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CASE REPORT

Unusual presentation of immunoglobulin G4-related disease: A case report

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is an inflammatory disease characterized by a tumor-like infiltration of IgG4 positive plasma cells and fibrosis in various organs. The exact pathogenesis remains unknown. In this article, we discuss the diagnostic management of IgG4-RD with reference to clinical, serologic, pathological and radiological data on a 17-year-old male patient with lumbar vertebral involvement.

Keywords: Fibrosis, immunoglobulin G4-related disease, lumbar vertebral involvement.

Immunoglobulin G4-related disease (IgG4-RD) is a condition characterized by the development of nodular/hyperplastic lesions and organ enlargement due to an increased infiltration of lymphocytes and plasma cells in various organs, accompanied by fibrosis. The disease can affect various organs, such as the pancreas, bile duct, lacrimal canals, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidneys, prostate, retroperitoneum, arteries, lymph nodes, skin and chest. Clinical symptoms vary depending on the affected organ.[1,2] The most common presentation type in children is IgG4-related orbital disease.[3] Bone involvement and central nervous system involvement are rare occurrences of the disease; most of these cases involve pachymeningitis, which presents as a localized or diffuse thickening of cranial or spinal cord dura mater.[4]

The exact pathogenesis is unknown, although it has been suggested that, unlike other IgG subgroups, IgG4 antibodies interact bivalently with other antibodies by changing half a molecule to form two arms that bind two different antigens, and thereby fail to form immune complexes, leading in turn to antiinflammatory rather than proinflammatory effects.[3]

The disease occurs more frequently in adults aged 50-80 years and in females, with a female-to-male ratio between 4:1 and 3:1.[2,5] The present case report discusses a pediatric case of IgG4-RD based on histopathological,

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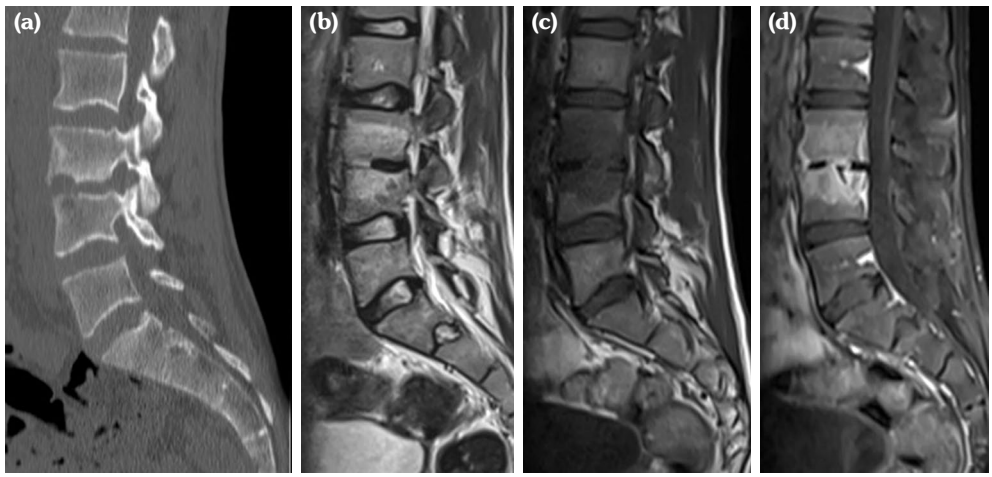

Figure 1. **(a)** Sagittal reconstructed computed tomography images show destructive lytic changes in end plates of L3 and L4 vertebral corpuses, and a modest loss of height accompanied by a decrease in disc space. **(b)** Sagittal T2 weighted (T2W) sequences show increased signal intensity, consistent with edema in affected vertebrae and intervertebral disc. **(c)** Sagittal T1W sequences prior to contrast enhancement show signal loss in vertebral corpuses. **(d)** Sagittal enhanced images show a diffuse contrast uptake in corresponding areas.

serologic and radiological findings, accompanied by the involvement of the lumbar spine, which is a rare occurrence in the literature. This case is unique because it is an example of a disease that is not seen very often in the pediatric population and that requires a good differential diagnosis. The differential diagnosis includes malignant tumors such as lymphoma and cancers, primary sclerosing cholangitis, multicentric Castleman's disease, sarcoidosis and antineutrophil cytoplasmic antibody (ANCA)-associated disease, as previously described.[6]

CASE REPORT

A 17-year-old Turkish male patient was admitted to our pediatric rheumatology outpatient clinic with severe lumbar pain, weight loss and fatigue for the last three months. A written informed consent was obtained from the patient's family for publication.

Physical examination identified tenderness in the lumbar vertebrae upon palpation. Laboratory

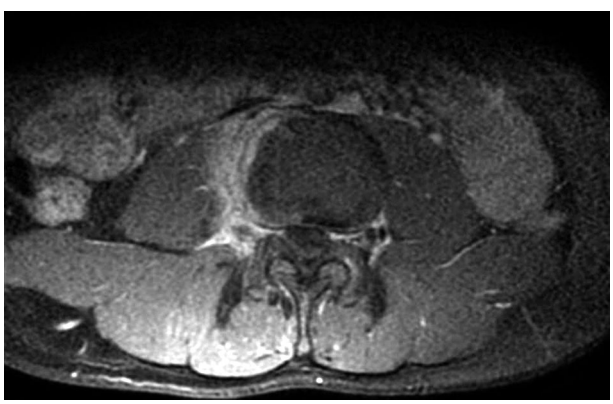

Figure 2. Axial enhanced images show involvement of right paravertebral and foraminal soft tissues, and increased signal intensity consistent with involvement of right L3 nerve.

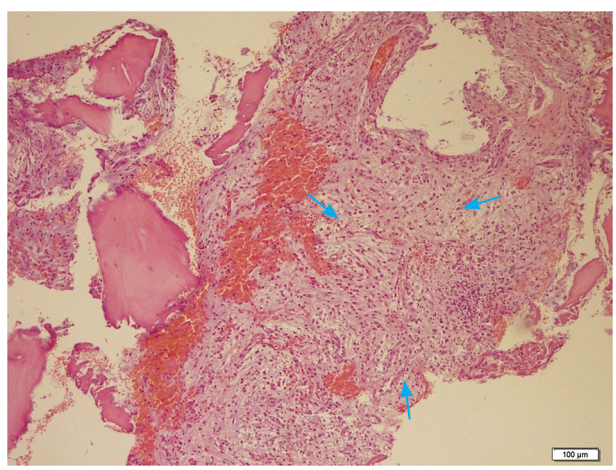

Figure 3. Tissue specimens show fibrotic tissue fragments and increased plasma cells (white arrows), lymphocytes, erythroid serial cells, bleeding areas in loose myxoid stroma between fractured bone spicules (H-E ×100).

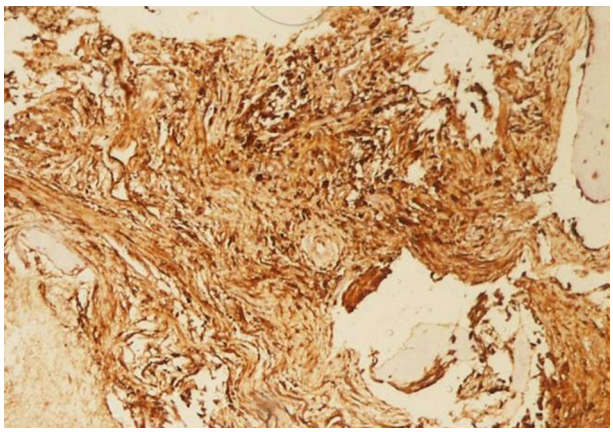

Figure 4. Partial immunoreactivity in plasma cells with immunoglobulin G4 (IgG4) staining that reveals 11 IgG4+ plasma cells per high-power field.

tests showed C-reactive protein of 8.7 mg/dL, erythrocyte sedimentation rate of 43 mm/h and procalcitonin level of 47.28 ng/mL. Peripheral blood smear and bone marrow examination revealed normal findings. Tuberculin skin test of 1 mm, quantiferon test and sputum stain for mycobacteria were negative, Rose Bengal and brucella tube agglutination were negative, brucella IgM was 0.40 (negative) and IgG was 0.75 (negative), no growth was detected in brucella culture and tuberculosis and brucella tests were negative. The autoantibodies including antinuclear antibodies, anti-double stranded deoxyribonucleic acid, ANCA and human leukocyte antigen B27 were negative.

Lumbar vertebral computed tomography revealed a decrease in the right half of the disc height at the L3-4 intervertebral disc level (Figure 1a). Lumbosacral spinal magnetic resonance imaging (MRI) revealed in sagittal T2A sequences increased signal intensity, consistent with edema in the affected vertebrae and intervertebral disc (Figure 1b). The sagittal T1A sequences prior to contrast enhancement showed signal loss in the vertebral corpuses (Figure 1c), while sagittal postcontrast images showed a diffuse contrast uptake in the corresponding areas (Figure 1d). The axial postcontrast images showed involvement of the right paravertebral

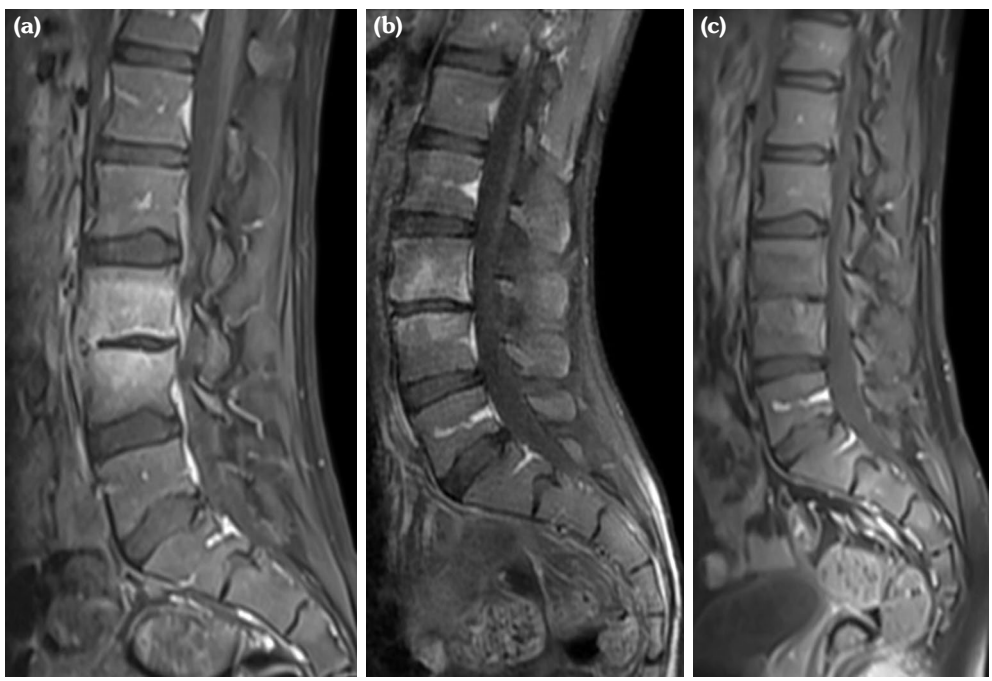

Figure 5. (a, b and c) Images show follow-up magnetic resonance imaging scans at approximately seven months. Sagittal enhanced T1A sequences show a decreased contrast uptake, edema and T2W hyperintensity over time (regression in radiological findings). Differential diagnosis includes malignant tumors such as lymphoma and cancers, infective and inflammatory disease and early stage Langerhans cell histiocytosis. In follow-up, due to regression in radiological findings, malign and infective diseases were excluded and further inflammatory diseases were considered.

and foraminal soft tissues, and increased signal intensity consistent with the involvement of the right L3 nerve (Figure 2). Radiological findings were consistent with spondylodiscitis.

Bone biopsy was performed due to increased signal intensity and the observation of lytic and destructive lesions on lumbovertebral MRI scans. Fibrotic tissue fragments were observed among the bone spicules in tissue samples. The increased number of plasma cells in these tissue fragments was remarkable (Figure 3). Immunostaining for IgG and IgG4 showed diffuse staining for IgG, and IgG4 11/high-power field (HPF) was observed (Figure 4). Serum IgG and serum IgG4 levels were found to be elevated according to Oxford immunology data (IgG4: 336 mg/dL [10-135 mg/dL], IgG: 1656 mg/dL [600-1600 mg/dL]).

Parotid and thyroid ultrasound revealed normal findings. Protein electrophoresis revealed polyclonal increase in gamma globulins (gamma protein: 19.4%; 11.1-18.8). Positron emission tomography (PET) showed increased metabolic activity with a heterogeneous character around the radiolucent areas (maximum standardized uptake value: 4.3).

According to the American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD, a score of 19 and above is the threshold for IgG4-RD. The patient fulfilled the criteria for the diagnosis of IgG4-RD with a total score of 19.4 points due to elevated serum IgG4 levels 2 to 5 times higher than normal (6.1 points) and the presence of lymphoplasmacytic infiltration and storiform fibrosis upon histopathological examination (13.3 points). The patient lacked fever, unresponsiveness to steroid therapy, leukopenia and thrombocytopenia, peripheral eosinophilia (>3,000 mm^3), ANCA or anti-Ro/SSA and anti-La/SSB positivity, infections, malignancy, rapid radiological progression and necrotizing vasculitis, primary granulomatous infiltration and malignant infiltration upon pathological examination, all of which were specified as exclusion criteria in the guidelines.

The patient was placed on steroid therapy, and a good response was achieved in terms of clinical and laboratory findings. Figures 1 and 5 present the MRI findings at baseline and during follow-up. Thus, early diagnosis provided good response to disease without organ damage.

DISCUSSION

The present study reports on a well-characterized case of biopsy-proven IgG4-related spondylodiscitis in the lumbar vertebrae. Local organ involvement was detected during a MRI, and PET scans provided further evidence of the involvement of a single organ with a low metabolic activity index in terms of malignancy.

An increase in serum polyclonal gamma globulins is observed in patients with IgG4-RD together with frequently elevated IgG and IgE levels. Hypocomplementemia can be observed.[1,2,7] Increased serum IgG4 levels can also present in other diseases (atopic dermatitis, pemphigus, asthma and multicentric Castleman's disease), and so are not specific to IgG4-RD. The patient's serum IgG4 was 336 mg/dL and his IgG was 1656 mg/dL. No elevated IgE levels or hypocomplementemia were observed.

In a study by Culver et al.,[8] a serum IgG4 level greater than 2.8 g/L was found to have a positive predictive value of 44.5% and a negative predictive value of 97.7% in differentiating between IgG4-RD and non-IgG4-RD. Furthermore, the analyses showed that the median serum IgG/IgG4 ratio was 3.78 and the median serum IgG1/IgG4 ratio was 2.18 in patients diagnosed with IgG4-RD. In our patient, the serum IgG/IgG4 ratio (4.92 g/L) and IgG1/IgG4 ratio (3.98 g/L) were found to be low.

In a study by Karim et al.,[3] the reported mean age of the patients was 13 years; 64% were female, 44% had orbital involvement and 12% had pancreatic involvement. Although all organs in the body are involved in pediatric patients, no bone involvement was observed in the study. In our patient, lumbar spine involvement was observed.

In a single-center study by Karadağ et al.[9] conducted on the Turkish population, the rate of females was equal to that of males, and retroperitoneal fibrosis was the most common finding. Of the total, 24 patients had localized involvement; pachymeningitis was observed in one patient; and no bone involvement was

reported, similar to the findings reported by Karim et al.[3]

Furthermore, in a study by Wallace et al.[10] involving a clinical and pathological assessment of 125 patients with biopsy-proven IgG4-related diseases, 23 different parts of the body were found to be involved while no data were available on bone tissue.

There is limited data on spinal involvement in the studies to date; however, in a study by Lu et al.,[4] cases of pachymenigitis related to a 6-year period were evaluated by literature review. A total of 38 patients were identified in this review. Intracranial involvement was observed in 80% of them, while eight patients had spinal pachymeningitis. The most commonly involved sites were the cervical and thoracic vertebrae. Only one patient was found to have lumbar vertebral involvement. To our knowledge, the present study is the first reported pediatric case with lumbar vertebral involvement.

Immunoglobulin G4-related disease may lead to irreversible organ damage if left untreated. Prednisolone is the primary option for treatment, being sufficient as a monotherapy in 43% of patients, whereas the remaining patients require maintenance immunosuppressive therapy.[3] In our case report, only prednisolone treatment was sufficient and no organ damage was observed with early diagnosis.

A diagnosis of IgG4-RD is definitive in patients with organ enlargement, mass or nodular lesions, or organ dysfunction, a serum IgG4 concentration >135 mg/dL, and histopathological findings of >10 IgG4+ cells/HPF and an IgG4+/IgG+ cell ratio >40%.[1]

The primary "take-away" lesson from this case report is that in unexplained inflammatory conditions, particularly tumor-like anomalies, the site of IgG4-RD should be excluded by imaging, physical and histopathological examination.

The strength of this case was that it confirmed the diagnosis with organ involvement and high serum IgG4 concentration while we were unable to evaluate tissue IgG4/IgG ratio because of lacking preparation and failure of lumbar puncture. Although there is no data to date about spinal involvement on histopathological findings, generally >10 IgG4+ cells/HPF is considered significant; thus, in this case, 11 IgG4+ cells/HPF confirmed the histopathological findings. To our knowledge, only a single adult patient with IgG4-RD and with lumbar vertebral involvement has been reported afterwards.

In conclusion, IgG4-RD is a recently described group of diseases that are not well recognized by pediatricians. It is possible to prevent progressive organ damage with early diagnosis and treatment. Fewer serologic and histological studies have been conducted to evaluate the treatment of pediatric patients than those conducted on adult patients; therefore, there is a need for further studies in this regard.

Declaration of conflicting interests

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