Multifocal Fibrosclerosis with Hypertrophic Pachymeningitis and a Soft Tissue Mass around the Thoracic Vertebral Bodies: A Case Report with Review of the Literature

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Abstract

Multifocal fibrosclerosis is the term used to represent a combination of similar fibrous lesions occurring at different anatomical sites. We herein report a hypertrophic pachymeningitis patient with a soft tissue mass around the thoracic vertebral bodies. A histopathological analysis of the biopsied tissues from both lesions showed dense fibrosis and a marked infiltration of lymphocytes and plasma cells, which lead to the diagnosis of multifocal fibrosclerosis. This pathological condition closely resembles that of IgG4-related disease and is a very rare combination of manifestations. Our case suggests that hypertrophic pachymeningitis patients need to also undergo a whole body examination.

Key words: multifocal fibrosclerosis, hypertrophic pachymeningitis, a soft tissue mass around thoracic vertebral bodies, IgG4-related disease, granulomatosis with polyangiitis

Introduction

Hypertrophic pachymeningitis is a rare disorder characterized by inflammatory thickening of the cerebral and/or spinal dura mater. Several causes have been recognized, including infections (tuberculosis and fungi), tumors, autoimmune diseases (granulomatosis with polyangiitis: GPA), and sarcoidosis (1-3). Multifocal fibrosclerosis is the term used to represent a combination of similar fibrous lesions occurring at different anatomical sites (4), and some conditions in this disease overlap with those of IgG4-related disease. There have been several reports on multifocal fibrosclerosis with hypertrophic pachymeningitis (5-8). We herein report a hypertrophic pachymeningitis patient with a soft tissue mass around the thoracic vertebral bodies, paying special attention to the similarities and differences between this disease and IgG4-related disease.

Case Report

A 68-year-old man presented with a dry cough that had continued for one month and was diagnosed with idiopathic organizing pneumonia in July 2007. He was treated with prednisolone (PSL) at a dose of 20 mg/day. The patient’s idiopathic organizing pneumonia improved and his oral PSL was tapered gradually to 6 mg/day. He presented with a left frontal throbbing headache and photophobia in September 2007 and was admitted to another hospital in October 2007 because his headache worsened. Laboratory investigations revealed increased the serum levels of C-reactive protein (CRP) (5.52 mg/dL, normal <0.10 mg/dL). The patient was suspected to be suffering from giant cell arteritis because of the visual disturbance in his right eye and the increase in his...
CRP level. He was treated several times with methylprednisolone pulse therapy followed by oral PSL at a dose of 80 mg/day in December, but his condition deteriorated. He was then transferred to our hospital for treatment in February 2008. Upon admission, he had a throbbing frontal headache and bilateral hearing impairment. There were no expanded temporal arteries, lymphadenopathy, skin rash, or arthritis noted. Laboratory investigations revealed increased serum levels of CRP (8.90 mg/dL). Other laboratory values including rheumatoid factor, myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA), proteinase 3 (PR3)-ANCA and angiotensin-converting enzyme, were within normal limits. His tuberculin skin test and interferon-γ release assay were negative. His cerebrospinal fluid (CSF) examination showed pleocytosis (10/mm³: 97% mononuclear cells), and elevated levels of protein (69 mg/dL) and IgG (31.4 mg/dL). A cytological examination of CSF revealed no evidence of malignancy and cultivation of bacteria, fungi and tuberculosis in CSF was negative. His CSF tuberculosis polymerase chain reaction was negative. The patient’s brain magnetic resonance imaging (MRI) revealed diffuse linear dural thickening and enhancement (Fig. 1-A). His cervical and thoracic spinal MRI also revealed dural thickening and enhancement. A biopsy of the dura mater from his right frontal brain was performed. The histopathological analysis of the biopsied tissues showed dense fibrosis and a marked infiltration of lymphocytes and plasma cells on the inner surface of the dura mater (Fig. 2-A and B). Neoplastic cells, vasculitis, granuloma, and infectious agents were not seen. Cultivation of bacteria, fungi and tuberculosis was negative. The patient was given a diagnosis of having idiopathic hypertrophic pachymeningitis and was treated with methylprednisolone pulse therapy followed by oral PSL at a dose of 50 mg/day. The patient was started on tacrolimus at a dose of 3 mg/day with oral PSL after his methylprednisolone pulse therapy because his condition could not be controlled by oral PSL alone. His headache and visual disturbance improved immediately. An MRI of his brain and the spine after therapy revealed a marked improvement of the diffuse linear dural thickening and enhancement (Fig. 1-B).

After the patient’s oral PSL had been tapered carefully to 9 mg/day, he presented with back pain and fever in June 2010. His chest computed tomography showed a soft tissue mass around the thoracic vertebral bodies. He was admitted to our hospital again. Laboratory investigations revealed he had increased serum levels of CRP (7.15 mg/dL). The MRI of the thoracic spine revealed a soft tissue mass around the thoracic vertebral bodies between T2 and T12 and enhancement of the mass (Fig. 3). The recurrence of hypertrophic pachymeningitis was not seen. Gallium-67 scintigraphy showed a strong accumulation of Gallium-67 in the mass (Fig. 4). A thoracoscopic biopsy of the mass was performed, and a histopathological analysis of the biopsied tissues showed dense fibrosis and marked infiltration of lymphocytes and plasma cells (Fig. 5-A). Neoplastic cells, vasculitis, granuloma, and infectious agents were not seen. The acid-fast bacilli staining of the biopsied tissues was negative; this finding was similar to that of the previously biopsied dura mater. An immunohistochemical analysis showed diffuse and scattered infiltration of IgG4-positive plasma cells (Fig. 5-B). We reexamined the biopsy tissues of the dura mater and they also showed diffuse and scattered infiltration of IgG4-positive plasma cells (Fig. 2-C). However, the ratio of IgG4+ / IgG+ plasma cells was about 10% in the dura mater, and about 30% in the soft tissue mass around the thoracic vertebral bodies. The patient’s serum IgG4 concentration was 19 mg/dL in July 2010. For com-
Comparison, we reexamined his serum IgG4 concentration from February 2008, which was 22.6 mg/dL. Therefore he did not fulfill the comprehensive diagnostic criteria for IgG4-related disease (9) and was finally given the diagnosis of multifocal fibrosclerosis. He was then treated with oral PSL at a dose of 30 mg/day and tacrolimus (3 mg/day); his back pain and fever improved immediately. After the patient’s oral PSL had been tapered carefully to 19 mg/day, he presented with back pain and fever again in August 2011. The laboratory investigations revealed increased serum levels of CRP (17.20 mg/dL). The patient was then treated with methylprednisolone pulse therapy followed by oral PSL at a dose of 30 mg/day. He was also started on methotrexate at a dose of 6 mg/week, which was increased to 8 mg/week. His back pain and fever improved immediately. His oral PSL was tapered carefully to 20 mg/day in August 2012. His serum level of CRP was within normal limits at that time and his symptoms did not reappear in that month.

**Figure 2.** The histopathological and immunohistochemical findings of the dura mater. The biopsied tissues showed dense fibrosis and a marked infiltration of lymphocytes and plasma cells on the inner surface of the dura mater (A and B) (Hematoxylin and Eosin staining). An immunohistochemical analysis showed a diffuse and scattered infiltration of IgG4-positive plasma cells (C).

**Figure 3.** The gadolinium-enhanced T1-weighted magnetic resonance image of the thoracic spine. The MRI revealed a soft tissue mass around the thoracic vertebral bodies between T2 and T12, and enhancement of the mass (arrows) (A and B). A recurrence of hypertrophic pachymeningitis was not seen.

**Figure 4.** Gallium-67 scintigraphy. Gallium-67 scintigraphy showed a strong accumulation of Gallium-67 in a soft tissue mass around the thoracic vertebral bodies.
IgG4-related disease includes a wide variety of diseases, such as Mikulicz’s disease, Riedel’s thyroiditis, interstitial pneumonia, autoimmune pancreatitis, interstitial nephritis, and retroperitoneal fibrosis (9-11). Recently, there have been several reports of multifocal fibrosclerosis with hypertrophic pachymeningitis (12-15). In some cases, multifocal fibrosclerosis and IgG4-related disease are considered as probably the same entity because they have a similar distribution of multiple organ involvement (9, 16, 17). We used the following comprehensive diagnostic criteria for IgG4-related disease that was established by the All Japan IgG4 team in 2011: A diagnosis of IgG4-related disease is definitive in patients with (a) organ enlargement, mass or nodular lesions, or organ dysfunction, (b) a serum IgG4 concentration >135 mg/dL, and (c) histopathological findings of >10 IgG4+ plasma cells / high-power field (HPF) and a ratio of IgG+ / IgG+ plasma cells >40%. Our patient did not fulfill these criteria and we therefore diagnosed his illness as multifocal fibrosclerosis. He had been treated with PSL when he was transferred to our hospital. We do not know how steroid therapy might have influenced his serum IgG4 concentration and IgG4+ plasma cells on his histopathology and thus do not know whether he had fulfilled the criteria before steroid therapy. Interstitial pneumonia preceded hypertrophic pachymeningitis in this case and since IgG4-related disease is one of the causes of interstitial pneumonia (18), we consider the interstitial pneumonia to be related to the multifocal fibrosclerosis.

Our patient had a soft tissue mass around the thoracic vertebral bodies. Only five cases of IgG4-related disease or multifocal fibrosclerosis with a soft tissue mass around the thoracic vertebral bodies have been previously reported (19-23). The clinical and demographic characteristics of the five cases are shown in Table. All five patients are men with an age range of 40 to 70 years. Serum IgG4 concentrations were measured in four cases and were more than 135 mg/dL in all four. Besides a soft tissue mass around the thoracic vertebral bodies, all patients had other organ involvement, such as the hypophysis, lacrimal glands, parotid glands, submandibular glands, and kidney. Only two patients underwent biopsies from the soft tissue mass around the thoracic vertebral bodies, while the other three patients underwent biopsies from other organ involvements. An immunohistochemical analysis showed an infiltration of IgG4-positive plasma cells in all cases. However, we are unable to determine whether all cases fulfilled the comprehensive diagnostic criteria for IgG4-related disease, as the number of IgG4+ plasma cells / HPF and the ratio of IgG4+ / IgG+ plasma cells were not shown in some cases. Four of the five cases received only steroid therapy and responded to treatment, while the other case received steroid and intravenous cyclophosphamide therapy because he had ANCA-associated glomerulonephritis (21). Our patient needed immunosuppressants with steroids because of his frequent relapses. We do not know whether the observed resistance to steroid therapy means that our patient had a different condition from these other cases. Several cases of GPA with a soft tissue mass around the thoracic vertebral bodies have been also reported previously (24-26). Our patient did not have sinusitis, lung nodules, or glomerulonephritis. His MPO-ANCA and PR3-ANCA were within normal limits. Granulomatous inflammation on the biopsied tissues from the soft tissue mass around the thoracic vertebral bodies and the dura mater was not seen. Therefore the patient’s results did not fulfill the American College of Rheumatology 1990 criteria for the classification of Wegener’s granulomatosis (27). To our knowledge, there has been only one report of an individual with soft tissue mass around the thoracic vertebral bodies and hypertrophic pachymeningitis, and the individual had not undergone a biopsy of the soft tissue mass nor from the dura mater (22). Hence, our case appears to be the first to involve biopsies from both lesions and we showed that both

Figure 5. The histopathological and immunohistochemical findings of the soft tissue mass around the thoracic vertebral bodies. The biopsied tissues showed dense fibrosis and a marked infiltration of lymphocytes and plasma cells (A) (Hematoxylin and Eosin staining). The immunohistochemical analysis showed a diffuse and scattered infiltration of IgG4-positive plasma cells (B).

Discussion

The term multifocal fibrosclerosis has been used to describe systemic inflammatory fibrosis, such as retroperitoneal fibrosis, sclerosing cholangitis, Riedel’s thyroiditis, and orbital pseudotumor (4). There have been several reports of multifocal fibrosclerosis with hypertrophic pachymeningitis (5-8). IgG4-related disease is a novel clinical disease entity characterized by elevated serum IgG4 concentration and the tumefaction or tissue infiltration by IgG4+ plasma cells. IgG4-related disease includes a wide variety of diseases, such as Mikulicz’s disease, Riedel’s thyroiditis, interstitial pneumonia, autoimmune pancreatitis, interstitial nephritis, and retroperitoneal fibrosis (9-11). Recently, there have been several reports of IgG4-related disease with hypertrophic pachymeningitis (12-15). In some cases, multifocal fibrosclerosis and IgG4-related disease are considered as probably the same entity because they have a similar distribution of multiple organ involvement (9, 16, 17). We used the following comprehensive diagnostic criteria for IgG4-related disease that was established by the All Japan IgG4 team in 2011: A diagnosis of IgG4-related disease is definitive in patients with (a) organ enlargement, mass or nodular lesions, or organ dysfunction, (b) a serum IgG4 concentration >135 mg/dL, and (c) histopathological findings of >10 IgG4+ plasma cells / high-power field (HPF) and a ratio of IgG4+ / IgG+ plasma cells >40%. Our patient did not fulfill these criteria and we therefore diagnosed his illness as multifocal fibrosclerosis. He had been treated with PSL when he was transferred to our hospital. We do not know how steroid therapy might have influenced his serum IgG4 concentration and IgG4+ plasma cells on his histopathology and thus do not know whether he had fulfilled the criteria before steroid therapy. Interstitial pneumonia preceded hypertrophic pachymeningitis in this case and since IgG4-related disease is one of the causes of interstitial pneumonia (18), we consider the interstitial pneumonia to be related to the multifocal fibrosclerosis.

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lesions had similar pathological conditions.

We report this case of hypertrophic pachymeningitis with a soft tissue mass around the thoracic vertebral bodies because this combination of manifestations is very rare and both lesions had similar pathological conditions. This case suggests that hypertrophic pachymeningitis patients may have other organ involvements even if they are diagnosed with idiopathic hypertrophic pachymeningitis and that they should therefore undergo a whole body examination.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

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Mitsuto Sato and Minori Kodaira contributed equally to this work.

**References**


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**Table. The Clinical and Demographic Characteristics of IgG4-related Disease or Multifocal Fibrosclerosis with a Soft Tissue Mass around Thoracic Vertebral Bodies.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years) / Sex</th>
<th>Serum IgG4 (mg/dL)</th>
<th>Histopathology (Biopsied organ)</th>
<th>Other organ involvements</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>61 / Male</td>
<td>583</td>
<td>Infiltration of many IgG4-positive plasma cells (Ureteropelvic junction)</td>
<td>Ureteropelvic junction</td>
</tr>
<tr>
<td>20</td>
<td>62 / Male</td>
<td>5,000</td>
<td>The ratio of IgG4+ / IgG+ plasma cells was 40-50% (Lacrimal gland)</td>
<td>Hypophysis, Orbital muscles, Lacrimal and submandibular glands</td>
</tr>
<tr>
<td>21</td>
<td>40 / Male</td>
<td>4,700</td>
<td>Up to 50% of plasma cells were IgG4-positive (A soft tissue mass around thoracic vertebral bodies)</td>
<td>Aortic arch Abdominal aorta</td>
</tr>
<tr>
<td>22</td>
<td>70 / Male</td>
<td>2,600</td>
<td>The majority of plasma cells were IgG4+ (Bronchus)</td>
<td>Dura mater, Bronchus, Lung, Parotid and submandibular glands</td>
</tr>
<tr>
<td>23</td>
<td>66 / Male</td>
<td>Not available</td>
<td>Abundant IgG4 positive plasma cells (A soft tissue mass around thoracic vertebral bodies)</td>
<td>Hypophysis Kidney</td>
</tr>
<tr>
<td>Present case</td>
<td>68 / Male</td>
<td>22.6</td>
<td>Diffuse infiltration of IgG4-positive plasma cells (A soft tissue mass around thoracic vertebral bodies)</td>
<td>Dura mater Lung</td>
</tr>
</tbody>
</table>