INTERNAL MEDICINE

□ CASE REPORT □

IgG4-related Autoimmune Prostatitis: Two Cases with or without Autoimmune Pancreatitis

Isao Nishimori[1], Takuhiro Kohsaki[1], Saburo Onishi[1], Taro Shuin[2], Shino Kohsaki[3], Yasuhiro Ogawa[3], Manabu Matsumoto[4], Makoto Hiroi[4], Hideaki Hamano[5] and Shigeyuki Kawa[6]

Abstract

Recently, autoimmune pancreatitis (AIP) has been reported with a variety of extra-pancreatic manifestations and infiltration of IgG4-positive cells into the affected organs. We report herein two cases with prostatitis. One was seen in a patient with typical AIP, and the other was observed without any clinical manifestation of AIP. Serum IgG4 levels were elevated in both cases. Histological examination of the prostates showed that parenchymal cells were partially or totally replaced with fibrosis and abundant infiltration of IgG4-positive cells. Significant uptake of [^{18}F] fluorodeoxyglucose by the prostate was seen in both cases. In the case with AIP, the uptake completely disappeared after steroid therapy. The findings observed in these cases suggest that the pathological mechanism for prostatitis is similar to the mechanism previously implicated in AIP, namely IgG4-related autoimmune prostatitis.

Key words: autoimmune pancreatitis, prostatitis, IgG4-related sclerosing disease, positron emission tomography with [^{18}F] fluorodeoxyglucose, steroid therapy

(DOI: 10.2169/internalmedicine.46.0452)

Introduction

Recently, autoimmune pancreatitis (AIP) has been proposed as a novel disease entity whose etiology may involve autoimmune mechanisms (1, 2). The disease concept of AIP originally arose from the characteristic findings on pancreatic imaging studies, such as diffuse enlargement of the pancreas and irregular narrowing of the main pancreatic duct, together with clinical evidence of dramatic improvement in the unusual configuration of the pancreas by the steroid therapy (1, 3). Some patients with AIP show hypergammaglobulinemia and non-specific autoantibodies, including antinuclear antibody and rheumatoid factor (2, 4). In addition, an increased level of serum IgG4 is reported to be a specific serological marker of AIP (5). Pathological studies of the pancreas in AIP patients show periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis that is designated as lymphoplasmacytic sclerosing pancreatitis (2, 4, 6, 7). Immunohistochemically, infiltration of an abundance of IgG4-positive plasma cells is seen in the pancreas of AIP patients (2, 4, 8-10).

The accumulation of clinical data in AIP patients has revealed a variety of extra-pancreatic involvement, including sclerosing cholangitis, lacrimal and salivary gland swelling (seronegative Sjögren's syndrome or Mikulicz's disease), hypothyroidism, hilar lymphoadenopathy, retroperitoneal fibrosis, interstitial pneumonia, and interstitial nephritis (11). Interestingly, infiltration of an abundance of IgG4-positive cells is also observed in these extra-pancreatic lesions. Based on these findings, systemic disease concepts, such as IgG4-related sclerosing disease (4, 12) or IgG4-associated multifocal systemic fibrosis (13), have been proposed.

We report herein two cases with prostatitis. Histological

[1]Department of Gastroenterology and Hepatology, Kochi Medical School, Nankoku, [2]Department of Urology, Kochi Medical School, Nankoku, [3]Department of Diagnostic Radiology and Radiation Oncology, Kochi Medical School, Nankoku, [4]Laboratory of Diagnostic Pathology, Kochi Medical School, Nankoku, [5]Department of Medicine, Gastroenterology, Shinshu University School of Medicine, Matsumoto and [6]Center for Health, Safety and Environmental Management, Shinshu University, Matsumoto

Received for publication July 15, 2007; Accepted for publication August 30, 2007

Correspondence to Dr. Isao Nishimori, nisao@kochi-u.ac.jp

DOI: 10.2169/internalmedicine.46.0452

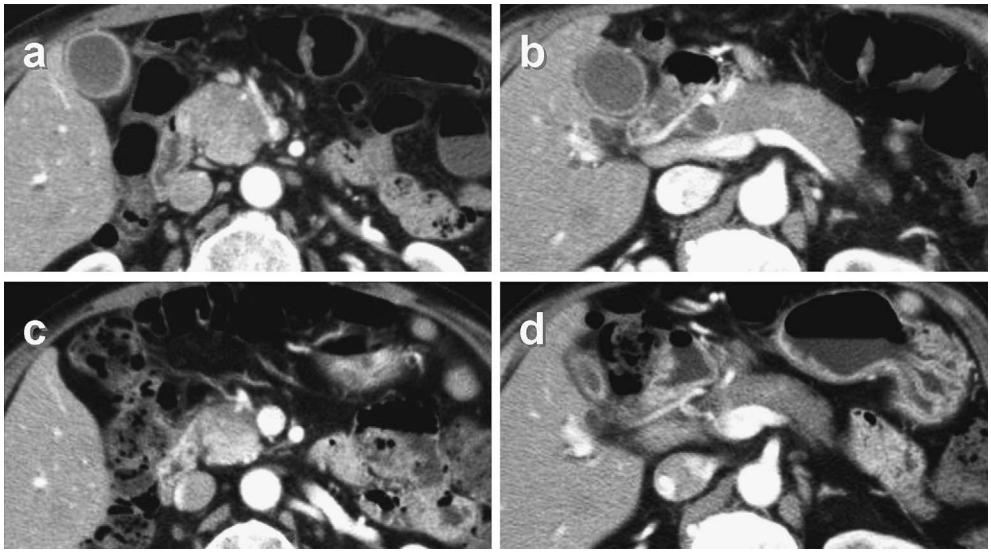

Figure 1. **Case 1. On admission, abdominal computed tomography with intravenous contrast reveals diffuse pancreatic enlargement (a and b). Following steroid therapy, the pancreatic swelling is markedly improved (c and d).**

examinations of the prostates yielded findings similar to those reported for AIP, including infiltration of IgG4-positive cells. Significant uptake of [^{18}F] fluorodeoxyglucose (FDG) by the prostate was seen in both cases. It is noteworthy that, in one case, the uptake of FDG completely disappeared after steroid therapy. The findings observed in these cases suggest a novel pathogenesis and therapeutic approach for prostatitis.

Case Report

Case 1

A 64-year-old man with elevated serum levels of hepatobiliary enzymes, as discovered by an annual health check, was referred to our hospital. Physical examination at the time of admission revealed no significant findings except for mild jaundice. At the age of 40 years, the patient was diagnosed as having benign prostatic hyperplasia with urinary frequency and dysuria; since then he has been treated with α-blocker. On the present admission, he had no complaints of genitourinary symptoms.

Laboratory examinations showed the following values (normal range): peripheral white cell count, 6,400/μL; peripheral eosinocyte count, 768/μL; C-reactive protein, 0.4 mg/dL (<0.3); total bilirubin, 5.4 mg/dL; alkaline phosphatase, 1,772 IU/L (100-340); γ-glutamyl transpeptidase, 847 IU/L (5-70); alanine aminotransferase, 175 IU/L (5-40); asparate aminotransferase, 201 IU/L (10-35); amylase, 108 IU/L (40-115); and lipase, 9 IU/L (13-60). Hepatitis B surface antigen and antibody to hepatitis C virus were negative. Serum γ-globulin, IgG, IgA, and IgM levels were 1.18 g/dL (0.7-1.6), 1,750 mg/dL (850-1,650), 196 mg/dL (110-450), and 22 mg/dL (45-190), respectively. The serum levels of the IgG subclasses were as follows: IgG1, 1,280 mg/dL (538-1,244); IgG2, 807 mg/dL (254-820); IgG3, 83 mg/dL (<70); and IgG4, 1,030 mg/dL (<117). Serum autoantibodies were all negative, including antinuclear antibody, rheumatoid factor, anti-Ro antibody (SS-A), anti-La antibody (SS-B), anti-mitochondrial antibody, and anti-smooth muscle antibody. The serum level of soluble IL-2 receptor was 1,140 IU/mL (220-530). Tumor marker levels were as follows: CEA, 4.6 ng/dL (<3.4); CA19−9, 25.9 U/mL (<37); and prostate-specific antigen, <0.01 ng/mL (<4). Proteinuria was not observed, and urinary sedimentation included neither red nor white blood cells.

Upon admission, abdominal computed tomography (CT) examination (Fig. 1a and 1b) revealed diffuse pancreatic enlargement. An endoscopic retrograde cholangiopancreatogram (ERCP) indicated diffusely irregular narrowing of the main pancreatic duct and segmental stricture of the lower common bile duct (Fig. 2a). Positron emission tomography with [^{18}F] fluorodeoxyglucose (FDG-PET) revealed significant uptake of FDG by the pancreas (standardized uptake value (SUV) of 4.4 at 60 min after the FDG injection) and prostate (SUV of 5.0) (Fig. 3a); the latter was reconfirmed as the prostate with small calcification by FDG-PET-CT (Fig. 3b).

Characteristic findings on the pancreatic imaging studies and a remarkably increased level of serum IgG4 fulfilled the diagnostic criteria for AIP proposed by a Japanese group (14) and a group at the Mayo Clinic (15). Accordingly, we started to treat the patient with 40 mg/day of oral prednisolone (PSL) and then tapered this dose by 5 mg every two weeks. Abdominal CT at 25 mg/day of PSL revealed improvement in the pancreatic swelling (Fig. 1c and 1d). ERCP at 20 mg/day of PSL also revealed improvements of irregular narrowing of the main pancreatic duct and segmental stricture of the lower common bile duct (Fig. 2b). FDG-PET (-CT) at 20 mg /day of PSL revealed complete disap-

DOI: 10.2169/internalmedicine.46.0452

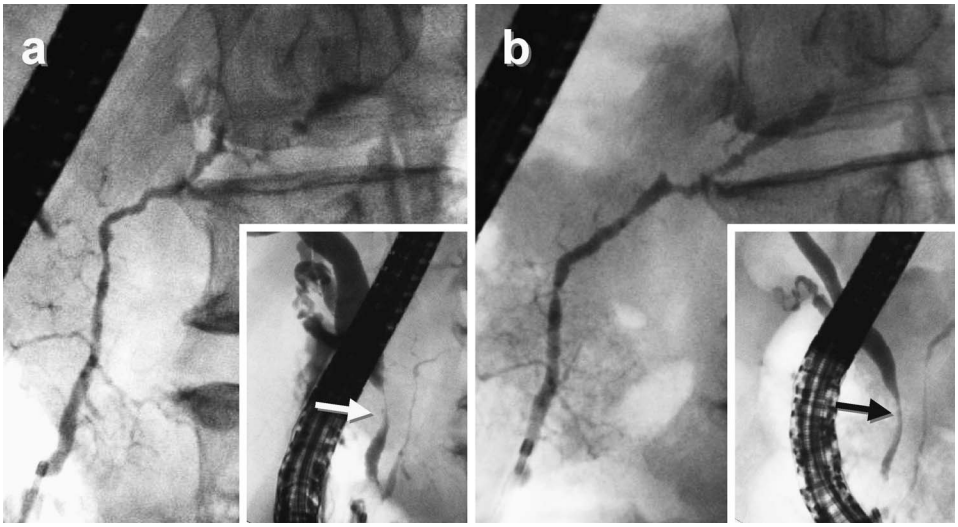

Figure 2. Case 1. On admission, endoscopic retrograde cholangio-pancreatogram reveals diffusely irregular narrowing of the main pancreatic duct and segmental stricture of the lower common bile duct (arrow) (a). Following steroid therapy, these findings are markedly improved (b).

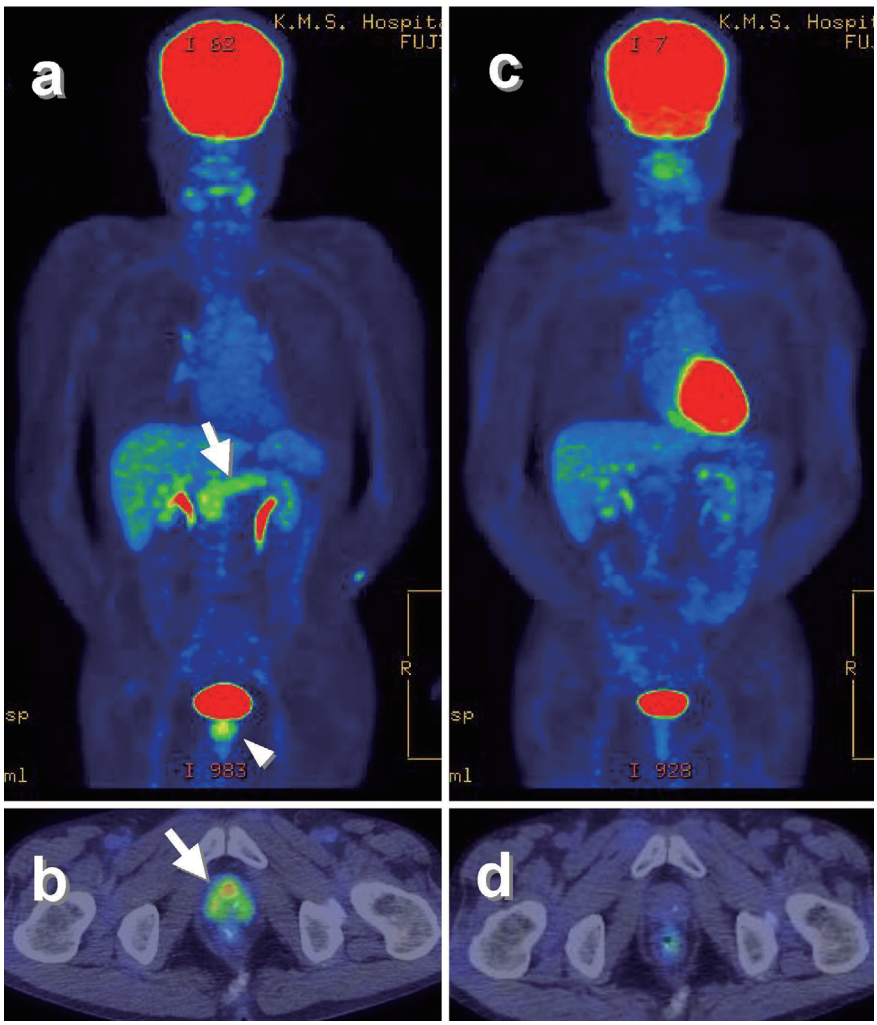

Figure 3. Case 1. On admission, positron emission tomography with [^{18}F] fluorodeoxyglucose (FDG-PET) reveals significant uptake of FDG by the pancreas (standardized uptake value (SUV) of 4.4 at 60 min after the FDG injection) (a) and prostate (SUV of 5.0) (b). Following steroid therapy, the FDG accumulation in the pancreas (c) and prostate (d) totally disappears.

DOI: 10.2169/internalmedicine.46.0452

pearance of FDG uptake by the pancreas and prostate (Fig. 3c and 3d). Serum levels of total bilirubin and hepatobiliary enzymes decreased into the normal range. Serum IgG4 level decreased to 341 mg/dL, but the prostate-specific antigen concentration has been lower than the detectable level (<0.01 ng/mL) under the maintenance of a PSL dose of 5 mg/day for 10 months.

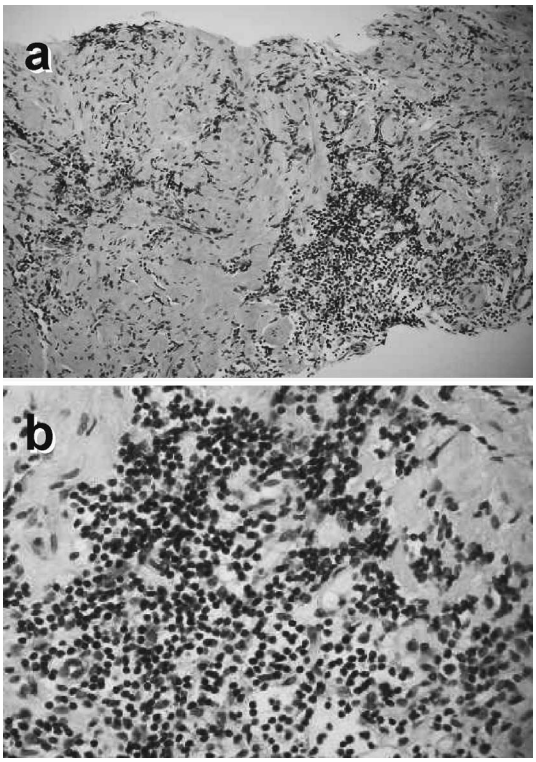

Figure 4. **Case 1. Prior to the steroid therapy, prostate tissue samples are obtained by a transurethral biopsy, which show few glandular structures, dense fibrosis, and infiltration of lymphocytes and plasma cells.**

Prior to the steroid therapy, prostate tissue samples were obtained by a transurethral biopsy, which showed scarce glandular structures, dense fibrosis, and infiltration of lymphocytes and plasma cells (Fig. 4). No findings were suggestive of prostatic carcinoma. The tissue samples were further studied for IgG subclass expression by immunohistochemistry using the avidin-biotin-peroxidase complex method. Formalin-fixed and paraffin-embedded sections were pretreated with a 0.1% solution of trypsin (Sigma Chemical, St. Louis, MO, USA) in Tris-HCl buffer containing 0.1% $CaCl_2$ at 37℃ for 10 min and then immunostained with sheep polyclonal antibody against human IgG1, IgG2, IgG3, and IgG4 (Binding Site, Birmingham, UK). In the results, a number of IgG4-positive cells were found to have infiltrated the prostate (Fig. 5d). There were fewer IgG1-positive cells than IgG4-positive cells (Fig. 5a). IgG3-positive cell infiltration was scattered (Fig. 5b) and IgG2-positive cells were rarely seen (Fig. 5c).

Case 2

A 67-year-old man wishing a pancreatic examination visited our hospital. Physical examination revealed no significant findings. At the age of 49 years, he complained of back pain and was admitted to our hospital for a pancreatic examination, but no remarkable abnormality was detected by a

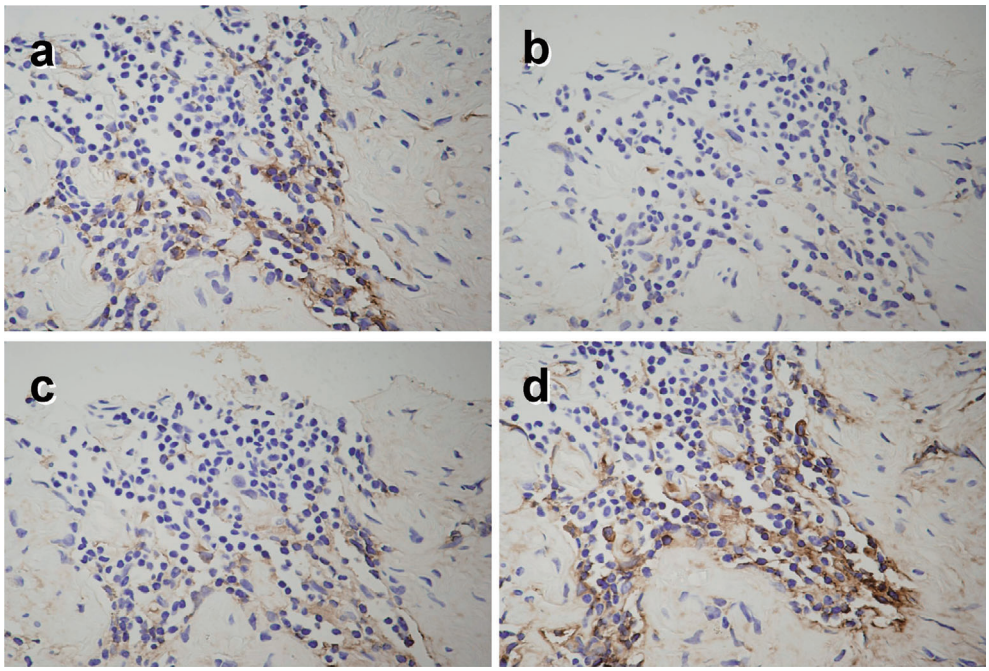

Figure 5. **Case 1. Immunohistochemical staining for the IgG subclasses expression. A number of IgG4-positive cells are found to infiltrate the prostate (d). There are fewer IgG1-positive cells than IgG4-positive cells (a). IgG3-positive cell infiltration is scattered (b) and IgG2-positive cells are rarely seen (c).**

DOI: 10.2169/internalmedicine.46.0452

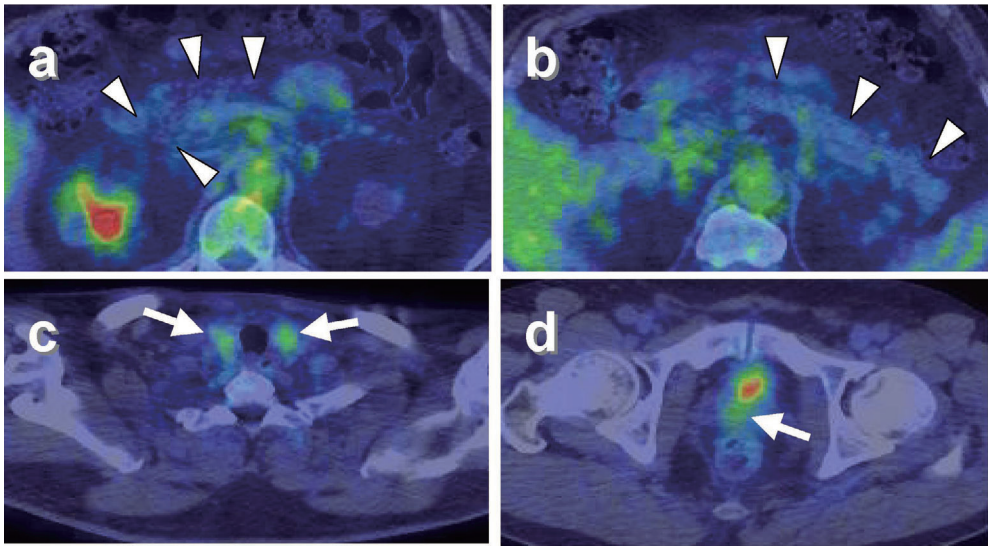

Figure 6. **Case 2. Positron emission tomography with [^{18}F] fluorodeoxyglucose (FDG-PET) reveals no uptake by the pancreas (a and b) but faint accumulation of FDG in the thyroid (standardized uptake value (SUV) of 4.0 at 60 min after the FDG injection) (c) and prostate (SUV of 3.4) (d).**

panel of examinations for the pancreas, including ERCP and CT. At that time, he was diagnosed as having acute prostatitis with tenderness of the prostate; he was treated with antibiotics. In addition, complication of chronic hypothyroiditis with euthyroid function was found with high levels of antimicrosome antibody (×12,800). At the age of 63 years, he underwent a transurethral prostatic resection under the diagnosis of benign prostatic hyperplasia.

Upon the present admission, laboratory examinations showed the following values (normal ranges are the same as those shown in case 1): peripheral white cell count, 4,900/μL; peripheral eosinocyte count, 196/μL; C-reactive protein, 0.1 mg/dL; and total bilirubin, 0.6 mg/dL. Hepato-biliary-pancreatic enzymes (same set as in case 1) were all in the normal range. Serum γ-globulin, IgG, IgA, and IgM levels were 1.77 g/dL, 2,000 mg/dL, 219 mg/dL, and 103 mg/dL, respectively. The serum levels of the IgG subclasses were as follows: IgG1, 1,100 mg/dL; IgG2, 895 mg/dL; IgG3, 43 mg/dL; and IgG4, 473 mg/dL. Serum autoantibodies were all negative, including antinuclear antibody, rheumatoid factor, anti-Ro antibody (SS-A), and anti-La antibody (SS-B). The serum level of soluble IL-2 receptor was 957 IU/mL. Thyroid function was normal, but the thyroid-stimulating hormone level was slightly elevated (9.29 μIU/mL; 0.47-4.33). Tumor marker levels were as follows: CEA, 4.6 ng/dL; CA19−9, 41 U/mL; and prostate specific antigen, 1.62 ng/mL. Urinalysis showed 30 mg/dL of protein but no sugar. Urinary sedimentation included 1-4 red blood cells and 10-19 white blood cells per high-power field.

CT examination revealed an atrophic pancreas with scattered fat infiltration but no tumor (data not shown). FDG-PET revealed no uptake by the pancreas (Figs. 6a and 6b) but faint accumulation of FDG in the thyroid (Fig. 6c) and prostate (Fig. 6d) with SUV of 4.0 and 3.4 at 60 min after the FDG injection, respectively.

Prostatic tissue samples, which were obtained by a transurethral resection 4 years earlier, were reevaluated and further stained with mouse monoclonal anti-IgG 4 antibody (clone HP6025, Zymed, San Francisco, CA). In this case, immunostaining was performed by an automated immunohistochemistry system (Discovery, Ventana Medical Systems, Tucson, AZ). For antigen retrieval, the section was pretreated with protease I (Ventana Medical Systems). Most part of resected prostate revealed hypertrophy of tubuloalveolar glands and smooth muscle bundles (Fig. 7a). In parts, massive infiltration of mononuclear cells was observed and dense fibrosis replaced the glandular structure. In such lesions, an abundance of IgG4-positive plasma cells were successfully stained (Fig. 7b).

Discussion

In this study, we presented two cases with an unusual histological type of prostatitis, characterized by infiltration of an abundance of IgG4-positive cells and replacement of the normal prostatic parenchyma with fibrosis. According to a consensus definition proposed by the National Institutes of Health in 1999 (16), prostatitis is classified into four groups: (i) acute bacterial prostatitis; (ii) chronic bacterial prostatitis; (iii) chronic-prostatitis/ chronic pelvic pain syndrome (CP/CPPS) (inflammatory and noninflammatory); and (iv) asymptomatic inflammatory prostatitis. The present two cases complained of neither genitourinary nor pelvic symptoms and showed no granulocyte infiltration in the prostatic tissue samples. In this regard, they are classified as asymptomatic inflammatory prostatitis. Histologically, Case 1 showed diffuse atrophy of the prostate, which has been introduced as sclerosing atrophy (17) and was agreeable with an undetectable serum level of the prostate-specific antigen. Case 2 showed hyperplasia of the gland and focal atrophy

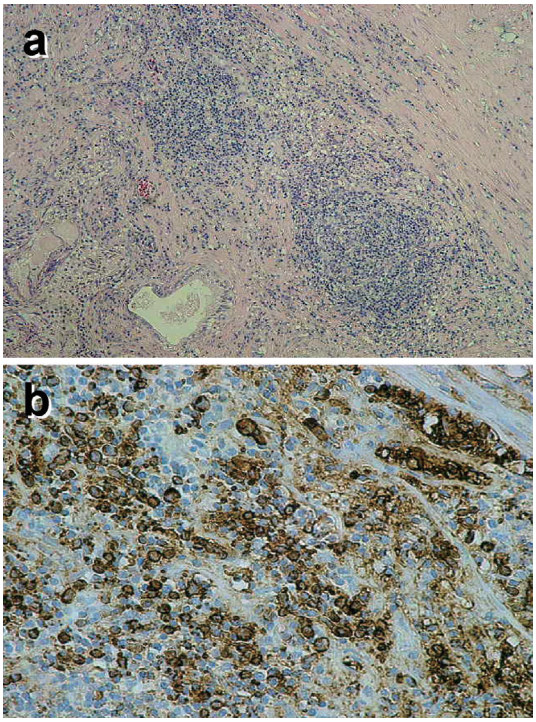

Figure 7. Case 2. Prostatic tissue samples obtained by a transurethral resection 4 years previously were re-evaluated. In most of the resected prostate, hypertrophy of tubuloalveolar glands and smooth muscle bundles are observed. In parts, massive infiltration of mononuclear cells is observed and dense fibrosis replaces the glandular structure (a). In such lesions, an abundance of IgG4-positive plasma cells are successfully stained by immunohistochemistry (b).

with chronic inflammation, which has been termed as proliferative inflammatory atrophy as previously reported (17). Asymptomatic inflammatory prostatitis is incidentally found in prostate biopsies in patients with possible prostatic cancer or infertility, and is still of unknown etiology (16, 18). Although an autoimmune process could be involved in this pathological condition, histochemical findings of IgG4-positive cell infiltration in the prostate have not been reported.

The histological findings observed in the prostate of the present two cases is similar to those reported in the pancreas and extra-pancreatic lesions of AIP patients, including abundant infiltration of IgG4-positive plasma cells (8-10, 12, 13). Both cases showed significantly increased serum levels of IgG4, reported to be a serological marker of AIP (5). Indeed, case 1 was complicated with AIP and showed typical findings of the pancreatic imaging study, such as diffuse enlargement of the pancreas and irregular narrowing of the main pancreatic duct (2, 4, 15). In addition, FDG-PET(-CT) revealed significant uptake of FDG by the pancreas in case 1; the same finding has been reported in AIP (19, 20). Interestingly, our two cases also showed intense accumulation of FDG in the prostate. It is noteworthy that, in case 1, the accumulation of FDG in the prostate totally disappeared after the steroid therapy, similar to the case of the pancreas. The diagnostic criteria for AIP proposed by a group at the Mayo Clinic included the following manifestations: (i) extra-pancreatic involvement, which is confirmed by the presence of abundant IgG4-positive cells; and (ii) response to steroid therapy, which is proven by resolution or marked improvement of pancreatic and/or extra-pancreatic lesions (15). Taken together, these findings strongly suggest that the pathological mechanism underlying prostatitis in the present cases was similar to that implicated in AIP, and was thus designated IgG4-related autoimmune prostatitis (21).

Case 2 failed to show significant findings suggestive for AIP on pancreatic imaging studies including FDG-PET-CT. Instead, positive accumulation of FDG by the thyroid gland was seen. Recently, a panel of extra-pancreatic lesions has been reported in AIP patients, including those with chronic thyroiditis (11). Further, extra-pancreatic lesions with IgG4-plasma cell infiltration have been reported to occur without any pancreatic manifestation (13). As with the prostatic lesion as described above, the chronic thyroiditis in case 2 might be one of extra-pancreatic manifestations of IgG4-related systemic disease.

A database search of the literature revealed only one case concomitantly affected by AIP and chronic prostatitis (21). The reported case underwent pancreaticoduodenectomy and tansurethral prostatic resection under tentative diagnoses of pancreatic cancer and benign prostatic hyperplasia, respectively (21). Histological analyses of the pancreas, prostate, and minor salivary gland yielded findings similar to those observed in our cases, including infiltration of IgG4-positive plasma cells into the glands. It is of greatest clinical significance that the disclosure of the clinical entity of AIP has made it possible to avoid unnecessary surgery of the pancreas, by virtue of the dramatic responsiveness of steroid therapy (2-4, 15). This is also possible in the cases of IgG4-related autoimmune prostatitis. Since case 1 was treated by oral prednisolone for the pancreatic lesion but had no complaints of genitourinary symptoms upon admission, the clinical outcome of steroid therapy on prostatic lesions is uncertain. However, the FDG accumulation in the prostate totally disappeared after the steroid therapy, indicating its effect on prostatic inflammation. As observed in case 2 and discussed above, IgG4-related autoimmune prostatitis could appear without complication of AIP, possibly pointing to a novel therapeutic approach for certain patients with solitary prostatitis.

In conclusion, the cases presented herein suggest that a mechanism similar to that implicated in AIP might extend from involvement in the pancreas to the prostate, leading us to propose a novel pathogenesis of prostatitis, namely IgG4-related autoimmune prostatitis. This new disease entity should be differentially diagnosed from prostatic cancer because of significant FDG uptake (22), but we can propose a novel therapeutic approach against prostatitis. From these points of view, we should carefully reevaluate patients with prostatitis and analyze clinical manifestations in a large number of patients with IgG4-related prostatitis.

DOI: 10.2169/internalmedicine.46.0452

Grant support: This work was supported by the Research Committee on Intractable Pancreatic Disease of the Ministry of Health, Labor and Welfare of Japan.

References

1. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci **40**: 1561-1568, 1995.
2. Okazaki K, Uchida K, Matsushita M, Takaoka M. Autoimmune pancreatitis. Intern Med **44**: 1215-1223, 2005.
3. Ito T, Nakano I, Koyanagi S, et al. Autoimmune pancreatitis as a new clinical entity. Three cases of autoimmune pancreatitis with effective steroid therapy. Dig Dis Sci **42**: 1458-1468, 1997.
4. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol **38**: 982-984, 2003.
5. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med **344**: 732-738, 2001.
6. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: A variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol **22**: 387-395, 1991.
7. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. Am J Surg Pathol **27**: 1119-1127, 2003.
8. Kamisawa T, Funata N, Hayashi Y, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut **52**: 683-687, 2003.
9. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. Mod Pathol **20**: 23-28, 2007.
10. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet **359**: 1403-1404, 2002.
11. Hamano H, Arakura N, Muraki T, et al. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. J Gastroenterol **41**: 1197-1205, 2006.
12. Kamisawa T, Funata N, Hayashi Y. Lymphoplasmacytic sclerosing pancreatitis is a pancreatic lesion of IgG4-related systemic disease. Am J Surg Pathol **28**: 1114-1124, 2004.
13. Tanabe T, Tsushima K, Yasuo M, et al. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. Intern Med **45**: 1243-1247, 2006.
14. Okazaki K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol **41**: 626-631, 2006.
15. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol **4**: 1010-1016, 2006.
16. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA **282**: 236-237, 1999.
17. Putzi MJ, De Marzo AD. Prostate pathology: histological and molecular perspective. Hematol Oncol Clin North Am **15**: 407-421, 2001.
18. Rivero VE, Motrich RD, Maccioni M, Riera CM. Autoimmune etiology in chronic prostatitis syndrome: an advance in the understanding of this pathology. Crit Rev Immunol **27**: 33-46, 2007.
19. Nakamoto Y, Saga T, Ishimori T, et al. FDG-PET of autoimmune-related pancreatitis: preliminary results. Eur J Nucl Med **27**: 1835-1838, 2000.
20. Nakamoto Y, Sakahara H, Higashi T, et al. Autoimmune pancreatitis with F-18 fluoro-2-deoxy-D-glucose PET findings. Clin Nucl Med **24**: 778-780, 1999.
21. Yoshimura Y, Takeda S, Ieki Y, Takazakura E, Koizumi H, Takagawa K. IgG4-associated prostatitis complicating autoimmune pancreatitis. Intern Med **45**: 897-901, 2006.
22. Palmedo H, Bucerius J, Joe A, et al. Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management. J Nucl Med **47**: 616-624, 2006.