the left limb and left face for one month. One week later, the patient developed progressive left limb weakness and constipation. On examination, his mental state was normal. However, his motor power was grade 4/5 in the left upper extremity and grade 2/5 in the left lower extremity. His pain sensations were impaired in the left face and left limbs. The deep tendon reflexes of his left lower extremity were decreased. The left Babinski sign was positive. The right Babinski sign and meningeal signs were negative.

Contrast-enhanced computed tomography (CT) scan of the chest showed enlargement of the mediastinal and bilateral axillary lymph nodes (Fig.1), while CT scan of the abdomen was unremarkable. Cervical ultrasonography proved enlargement of the bilateral cervical, supraclavicular and subclavian lymph nodes. Magnetic resonance imaging (MRI) revealed multiple enhanced lesions (including the right brainstem, the right temporal-parietal lobe and the left periventricular white matter) in the brain parenchyma on the T1-weighted imaging (T1WI) (Fig.2, A and B). Spine MRI showed T1-hyperintense lesions in the spinal cord that extended contiguously from the thoracic spine (T6–7) to the conus medullaris (Fig.2, C and D). A lumbar puncture revealed the following: white blood cell 10 cells/mm^3 (normal value < 8 cells/ mm^3); protein 0.68 g/L (normal range: 0.15–0.45 g/L) and intrathecal IgG synthesis 8.725 mg/day (normal value < 5.81 mg/day). Laboratory examinations further excluded central nervous system

Table 1
Additional auxiliary examination results.

Hematologic test results	
Serum amylase	(−)
Serum lipase	(−)
Oral glucose tolerance test	(−)
HIV	(−)
CMV	(−)
EBV	(−)
Parasite	(−)
Syphilis	(−)
Tuberculosis	(−)
Tumor markers	
α-fetoprotein	(−)
Carcino-embryonic antigen	(−)
Cancer antigen15–3	(−)
Cancer antigen 19–9	(−)
Cancer antigen −125	(−)
Cancer antigen 72–4	(−)
Total prostate-specific antigen	(−)
Free prostate specific antigen	(−)
Neuron-specific enolase	(−)
Cytokeratin 19 fragment antigen 21–1	(−)
Immunological test results	
ANA	(−)
Anti-ds-DNA	(−)
c-ANCA(IgG)	(−)
p-ANCA (IgG)	(−)
MPO ANCA (IgG)	(−)
PR3ANCA (IgG)	(−)
Rheumatoid factor (IU/mL)	(−)
AKA	(+)
Anti-SS-A	(−)
Anti-SS-B	(−)
Anti-Scl-70	(−)
Anti-Jo-1	(−)
Anti-RNP-70	(−)
Anti-RNP/SM	(−)
Anti-ACA	(−)
Serum lipase	(−)
Serum protein electrophoresis	(−)
Immunofixation electrophoresis	(−)
Urine and serum light chain (kappa/lambda)	(−)
Urine Bence-Jones protein	(−)
Oligoclonal band (CSF /Serum)	(−/−)
Autoantibodies against aquaporin 4 (CSF /serum)	(−/−)
Myelin oligodendrocyte glycoprotein antibodies (CSF /serum)	(−/−)
Myelin basic protein antibodies (CSF /serum)	(−/−)
Glial fibrillary acidic protein antibodies (CSF /serum)	(−/−)
Anti-flotillin-1 antibodies (CSF /serum)	(−/−)
Anti-flotillin-2 antibodies (CSF /serum)	(−/−)
Anti-ganglioside antibodies (CSF /serum)	
Anti-GQ1b antibodies	(−/−)
Anti-GT1a antibodies	
Anti-GT1b antibodies	(−/−)
Anti-GD1a antibodies	(−/−)
Anti-GD1b antibodies	(−/−)
Anti-GD2 antibodies	(−/−)
Anti-GD3 antibodies	(−/−)
Anti-GM1 antibodies	(−/−)
Anti-GM2 antibodies	(−/−)
Anti-GM3 antibodies	(−/−)
Anti-GM4 antibodies	(−/−)
Anti-sulfatide antibodies	(−/−)
Cerebrospinal fluid	
Glucose	(−)
Fungus (smear/culture)	(−/−)
Bacteria (smear/culture)	(−/−)
Acid-fast bacilli cultures	(−)
Malignant cell	(−)
Flow cytometry	CD45, CD5 and CD34 were negative

HIV = human immunodeficiency virus; CMV = human cytomegalovirus; EBV = Epstein-Barr virus; ANA = anti-nuclear antibody; dsDNA = double-stranded deoxyribonucleic acid; ANCA = anti-neutrophil cytoplasmic antibodies; AKA = anti-keratin antibodies; Anti-SS-A and SS-B = anti-SS-A(Ro) and anti-SS-B(La) autoantibodies; Anti-SM = anti-Smith antibodies; Anti-ACA = anti-anticardiolipin antibodies; CSF: cerebrospinal fluid.

demyelinating diseases, connective tissue diseases, blood system diseases, infectious diseases and neoplastic diseases (Table 1); however, increased values were found for the serum concentrations of IgG4 235 mg/dL (normal < 135 mg/dL), white blood cells 10.3 × 10^9/L (normal = 3.5–9.5 × 10^9/L), erythrocyte sedimentation rate 26 mm/h (normal range: < 21 mm/h), C-reactive protein 8.43 mg/L (normal range: < 5 mg/L) and anti-cyclic citrullinated peptide antibodies > 500 U/mL (normal range: < 17 U/mL). The findings of bone marrow biopsy, Montreal Cognitive Assessment test, Mini-Mental State Examination, electroencephalography, ultrasonography of salivary glands, whole-body bone single-photon emission computed tomography/computed tomography (SPECT/CT) and brain contrast-enhanced magnetic resonance angiography showed no abnormalities.

Samples from the enlarged left axillary lymph node were stained with hematoxylin-eosin and various immunohistochemical stains for immune cells. The biopsy specimens showed infiltration of plasma cells and eosinophils (Fig.2, E). In addition to CD20+, CD3+ and CD138+ cells were present in the lymph node. Immunohistochemical staining for IgG4 demonstrated that the number of IgG4-positive plasma cells was 50–60 cells/HPF and the ratio of IgG4+/IgG+ cells > 40% (Fig.2, F). Brain biopsy, which was not performed until 11 days after glucocorticoid treatment (intravenous methylprednisolone 1000 mg/d for 5 days followed by oral prednisone 60 mg/d) because of the rapid progression of the disease, revealed perivascular lymphoplasmacytic infiltrate (Fig.2, G), with most being composed of T cells (CD4+, CD3+ and CD8+ cells) and a few consisting of B cells (CD20+ cells). However, IgG4 immunoreactivity was negative in multiple foci of dense inflammatory infiltrates. Microorganisms, granulomas or malignant tissues were not revealed.

Two weeks after glucocorticoid treatment, the patient's walking was improved. Eight months later, the patient could walk independently with the gradual reduction of prednisone, and his numbness subsided and his constipation was alleviated. A repeat MRI performed showed that the previous lesions nearly resolved (Fig.2, H–K). The serum level of IgG4 at this point decreased to 142 mg/dL.

3. Discussion

In the presented case, the diagnosis of IgG4-RD was made based on histological features, multi-organ involvement and high serum IgG4 levels. The patient also had evidence of RA. However, rheumatoid encephalomyelitis could be excluded because of the lack of rheumatoid pathology, which mainly present with granuloma.(Kamio et al., 1996) In fact, the co-occurrence of IgG4-RD and RA has been previously reported.(Mehta et al., 2014) To date, only one case with brain parenchyma (left mesial temporal lobe, bilateral periventricular white matter and right dorsal frontal lobe) but not spinal cord involvement has been reported.(Regev et al., 2014)

Due to the non-specific clinical manifestations and imaging features, IgG4-related disease with multifocal neurological lesions is easily misdiagnosed. In this case, the non-specific clinical manifestations and imaging studies suggest the need for brain biopsy and pathological study to confirm diagnosis. Though the brain biopsy sample found no accumulation of IgG4-positive cells, the samples from lymph node biopsies revealed lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells, which suggests the diagnosis of IgG4-related systemic disease was confirmed.(Deshpande et al., 2012) The lack of IgG4-positive cells in the brain sample could be due to the effects of previous steroid therapy and the limited needle biopsy sample.

Our case broadens the phenotypic presentation for the neurological sequelae of IgG4-RD. The present case reminds the neurologist to consider IgG4-RD in patients with unusual cerebral parenchyma or spinal cord impairment, as appropriate glucocorticoid therapy can reverse the symptoms and may be beneficial for long-term remission. (Khosroshahi et al., 2015)

Data statement

Further anonymized data can be made available to qualified investigators upon request to the corresponding author.

Author contributions

J. Lin and L. Zheng collected data and drafted the manuscript. D. Zhou revised the manuscript. Z. Hong conceptualized and revised the manuscript.

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Disclosure

None of the authors have any conflict of interest to disclose.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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