

Usefulness of PET/CT Imaging in Systemic IgG4-related Sclerosing Disease. A Report of Three Cases

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Summary

Autoimmune pancreatitis is the pancreatic manifestation of a novel clinicopathological disorder called systemic IgG4-related sclerosing disease. Beside the pancreas, this entity affects other sites (salivary glands, orbit, lung, thyroid, gallbladder, biliary tree system, kidney, abdominal aorta, retroperitoneum, prostate, and lymph node) by infiltration with IgG4-positive plasma cells. Several case reports and small case series have demonstrated the utility of integrated positron emission tomography/computed tomography (PET/CT) in monitoring therapy and documenting relapse and flare-up of autoimmune pancreatitis. However, there are no reports on the usefulness of PET/CT in selecting extrapancreatic sites for tissue sampling. We herein demonstrate the clinical utility of integrated PET/CT in 3 cases of systemic IgG4-related sclerosing disease for targeting extrapancreatic biopsy sites.

Introduction

Autoimmune pancreatitis is a rare type of chronic pancreatitis with presumed autoimmune etiology characterized by pancreatic fibrosis and inflammation due to infiltration of immunoglobulin G4 (IgG4)-positive plasma cells [1]. It was first described by Sarles *et al.* in 1961 [2]. In 1995, a Japanese group introduced the term “autoimmune pancreatitis” as we know it today [3]. Since then, there is a growing interest in this disease, and many cases have been reported around the world. In 2002, Hamano *et al.* were first to perform immunohistochemical analysis of ureteral lesions in patients with autoimmune pancreatitis and showed that these lesions were infiltrated with rich IgG4-positive plasma cells similar to pancreatic lesions [4]. In 2003, Kamisawa *et al.* performed a similar study on other extrapancreatic organs in patients with autoimmune pancreatitis and found the same result [5]. Therefore, they proposed a new clinicopathological disorder called systemic IgG4-related sclerosing disease which autoimmune

pancreatitis is the pancreatic manifestation of this entity [5]. Sometimes, as seen in one of the 3 cases below, systemic IgG4-related sclerosing disease can occur without pancreatic involvement.

Integrated positron emission tomography/computed tomography (PET/CT) is not only a valuable imaging technique for distinguishing neoplastic from benign lesions but also a useful tool for workup of inflammatory processes. Several case reports and small case series in the East (Japan, South Korea) have documented the utility of PET/CT in diagnosing and monitoring therapy of autoimmune pancreatitis and its extrapancreatic lesions [6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. However, there are no reports on the ability of PET/CT imaging in localizing the best target sites for tissue sampling in order to confirm the diagnosis so invasive surgical procedures can be avoided. We herein reported 3 cases of using PET/CT imaging to select the biopsy sites and monitor response to corticotherapy.

Case Reports

Case #1

A 52-year-old Chinese male was referred to our center for further workup of acute pancreatitis and common bile duct stricture. His medical problems included asthma, chronic cough, allergic rhinitis, and chronic rhinosinusitis for approximately 20 years; recently, these conditions worsened. At our center, the patient underwent pancreas protocol computed tomography (CT) scan, endoscopic ultrasound (EUS), and endoscopic cholangiopancreatography (ERCP). CT scan of the abdomen was negative for pancreatic lesion. EUS showed one hypoechoic lesion (2.6x1.8

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Abbreviations CyBor-D: cyclophosphamide, bortezomib, and dexamethasone

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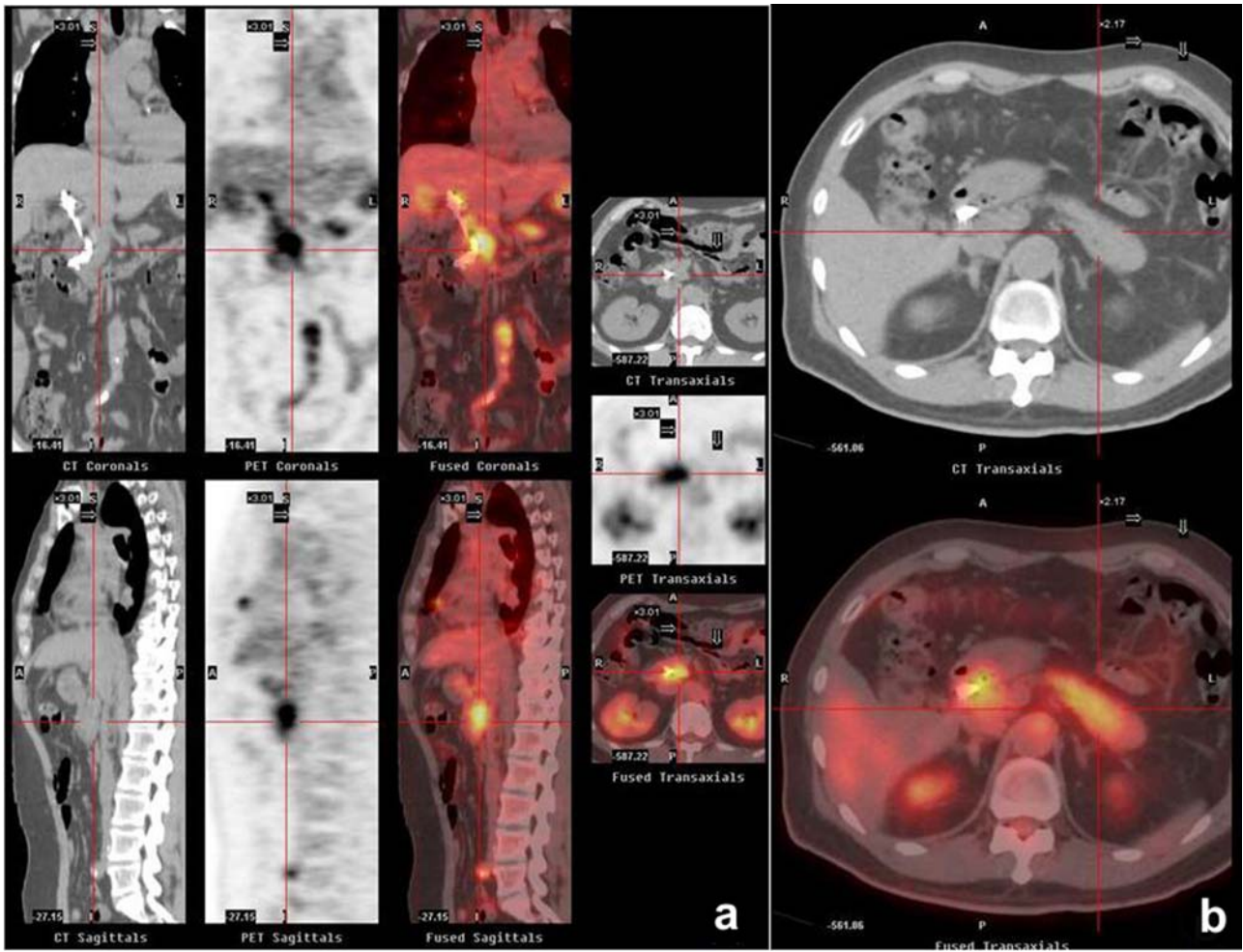


Figure 1. PET/CT composite (a.) and axial PET/CT images (b.) show diffuse tracer uptake by the pancreas (crosshairs). Case#1.

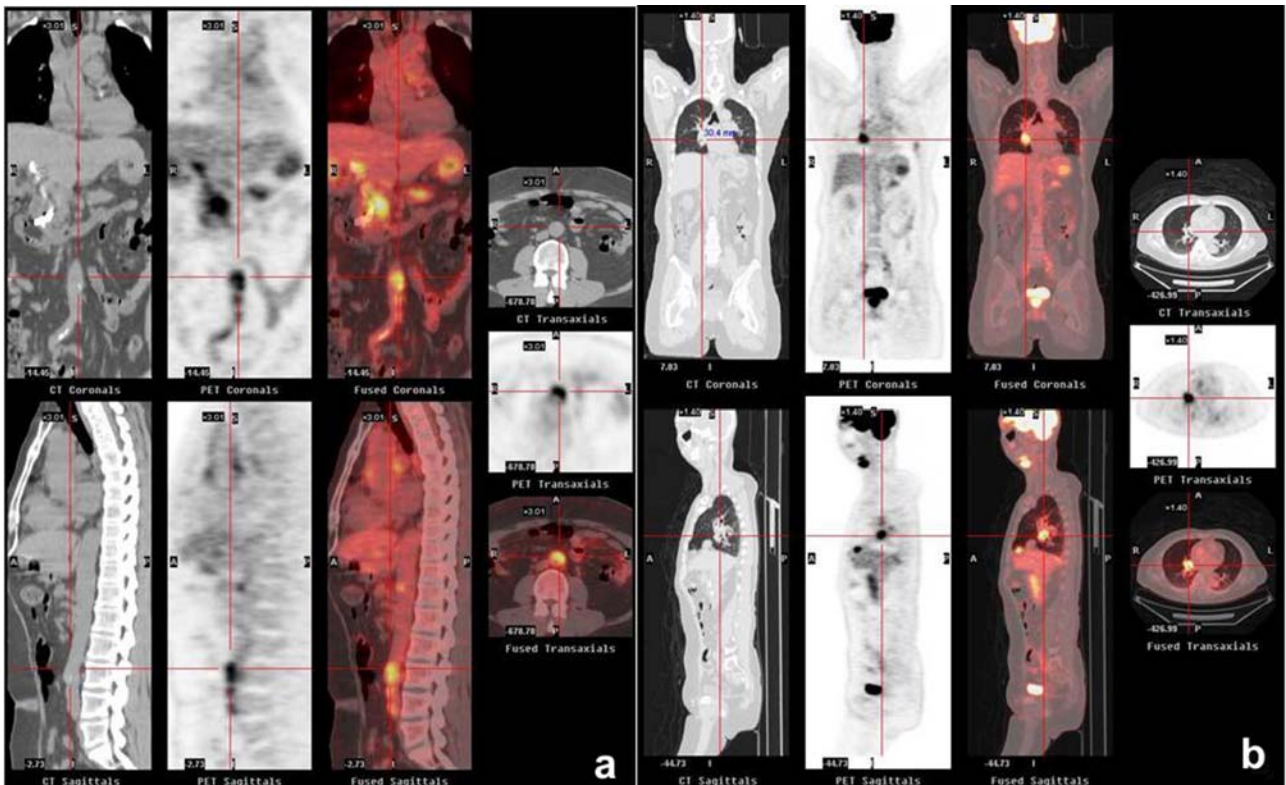


Figure 2. Composite PET/CT images show hypermetabolic peri-aortitis (a. crosshair) and right peri-hilar lesion (b. crosshair). Case#1.

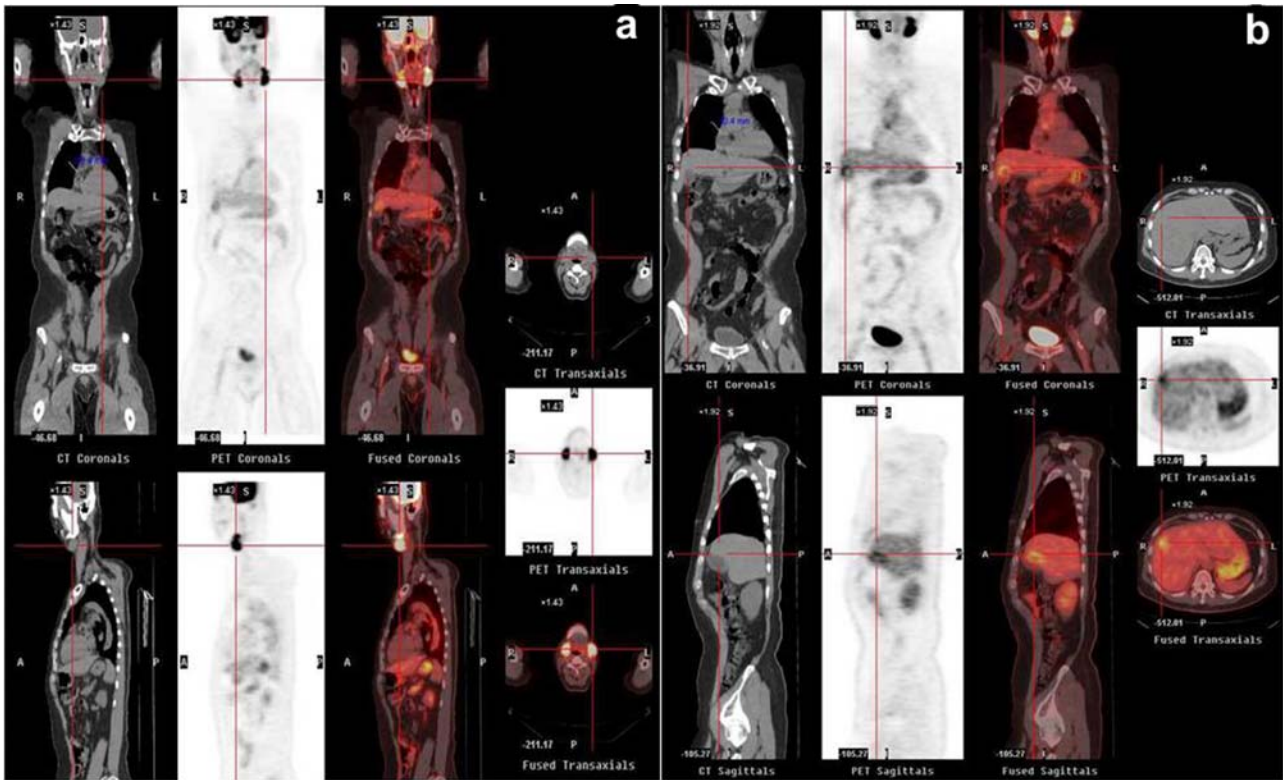


Figure 3. Composite PET/CT images show hypermetabolic lesions of the bilateral salivary glands (a. crosshair) and of the gallbladder (b. crosshair). Case#1.

cm) in the head and another hypoechoic lesion (2.2x2.2 cm) in the body of pancreas; (EUS)-guided fine needle aspiration (EUS-FNA) of the two lesions was negative for pancreatic neoplasm. ERCP demonstrated a high grade common bile duct stricture, which was treated with stent placement; common bile duct brushing cytology was also negative for cancer. At this juncture, pancreaticoduodenectomy was contemplated because he may have pancreatic cancer or cholangiocarcinoma despite above negative workup. In the interim, PET/CT was performed. PET/CT revealed diffuse inflammation in the pancreas (Figure 1). Extrapancreatic lesions in the abdominal aorta, hilar region of lungs, salivary glands, and gallbladder were also observed on PET/CT (Figures 2 and 3). Because of these findings, the patient was suspected to have systemic IgG4-related sclerosing disease. As a result, immunoglobulin G (IgG) and IgG4 levels were measured. Only IgG level was elevated (IgG: 2,430 mg/dL, reference range: 767-1,590 mg/dL; IgG4: 41.2 mg/dL, reference range: 2.4-121.0 mg/dL). Immunoglobulin E (IgE) was 527 KU/L (reference range: 0-127.0 KU/L), and the carbohydrate antigen 19-9 (CA 19-9) was 37 U/mL (reference range: 0-37 U/mL). In order to support the suspected diagnosis, CT-guided biopsy of the left submandibular gland was performed and immunochemical staining was consistent with IgG4-related sclerosing disease (more than 30 IgG4-positive cells per high power field). Therefore, he was treated with prednisone 40 mg daily. After one month of corticotherapy, a repeated PET/CT showed resolution (Figure 4); however, there was an

increase in IgG4 level (546 mg/dL) with a decrease in IgG (1,310 mg/dL). The patient's symptoms resolved with steroid and the scheduled pancreaticoduodenectomy was canceled. Subsequently, prednisone was tapered off and azathioprine 175 mg (2 mg/kg) daily was initiated for maintenance therapy. After one year of treatment, he was asymptomatic.

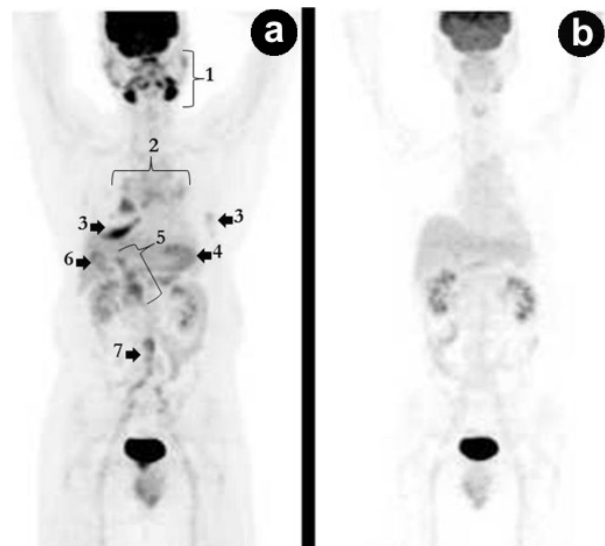


Figure 4. Serial PET coronal maximum intensity projection (MIP) shows pre-corticotherapy (a.) and 1-month post-corticotherapy with resolution of all hypermetabolic IgG4-related lesions (b.). Case#1. 1: salivary glands; 2: bilateral peri-hilar regions; 3: bilateral lower lungs; 4: pancreas; 5: porta-hepatitis/common bile duct; 6: gallbladder; 7: abdominal aorta

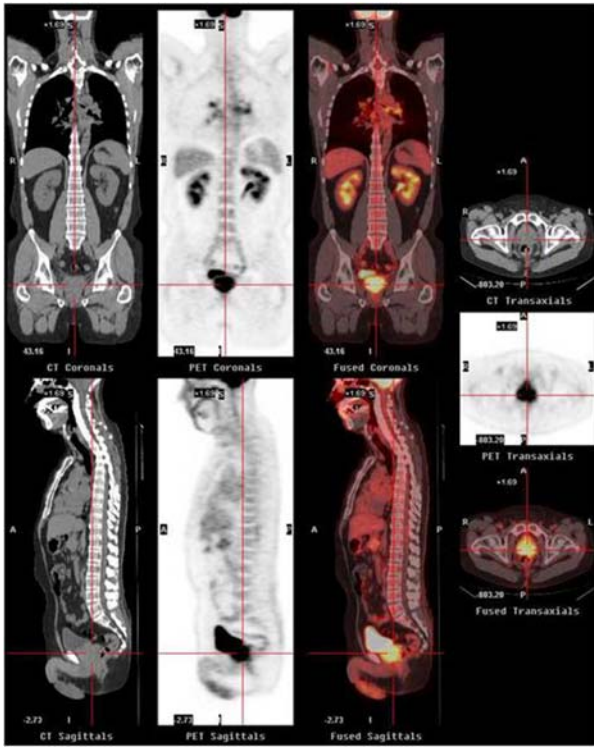


Figure 5. Composite PET/CT images show an intense tracer uptake by the prostate. Case#2.



Figure 6. Axial fused PET/CT images show hypermetabolic lesions of the salivary glands (a.) and thyroid (b.). Case#2.

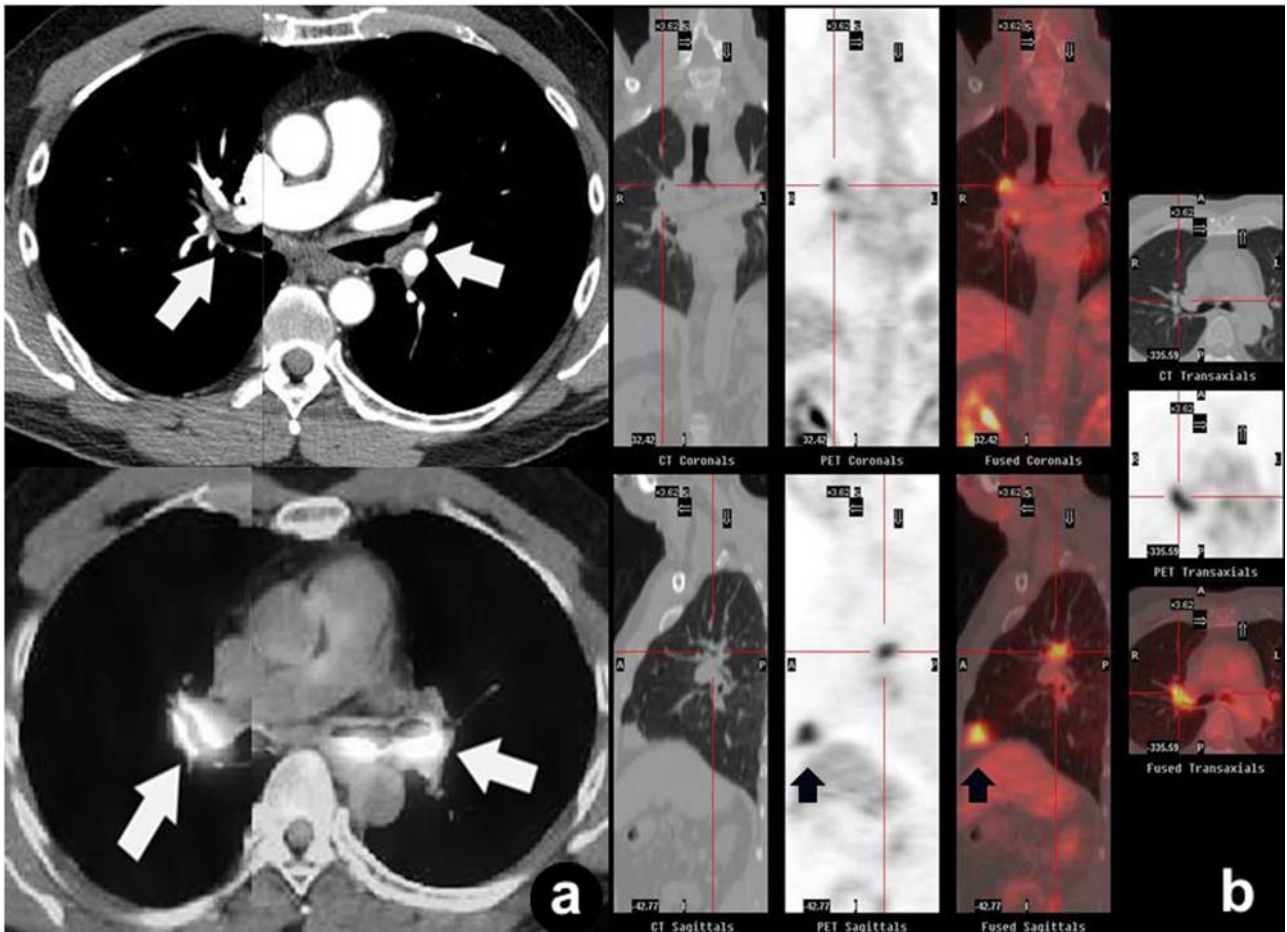


Figure 7. a. Contrast-enhanced CT (top) and fused PET/CT (bottom) axial images show hypermetabolic soft tissue thickening (arrows) with narrowing of the bronchial lumen bilaterally. **b.** Composite PET/CT images show lesions of the right hilar nodes (crosshair) and right middle pulmonary lobe (arrows). Case#2.

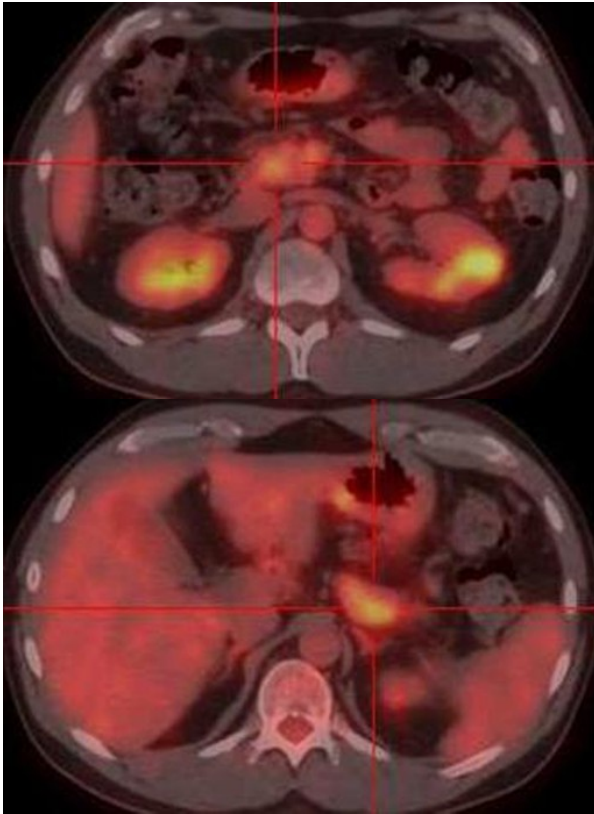


Figure 8. Axial fused PET/CT images show diffuse pancreatic tracer uptake (crosshair). Note that the patient only has diabetes mellitus type 2 but does not have any clinical symptoms of pancreatitis. Case#2.

Case #2

A 53-year-old white male, nonsmoker, was self-referred to our clinic for an enlarged prostate. Past medical history was significant for “idiopathic” pancreatitis (10 years ago), which resulted in diabetes mellitus type 2, benign prostate hypertrophy (for 4 years), asthma, and hypothyroidism. He complained of having a weak urine stream for 4 months. Prior to coming to our institution, the patient had a biopsy of the hard palate secondary to soft tissue inflammation; immunostaining was positive for IgG4 cells. Hence, systemic IgG4-related sclerosing disease was suspected. PET/CT, which was performed at our center, showed a diffuse tracer uptake by the prostate (Figure 5). In addition, it also revealed several hypermetabolic lesions in the salivary glands, thyroid (Figure 6), both bronchi, right hilar lymph nodes, right middle lung lobe (Figure 7), pancreas (Figure 8), and left kidney (Figure 9). PET/CT images were consistent with systemic IgG4-related sclerosing disease. Also, immunostaining of the prostate at our institution demonstrated a high number of IgG4-positive cells in high power field (Figure 10). IgG level was high (2,260 mg/dL); IgG4 level was not obtained. IgE was elevated (IgE: 1,125 KU/L). Prostate-specific antigen was normal (0.13 ng/mL; reference range: 0-4.00 ng/mL). Prednisone 40 mg daily was initiated and benign prostate hypertrophy symptoms resolved after one month of treatment. A two-month follow-up PET/CT showed resolution (Figure 11). Currently, the patient has been tapering off the prednisone and is asymptomatic.

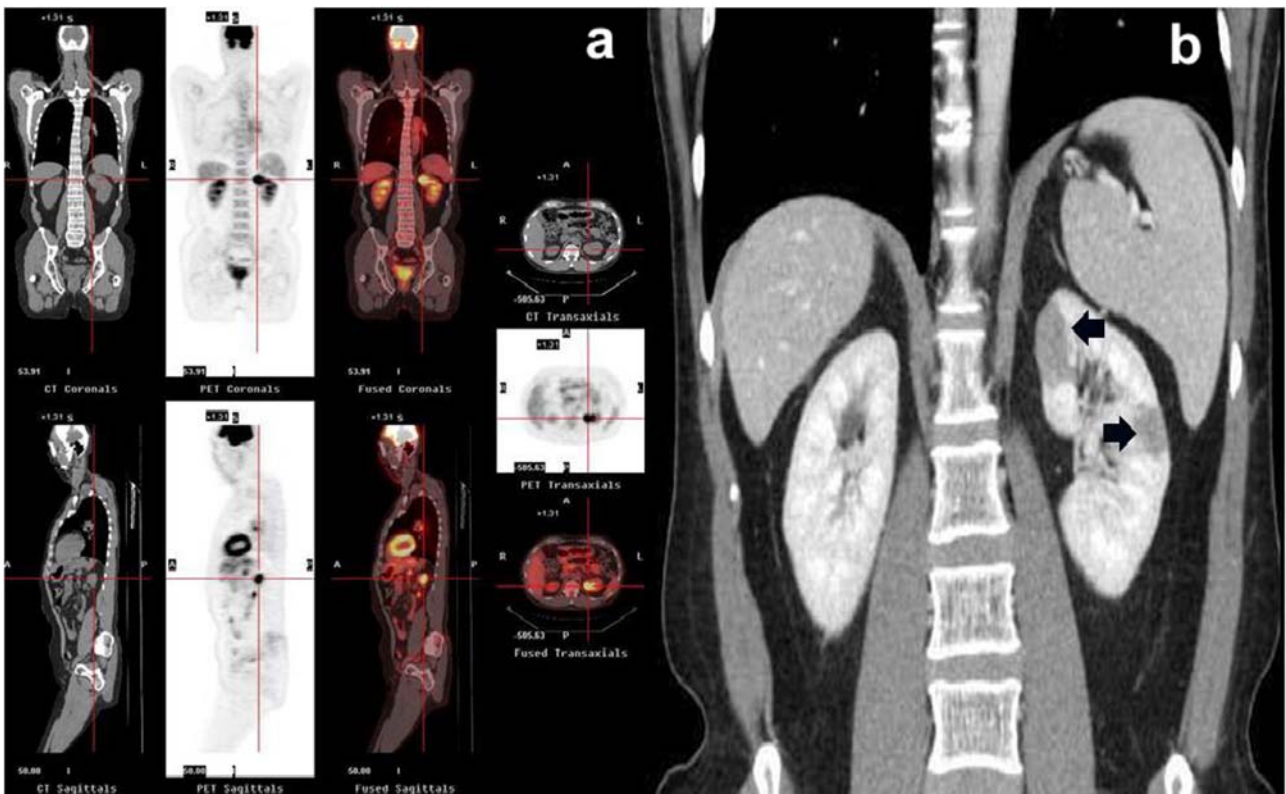


Figure 9. Composite PET/CT (a. crosshair) and coronal CT (b. arrows) show lesions of the left kidney. Case#2.

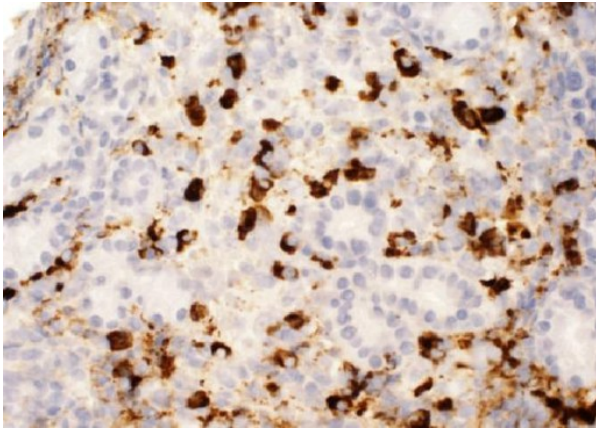


Figure 10. IgG4-immunostaining of the prostate shows a high number of IgG4-positive cells in high power field (magnification: 400x). Case#2.

Case #3

A 57-year-old white female was referred to our center for recurrent systemic IgG4-related sclerosing disease. She complained of right posterior pleuritic chest pain for 3 weeks. Three years prior to her present illness, the patient noticed that her right eyelid was drooping. PET demonstrated bilateral retro-orbital hypermetabolic lesions (Figure 12). She underwent a complete retro-orbital tumor resection of the right eye. Immunostaining of the lesion was consistent with IgG4-related sclerosing disease. After surgery, no steroid was initiated and she was asymptomatic. One year later, the patient had recurrent bouts of pneumonia. CT of the chest revealed a right lung mass (7.8x6.3 cm). Bronchoscopy was negative for malignant cells. According to the patient, CT-guided biopsy was “positive for cancer” (we were unable to obtain the

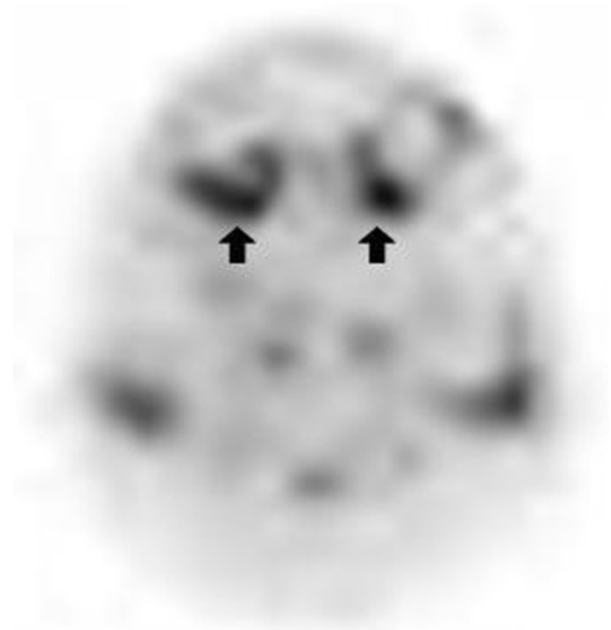


Figure 12. Axial PET image show bilateral retro-orbital hypermetabolic lesions (arrows). Case#3.

official pathology report). PET showed a mass of intense tracer uptake in the right lower lung extending to the pleura (Figure 13). As a result, she underwent right middle lobe/lower lobe lobectomy. Again, immunostaining of the lung mass was consistent with systemic IgG4-related sclerosing disease. The patient was not on any postoperative cortico- or chemotherapy and was asymptomatic for 5 months. She then became dyspneic and complained of right posterior pleuritic chest pain; a repeat radiographic imaging revealed recurrent IgG4-related sclerosing disease. She was placed on prednisone 40 mg daily, which was

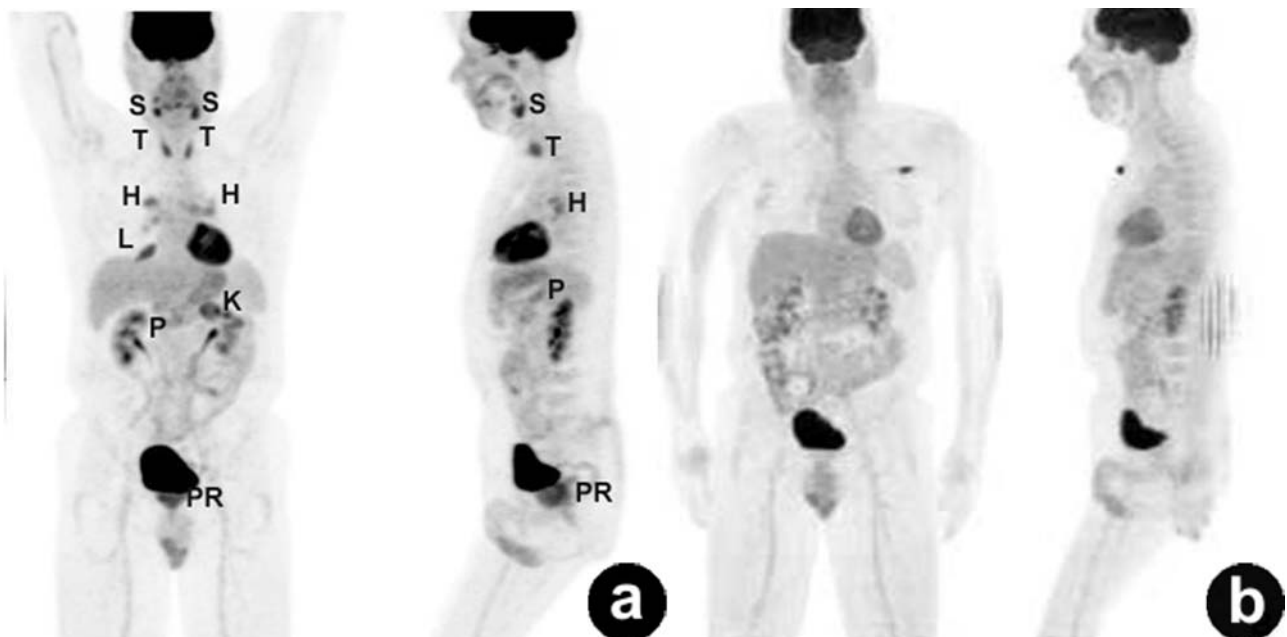


Figure 11. Serial coronal and sagittal pre- (a.) and post-corticotherapeutic (b.) PET maximum intensity projection (MIP) images show complete resolution of the diffuse hypermetabolic lesions of systemic IgG4-related sclerosing disease. The focus at the left upper anterior chest wall represents an artifact (b.). Case#2.

S: salivary glands; T: thyroid gland; H: bilateral hilar nodes; L: right middle pulmonary lobe; K: upper pole of the left kidney; P: pancreas; PR prostate

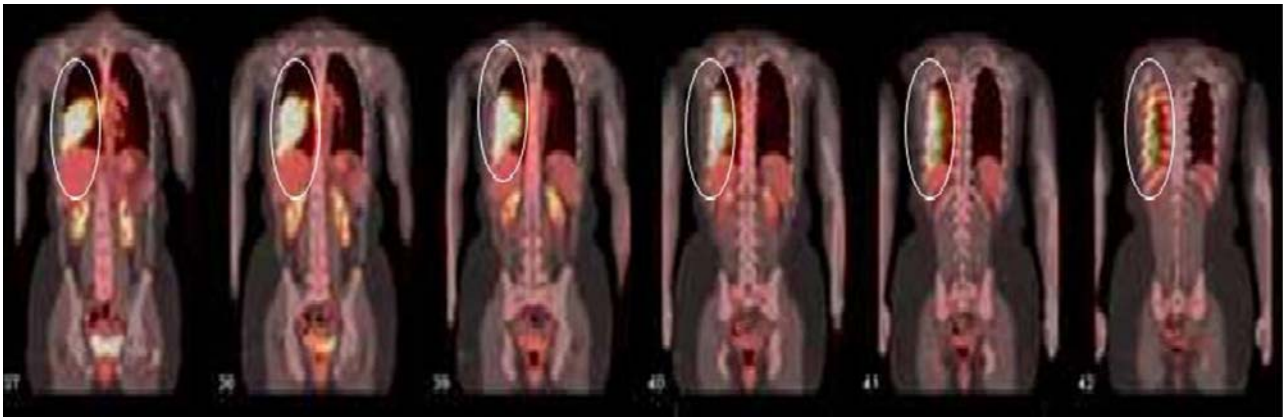


Figure 13. Coronal fused PET/CT images show extensive right lower lung and pleura hypermetabolic lesions (circle). Case#3.

tapered off over a two-month period. Her symptoms were fairly controlled for another 5 months. However, she was referred to our center for recurrent symptoms secondary to uncontrolled systemic IgG4-related sclerosing disease. At our center, IgG, IgG4, IgE levels were normal (IgG: 844 mg/dL; IgG4: 28.3 mg/dL; IgE: 61.3 KU/L). These labs were not performed by the outside center. Because of similarity between systemic IgG4-related sclerosing disease and multiple myeloma due to plasma cell proliferation, she was treated with 4 cycles of a chemotherapy regimen, CyBor-D (cyclophosphamide, bortezomib, and dexamethasone). Clinical improvement was observed after the third cycle. After 4 cycles of CyBor-D, she remained asymptomatic.

Discussion

Autoimmune pancreatitis is a pancreatic manifestation of the systemic IgG4-related sclerosing disease. It affects other extrapancreatic sites (50-85%) such as salivary glands (sclerosing sialadenitis), orbit (orbital pseudotumor), lungs (inflammatory pseudotumors, interstitial pneumonia), thyroid (thyroiditis), gallbladder (cholecystitis), biliary tree system (sclerosing cholangitis), kidney (tubulointerstitial nephritis), abdominal aorta (lymphoplasmacytic aortitis), retroperitoneum (retroperitoneal fibrosis), prostate (prostatitis), and lymph node (lymphadenopathy) [10, 16, 17]. At the present time, there is no international consensus on the diagnostic criteria for autoimmune pancreatitis. Currently, three different sets of criteria have been proposed to diagnose autoimmune pancreatitis [18]. One important immunohistological criterion in these three sets is the presence of Ig4-positive cells in the pancreas (more than 10 cells/high power field). According to experts around the world, cytology obtained by EUS-FNA is only adequate to diagnose pancreatic cancer; it is not able to establish the presence of autoimmune pancreatitis [19]. Histological tissue of the pancreas obtained by EUS-guided Trucut biopsy can diagnose autoimmune pancreatitis, but this technique is challenging and only available at a few centers. Preoperative differentiation of pancreatic cancer from autoimmune pancreatitis is important because 3-11% of Whipple procedures are

performed on patients with autoimmune pancreatitis, which can be medically treated with corticosteroid [20, 21]. Because of whole-body PET/CT imaging ability, it can target extrapancreatic sites for tissue sampling. This utility of PET/CT was illustrated in Cases #1 and #2. In Case #1, PET/CT changed the management from Whipple procedure to corticotherapy.

Most patients with autoimmune pancreatitis have elevated IgG and IgG4 levels. In 2001, Hamano *et al.* demonstrated that IgG4 is more than sensitive than total IgG for diagnosing autoimmune pancreatitis [22]. The sensitivity and specificity of elevated IgG4 (cut-off: 135 mg/dL) for diagnosing autoimmune pancreatitis are approximately 70% and 90%, respectively [23, 24, 25]. In addition, Hamano *et al.* also showed that serum IgG4 in patients with autoimmune pancreatitis decreased after one month of corticotherapy [22]. This was not observed in Case #1. Prior to steroid treatment, IgG4 was 41.2 mg/dL; however, after one month of corticotherapy, it increased to 546 mg/dL. Only IgG decreased from 2,430 mg/dL to 1,310 mg/dL. One possible explanation of the difference between our observation and that of Hamano *et al.* is that the authors compared IgG4 levels of pre- and post-corticotherapy in only 12 out of 20 patients with autoimmune pancreatitis [22]. Our result seems to support the conclusion of a meta-analysis on the utility of IgG4 in follow-up autoimmune pancreatitis post steroid therapy. IgG4 is useful in therapeutic monitoring only when the IgG4 level of pre-corticotherapy is high [26]. Despite elevated IgG4 during post-corticotherapy, PET/CT is valuable in demonstrating resolution of IgG4-related lesions (Figure 4). After reviewing records from the outside, we noticed that serum IgG and IgG4 levels were not measured in cases where systemic IgG4-related sclerosing disease was confirmed by immunohistopathology (Cases #2 and #3). Clinicians should be aware of this new entity because corticosteroid is the treatment of choice, not invasive surgery.

Currently, pathogenesis of autoimmune pancreatitis is still an enigma. Studies indicate there is a close relationship between allergic disease and autoimmune pancreatitis [27]. Kamisawa *et al.* showed that 44% of patients with autoimmune pancreatitis had allergic

disorders and high serum IgE level [28]. Two of our patients (Cases #1 and #2) had a history of asthma, chronic cough, allergic rhinitis, chronic rhinosinusitis, and elevated IgE. Systemic IgG4-related sclerosing disease should be on the differential diagnosis list during the diagnostic workup of suspected cancer patients with allergic conditions.

Several different pulmonary patterns in patients with systemic IgG4-related sclerosing disease have been reported. These are interstitial/nodular infiltration, bronchial/interlobular wall thickening, and inflammatory pseudotumor [29, 30, 31, 32]. A study reported 9 cases of IgG4-related lung pseudotumors [30]. Similar to our Case #3, Zen *et al.* observed that 7 out of 9 pseudotumors located adjacent to pleura [30]; PET was only performed in Case #7 and it showed an intense tracer uptake by the pseudotumor as seen in our Case #3 (Figure 13). Eight out of 9 patients underwent either partial resections or lobectomies. Whether or not lung cancer was the preoperative diagnosis in these 8 patients was unclear. Only one patient (Case #9) did not undergo surgery and correctly diagnosed by transbronchial lung biopsy. For this case, after one month of corticosteroid treatment, the pseudotumor size was markedly decreased, and the patient's symptomatology (hemoptysis) resolved. In our Case #3, the patient would have spared from lobectomy if she was diagnosed with systemic IgG4-related sclerosing disease preoperatively. As demonstrated in Figures 12 and 13, PET/CT imaging should be considered prior to any surgical resection in patients with a history of IgG4-related sclerosing disease because it helps to reach the correct diagnosis by targeting biopsy sites.

Corticosteroid is the treatment of choice for patients with systemic IgG4-related sclerosing disease. The response to steroid was incorporated in the American, Japanese, and Korean diagnostic criteria of autoimmune pancreatitis [18]. However, there is no consensus on the standard regimen or duration of corticotherapy. Normally, prednisolone (30-40 mg/day) is initiated and tapered by 5 mg every 2-4 weeks [16]. Because of the ability of PET/CT to image the whole body, it is a valuable tool for monitoring therapy and demonstrating sites of relapse or flare-up as seen in Figures 4 and 10.

When flares or relapses occur while patients are on steroids, a few small studies suggest that azathioprine and rituximab (a monoclonal antibody against CD20 antigen on B lymphocytes) may be effective [33, 34, 35, 36]. In Case #1, the patient was treated with azathioprine for maintenance therapy to prevent relapses because some evidences indicate that patients with Ig4-related cholangitis have a high rate of relapse (53%) after steroid withdrawal [33]. In Case #3, the rationale for using bortezomib-based chemotherapy regimen (CyBor-D), which has been shown to be effective in managing of multiple myeloma [37], was that plasma cell proliferation was the underlying

pathogenesis of both disorders. Accumulating evidence indicates that long-lived plasma cells can cause autoimmune diseases by producing autoreactive antibodies [38]. These long-lived plasma cells are resistant to immunosuppression therapy [38]. In addition, they are refractory to rituximab because these cells lack CD20 expression [38]. It has been shown that bortezomib effectively depleted both short-lived and long-lived plasma cells [39]. As a result, CyBor-D may be useful in treating systemic IgG4-related sclerosing disease. Larger studies are warranted to identify the standard treatment for this disease.

Conclusion

Systemic IgG4-related sclerosing disease is a new disorder which is characterized by infiltration of pancreas and extrapancreatic sites with IgG4-positive plasma cells. Correct diagnosis of this condition is crucial because corticotherapy is effective. Besides monitoring therapy and demonstrating relapse, PET/CT is a useful adjunctive imaging technique for targeting extrapancreatic biopsy sites.

Conflict of interest The authors have no potential conflicts of interest

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