EDORIUM Journals

Int J Hepatobiliary Pancreat Dis 2023;13(1):1–6.
www.ijhpd.com

RESEARCH ARTICLE PEER REVIEWED | OPEN ACCESS

IgG4-related inflammatory pseudotumor of the liver presenting as an incidental solitary liver mass

Mohammed Omer Mirghani, Zergham Zia, Mohammad Haytham Mawardi, Zuhoor Almansouri, Niaz Ahmad

ABSTRACT

Inflammatory pseudotumor is increasingly being recognized as a definitive pathological entity affecting many organ systems and often difficult to distinguish from malignancy. We report a case of a 48-year-old female who presented with right hypochondrial pain associated with nausea and vomiting and recent weight loss. An ultrasound scan demonstrated gallstones without evidence of cholecystitis and an incidental 1.5 cm mass in the left liver lobe. A computed tomography (CT) and a magnetic resonance imaging (MRI) scan described the mass suspicious of a malignant tumour. An ultrasound-guided biopsy confirmed a benign inflammatory mass with lymphoplasmacytic infiltration staining for IgG4 and no evidence of malignancy. The patient had an elevated serum IgG4 levels. The patient was kept under surveillance. She underwent a laparoscopic cholecystectomy and at 18 months following the initial presentation the patient remains asymptomatic with stable liver lesion on ultrasound scan.

Mohammed Omer Mirghani[1], Zergham Zia[2], Mohammad Haytham Mawardi[3], Zuhoor Almansouri[4], Niaz Ahmad[1]

Affiliations: [1]Departmet of Surgery, Section of Hepatobiliary and Transplantation Surgery, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia; [2]Department of Radiology, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia; [3]Department of Medicine, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia; [4]Department of Anatomic Pathology, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia.

Corresponding Author: Niaz Ahmad MD, FRCS, Department of Surgery, Section of Transplantation & HPB Surgery, King Faisal Specialist Hospital and Research Centre, PO Box 40047, Jeddah 21499, Saudi Arabia; Email: niazahmad@kfshrc.edu.sa and niazamad@hotmail.com

Received: 12 June 2022
Accepted: 06 February 2023
Published: 02 March 2023

Keywords: Inflammatory pseudotumor, IgG4, Liver, Plasma cell

How to cite this article

Mirghani MO, Zia Z, Mawardi MH, Almansouri Z, Ahmad N. IgG4-related inflammatory pseudotumor of the liver presenting as an incidental solitary liver mass. Int J Hepatobiliary Pancreat Dis 2023;13(1):1–6.

Article ID: 100101Z04MM2023

****

doi: 10.5348/100101Z04MM2023CR

INTRODUCTION

An incidental solid mass in a non-cirrhotic liver in the absence of a primary tumor elsewhere poses a diagnostic challenge. Inflammatory pseudotumor (IPT) is increasingly being recognized as a unique pathological entity affecting many organ systems and often presenting as a tumor that mimics malignancy. Inflammatory pseudotumor was first described in the lungs in 1939 [1]. Subsequently IPT has been described in other organs and systems such as the central nervous system, salivary glands, kidneys, liver, omentum, ovaries, larynx, urinary bladder, breasts, pancreas, spleen, lymph nodes, skin, soft tissues, and the orbit of the eye [2]. An IPT of the liver (IPTL) was first reported by Pack and Baker in 1953 as a rare benign lesion characterized by infiltration of inflammatory cells and fibrosis that mimics a malignant tumor requiring surgery [3]. Inflammatory pseudotumor of the liver presents with non-specific symptoms and often diagnosed incidentally. The etiology and pathogenesis of IPTL are unknown and there are no characteristic laboratory or radiological diagnostic features.

An IPTL in the liver hilum is usually a diffuse infiltrative lesion along the intra or extrahepatic biliary tree that may lead to biliary obstruction, portal

hypertension, even cirrhosis and is often difficult to distinguish from sclerosing cholangitis or a malignant Klatskin tumor [4, 5]. An intrahepatic IPTL may mimic a malignant tumor on imaging, particularly a metastatic disease, a hepatocellular carcinoma, or intrahepatic cholangiocarcinoma [6, 7]. It is often a solitary tumor with a predilection for the right lobe; however, multiple lesions in both hepatic lobes have been described [7].

Recent studies have suggested IPT and IPTL to be associated with autoimmune IgG4-related disease (IgG4RD). This is a fibroinflammatory disease characterized by a tendency to form tumor like lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4; storiform fibrosis; and often but not always an elevated serum IgG4 concentrations [8, 9]. These cases often respond to corticosteroid and NSAID. Many previously described autoimmune related inflammatory condition such as Mikulicz's disease, Kuttner's tumor, Hashimoto's thyroiditis, autoimmune pancreatitis, sclerosing cholangitis, interstitial nephritis, retroperitoneal fibrosis, and others can be reclassified as belonging to this group connected by the unique pathological features described above.

The diagnosis of IPTL associated with IgG4RD is established by a biopsy. The characteristics features include a dense lymphoplasmacytic infiltration staining positive for IgG4 in the background of storiform fibrosis. The serum IgG4 may also be elevated. An absence of a suspicion for primary or secondary malignancy, liver cirrhosis and normal tumor marker may act as proxy for the diagnosis of IPTL in combination with imaging and histological criteria and help avoid unnecessary surgery [7, 8].

CASE REPORT

We report a case of a 48-year-old female with no known comorbidities presented with right hypochondrial pain, nausea, and vomiting associated with a weight loss of 3 kg over one month. Her abdominal examination was unremarkable. She had a normal blood count, renal, and hepatic profiles. An ultrasound scan demonstrated a fatty liver, multiple gall stones without the evidence of cholecystitis, and an incidental 1.5 cm hypodense mass in the left liver lobe (Figure 1A).

Computed tomography abdomen demonstrated a 1.6 cm hypoattenuating lesion in segment II of the liver with arterial enhancement and delayed washout suspicious for a hepatocellular carcinoma. The background liver did not appear cirrhotic, without portal hypertension or biliary obstruction. An MRI scan of the liver again confirmed the left lobe liver lesion with restricted diffusion and ring enhancement post-gadolinium highly suspicious of malignancy (Figure 1B and C).

A screening for primary malignancy elsewhere was negative including a CT scan of chest and pelvis, upper and lower gastrointestinal endoscopy, a mammogram, and a thyroid scan. Tumor markers including AFP, CEA, CA19-9, and CA125 were within normal range. Viral screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) were also negative.

An ultrasound-guided tru-cut biopsy of the liver lesion showed focal area of fibrosis with a dense lymphoplasmacytic infiltration but no malignant cells. Staining for IgG4 was positive in up to 12 plasma cells per high power field in the densest areas of plasma cell infiltrate (Figure 2A–C).

Autoimmune screen showed elevated IgG4 level of 18.49 g/dL (normal range 7–16 g/dL) (Figure 3) and a high anti-RNP antibody of 37 (normal range 0–16). Antinuclear antibodies (ANAs) and smooth muscle antibodies (SMAs) were also positive. Microsomal antibodies (TPOs) and antimitochondrial antibodies (AMAs) were negative. An upper gastrointestinal (GI) endoscopy was unremarkable. Biopsies taken from the stomach, duodenum, and ampulla of Vater were positive for *Helicobacter pylori*. The patient received helicobacter eradication treatment.

A repeat MRI scan at three months again demonstrated a stable 1.5 cm solid lesion in the left liver lobe. Repeat biopsy with a 14 G needle corroborated the earlier pathological findings of focal fibrosis with dense lymphoplasmacytic infiltration and positive IgG4 staining.

A multidisciplinary review of the case concluded that the patient's initial symptoms were likely related to biliary colic and the liver lesion was incidental and benign. The patient was not given any steroid or anti-inflammatory treatment in the absence of symptoms and stable liver lesion. A laparoscopic cholecystectomy was performed one year after the initial presentation with uneventful recovery. Serum IgG4 at one year was normal at 14 g/dL. At 18 month, the patient remains symptom free, and the

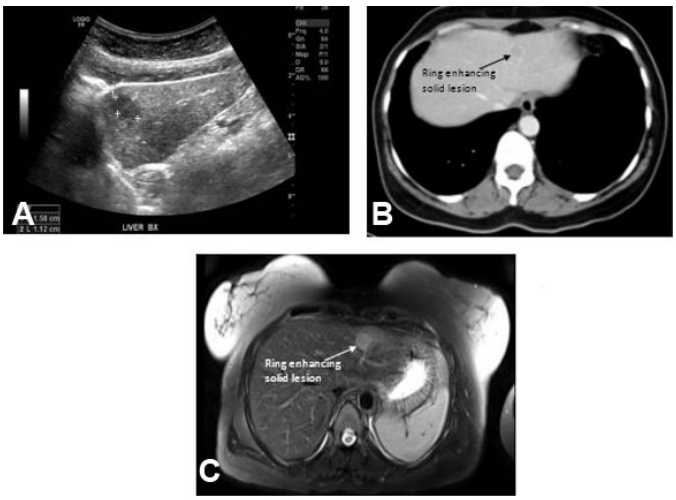

Figure 1: (A) Ultrasound scan of liver demonstrating a 1.6 cm hypoechoic lesion in the left liver lobe, (B) CT scan demonstrating an enhancing lesion in the segment II of liver (portal venous phase), (C) MRI scan demonstrating the same lesion with restricted diffusion and ring enhancement suggesting a malignant tumor (T2).

liver lesion is stable. The final diagnosis was consistent with IgG4-related IPTL in the absence of systemic IgG-4 disease.

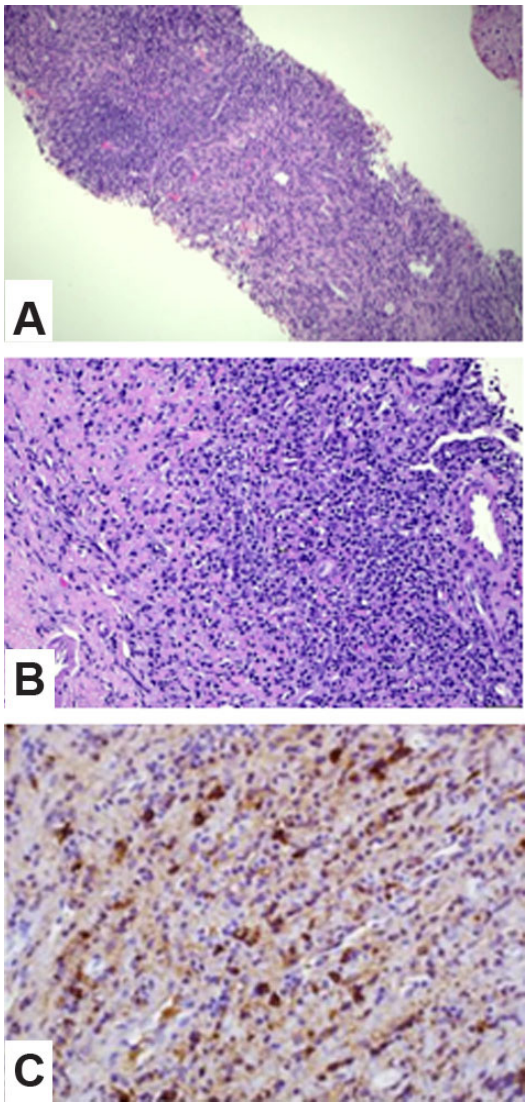

Figure 2: (A–C) Histopathology of IPTL, (A) low power (×100), (B) high power (×400) with heamtoxylin and eosin (HE) staining showing dense lymphoplasma cell infiltrate and fibrosis. (C) Showing IgG4 staining plasma cells (×400 magnification).

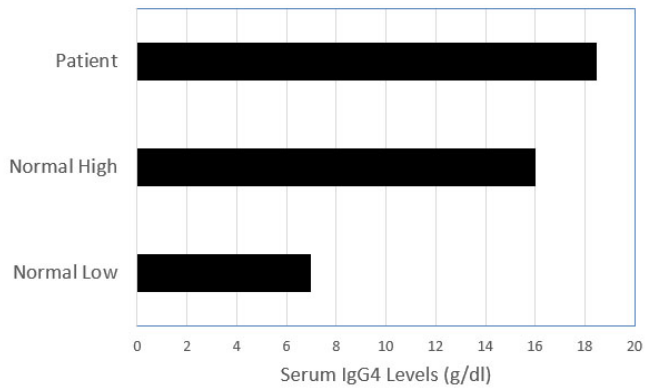

Figure 3: Serum IgG4 levels were elevated in our patient.

DISCUSSION

A case of IPTL associated with IgG4RD is reported that presented as an incidental solid tumor in the liver. The diagnosis was established by a biopsy of the lesion and major surgery was avoided.

Inflammatory pseudotumor is a chronic inflammatory condition of unknown etiology that can mimic a tumor. It is also variably known as an inflammatory myofibroblastic tumor, plasma cell granuloma, xanthomatous pseudotumor, and inflammatory fibrosarcoma. According to histology, three different types of IPTL have been described: xanthogranuloma, plasma cell granuloma, and sclerosing pseudotumors [10]. The lesions may be solitary or multiple and, radiologically, may mimic malignancy. Histologically, an IPT is characterized by spindle-shaped cells, myofibroblasts, and mixed inflammatory cells including plasma cells, lymphocytes, and histiocytes. Inflammatory pseudotumor of the liver accounts for 0.7% of liver tumors and 8% of all extrapulmonary IPTs [11]. Inflammatory pseudotumor of the liver commonly occurs in childhood and early adulthood with some reports of a male preponderance [11] and appears to be more common in non-European populations [12].

The etiology and pathogenesis of IPTL remain uncertain. Reported conditions associated with IPTL include infections, trauma, ischemia, and autoimmune disorders. A chronic abscess or an inflammation of liver may also lead to the development of an IPTL. In IPTL of inflammatory or infectious origin, the lesion appears to develop from a healing abscess or an inflammation [11]. Hydatid cyst of the liver also forms an important differential diagnosis.

The diagnosis of IPTL in our cases conformed to the recently described IgG4-related disease [8, 9]. The histopathology confirmed fibrosis with a dense lymphoplasmacytic infiltrate positive for IgG4. The fibrosis did not have classically described storiform pattern which may be due to biopsy sampling. The lesion did not demonstrate obliterative phlebitis, an optional feature for diagnosis. There were no neutrophils and epithelioid cells as these features do not support the diagnosis of IgG4RD [13]. Serum IgG4 level was also elevated. Inflammatory pseudotumor of the liver, therefore, can be included in the spectrum of IgG4RD that can affect virtually any organ system of the body and are connected by the unique histopathological characteristics.

Inflammatory pseudotumor of the liver is often asymptomatic and is discovered as incidental finding on imaging. Common symptoms of IPTL include abdominal pain, fever, and weight loss. Inflammatory pseudotumor of the liver involving the biliary tree may present with intra or extrahepatic biliary obstruction and may mimic sclerosing cholangitis or a malignant Klatskin tumor [4, 5].

The diagnosis of IPTL is difficult. Ultrasound and CT scans are not specific, revealing variable patterns of echogenicity of a liver mass mimicking hepatocellular

cancer, metastasis, cholangiocarcinoma, or an abscess [14–16]. The CT scan features of an IPTL may mimic a malignant tumor with variable contrast enhancement. A delayed enhancement can also be seen as in metastatic liver tumors and cholangiocarcinoma. A low signal intensity on T1-weighted images, moderate to high signal intensity on a T2-weighted images and ring enhancement post-gadolinium can lead to the diagnosis of a malignant tumor. A histology is needed to confirm the diagnosis of IPTL but has the inherent problem of inadequate, inappropriate, or missed sampling. A biopsy, therefore, may represent a perilesional area of an un-sampled tumor. Clinical and radiological correlation and a repeat biopsy are often required. A repeat biopsy in our case confirmed the earlier histological findings and major surgery was avoided. In many cases such a diagnosis is confirmed after the surgical resection of the tumor.

IgG4 staining of the plasma cell is diagnostic feature and should be quantified. A count of 10 positive cells per high power field in the densest area of plasma cell infiltrate support the diagnosis of IPTL associated with IgG4RD. some authors suggest using the ratio of IgG4/IgG staining of plasma cell and a ratio of 40% or more to be diagnostic [17].

The serum IgG4 levels were raised in our patients, but this may be normal in up to 40% of patients diagnosed with IgGRD [18]. The presence of other biomarkers such as FoxP3 and Th2-type cytokines, such as IL4, IL5, IL10, and IL13 also support the diagnosis of IgG4RD [13, 19].

The natural history of IPT is one of disease regression. Inflammatory pseudotumor of the liver frequently resolves spontaneously with no long-term consequences [6, 11]. A multidisciplinary approach involving the physician, the pathologist, and the radiologist is required to manage these cases. Following the confirmation of diagnosis, the patients with IPT can be observed with surveillance of symptoms and appropriate imaging to monitor the size of the tumor. For IPTL an USS surveillance is often adequate, where indicated, symptomatic patients with confirmed IgG4RD associated IPTL may be treated with steroid, immunosuppression, and non-steroidal anti-inflammatory drugs (NSAIDs) with variable response [8, 9, 11]. Surgical resection is not required in most cases but may become essential if the diagnosis is uncertain. Treatment with steroid and/or NSAID may help to confirm the diagnosis and stop progression of the disease in initially asymptomatic cases. The indication for surgery in IPTL includes: (a) persistent and unresolving symptoms, (b) tumor growth, (c) hilar tumor with biliary obstruction and/or portal hypertension [20, 21].

Recurrence after resection and malignant transformation IPTL have been reported to occur [22, 23] though at least some of these may be "missed tumor" at the initial diagnosis. A long-term follow-up is recommended even for patients who have been successfully treated by surgical resection.

CONCLUSION

Inflammatory pseudotumor of the liver is a rare inflammatory tumor of liver associated with IgG4-related disease that may mimic a malignant tumor and should be included in the differential diagnosis of liver tumor; where the diagnosis is confirmed, the patient should be treated medically and managed by surveillance. Surgical treatment should be offered where symptoms persist, or progress, and doubts exist regarding the diagnosis. In the absence of a definitive diagnosis many of the IPTLs will be diagnosed after surgery.

REFERENCES

1. Brunn H. Two interesting benign lung tumors of contradictory histopathology: Remarks on the Necessity for Maintaining the Chest Tumor Registry. J Thorac Surg 1939;9(2):119–31.
2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366(6):539–51.
3. Pack GT, Baker HW. Total right hepatic lobectomy; Report of a case. Ann Surg 1953;138(2):253–8.
4. Goldsmith PJ, Loganathan A, Jacob M, et al. Inflammatory pseudotumours of the liver: A spectrum of presentation and management options. Eur J Surg Oncol 2009;35(12):1295–8.
5. Zen Y, Harada K, Sasaki M, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: Do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004;28(90):1193–203.
6. Puri Y, Lytras D, Luong TV, Fusai GK. Rare presentation of self-resolving multifocal inflammatory pseudotumour of liver. World J Clin Cases 2014:2(1):5–8.
7. Rosa B, Moutinho-Ribeiro P, Pereira JM, et al. Ghost tumor: An inflammatory pseudotumor of the liver. Gastroenterol Hepatol (N Y) 2012;8(9):630–3.
8. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25(9):1181–92.
9. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): General concepts and details. Mod Rheumatol 2012;22(1):1–14.
10. Someren A. Inflammatory pseudotumor of liver with occlusive phlebitis: Report of a case in a child and review of the literature. Am J Clin Pathol 1978;69(2):176–81.
11. Lévy S, Sauvanet A, Diebold MD, Marcus C, Da Costa N, Thiéfin G. Spontaneous regression of an inflammatory pseudotumor of the liver presenting as an obstructing malignant biliary tumor. Gastrointest Endosc 2001;53(3):371–4.
12. Koea JB, Broadhurst WG, Rodgers MS, McCall JL. Inflammatory pseudotumor of the liver: Demographics, diagnosis, and the case for nonoperative management. J Am Coll Surg 2003;196(2):226–35.
13. Zen Y, Fuji T, Harada K, et al. Th2 and regulatory

immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology 2007;45(6):1538–46.
14. Caramella T, Novellas S, Fournol M, Saint-Paul MC, Bruneton JN, Chevallier P. Imaging of inflammatory pseudotumors of the liver. [Article in French]. J Radiol 2007;88(6):882–8.
15. Herek D, Karabulut N. Education and imaging. Hepatobiliary and pancreatic: Inflammatory pseudotumors of the liver. J Gastroenterol Hepatol 2011;26(7):1217.
16. Park JY, Choi MS, Lim YS, et al. Clinical features, image findings, and prognosis of inflammatory pseudotumor of the liver: A multicenter experience of 45 cases. Gut Liver 2014;8(1):58–63.
17. Cheuk W, Chan JKC. IgG4-related sclerosing disease: A critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol 2010;17(5):303–32.
18. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. Curr Opin Rheumatol 2011;23(1):108–13.
19. Miyake K, Moriyama M, Aizawa K, et al. Peripheral CD4+ T cells showing a Th2 phenotype in a patient with Mikulicz's disease associated with lymphadenopathy and pleural effusion. Mod Rheumatol 2008;18(1):86–90.
20. Lu CC, Chen CC, Hsia CY, et al. A progressive growing inflammatory pseudotumor of the liver. Zhonghua Yi Xue Za Zhi (Taipei) 2001;64(12):725–30.
21. Kaneko K, Ando H, Watanabe Y, et al. Aggressive preoperative management and extended surgery for inflammatory pseudotumor involving the hepatic hilum in a child. Surgery 2001;129(6):757–60.
22. Pecorella I, Ciardi A, Memeo L, et al. Inflammatory pseudotumour of the liver—Evidence for malignant transformation. Pathol Res Pract 1999;195(1):115–20.
23. Zavaglia C, Barberis M, Gelosa F, et al. Inflammatory pseudotumour of the liver with malignant transformation. Report of two cases. Ital J Gastroenterol 1996;28(3):152–9.

****

Author Contributions

Mohammed Omer Mirghani – Design of the work, Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Zergham Zia – Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mohammad Haytham Mawardi – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Zuhoor Almansouri – Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Niaz Ahmad – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

ABOUT THE AUTHORS

Article citation: Mirghani MO, Zia Z, Mawardi MH, Almansouri Z, Ahmad N. IgG4-related inflammatory pseudotumor of the liver presenting as an incidental solitary liver mass. Int J Hepatobiliary Pancreat Dis 2023;13(1):1–6.

Niaz Ahmad, MBBS, FRCSEd, MD, FRCS is a consultant transplant and hepatobiliary surgeon at Sheikh Khalifa Medical City, Abu Dhabi. He is also an honorary professor of transplantation at the Dow University of Health Sciences, Pakistan. Previously he has worked as a consultant surgeon at King Faisal Specialist Hospital, Jeddah, Saudi Arabia and St. James's University Hospital, Leeds, UK. Dr. Niaz Ahmad is widely recognized for his clinical and research work in the field of liver and renal transplantation. His research interests include ischemia-reperfusion injury in transplant, organ preservation, extended criteria donor organ, tissue engineering, and tumor biology. He is credited with performing kidney transplant from the youngest donor which is listed in Guinness World Record since 2016.