IgG4-Related Sclerosing Diseases in the Abdomen: Imaging Findings with Pathologic Correlations

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Learning objectives

1. Review of multi modality imaging spectrum of Immunoglobulin G4 (IgG4) related sclerosing diseases of abdominal organs.

2. Description of Radio-pathological correlations of IgG4 related diseases of abdominal organs.
Background

Immunoglobulin G4 (IgG4) related diseases are of unknown etiology which can affect any organ from head to toe. It is characterised by diffuse or focal tumor like lesions with lymphoplasmacytic infiltrate enriched with IgG4 positive plasma cells and fibrosis. They are often associated with elevated serum IgG4 levels.

It predominantly affects males in their 4-6 decades however exact incidence is unknown.

It is a great mimicker with varying differential diagnosis on imaging, ranging from inflammatory lesions to malignancy.

Recognition of imaging findings can suggest a diagnosis, which can be confirmed on serology and histopathology. This is of paramount importance as the disease responds to immuno-suppressive therapy and thus unwarranted surgeries can be avoided.

In this context our experience (at Postgraduate Institute of Medical Education and Research, Chandigarh, India--a tertiary care centre) with IgG4 related sclerosing diseases of abdomen and multi-modality imaging findings with pathological correlations is presented here.
INTRODUCTION

IgG4 related diseases of abdomen most commonly affects pancreas followed by biliary system, kidneys and retroperitoneum. Rarely prostate and lymph nodes can also be involved.

Table 1: shows spectrum of IgG4 related diseases affecting abdominal organs (Table 1 on page 8).

STUDY DESIGN

Retrospective analysis of IgG4 related diseases affecting abdominal organs diagnosed between July 2006 and February 2016 at our institute- Postgraduate Institute of Medical Education and Research (P.G.I.M.E.R), Chandigarh, India revealed 21 cases: autoimmune pancreatitis (AIP) - 17, peri-aortitis-2, cholecystitis- 2.

This included 15 men and 6 women (45 to 66 years). Diagnosis was established based on imaging, serological, cytological and histopathological findings.

Imaging included ultrasound, CT, MRI, contrast enhanced ultrasound, PET-CT and/or endoscopic retrograde cholangiopancreatography (ERCP).

MULTI-MODALITY IMAGING SPECTRUM OF IgG4 DISEASES OF ABDOMEN

PANCREAS (Autoimmune Pancreatitis- AIP)

Incidence: Accounts for 2-11% of all chronic pancreatitis.

Imaging: Imaging depends on type of involvement which can be focal (tumor like) or multifocal or diffuse.

Most common is diffuse type where pancreas is diffusely enlarged and appears "sausage like" with sharp margins and loss of normal lobular contour and clefts (Fig. 1 on page 8, Fig. 2 on page 9, Fig. 5 on page 12). The tail typically appears truncated (Fig. 1 on page 8, Fig. 5 on page 12). Sometimes characteristic capsule like halo/ rim can be seen especially on CT/MRI (Fig. 1 on page 8). On imaging pancreas appears hypoechoic on ultrasound, hypoattenuating on CT and hypointense
on T1 Weighted MR Imaging (Fig. 1 on page 8, Fig. 2 on page 9, Fig. 5 on page 12, Fig. 6 on page 13). Focal involvement is less common, predominantly affects head region and mimicks malignancy.

The main pancreatic duct can show segmental narrowing in the affected region/s which is best demonstrated on Endoscopic Retrograde Pancreatocholangiography (ERCP) or Magnetic Retrograde Pancreatocholangiography (MRCP) (Fig. 3 on page 10).

Usually ductal or parenchymal calcifications, pseudocyst formation, and/or peri-pancreatic inflammation is rarely seen.

**BILIARY SYSTEM (Extra-pancreatic manifestations)**

Bile ducts are the the second most organ system to be involved, where the intra-pancreatic portion of common bile duct (CBD) is involved (Fig. 3 on page 10, Fig. 5 on page 12). Sometimes multi-focal segmental strictures of CBD and intra-hepatic ducts can be seen (Fig. 3 on page 10). The involved biliary segments demonstrates concentric thickening, stenosis and post contrast enhancement. These abnormalities reverses after immuno-suppressive therapy (Fig. 3 on page 10, Fig. 6 on page 13).

**GALL BLADDER**

Involvement of gall bladder can be either diffuse (Fig. 1 on page 8) or focal (Fig. 7 on page 14). Focal involvement mimick malignancy.

Diffuse form appears as circumferential symmetric wall thickening that appears hypoechoic on ultrasound and hypointense on T2 Weighted MR Imaging with delayed contrast enhancement due to fibrosis. In active stage it shows avid PET activity (Fig. 7 on page 14).

Focal involement shows asymmetric wall thickening however without any contiguous hepatic infiltration unlike malignancy (Fig. 7 on page 14). Needless to mention most of the cases are reported post operatively. On histopathogical evaluation inflammatory cells are IgG4 positive on IHC (Fig. 8 on page 15).

**KIDNEYS**

Renal involvement is usualy seen in about 1/3"rd of cases with autoimmune pancreatitis.

There are four patterns of renal involvement: round or wedge shaped cortical nodules, peripheral cortical lesions, mass-like lesions and renal pelvic invoielement (pyelitis) (Fig. 2 on page 9, Fig. 5 on page 12, Fig. 6 on page 13). The lesions represent lymphoplasmacytic infiltrates or interstitial nephritis that progresses to scars if goes untreated.
Lesions appear hypoechoic on ultrasound (Fig. 2 on page 9), hypoattenuating on CT (Fig. 2 on page 9, Fig. 5 on page 12) and hypointense on T2 Weighted MR Imaging (Fig. 6 on page 13). Lesions may show enhancement after intravenous contrast administration.

**PERI-AORTITIS**

The spectrum of IgG4 related diseases in retro-peritoneum are retro-peritoneal fibrosis, aortitis (Fig. 9 on page 16, Fig. 10 on page 17) and aortic aneurysms (Fig. 10 on page 17, Fig. 11 on page 18).

Three imaging patterns are recognised 1) peri-aortic soft tissue mass, 2) peri-ureteric mass, and 3) plaque like mass.

On imaging a soft tissue like mass is seen encasing aorta and its branches (Fig. 9 on page 16), typically without any luminal compromise unlike aorto-arteritis. The soft tissue is hypodense on CT (Fig. 9 on page 16) and demonstrates varying signal intensity on MR depending on degree and stage of fibrosis.

On pathology the lymphoplasmacytic cells are IgG4 positive with negative CD3 and CD20 staining, which are markers for T-cell and B-cell related inflammation respectively and are positive in aorto-arteritis (Fig. 12 on page 19).

**LYMPH NODES**

Lymph nodes involvement is seen in 80% of cases of autoimmune pancreatitis with most commonly involved lymph nodal groups are mediastinal and peri-pancreatic groups (Fig. 2 on page 9).

**SUMMARY OF RESULTS IN THE PRESENT SERIES**

**Autoimmune Pancreatitis**

12/17 cases of AIP showed diffuse bulky sausage shaped pancreas with loss of lobulations and a capsule like thin hypodense rim (4/12). 5/17 had focal mass like enlargement of pancreas (4- head and 1- body). Other findings were: benign strictures in lower common bile duct (11/17) and distal pancreatic duct (4/17), hypoattenuating nodules in kidneys 10/17 and enlarged hypodense mediastinal and peri-esophageal lymph nodes in 2/17.

**Cholecystitis**
One case of cholecystitis showed circumferential mural thickening in association with AIP (diffuse), while 2/2 revealed focal mural thickening mimicking malignancy.

**Peri-aortitis**

Cases of peri-aortitis showed a plaque like soft tissue along abdominal aorta and its visceral branches in one case and with aneurysm and rupture in another.
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Spectrum of diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Autoimmune pancreatitis</td>
</tr>
<tr>
<td>Hepatobiliary system</td>
<td>cholecystitis, Sclerosing cholangitis, focal mass like inflammatory pseudotumors within liver parenchyma, IgG4 related hepatitis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Inflammatory pseudotumors, sclerosing pyelitis, nephropathy</td>
</tr>
<tr>
<td>Prostate</td>
<td>prostatitis</td>
</tr>
<tr>
<td>Retroperitoneum and vascular structures</td>
<td>Retroperitoneal fibrosis, sclerosing mesentetitis, periaortitis, aortic aneurysms</td>
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</tbody>
</table>

**Table 1:** Table 1: shows spectrum of IgG4 related diseases affecting abdominal organs.

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Fig. 1: Figure 1: 57 year male patient presenting with pruritis and yellowish discoloration of skin and conjuctiva, diagnosed to have obstructive jaundice. (a to c) Ultrasound,(d to h)- axial contrast enhanced computed tomography images. Pancreas is bulky and "sausage" shaped with truncated tail (white asterik in a, c and f images) with characteristic hypodense rim sign ( white arrow in f). Intrahepatic biliary radical dilatation ( blue arrow in d) with dilated CBD with associated lower CBD stricture). Mild concentric wall thickening of gall baldder is also seen (red arrow in b and e). Imaging diagnosis of autoimmune pancreatitis with cholecystitis (diffuse form) was suggested and confirmed with raised serum total IgG (1971 mg/dL) and IgG4 levels (251 mg/dL). Patient was treated with oral corticosteroids and responded well to therapy.

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Fig. 2: Figure 2: 50 year male patient presenting with obstructive jaundice, was diagnosed to have CBD strictures (sclerosing cholangitis) and underwent CBD stenting .(a to c)- Ultrasound and (d to h)- axial contrast enhanced computed tomography images. Pancreas is bulky and sausage shaped with minimal peri-pancreatic stranding (red asterisk in a and d images). Intrahepatic biliary radical dilatation (red arrow in b and e). Renal lesions in both kidneys (blue arrow in c,f,h) The lesions are hypoechoic on ultrasound (c)and hypo-attenuating on CT (f,i). CBD stent seen in situ (long white arrow in i). Discrete enlarged hypodense lymph nodes are seen at right hilar and peri-esophageal locations (white block arrows in g and h). Imaging diagnosis of autoimmune pancreatitis was suggested which was further confirmed on guided fine needle aspiration cytology from pancreas (Figure 4), raised serum total IgG (2199mg/ dL)and IgG4 (129mg/dL) levels. Patient was started on oral corticosteroids and responded well to therapy (Figure 3).

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Fig. 3: Figure 3: a and b- MRCP and c (pre-treatment) and d (post-treatment) ERCP of the same patient in figure 2, reveals stricture in proximal CBD (short arrow in a to c) and distal CBD (long arrow in a to c) with presence of intrahepatic biliary radical dilatation. Post treatment ERCP image (d) shows resolution of the CBD strictures with non-dilated biliary radicals.

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Fig. 4: Figure 4: Panel of micro-photographs showing fine needle aspiration cytological features in autoimmune pancreatitis. a) Pancreatic ductal epithelial fragments and stromal fibro-inflammatory fragments, b) Pancreatic acinar cell cluster with lymphocytes and plasma cells in the background, c) Cellular stromal fibro-inflammatory fragments, and d) Hyalinised stromal fragment (a, c, d: Hematoxyline-Eosin stain.: b.May-Grunwald Giemsa stain: a:x 100: b:x 200, c and d:x 400)

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**Fig. 5:** Figure 5: 51 year female patient presenting with occasional mild pain abdomen with yellowish discoloration of skin and conjunctiva, diagnosed to have CBD stricture and underwent CBD stenting. (a)- grey scale ultrasound image, (b and c): ERCP and CBD stenting. (d to f)- contrast enhanced computed tomography images(axial and coronal). Pancreas is bulky and sausage shaped with minimal peri-pancreatic stranding (white asterisk in a and d). Short segment lower CBD stricture (red arrow in b and placement of CBD stent in c). Intrahepatic biliary radical dilatation with CBD stent in-situ (black arrow in e). Hypodense renal lesions in both kidneys (white arrow in f). Imaging diagnosis of autoimmune pancreatitis was suggested when patient was re-scanned after ERCP for evaluation of disease status, thereafter patient was started on oral corticosteroids to which she responded well with resolution of clinical symptoms and regression of radiological lesions (next image). At diagnosis there were elevated total serum IgG (2850 mg/dL)levels but serum IgG4 were normal (81 mg/dL).

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Fig. 6: Figure 6: MR images of same patient as in figure 5, a to c pre treatment MR images and d to f- post treatment MR images. There is significant reduction in the intrahepatic biliary radicle dilatation (coronal T2 weighted MR images with blue arrow showing lower CBD stricture in a and c), reduced bulk of pancreas with prominent MPD (axial T1 weighted images showing white asterisk in b and e) and reduction in size of renal lesions (coronal T2 weighted image with red arrow in c and f).

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Fig. 7: Figure 7: 45 year female patient presenting with vague abdominal pain, incidentally detected gall bladder wall thickening. a,b - ultrasonography, c - contrast enhanced ultrasonography, d to f - axial contrast enhanced computed tomographic images, g to i- axial PET CT images. Asymmetrical wall thickening is seen involving fundus and distal body of gall bladder (red arrow) with intense FDG uptake in PET-CT images. Pre-operative diagnosis of malignant GB wall thickening was made and patient underwent surgery, histopathology revealed IgG4 related autoimmune cholecystitis. Follow-up ultrasound (not shown here) revealed no evidence of any recurrence.

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Fig. 8: Figure 8: Panel of photomicrographs showing a) fibro-inflammatory process involving the gall bladder fossa and portal tract inflammation, b) inflammatory cells composed of numerous plasma cells, c) obliterative phlebitis along with fibrosis and inflammation, and d) IgG4 Immunohistochemistry (IHC) highlights many IgG4 positive plasma cells.

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Fig. 9: Figure 9: 54 year male patient presented with vague pain abdomen. (a to d) - contrast enhanced axial computed tomography images in arterial phase, (e and f) - coronal and sagittal reconstructed images of aorta and its branches respectively. Ill defined soft tissue is seen in pre-aortic location (red arrow in a) and this soft tissue is seen encasing the celiac artery from its origin (red arrow in b) and also superior mesenteric artery (SMA) and its branches from origin (red arrow in c to f) without any luminal compromise of these arteries.

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Fig. 10: Figure 10: 63 year male patient presented with sudden onset pain abdomen and hypotension. a and b - non contrast axial computed tomography images, c to f- axial contrast enhanced computed tomographic angiographic images, g- reconstructed volume rendered (VR) image of abdominal aorta. Fusiform infrarenal abdominal aortic aneurysm seen (black asterisk in c,d and g) with active contrast leak (block red arrow in d) associated hyperdense hematoma (red arrow in e and f) and associated significant periaortic stranding (white arrow in a and b). Patient expired on day 2 of admission and a diagnosis of IgG4 peri-aortitis was made on autopsy.

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Fig. 11: Autopsy specimen shows a) gross specimen with evidence of blood collection in the area of aortic rupture confirmed b & c) by cross sections at the site of rupture and histopathology (arrow) c). Note thrombus in left common iliac artery (b) corresponding to CT angiographic images.

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Fig. 12: Figure 12: Photomicrograph shows a) inflammatory peri-aortitis which had b) evidence of fibrosis and c) venulitis. Plasma cells were IgG4 positive. Stains for CD 3 and CD20 were negative (positive in aorto-arteritis).

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Conclusion

(1). IgG4 related sclerosing diseases are rare and recently recognized entities which are potentially curable with appropriate (immuno-suppressive) therapy.

(2). On imaging, findings can be varied and can simulate malignancy especially with focal involvement. Therefore awareness of imaging spectrum by Radiologists is of paramount importance in suggesting a diagnosis. The disease responds to immunosuppressive therapy and therefore correct diagnosis is desirable.

(3). In this series correct pre-operative diagnosis was established in 18/21 cases (all AIP and one peri-aortitis), cases of focal cholecystitis was diagnosed on surgical specimens while one case of peri-aortitis was diagnosed on autopsy.

(4). In appropriate clinical context, recognition and awareness of imaging features are diagnostic, when supported by laboratory findings.
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References

