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IGg4 Related Autoimmune Pancreatitis in a Patient with Silicosis

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Abstract

Background: Exposure to silica is a well known occupational and environmental risk factor for the development of pulmonary disease. Moreover, it is known to be associated with the development of autoimmune manifestations.

Case presentation: We report a case of IgG4 related autoimmune pancreatitis in patient with interstitial lung disease secondary to silicosis, who presented to the emergency room with a two month history of epigastric pain. Investigation including laboratory studies and magnetic resonance cholangiopancreatography (MRCP) revealed elevated liver enzymes, CA 19-9 and a pancreatic head mass. Biopsies taken via fine needle aspiration through endoscopic ultrasound did not show any evidence of malignancy or infection. Finally, following steroid therapy for a respiratory parenchymal infection, the patient improved clinically. This paralleled improvements in liver enzymes, CA19-9 and resolution of the pancreatic masses assessed by computerized tomography. Further investigation revealed elevated serum immunoglobulin levels, particularly IgG4.

Conclusion: this is the first case report documenting the occurrence of IgG4 related autoimmune pancreatitis in a patient with silicosis. The combination of both elevated immunoglobulin levels prior to steroid administration coupled with clinical, laboratory and radiological improvement following treatment strongly suggests an autoimmune mediated disease.

Keywords
IgG4; silicosis; autoimmune pancreatitis

Abbreviations

ALT: Alanine Transaminase; ANA: Antinuclear Antibody; ANCA: Anti-neutrophil Cytoplasmic Autoantibody; AIP: Autoimmune Pancreatitis; CBD: Common Bile Duct; ERCP: Endoscopic Retrograde Cholangiopancreatography; EUS: Endoscopic Ultrasound; FNA: Fine Needle Aspiration; GGT: Gamma Glutamyl Transferase; MRCP: Magnetic Resonance Cholangiopancreatography; ULN: Upper Limit of Normal

Background

Free silica (SiO_2), or crystalline quartz, is an abundant mineral found in sand, rock, and soil. major occupational exposures include mining, stonecutting, sandblasting, glass, and cement manufactering,

foundry work, packing of silica flour, and quarrying, particularly of granite [1,2]. In addition to being a major cause of occupational pulmonary disease, silica is well known as an environmental factor involving autoimmunity. Reported autoimmune complications of silicosis include rheumatoid arthritis, *i.e.* Caplan's syndrome [3], systemic lupus erythematosus [4,5], systemic sclerosis [6], and anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis/ nephritis [7,8].

Compounds containing silica are potent stimulators of immune reactions, by several mechanisms. Silicon may induce apoptosis, which triggers the cascade of release of proteolytic enzymes causing tissue damage, activation of polymorph nuclear cells, and eventual release of intracellular proteins that become targets for autoimmune reactions [7]. Several antibodies have been detected in serum of silica-exposed patients, including antinuclear antibody (ANA), rheumatoid factor, anti-topoisomerase I, anti-desmoglein, anti-caspase 8, anti-CD95/Fas, ANCA, and immune complexes (9,10,7). Of note, in a study by Bartunkova et al., demonstrating ANCA positivity associated with silicosis, the majority of patients were p-ANCA positive, which is associated with a variety of autoimmune and inflammatory conditions. Therefore, it was suggested that p-ANCA positivity reflects a chronic inflammatory condition induced by silica rather than a specific disease-associated marker [7]. This humoral immunologic response in silicosis patients is accentuated due to hyperactive macrophages that secrete the inflammatory cytokines tumor necrosis factor (TNF) and interleukin 1(IL-1) , in turn activating helper T cells to facilitate B cell antibody production [2]. Indeed, silica has been shown to increase immunoglobulin levels in vitro [11], and elevated immunoglobulin levels have been documented in silicosis patients [9]. Auto antibodies are formed not only due to exposure to silica dust but also to other silicon-containing chemicals, such as asbestos [12] or organic silicon compounds in breast implants [13].

Several studies have demonstrated inhibition of Fas-mediated apoptosis in silicosis patients by elevated levels of soluble Fas and Decoy Receptor 3 (DcR3). This may result in delayed activation-induced cell death of self-antigen-activated T lymphocytes, thus increasing the risk of autoimmune conditions [10]. Chronic activation of responder T cells in silicosis patients is also supported by findings of elevated soluble interleukin-2 receptor(sIL-2R), a marker for activation of T cells under certain pathophysiological states including autoimmune diseases, as well as chronic activation and earlier FAS-mediated apoptosis of regulatory T cells [14].

The association between silica exposure and autoimmune diseases is well documented. However, since it affects only some individuals, there seems to be a genetic component. Brown *et al.* examined the effects of silica instillation in comparison to saline and titanium dioxide controls in New Zealand Mixed mice, autoimmune prone mice that develop features of systemic lupus erythematosus. They demonstrated disease acceleration in the silica exposed mice by several parameters – increased mortality, proteinuria, autoantibody levels, circulating immune complexes, pulmonary fibrosis, immune complex deposition and complement C3 deposition within the kidney [15]. A recent study reproduced these results in NZBWF1 mice, another lupus-prone strain with a less penetrant phenotype of autoimmunity, as well as demonstrated formation of ectopic lymphoid tissue, hypothesized to contribute to early triggering of lupus. Lung and renal pathology following silica instillation had also developed in C57Bl/6 mice, however to a lesser extent than the lupus-prone mice, supporting the contribution of genetic predisposition [16].

The term "IgG4-related disease" was first coined in 2003 [17] in relation to autoimmune pancreatitis, but has since been recognized as a fibro inflammatory condition affecting virtually every organ system, encompassing many conditions that were previously regarded as isolated single organ diseases [18,19]. IgG4-related diseases mainly affect middle-aged to elderly men, notably opposed to most autoimmune diseases. The clinical symptoms are relatively mild and sub acute, and result from organ swelling or damage. One or more organs may be involved, synchronously or metachronously. Comprehensive clinical diagnostic criteria for IgG4-related disease, as proposed by the Umehara study group, include 1- clinical examination showing characteristic diffuse/ localized swelling or masses, 2- elevated serum IgG4 (≥135 mg/dL), and 3- histopathological examination with marked lymphocyte and plasmacyte infiltration and fibrosis or infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells per high power field; defining "definite" if all criteria are met, "probable" if criteria "1" and "3" are met, and "possible" if criteria "1" and "2" are met. Importantly, malignant tumors and similar diseases must be differentiated from IgG4-related diseases, and organ-specific diagnostic criteria may diagnose patients that do not meet these general criteria and should be used concurrently (for autoimmune pancreatitis, sclerosing cholangitis, and kidney disease) [20-23]. The mainstay of treatment of IgG4-related diseases is corticosteroid treatment.

Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis and therapeutically by a dramatic response to steroids [21]. Since the acknowledgment of IgG4-related pancreatitis, AIP has been divided into two subtypes, based on clinical and histopathological profiles. In 2011, the international consensus diagnostic criteria for AIP were published, defining type 1 and type 2 AIP [21]. In general, type 1 AIP, synonymous with IgG4-related AIP, is characterized by the classic histopathological findings of lymphoplasmacytic sclerosing pancreatitis. Type 2 AIP is not an IgG4-related disease but rather idiopathic duct-centric chronic pancreatitis, and is identified on the basis of histological features of neutrophilic infiltration into the epithelium of the pancreatic duct. These criteria take in account a combination of parenchymal and ductal imaging, serum IgG4 concentrations, extra pancreatic disease, pancreatic histology, and glucocorticoid responsiveness, resulting in "definite" or "probable" diagnosis of each type.

Type 2 AIP, the less common of the two subtypes of AIP, is typically diagnosed at a younger age (40 compared to 61 years in type 1 AIP), the incidence in males and females is approximately equal, and is not associated with other organ involvements. Since type 2 AIP is very rare, to date very little is known about the pathogenesis of this disease or risk factors, however, concurrent inflammatory bowel disease is found in 10-20% of patients. This subtype responds rapidly to corticosteroid treatment, as does type 1 AIP, however differs from the latter in that relapse rates are low (< 10%) and maintenance therapy is not indicated [24].

Herein, we present the first case report documenting the occurrence of IgG4-related autoimmune pancreatitis in a patient with known silicosis.

Case Presentation

A 59-year-old man presented to the emergency department with intolerable epigastric pain radiating to the back that began two months prior to his admission. This pain initially improved with

omeprazole but worsened over time. Past medical history is significant for interstitial lung disease due to silicosis and benign prostate hypertrophy, as well as smoking which he ceased 3 years earlier. Ultrasound performed in the emergency department demonstrated cholelithiasis however, upon admission repeat ultrasound demonstrated a small amount of sludge without bile stones or signs of cholecystitis. Liver enzymes at this time were within normal limits. The patient was discharged but returned a few days later due to worsening pain, serum amylase was elevated at 207 U/L (upper limit of normal (ULN) 100 U/L). Computerized tomography did not show signs of pancreatitis or pancreatic duct dilatation; however, lymphadenopathy in the liver hilum and increased size of known lymphadenopathy in the mesenteric root was seen. Endoscopy revealed a 1.5 cm antral mass with central excavation and thick prepyloric folds, pathology from the antral mass demonstrated normal mucosa while pathology from the pyloric area revealed hyperplasia of Brunner glands and mild chronic inflammation. Staining for *Helicobacter pylori* was negative. One week later, the patient developed obstructive jaundice, with bilirubin up to 140 mcM (normal range 0-17 mcM) and elevated hepatocellular and cholestatic enzymes (peak values of ALT 260 U/L (ULN 40 U/L), GGT 2133 U/L (ULN 61 U/L)). Magnetic resonance cholangiopancreatography (MRCP) demonstrated a 2.5 cm mass at the head of the pancreas, as well as mild dilatation of intrahepatic bile ducts, common hepatic duct, and common bile duct (CBD), and narrowing of the central and distal CBD. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, during which the stricture appeared to be benign secondary to inflammation. Papillotomy and biliary stenting was performed, with resolution of the laboratory abnormalities. Brush biopsy demonstrated normal epithelial cells. Due to the mass seen in the MRCP, endoscopic ultrasound (EUS) was performed demonstrating signs of cholecystitis, and fine needle aspiration (FNA) was taken from the pancreatic head, although a mass was not clearly demonstrated during the endoscopy. Pathology reported pancreatic tissue with focal necrosis and minimal chronic active inflammation, no malignancy was seen. Few cells had stained positively for IgG, of which some were positive for IgG4.

On follow-up, the patient continued to complain of severe pain despite analgesics and had lost 14 kg in two months. CA19-9 levels had increased from 112 to 846 U/mL (ULN 37 U/mL) in one month, and along with the pancreatic mass visualized on MRCP, he was considered for Whipple's procedure. However, the surgery was postponed due to pneumonia. Importantly, during treatment for pneumonia the patient was also treated with steroids due to expiratory wheezes. After recovery from the pneumonia, while still on steroid treatment, on repeated evaluation the CA19-9 had spontaneously lowered to 143U/mL. Elevated serum IgG levels (X 1.3 ULN) were measured, with elevated IgG4 of more than 162 mg/dL (over X 1.7 ULN) as well as IgG1 (X 1.7 ULN) and IgG3 (X 1.5 ULN). Repeat computerized tomography showed decreased pancreatic swelling. Taken together, the laboratory, radiographic, and pathological findings consistent with inflammatory pancreatitis, with emphasis on the lack of malignancy upon several biopsies and resolution of the findings following steroid treatment, led to the diagnosis of autoimmune pancreatitis, in a patient with silicosis.

Discussion

To date, silicosis per se has not been directly linked to IgG4-related disease, however, several reports present data that suggest an association between the two. IgG production is known to be increased in silica-exposed individuals, in mice [16] and in humans [2,9]. In 1992, Tschopp *et al*.

described a case of an alpine miner with pulmonary silicosis who developed a retroperitoneal mass invading the head of the pancreas. On resection, many silicotic nodules were found in the retro pancreatic region, with silica particles seen under polarized light [25]. Argani et al. reported a series of five men with reactive mediastinal spindle cell proliferations pathologically resembling inflammatory pseudo tumors, associated with anthracosis and anthracosilicosis, two with confirmed exposure to silica [26]. Only a few years later was the entity of IgG4-related diseases described. Since then, there have been sporadic reports of lung and mediastinal pseudotumors associated with silicosis [27,28], however an association to IgG4 was not sought. Recently, an increased occupational exposure among a Danish cohort of 25 patients with IgG4-related autoimmune cholangitis has been observed, of which three were exposed to silica dust, two to asbestos, and two to both [29]. Of note, exposure to asbestos, composed of hydrated magnesium silicates, has been linked to pulmonary, pleural, and retroperitoneal fibrosis [30], and IgG4-related lung disease has been suggested in a patient with occupational exposure to asbestos [31].

The silicosis patient presented herein presented initially with features highly suspicious for pancreatic cancer, despite FNA *via* EUS that was negative for malignancy. However, the planned Whipple's procedure was postponed due to pneumonia, during which steroids were added for concurrent airway obstruction. Following the acute illness, repeat CA19-9 had decreased significantly and pancreatic swelling had decreased, thus the diagnosis was corrected to autoimmune pancreatitis. The pathology results did not demonstrate classical characteristics of either type of AIP, which may be due to sampling error, known to occur frequently due to patchy involvement of the pancreas resulting in focal sparing of varying percentages and sizes [32]. However, the clinical profile better fits the characteristics of type 1 AIP (older age, male), further supported by the elevated serum IgG4 levels [33,34]. According to the international consensus diagnostic criteria for AIP [21], this case meets the criteria for probable type 1 AIP (focal enlargement of the pancreas, serum IgG4 X1-2 ULN, and response to steroids). Of note, for technical reasons, the serum IgG4 results were not a definitive value but rather "more than" 162 mg/dL (X 1.7 ULN). If this value were in fact higher than twice the ULN, the case would meet the criteria for definitive type 1 AIP. The features were not diagnostic for type 2 AIP.

To the best of our knowledge, the present case is the first to describe AIP in a patient with silicosis. As the case is suggestive of type 1 AIP, this is the first case to directly link silicosis and IgG4-related disease. The case suggests additional mechanisms by which immune-mediated pancreatitis can develop in these patients. Moreover, this case supports the hypothesis that occupational exposure may contribute to development of IgG4-related diseases. Further studies are required for determining the mechanism involved in the silicosis-mediated pancreatitis and silicosis-associated IgG4-related diseases.

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