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Autoimmune pancreatitis - Case series

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Abstract

Autoimmune pancreatitis is an infrequently diagnosed disease. Type 1 AIP is the prototypic IgG4 related disorder. The affected tissues share particular pathologic, serologic, and clinical features, regardless of the organ involved. Multiple organs may be involved like pancreas, liver, salivary glands, orbital involvement, retroperitoneal involvement and renal system. We present three interesting cases of autoimmune pancreatitis encountered in our hospital. Each patient had peculiar findings with varied clinical presentation and organ involvement. Their clinical presentation, disease course and management have been briefly discussed. The learning point in our patients was that one has to work up for an etiology in all patients with pancreatitis especially having a high degree of suspicion for autoimmune pancreatitis. If pancreatitis is associated with sclerosing cholangitis like picture then autoimmune etiology should be ruled out. It is most important to differentiate between the PSC and autoimmune pancreatitis with sclerosing cholangitis because with the latter the patient dramatically responds to steroids. Serum IgG4 levels need not be elevated in all patients of autoimmune pancreatitis. Renal involvement or multisystem involvement in a patient with pancreatitis should also alert the clinician about the autoimmune nature of the disease.

Keywords

autoimmune pancreatitis; IgG4; sclerosing cholangitis; pancreatic head mass; steroids

Introduction

Autoimmune pancreatitis is an infrequently diagnosed disease. Type 1 AIP is the prototypic IgG4 related disorder. The affected tissues share particular pathologic, serologic, and clinical features, regardless of the organ involved. Multiple organs may be involved like pancreas, liver, salivary glands, orbital involvement, retroperitoneal involvement and renal system. We present three interesting cases of autoimmune pancreatitis encountered in our hospital. Each patient had peculiar findings with varied clinical presentation and organ involvement. Their clinical presentation, disease course and management have been briefly discussed.

Case Vignette 1

In 2009, a 21 year old female had pancreatic type of acute abdominal pain. Her amylase and lipase were elevated and ultrasound abdomen had revealed bulky and an edematous pancreas.

Patient was treated symptomatically. She improved after a short course of analgesics and proton pump inhibitors. Patient was on irregular follow up and the cause was not evaluated then.

In 2013, she was pregnant and at 36 weeks of pregnancy she again developed pancreatic type of abdominal pain. Serum amylase and lipase were elevated. MRCP had revealed mild bulky pancreas with a normal common bile duct and pancreatic duct. Patient was treated symptomatically and improved. Following delivery she was advised etiological work up but she was lost to follow up.

In November 2015, she presented to us with history of progressive jaundice for 2 months. She had high fever, pruritus, and pale stools. She also gave history of amenorrhea for 6 weeks and the urine pregnancy test was positive. On physical examination she had icterus and hepatomegaly. LFT revealed cholestatic pattern with a total bilirubin of 18mgs, a direct fraction of 14 mgs and alkaline phosphatase was 324 IU/L . Ultrasound abdomen showed dilated IHBR with calcification in the head and body of pancreas. HBsAg, Anti HCV, HIV were negative. Fasting lipid profile, serum calcium and PTH was normal.

Since the patient was in cholangitis, ERCP was performed with a lead shield to protect the fetus. Biliary sphincterotomy was done and 7 F x 8 cm double pig tail plastic stent was deployed and free flow of bile was noted. Following ERCP, abdominal pain and pruritus resolved but jaundice persisted. Meanwhile patient had spontaneous abortion for which suction evacuation was done by the obstetrician. Patient continued to have fever and increasing jaundice. She was instituted on higher end antibiotics, Vitamin K, intravenous fluids and ursodeoxycholic acid.

MRCP was done which revealed multifocal areas of cystic dilatation and narrowing of intrahepatic bile ducts in segments VIII, VII and V of right lobe and segment II of left lobe with mid CBD Stricture. The pancreas appeared diffusely atrophic with dilated pancreatic duct and multiple pancreatic calcifications. She was submitted for the 2nd sitting of ERCP and this time we did a cholangiogram which revealed multiple strictures and dilatations of intrahepatic biliary radicals with mid CBD stricture. A brush cytology was taken, the old stent was removed and a new 7 F x 8 cm double pig tail stent was deployed. Following the procedure, fever also subsided, but patient's bilirubin was persistently elevated.

We did a complete autoimmune profile considering the recurrent episodes of pancreatitis with jaundice in a young female patient. We found that anti Ro antibody was strongly positive. All other autoimmune markers were negative. Schrimer's test was positive. IgG4 levels were within normal limits. Since the patient had sclerosing cholangitis like picture we did a colonoscopy which revealed normal mucosa and vascular pattern. Random mucosal biopsies of the colon were also negative. Upper GI endoscopy was also normal.

The brush cytology report was also not contributory. An ultrasound guided liver biopsy was also done for this patient. Liver histopathology showed hepatic lobules with preserved architecture, with hepatocytes exhibiting feathery degeneration, focal microvesicular steatosis with numerous hepatocytes exhibiting intrahepatic bile staining. Bile plugs were seen in biliary canaliculi and Kupfer cell hyperplasia was present. Periportal inflammatory infiltrate composing of lymphocytes and plasma cells were seen. An impression of cholestatic liver disease was given.

Patient's general condition was deteriorating. The jaundice was deepening and she had enlargement of spleen. She developed small pseudoaneurysm of the subcostal artery as a complication of

liver biopsy which was obliterated using coils by our interventional radiologist. Surprisingly the CT angiograpy which was done for intervention showed a newly developed mass lesion in the head of pancreas (fig.1.1). CA 19-9 was within normal limits.

At this juncture, we had a 27 year old female with recurrent pancreatitis with evidence of inflammatory mass in the head of pancreas, obstructive jaundice with multiple strictures and dilatations of intrahepatic biliary radicals and CBD stricture with anti Ro positivity. We strongly suspected autoimmune pancreatitis with sclerosing cholangitis in our patient.

We started the patient on Prednisolone 40 mg once daily, and UDCA was continued. Patient improved significantly and serum bilirubin decreased from 22 mg/dl to 2.4 mg/dl in 2 weeks. MRCP showed resolution of multiple cystic dilatation and narrowing of intrahepatic bile ducts. She is in remission and on regular follow up with us.

Our patient fulfilled 3 out of 6 in the HISORT criteria for diagnosis of autoimmune pancreatitis (one or more strictures involving intra hepatic, extra hepatic or intra pancreatic biliary tree, imaging features of autoimmune pancreatitis – inflammatory mass lesion of head of pancreas, normalization of liver enzymes or resolution of biliary duct stricture following steroid therapy). So after considering all these we made a final diagnosis of autoimmune pancreatitis probably type 1 with sclerosing cholangitis with secondary Sjogren's syndrome in our patient.

Case Vignette 2

18 year old male was admitted in our hospital with complaints of severe abdominal pain radiating to back and vomiting. The pain had decreased on stooping forward There was no hematemesis or malena. He was not an alcoholic or smoker. There were three similar episodes in the past for which he was treated in a local hospital. On examination patient had epigastric tenderness and no organomegaly or free fluid in the abdomen. His amylase and lipase were elevated. An ultrasound abdomen showed a bulky pancreas. Patient was kept nil per oral and was given analgesics and intravenous fluids. He improved significantly. Etiological work up showed a normal serum triglycerides, calcium , parathormone levels. MRCP revealed bulky pancreas with a prominent main pancreatic duct and multiple wedge shaped T2 hyperintense lesions (right > left) in the kidneys. The serum IgG4 levels were elevated (3.31 g/L). Patient did not have any symptoms of renal involvement and his blood urea, serum creatinine and urine analysis were well within normal limits. Since the patient had improved significantly on symptomatic treatment alone we have not started him on steroids. He is on regular follow up with us.

Case Vignette 3

28 year old male was admitted with severe abdominal pain and vomiting and decreased urine output. On examination he had severe epigastric tenderness without any organomegaly or free fluid in the abdomen. He was evaluated for seizures and hypertension one year ago at a local hospital but was not on any medications. His serum creatinine was 5 mg/dl, blood urea was 92 mg/dl and hemoglobin was 6 gm/dl. The serum amylase was 751 IU/L serum lipase was 3726 IU/L. His serum calcium was 8.4 g/dl. The fasting lipid profile was normal. Plain CT abdomen showed multiple loculated collection in the head, body and tail of pancreas with gross ascites and left sided pleural effusion suggestive of acute necrotizing pancreatitis. A MRCP showed acute necrotic intra pancrewatic collection with ascites. He was started on

higher end antibiotics and hemodialysis and supportive care. He had significant proteinuria (4+) with granular casts and few RBC in the urine. Protein creatinine ration was 5.9. His total count was elevated (17,900) with predominat neutrophils. Ascitic fluid analysis showed a high protein ascites (5.4 g) with 150 cells/cumm. Ascitic fluid culture was negative. After stabilizing the patient a renal biopsy was done which revealed membranous nephropathy with moderate interstitial nephritis and tubular atrophy. IgG (+3) and c3 (+1) immunoflorescence staining revealed a granular positivity over the capillary walls. It was negative for anti phospholipase A2 receptor. Serum IgG4 levels were elevated (5.31g/dl). Serum Ig E was also elevated (456.5 IU/ml). The TSH level was high (12.84 mIU/ml) with low T3 and T4. So a diagnosis of autoimmune pancreatitis with hypothyroidism with IgG4 related kidney disease was made. After patient was stabilized, he was started on oral prednisolone 40 mgs and he improved symptomatically. He was discharged and awaiting follow up results from him.

Literature

The three important features of Immunoglobulin G4related disease (IgG4RD) are tumor like swelling of involved organs, a lymphoplasmacytic infiltrate with IgG4 positive plasma cells and a "storiform fibrosis" pattern [1,2]. In these patients the serum concentrations of IgG4 are elevated in 60 to 70 percent. Response to glucocorticoid treatment has also been considered as one diagnostic criterion for the disorder. TYPE 1 AIP is the prototypic IgG4related disorder. The affected tissues share particular pathologic, serologic, and clinical features, regardless of the organ involved. Many other organs may be involved like salivary glands, orbital involvement, retroperitoneal involvement and renal disease. Immunoglobulin G4related disease (IgG4RD) generally occurs most commonly in middle aged and older men. Immune complex deposition in the pancreas, kidneys, and certain other affected tissues has been reported [3].

Patients fulfilling criteria for both Sjogren Syndrome and IgG4RD have been reported in literature. Increased IgG4 serum levels (>135mg/dL) were present in 7.5 percent of the 133 patients with well defined primary Sjogren Syndrome [4]. The patients having elevated levels of IgG4 levels had a higher frequency of IgG4RD clinical features (autoimmune pancreatitis, autoimmune cholangitis, and interstitial nephritis) and lower rates of ANA , antiRo/ SSA, and antiLa/ SSB antibodies. In addition, 2.3% of patients studied had increased numbers of IgG4 (+) plasmacytes in labial minor salivary gland biopsies. Most of these patients probably represent IgG4RD patients misclassified as having SS.

IgG4RD can present as dacryoadenitis or orbital pseudotumors in the eye [5,6,7], noninfectious aortitis, retroperitoneal fibrosis, Reidel's thyroiditis (IgG4related thyroid disease) and the fibrous variant of Hashimoto's thyroiditis. Renal involvement in patients with IgG4RD have been described; the most common finding is tubulointerstitial nephritis [8,9,10,11,12]. On CT or MR, renal lesions are commonly bilateral and multiple, predominantly involving renal cortex . Renal parenchymal lesions can be classified as small peripheral cortical nodules, round or wedge-shaped lesions, and diffuse patchy involvement. Renal lesions may present as a large solitary mass which mimics primary renal neoplasm. Retroperitoneal fibrosis is seen in 10% of cases in one study. The serum IgG4 level was raised (>135 mg/dL) in 86 percent of 114 patients in a study by Nakanuma [13]. The degree of IgG4 elevation does not correlate with the degree of disease activity. The serum IgG4 concentration tends to increase with the number of organs involved. The diagnosis of IgG4RD is based the histopathology in the biopsy specimen,

typical imaging findings and serum IgG4 levels and the characteristic response to treatment.

Additional organ involvement may be identified through a careful history, physical examination, routine laboratory testing, and selected imaging studies. All patients with symptomatic, active IgG4RD require treatment. Glucocorticoids are the first line agent used for remission induction in all patients with active, untreated IgG4RD, unless contraindications to such treatment are present.

After successful course of induction therapy, some patients may benefit from maintenance therapy. Most patients respond to glucocorticoids within several weeks, typically with symptomatic improvement, reductions in the size of masses or organ enlargement, improvement in organ function, and often a decrease in serum levels of IgG4. Retreatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction. Steroid sparing agents may be used for continuation in the remission maintenance period following a relapse.

Many cases of chronic pancreatitis associated with bile duct strictures have been reported in literature. The commonest involvement described is distal common bile duct stricture leading on to obstructive jaundice. But in some cases the biliary ductal involvement would be multiple with a sclerosing cholangitis like picture. There were earlier reports where they had described sclerosing cholangitis like picture was associated with pancreatitis having features resembling autoimmune pancreatitis. For example they had a mass like swelling of the pancreas or there was involvement of salivary glands or multiple organs were involved and most importantly they had responded to steroids. Hence they could have represented autoimmune pancreatitis.

Kojima *et al*. have proposed that lesions reported as PSC associated with chronic pancreatitis should be regarded as a different entity from PSC [14]. Kawaguchi had demonstrated lymphoplasmacytic sclerosing inflammatory disease involving the total pancreas, common bile duct, gallbladder and minor salivary gland of the lip in patients with variant forms of PSC. Wakabayashi *et al*. have suggested that steroid therapy for autoimmune pancreatitis is particularly indicated in those with common bile ducts strictures or immunoserological abnormality [15]. The table 1.1 differentiates sclerosing cholangitis that occurs in autoimmune pancreatitis from that of PSC based on the clinical, serology and the response to therapy.

During the first week after the onset of AP, treatment is medical. Surgery is not indicated during this phase, unless a suspicion of ischemia or perforation as a secondary complication arises. Surgery during this first phase aggravates the multiorgan failure and results in a greater rate of complications, such as intestinal hemorrhage or fistula. Most common indications for surgery of pancreatic necrosis are infection and single or multiorgan failure. A persistent single- or multiorgan failure refractory to support treatment may constitute an indication for surgery. Numerous studies have shown that in this context, oppositely to what happens when infection constitutes the indication for surgery, necrosectomy does not provide a significant benefit regarding mortality, and thus, it must be considered as the last resource in a patient in whom maximum medical support does not result in clear improvement. The management of pancreatic stump after distal pancreatectomy is an hard challenge, even for the most expertise gastrointestinal surgeons. No single method of reconstruction is suitable for all patients. Based on literature review, pancreatic duct occlusion techniques are associated with highest rate of postoperative complications, especially pancreatic fistula [16]. Pancreatic fistula after pancreatoduodenectomy

represents the major source of morbidity. Derivative procedures are preferred by pancreatic surgeons, but the optimal management of remnant pancreatic stump remains controversial [17].

Conclusion

The learning point in our patients was that one has to work up for an etiology in all patients with pancreatitis especially having a high degree of suspicion for autoimmune pancreatitis. If pancreatitis is associated with sclerosing cholangitis like picture then autoimmune etiology should be ruled out. It is most important to differentiate between the PSC and autoimmune pancreatitis with sclerosing cholangitis because with the latter the patient dramatically responds to steroids. Serum IgG4 levels need not be elevated in all patients of autoimmune pancreatitis. Renal involvement or multisystem involvement in a patient with pancreatitis should also alert the clinician about the autoimmune nature of the disease.

Tables

Table 1: Differentiation between PSC and SC-AIP

	PSC	SC-AIP
Age group	young	Older
Presentation as Obstructive jaundice	Less frequent	More frequent
Associated Complications	IBD	Extra pancreatic lesions
Serum IgG4 level	normal	High
IgG4-bearing plasma cell infiltration	Not seen	Seen
Steroid therapy	Not effective	Effective

Figures

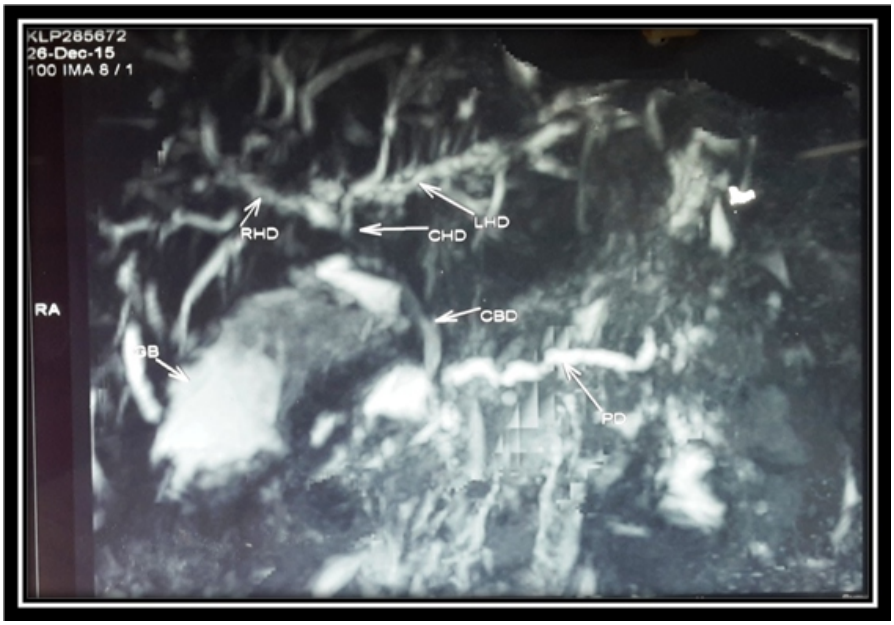

Figure 1.1: MRCP showing multifocal areas of cystic dilatation and narrowing of intrahepatic bile ducts in segments VIII, VII and V of right lobe and segment II of left lobe with mid CBD Stricture. The pancreas appeared diffusely atrophic with dilated pancreatic duct and multiple pancreatic calcifications.

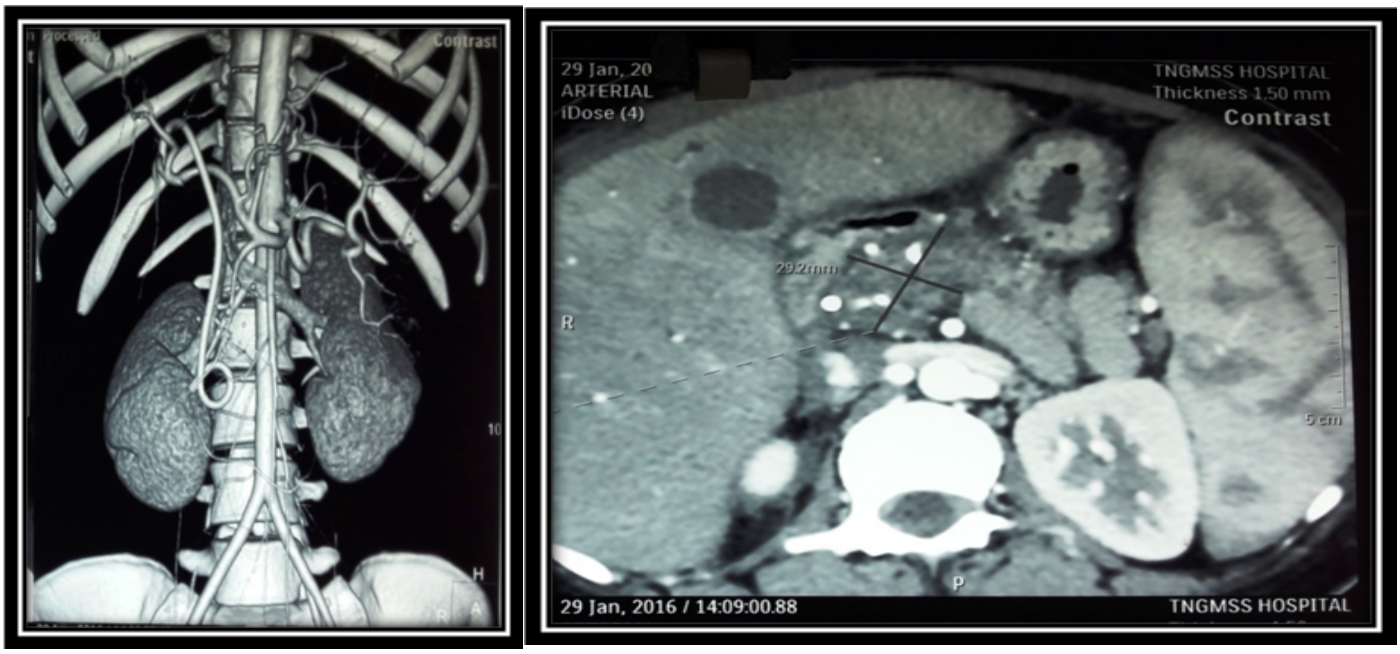

Figure 1.2: CT angiogram showing the biliary stent and the newly developed pancreatic head mass

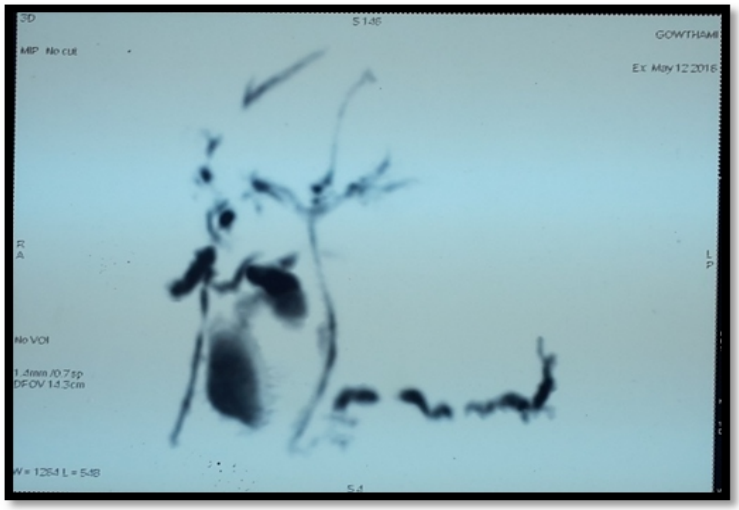

Figure 1.3: MRCP done post steroid therapy showing resolution of the cystic dilatation and narrowing of intrahepatic bile ducts

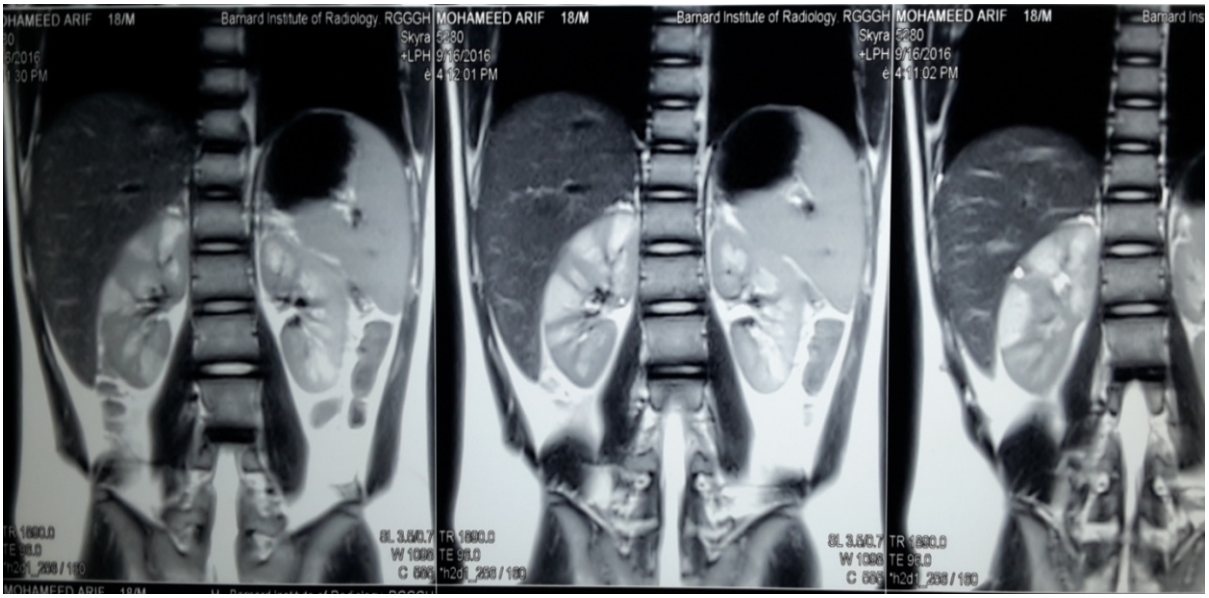

Figure 2.1: MRCP picture showing multiple wedge shaped T2 hyperintense lesions (right > left) in the kidneys

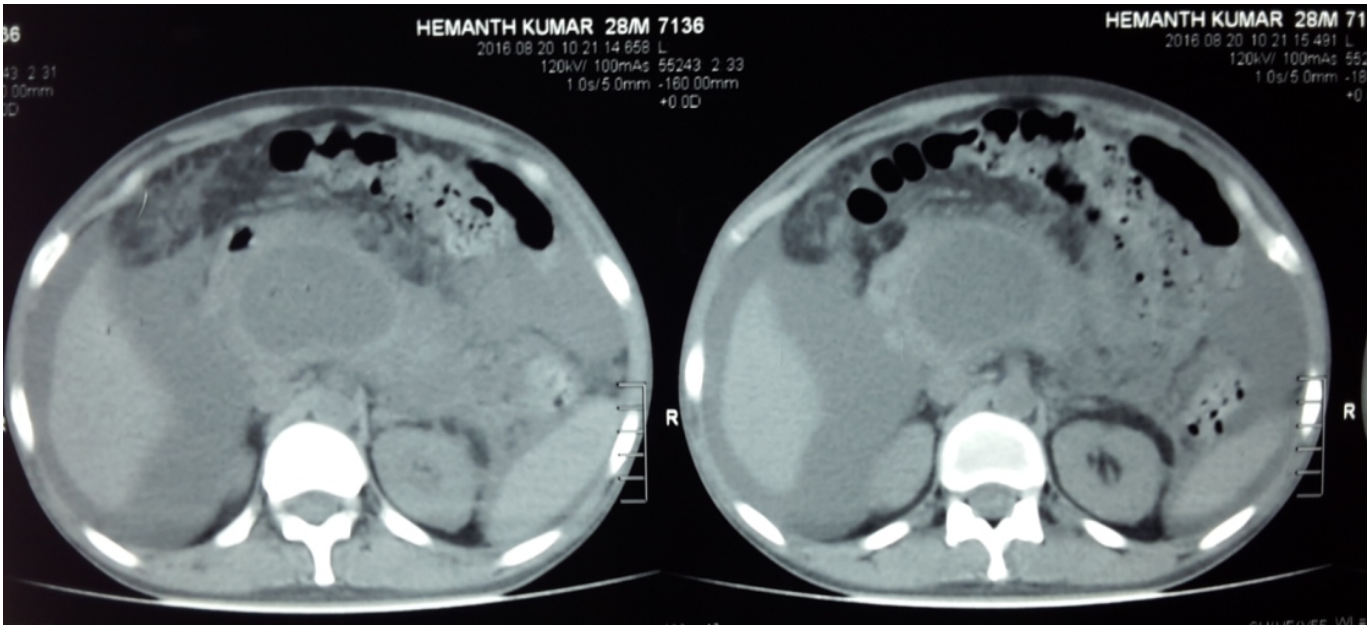

Figure 3.1: CT film showing bulky pancreas with cystic collection in the head of pancreas with ascites

References

1. Cheuk W, Chan JK. IgG4related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol 2010; 17:303

2. Smyrk TC. Pathological features of IgG4 related sclerosing disease. Curr Opin Rheumatol 2011; 23:74.

3. Deshpande V, Chicano S, Finkelberg D, et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. Am J Surg Pathol 2006; 30:1537

4. Mavragani CP, Fragoulis GE, Rontogianni D, et al. Elevated IgG4 serum levels among primary Sjögren's syndrome patients: do they unmask underlying IgG4 related disease? Arthritis Care Res (Hoboken) 2014; 66:773.

5. Sato Y, Ohshima K, Ichimura K, et al. Ocular adnexal IgG4related disease has uniform clinicopathology. Pathol Int 2008; 58:465.

6. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4related Sclerosing disease? Am J Surg Pathol 2007; 31:643.

7. Andrew NH, Sladden N, Kearney DJ, Selva D. An analysis of IgG4 related disease (IgG4RD) among idiopathic orbital inflammations and benign lymphoid hyperplasias using two consensusbased diagnostic criteria for IgG4RD. Br J Ophthalmol 2015; 99:376.

8. Rudmik L, Trpkov K, Nash C, et al. Autoimmune pancreatitis associated with renal lesions mimicking metastatic tumours. CMAJ 2006; 175:367.

9. Murashima M, Tomaszewski J, Glickman JD. Chronic tubulointerstitial nephritis presenting as multiple renal nodules and pancreatic insufficiency. Am J Kidney Dis 2007; 49:e7.

10. Watson SJ, Jenkins DA, Bellamy CO. Nephropathy in IgG4related systemic disease. Am J Surg Pathol 2006; 30:1472.

11. Saeki T, Nishi S, Imai N, et al. Clinicopathological characteristics of patients with IgG4related tubulointerstitial nephritis. Kidney Int 2010; 78:1016.

12. Takahashi N, Kawashima A, Fletcher JG, and Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. Radiology 242: 791-801, 2007.