Proteinase 3 Anti-Neutrophil Cytoplasmic Antibody (PR3-ANCA) Positive IgG4-Related Retroperitoneal Fibrosis: Utility of PET-CT with 18F-Fluorodeoxy Glucose (FDG)

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Abstract

A 55-year-old man showed a serum creatinine level of 1.51 mg/dL, CRP of 0.79 mg/dL, and proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) of 43.9 EU (normal range: below 10). The serum levels and ratios of IgG1, IgG2, IgG3, and IgG4 to total IgG were 1,570 mg/dL (49%), 1,190 mg/dL (37%), 82 mg/dL (3%), and 351 mg/dL (11%), respectively. Positron emission tomography and CT with 18F-fluorodeoxyglucose (PET-CT) demonstrated retroperitoneal fibrosis. After a diagnosis of IgG4-related retroperitoneal fibrosis with PR3-ANCA was made, oral prednisolone improved serum creatinine and the titer of PR3-ANCA to normal levels, with no abnormal findings on PET-CT.

Key words: IgG4-related retroperitoneal fibrosis, PET-CT with FDG, PR3-ANCA


Introduction

Retroperitoneal fibrosis was first described by Albarran in 1905 (1). Two additional cases described by Ormond established the disease entity of retroperitoneal fibrosis in 1948 (2). Recently, retroperitoneal fibrosis is reported to belong to IgG4-related diseases, which is proposed as a new disease entity by many Japanese physicians, based on the criteria of IgG4 greater than 135 mg/dL (3, 4). On the other hand, proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) is a well known disease marker autoantibody found in Wegener’s granulomatosis (5). However, several other diseases are reported to be associated with PR3-ANCA (6-8).

Here we report the first case of PR3-ANCA positive IgG4-related retroperitoneal fibrosis and review the literature.

Case Report

A 55-year-old man was admitted to Kizawa Memorial Hospital for low back pain and abdominal discomfort. Nine years prior to admission, he was diagnosed with chronic pancreatitis based on elevated trypsin and pancreatic phospholipase A2 levels. At that time, abdominal discomfort improved with camostat mesilate (CM), a newly synthesized oral protease inhibitor. Two months prior to admission, he was diagnosed with chronic sinusitis with thickened sinusoidal walls and underwent endoscopic surgery. Pathological examination of the nasal polyp specimens demonstrated chronic inflammation with lymphocyte and plasma cell infiltration without granulomatous changes and vasculitis, however, there was no information obtained on the rate of IgG4 positive plasma cells. One month prior to admission, he visited a neighborhood medical clinic for abdominal discomfort without complains of dry eyes or dry mouth, and a gastroduodenal fiberscopic study revealed no abnormalities. He

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aminotransferase and alanine aminotransferase levels were
enhanced CT scan revealed a soft tissue density surrounding
right hydronephrosis and hydroureter (Fig. 1A). An en-
tively.
IgG to total IgG were 49%, 37%, 3%, and 11%, respec-
351 mg/dL, respectively. The ratio of IgG1, IgG2, IgG3, and
IgG4 were 1,570 mg/dL, 1,190 mg/dL, 82 mg/dL, and
2,928 mg/dL, 467 mg/dL, and 44 mg/dL, respectively.
Blood chemistry revealed sodium of 137 mEq/L, potassium of
4.6 mEq/L, chloride of 99 mEq/L, amylase of 138 IU/L (normal
range: 60-200 IU/L), C-reactive protein (CRP) of 0.79 mg/dL (normal range:
below 0.3 mg/dL), and IgG, IgA, IgM antibody levels of
below 10). The serum levels of IgG1, IgG2, IgG3,
and IgG4 were 1,570 mg/dL, 1,190 mg/dL, 82 mg/dL, and
351 mg/dL, respectively. The ratio of IgG1, IgG2, IgG3,
and IgG4 to total IgG were 49%, 37%, 3%, and 11%, respec-
tively.
Abdominal computed tomography (CT) demonstrated
right hydronephrosis and hydroureret (Fig. 1A). An en-
hanced CT scan revealed a soft tissue density surrounding
the abdominal aorta (Fig. 1B). Positron emission tomogra-
phy (PET) and CT (PET-CT) with 18F-fluorodeoxyglucose
(FDG) showed accumulation of FDG in the lower abdomen,
corresponding to the soft tissue density around the abdomi-
nal aorta seen on CT (Fig. 2A, 2C), and in the salivary
glands, but not in the nasal area or pancreas.
In the context of high levels of IgG4 and abdominal CT
and PET-CT scan findings, a diagnosis of retroperitoneal fi-
brosis was made. The patient was started on 40 mg/day of
prednisolone (PSL) for 10 days. PSL was then decreased to
30 mg/day for 20 days, after which PSL was decreased to
25 mg/day and 50 mg/day of azathiopurin was started for 30
days. After 60 days of treatment, serum creatinine, initially
1.51 mg/dL, decreased to 0.8 mg/dL, estimated GFR improved
from 39.1 to 78.4 mL/min/m². Ri

Discussion

There are three unique aspects in the present case. The first is retroperitoneal fibrosis with high levels of IgG4. The second is a positive finding on PET-CT prior to treatment. The third is the presence of elevated PR3-ANCA on admission.

The concept of IgG4-related disease (3), which includes
Table 1. Cases of PR3-ANCA or c-ANCA Positive Retroperitoneal Fibrosis in the Literature

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Age/sex</th>
<th>ANCA titer</th>
<th>Imaging study</th>
<th>Related disease</th>
<th>Serum IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ter Maaten (1993)27</td>
<td>49/M</td>
<td>PR3 ANCA 1:64</td>
<td>N/A</td>
<td>Wegener’s granulomatosis, granulomatous prostatitis</td>
<td>N/A</td>
</tr>
<tr>
<td>Kaipiainen-Seppänen (1996)28</td>
<td>52/M</td>
<td>c-ANCA 100 IU (&lt;10)</td>
<td>CT</td>
<td>atrial fibrillation, bronchial asthma</td>
<td>N/A</td>
</tr>
<tr>
<td>Vaglio (2002)29</td>
<td>74/F</td>
<td>c-ANCA1:160; PR3 negative</td>
<td>CT</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>de Roux-Serratrice (2002)30</td>
<td>47/M</td>
<td>PR3-ANCA 62 IU/mL (&lt;20)</td>
<td>CT</td>
<td>Wegener’s granulomatosis (six months later)</td>
<td>N/A</td>
</tr>
<tr>
<td>Aslangul (2003)31</td>
<td>82/F</td>
<td>PR3-ANCA 1518 U/mL (&lt;10)</td>
<td>CT</td>
<td>intestinal bleeding, pelvic mass</td>
<td>N/A</td>
</tr>
<tr>
<td>Mavragani (2007)32</td>
<td>52/M</td>
<td>PR3-ANCA three times the upper limit of normal</td>
<td>CT</td>
<td>Riedel’s disease (thyroidectomy)</td>
<td>N/A</td>
</tr>
<tr>
<td>Martinez-Odriozola (2008)33</td>
<td>46/M</td>
<td>PR3-ANCA 179 U/mL</td>
<td>CT</td>
<td>crescentic GN, intracranial hemorrhage, death</td>
<td>N/A</td>
</tr>
<tr>
<td>Present case</td>
<td>55/M</td>
<td>PR3-ANCA 43.9 U/mL (&lt;10)</td>
<td>CT and PET-CT</td>
<td>chronic sinusitis 351 mg/dL, 11% of total IgG</td>
<td></td>
</tr>
</tbody>
</table>

chronic pancreatitis (9, 10), Mikulicz’s disease (11), sclerotic cholangitis (12), interstitial nephritis (13, 14), and retroperitoneal fibrosis (15, 16), has been presented by many Japanese physicians as a new disease entity. Essential diagnostic criteria proposed include a serum level of IgG4 greater than 135 mg/dL, an increased number of IgG4-positive cells observed in involved tissues, and sclerotic changes in involved tissues. The present case is compatible with IgG4-related disease, given the elevated level of IgG4 (351 mg/dL); however, it is difficult to perform biopsy of retroperitoneal tissue. We made a diagnosis of retroperitoneal fibrosis based on the findings on plain and contrast-enhanced abdominal CT.

PET-CT has recently been reported as a useful imaging modality in retroperitoneal fibrosis. Usually PET shows a hot spot with accumulation of the labeled substance but it is difficult to identify the involved organ. The combination of PET and CT clearly demonstrates involved organs and tissues. Since 2002, there are several reports on PET-CT performed in patients with retroperitoneal fibrosis (17-21). The current case shows the utility of PET-CT with FDG in the diagnosis and follow-up evaluation of patients with retroperitoneal fibrosis.

PR3-ANCA is a well-known disease marker of Wegener’s granulomatosis. However, the sensitivity and specificity of PR3-ANCA for Wegener’s granulomatosis have been reported to be 30-50%, and 90%, respectively (22-24). In the context of infection, proteinase 3 (PR3), a serine protease located in the cytoplasm of neutrophils, moves to the cell surface, and is secreted by neutrophils. Secreted PR3 is neutralized by serine protease inhibitors such as anti-trypsin. When the neutralization mechanism is impaired, PR3 itself injures cells or tissues, and anti-PR3 antibody, namely PR3-ANCA, reacts with PR3 on cell surfaces. These reactions accelerate inflammation (25, 26). Other than in Wegener’s granulomatosis, PR3-ANCA is known to be elevated in patients with infectious endocarditis (6), drugs such as sulphasalazine (7), and parvovirus B19 infection (8). This present case indicates that PR3-ANCA is also positive in patients with retroperitoneal fibrosis or IgG4-related disease.

The current patient has a history of chronic sinusitis; however, the surgical specimen for sinus surgery showed no specific findings compatible with Wegener’s granulomatosis; however, the surgical specimen for sinus surgery showed no specific findings compatible with Wegener’s granulomatosis, and systemic examination revealed no signs of lung and kidney involvement. Unfortunately no analysis for IgG subclasses was undertaken.

An extensive review of the literature revealed eight cases including the present case with PR3-ANCA positive retroperitoneal fibrosis (27-33). Two cases showed signs of Wegener’s granulomatosis, and one had Riedel’s disease, an
IgG4-related disease. Although the previous authors did not comment on the serum levels of IgG4, these reports are generally thought to be cases of IgG4-related disease, even though this is the first reported case with a combination of IgG4-related retroperitoneal fibrosis and elevated PR3-ANCA (Table 1). Regarding the relationship between IgG4 and PR3-ANCA, recent several analyses demonstrate the importance of IgG4 subclass of PR3-ANCA, which induces inflammation in patients with Wegener’s granulomatosis (5, 34, 35). Further accumulation of similar cases will help clarify the mechanisms of retroperitoneal fibrosis and the relationship between PR3-ANCA and IgG4.

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

References