Clinical and radiological features of IgG4-related perineural disease

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Purpose

IgG4-related disease is a newly designated disease entity, which can be defined as an idiopathic fibro-inflammatory condition rich in IgG4⁺ plasma cells. This disease affects a variety of organs including the salivary gland [1], pancreas [2], bile duct [3], lung [4], kidney [5], and aorta / artery [6, 7]. IgG4-related disease shares clinicopathological characteristics irrespective of the affected organs. Clinical features can be summarized as occurring predominantly in adult male patients, elevated serum IgG4 concentrations, responsive to steroid therapy, and synchronous or metachronous association with IgG4-related disease in other organs [8, 9].

IgG4-related disease is histologically characterized by diffuse lymphoplasmacytic infiltration rich in IgG4⁺ plasma cells, storiform fibrosis, obliterative phlebitis, and moderate tissue eosinophilia [1, 3-6, 10]. IgG4-related disease predominantly develops in glandular organs, but non-glandular tissue like retroperitoneum can be affected as well [11, 12].

For the diagnosis of IgG4-related disease, imaging examination plays an important role [13, 14]. Imaging features of renal, pulmonary or arterial lesions have been also well characterized [15-18]. Recently, a few papers have described the peripheral nerve involvement in IgG4-related disease [19-21]. However, the radiological features of IgG4-related peripheral nerve lesions remain to be clarified.

In this study, we retrospectively examined IgG4-related disease involving the peripheral nervous system. The purpose of this study is to elucidate the clinicopathological and radiological characteristics of IgG4-related peripheral nerve lesions.

Methods and Materials

Case selection

We selected consecutive 105 patients (87 men and 18 women; median 68 years, range 38-86 years) that showed radiological features consistent with IgG4-related disease in our hospitals and related institution from the period between September 1998 and May 2011. Another case with IgG4-related peripheral nerve disease (case 6) was obtained from a radiology consultation file.

We retrospectively reviewed radiology and pathology data of 106 patients with IgG4-related disease collected regarding the presence or absence of macroscopic peripheral
nerve abnormalities. A total of 7 patients with peripheral nerve involvement were found and enrolled in this study. All patients were male with a median age of 58 years (range: 44-74 years). Clinical features of these patients are summarized in Table 1. Follow-up data were also examined particularly in terms of the presence or absence of recurrences and neurological symptoms by reviewing inpatient and outpatient records, and follow up imaging.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Symptom</th>
<th>IgG (mg/dL)*</th>
<th>IgG4 (mg/dL)†</th>
<th>ANA (titer)</th>
<th>IgE (IU/mL)‡</th>
<th>Initial dose of steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Male</td>
<td>Double vision, subcutaneous nodule in cheek</td>
<td>4845</td>
<td>2050</td>
<td>×40</td>
<td>988</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>Male</td>
<td>Left proptosis, double vision</td>
<td>NA</td>
<td>372</td>
<td>×40</td>
<td>NA</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Male</td>
<td>Lacrimal gland enlargement</td>
<td>1450</td>
<td>463</td>
<td>&lt;40</td>
<td>4608</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Male</td>
<td>Right proptosis, double vision, lacrimal gland enlargement</td>
<td>1146</td>
<td>325</td>
<td>&lt;40</td>
<td>151</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Male</td>
<td>Epigastralgia</td>
<td>2850</td>
<td>1280</td>
<td>NA</td>
<td>NA</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>Male</td>
<td>Lacrimal gland enlargement, cervical lymph node enlargement</td>
<td>6024</td>
<td>2550</td>
<td>NA</td>
<td>NA</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>Male</td>
<td>Palpable left</td>
<td>7364</td>
<td>3440</td>
<td>×2560</td>
<td>1146</td>
<td>40 mg/day</td>
</tr>
</tbody>
</table>
Diagnosis of IgG4-related disease

The diagnosis of IgG4-related disease was made based on serological, imaging, and histological examinations. Serum IgG4 concentrations were elevated in all patients (median 1280 mg/dL; range 325-3440 mg/dL, normal range <135 mg/dL). Five patients (cases 3-7) had histological examination for specimens taken from the lacrimal gland (surgical biopsy; cases 3, 4, 6), kidney (needle biopsy; cases 5, 6, 7), hepatic mass (needle biopsy; case 5), and cervical lymph node (surgical biopsy; case 6). Cases 1 and 7 had surgical biopsies from peripheral nerve lesions. Case 2, who did not have histological examination, was diagnosed as IgG4-related ophthalmic disease based on the clinical presentation with left proptosis, imaging features, and a high serum IgG4 concentration (372 mg/dL).

All resected or biopsied specimens were reviewed by a pathologist and confirmed features consistent with IgG4-related disease including diffuse lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, occasional eosinophils, numerous IgG4\(^+\) plasma cell infiltrates, and high IgG4\(^+\)/IgG\(^+\) plasma cell ratios (>40%) [1, 3, 5, 6].

Radiological examinations

All images were reviewed by two radiologists and decisions were reached by consensus. Because of the retrospective nature of this study, the imaging examinations performed were not consistent. Imaging examinations evaluable for neural lesions performed were CT in six patients (cases 1-6), MRI in five (cases 1-4, 6), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in one (case 5). Case 7 did not undergo radiological examination for the neural lesion. Images were reviewed in terms of the location, shape, and size of each lesion, configuration of the border to surrounding adipose tissue (well circumscribed or infiltrative), and the presence or absence of radiologically detectable nerve fibers within the lesion. The size of lesions was defined as the maximum diameter measured in the vertical imaging plane to the peripheral lesions.

Results

Clinical characteristics
**Location:** A total of 21 peripheral nerve lesions were identified in 7 patients. Locations and radiological features are summarized in Table 2. Of 7 patients, 5 (71%) had two or more lesions simultaneously. Twenty lesions (95%) were located in orbital or paravertebral area, involving infraorbital (n=5), supraorbital (n=4), optic (n=4), lumbar spinal (n=3), sacral spinal (n=3), and cervical spinal nerves (n=1). The remaining lesion was involvement of great auricular nerve in a cervical mass in case 7.

Table 2. Characteristics of perineural lesions

<table>
<thead>
<tr>
<th>Case</th>
<th>Affected nerve</th>
<th>Performed imaging examinations</th>
<th>Size</th>
<th>Shape</th>
<th>Involved nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right supraorbital nerve</td>
<td>CT (P), MRI (P)</td>
<td>15 mm</td>
<td>Round</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Right infraorbital nerve</td>
<td>CT (P), MRI (P)</td>
<td>25 mm</td>
<td>Lobular</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Left infraorbital nerve</td>
<td>CT (P), MRI (P)</td>
<td>26 mm</td>
<td>Lobular</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Left optic nerve</td>
<td>CT (P), MRI (P)</td>
<td>12 mm</td>
<td>Lobular</td>
<td>Identifiable (MRI)</td>
</tr>
<tr>
<td>2</td>
<td>Left optic nerve</td>
<td>CT (P), MRI (CE)</td>
<td>14 mm</td>
<td>Lobular</td>
<td>Identifiable (MRI)</td>
</tr>
<tr>
<td>3</td>
<td>Left supraorbital nerve</td>
<td>CT (P), MRI (P)</td>
<td>10 mm</td>
<td>Round</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Left optic nerve</td>
<td>CT (P), MRI (P)</td>
<td>10 mm</td>
<td>Lobular</td>
<td>Identifiable (MRI)</td>
</tr>
<tr>
<td>4</td>
<td>Right infraorbital nerve</td>
<td>CT (P), MRI (CE)</td>
<td>8 mm</td>
<td>Round</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Right optic nerve</td>
<td>CT (P), MRI (CE)</td>
<td>30 mm</td>
<td>Lobular</td>
<td>Identifiable (MRI)</td>
</tr>
<tr>
<td>5</td>
<td>Left C6 nerve</td>
<td>C6 (P), FDG-PET</td>
<td>9 mm</td>
<td>Round</td>
<td>Not visible</td>
</tr>
<tr>
<td></td>
<td>Right L5 nerve</td>
<td>CT (CE), FDG-PET</td>
<td>13 mm</td>
<td>Round</td>
<td>Not visible</td>
</tr>
<tr>
<td>Case</td>
<td>Other organ manifestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Enlargement of the left extra-ocular muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Enlargement of the left extra-ocular muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Dacryoadenitis, sialadenitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other organ involvement: All patients were found to have IgG4-related lesions in other organs, all but one of which were identified at the same time as the neural lesions (Table 3).
Dacryoadenitis

Hepatic inflammatory pseudotumor, tubulointerstitial nephritis

Dacryoadenitis, mediastinal lymphadenopathy, tubulointerstitial nephritis, enlargement of the bilateral extra-ocular muscle

Dacryoadenitis, lung lesions, tubulointerstitial nephritis

*, a single lesion identified before the episode of perineural disease.

**Symptoms:** All patients presented symptomatically (Table 1). Symptoms were related to other organ lesions or mass effects of peripheral nerve lesions. Real neurological signs such as paralysis were not evident in any cases at the first presentation.

**Treatment and recurrence:** Steroid therapy at an initial dose of 20 to 40 mg/day was effective for all patients, making peripheral nerve lesions decrease in size in conjunction with decreased size of other organ lesions. Recurrent perineural lesions were confirmed during steroid taper in two patients (cases 2, 4). In case 2, the recurrent lesion, which compressed the left optic nerve in the optic bony canal, caused failing vision and papilledema. The recurrent lesion promptly responded to an increased dose of steroid. Visual acuity and papilledema were fully recovered. Recurrent lesions involving right optic and infraorbital nerves in case 4 also decreased in size with an increased dose of steroid.

**Imaging characteristics**

Radiological examination was performed for peripheral nerve lesions in 6 patients (cases 1-6). All lesions were radiologically characterized by distinct masses along the affected nerve fascicles (Figures 1-4). The size of the lesions ranged from 8 to 30 mm (median 13 mm). In case 1, bilateral orbital masses extended to the subcutis of the cheek along infraorbital nerves and their branches (Figure 1a, c-f). Spinal nerve lesions in cases 5 and 6 involved nerve fascicles mainly within and distal to intervertebral foramen, and portions proximal to the foramen, which anatomically correspond to nerve roots, were affected only in cervical nerve lesion of case 5. All lesions were well circumscribed with a round or lobular shape. The latter was common in optic nerve lesions (Table 3). On CT images, all lesions showed iso-density compared with those of skeletal muscles. Peripheral nerve lesions showed iso-intensity in T1-weighted MRI images and iso- to slightly high-intensity in T2-weighted images compared with those of skeletal muscles (Figure 1-4). All lesions were homogeneously enhanced (Figure 2c, d and 3c). Calcification or necrosis was not a feature in any lesion.
Histopathological features of the perineural lesions

Histopathological examinations in perineural lesions were performed in cases 1 and 7. The pathology specimen consisting of perineural soft tissue showed severe lymphoplasmacytic infiltration, irregular fibrosis, and occasional eosinophils. Obliterative phlebitis was not identified. Immunostaining revealed a large number of IgG4+ plasma cells and an IgG4/IgG ratio was 61.8%.

Case 7, who did not undergo radiological examination of the peripheral nerve lesion, had IgG4-related disease in bilateral lacrimal glands, lung (interstitial pneumonia), and kidney. He noticed a palpable mass in the left neck, which was surgically resected on suspicion of an enlarged lymph node. Macroscopically, the resected lesion was a well circumscribed spherical mass measuring 15 mm in the maximum diameter. Histologically, the specimen was not a lymph node but an inflammatory nodule centered on large nerve fascicles (Figure 5a, b), which were considered to be the great auricular nerve. The epineurium was extensively enlarged with massive lymphoplasmacytic infiltration rich in IgG4+ plasma cells (Figure 5c, d). Penetrating nerve fibers, which were separated from the inflammatory process by the perineurium, were histologically unremarkable with scarce intraneural inflammatory cell infiltration (Figure 5b).

Compared radiological features and histological findings, perineural masses corresponded to the expanded perineurium affected by the IgG4-related inflammatory process. Homogeneous enhancement on imagings was supposed to represent massive inflammatory cell infiltration in the perineurium.

Images for this section:
Fig. 1: Figure 1: CT (a) and MRI (b, d; T2 weighted images; c, e, f, T1 weighted images) of orbital space in 55-year-old man (case 1). CT image reveals soft tissue around the bilateral infra orbital nerve (a; arrows). MRI shows soft tissue around the left orbital nerve (b-d; small arrows), bilateral infra orbital nerve (c-f; arrows), and right supra orbital nerve (c, d; arrowheads). Left orbital nerve can be detected in the lesion (b, d).
Fig. 2: Figure 2: CT (a) and MRI (b, T2 weighted image; c and d, contrast-enhanced T1 weighted images) of orbital space in 44-year-old man (case 4). Soft tissue mass is detected in the right orbital space (a; arrow). This lesion extends along the right optic nerve in MRI (b-d; arrows). The right optic nerve penetrating in the lesion is detectable in MRI (b, d; small arrows). Soft tissue mass along the right infraorbital nerve is also noted (a-c; arrowheads).
**Fig. 3:** Figure 3: MRI (a and d, T2 weighted images; b, T1 weighted image; c, contrast-enhanced T1 weighted image) of orbital space in 61-year-old man (case 3). MRI shows the soft tissue around the left supra orbital nerve (a-c; arrows) and optic nerve (c, d; arrowheads). The left optic nerve can be detected in the lesion.
Fig. 4: Figure 4: CT (a, c, e) and FDG-PET (b, d, and f, fusion images; g, coronal MIP image) of whole body in 58-year-old man (case 5). CT shows soft tissue density around the left C6 (a; arrow), right L5 (c; arrows), and S1 nerves (e; arrow). High FDG uptakes are identified as perineural masses (b, d, f, g; arrows).
Fig. 5: Figure 5: Histological features of resected IgG4-related perineural disease. 61-year-old man (case 7). (a) The epineurium is involved in a massive inflammatory process, where nerve fascicles (*) are embedded. (b) The endoneurium is unremarkable without inflammatory cell infiltration. (c) Inflammatory cells consist predominantly of lymphocytes and plasma cells. (d) Immunostaining for IgG4 reveals a large number of IgG4+ plasma cells.
Conclusion

The obtained results can be summarized as follows: (1) IgG4-related disease can rarely involve peripheral nerves particularly in ocular or paravertebral area, the former usually associated with ophthalmic lesions. (2) IgG4-related neural lesions are radiologically characterized by nerve-centered distinct soft tissue masses. (3) Histological features are massive lymphoplasmacytic infiltrates rich in IgG4+ plasma cells predominantly affecting the epineurium, suggesting "IgG4-related perineural disease" to be an appropriate term to describe these lesions. (4) Neurological symptoms are only rarely noted in this retrospective study.

The predominant radiological feature of IgG4-related perineural disease was a well-circumscribed mass, seen as soft tissue intensity on MRI. Interestingly, MRI demonstrated unremarkable optic nerves penetrating the perineural masses, suggesting little, if any, damage to the nerve fascicles themselves. This is in keeping with the fact that nerve fibers entrapped in the lesion were histologically unremarkable, and neurological symptoms were rare. However, smaller nerves, such as the infraorbital nerve, were difficult to visualize on MRI. It is not yet conclusive to what extent FDG-PET is useful in detecting IgG4-related perineural disease like as reported in other organs [22], but this functional imaging helped us to recognize spinal nerve lesions, which were overlooked by other modalities, in case 5.

It is interesting that 13 of 21 (62%) perineural lesions were seen in the orbital area, where branches of the trigeminal nerve were commonly involved (43%). Affected nerves described in previous papers were also trigeminal or optic nerve branches [19-21]. One possible explanation of this site predilection is that IgG4-related ophthalmic disease more commonly shows perineural extension than other organ manifestations.

In conclusion, IgG4-related disease of the peripheral nervous system, which can be called IgG4-related perineural disease, is characterized by orbital and paravertebral localization, perineural mass formation detectable as soft tissue intensity in MRI images, and rare neurological symptoms.

Personal Information

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References


