IgG4 related Inflammatory Pancreatic Head Pseudotumor Mirror Pancreatic Carcinoma: A Novel Case Series with a Review of the Literature

Faheemullah Khan[1], Jehanzeb Shahid[1], Amna Saleem[2], Uzzam Ahmed Khawaja[2], Wasim Ahmed Memon[3], Uffan Zafar[1], Tariq Abdul Hameed[4], and Khabab Mohamed Ahmed[5]

[1]The Aga Khan University Hospital
[2]Jinnah Medical and Dental College
[3]The Aga Khan University
[4]Indiana University School of Medicine
[5]University of Khartoum Faculty of Medicine

April 5, 2023

IgG4 related Inflammatory Pancreatic Head Pseudotumor Mirror Pancreatic Carcinoma: A Novel Case Series with a Review of the Literature

Faheemullah Khan, MBBS, MD[1], Jehanzeb Shahid, MBBS, FCPS[2], Amna Saleem, MBBS[3], Uzzam Ahmed Khawaja, MBBS[4], Wasim Ahmed Memon, MBBS, FCPS[5], Uffan Zafar, MBBS[6], Tariq Abdul Hameed, MD, DABR[7], Khabab Abbasher Hussien Mohamed Ahmed, MBBS[8*]

[1,2,5,6]Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan.

[3,4]Jinnah Medical and Dental College, Karachi, Pakistan.

[7]Department of Radiology, Indiana University School of Medicine, Indiana, US.

[8]Faculty of Medicine, University of Khartoum, Khartoum, Sudan

Faheemullah Khan : Email: islamianfellow@hotmail.com, ORCID:*https://orcid.org/0000-0001-6369-743X*

Jehanzeb Shahid: Email:*jehanzeb.shahid@aku.edu*

Amna Saleem: Email: amna.saleem41@hotmail.com

Uzzam Ahmed Khawaja: Email: uzzamahmedkhawaja@gmail.com

Wasim Ahmed Memon: Email:*wasim.memon@aku.edu*

Tariq Abdul Hameed: Email: thameed@iupui.edu

Khabab Abbasher Hussien Mohamed Ahmed: Email: khabab9722@gmaail.com, ORCID:

https://orcid.org/0000-0003-4608-5321

Article type : Case Series

Abstract: 105

Main text : 1907 (Main document)

Tables : 0

Figures : 5

References : 27

Pages : 10

Short running title

IgG4 related inflammatory pancreatic head pseudotumor.

Declarations:

-Consent statement: Written informed consent was obtained from the patients to publish this report in accordance with the journal's patient consent policy.

-Competing interests: None to declare.

-Funding: Not applicable.

-**Acknowledgement** : None to declare.

-Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Corresponding Author:

Khabab Abbasher Hussien Mohamed Ahmed, Email: Khabab9722@gmail.com, ORCID: https://orcid.org/0000-0003-4608-5321, ZIP code: 11111, Khartoum, Sudan

Abstract

Inflammatory pseudo tumor is an entity of pancreatic carcinoma composed of inflammatory cells and myofibroblastic spindle cells. In our novel case series, we report four such cases of pancreatic pseudo tumors with patients ranging from 30 to 70 years of age.

Keywords: Pseudo tumor, pancreatic carcinoma, abdominal CT, Serum IgG4

Key Clinical message:

In this noteworthy case series regarding pancreatic pseudo tumors, we intend to spread knowledge among physicians for the diagnostic and therapeutic approach and eventual disease prognosis

Introduction

Radiologists are finding it difficult and challenging to detect the pancreatic pathologies as the diverse range of diseases impersonates pancreatic neoplasm [1–3]. Such maladies are mostly signified as pancreatic pseudotumors. Multiple illnesses fall under the umbrella of the pancreatic pseudo-tumors including autoimmune pancreatitis, intra-pancreatic accessory spleen, abrupt pancreatic hemorrhage, chronic pancreatitis, groove pancreatitis and fatty replacement of the pancreas [4–6]. Non-cancerous lesions, often indicated as pseudotumors are revealed in around 5-10% patients undergoing pancreatectomies on account of a conjecture diagnosis of malignancy entrenched via radiology [7,8].

The usual pathogenesis of this disease is secondary to chronic inflammatory conditions. It may result due to a genetic or developmental defect, several infections, physical injuries and lympho-proliferative disorders [8, 9]. The degree to which pseudo-tumors imitate life taking diseases can lead to interventions that can jeopardize the patient's health, thereby increasing the mortality rates. Moreover, the wide range of differentials further complicates the process of reaching to a definitive diagnosis [10]. Hence, it is essential to initiate a prompt medical assessment in order to extract the final diagnosis followed by a rapid treatment for each patient diagnosed with a pancreatic mass [10].

Herein, we present a set of patients presenting with a pancreatic mass on abdominal CT scan indicative of a pancreatic pseudo tumor. The purpose is to highlight the imaging features and biochemical markers of autoimmune pancreatitis/IgG4 related pancreatic disease that helps to differentiate this entity from a true pancreatic tumor.

Case Presentation

Case 1

A 72-year-old male patient with co-morbids including diabetes mellitus, ischemic heart disease and benign prostatic hyperplasia came to our hospital with complaints of yellow discoloration of sclera, dark colored urine, and pale colored stools for 15 days. Patient history included coronary artery bypass grafting (18 years ago) and carotid endarterectomy (19 years ago). On arrival the patient was stable except having jaundice. CT scan abdomen with contrast showed heterogeneous appearing lesion involving the uncinate process of the pancreas likely representing a neoplastic lesion (**Figure 1**). Few small pulmonary pleural based soft tissue density nodules were also noted suspicious for metastatic deposits. His blood CA19-9 was 42.07 U/mL (Normal: non-detectable to 39 U/mL). PET-CT showed low FDG avid soft tissue lesion involving uncinate process of pancreas and non-FDG avid predominantly sub pleural subcentimeter bilateral lung nodules.

Post-procedure, the patient was shifted to intensive care unit for post-surgical care. He became hypotensive therefore was kept on dual inotropic support. Patient had raised troponin level of 25 and developed atrial fibrillation. He was managed with intravenous fluids, analgesics, antibiotics, Vitamin K, Amiodarone, and anti-emetics. Chest x-ray revealed left sided pleural effusion which was aspirated under ultrasound guidance. His Jackson Pratt drain was removed on 9th post-operative day. Patient had complaints of bloating and abdominal pain, therefore CT scan abdomen and pelvis with contrast was done, which did not report any anastomotic leak or abdominal collection. His Jackson Pratt drain was then removed on 9th post-operative day. He was eventually mobilized out of bed. Incentive spirometry and chest physiotherapy were done. His diet was progressed gradually which he tolerated well. The patient was in stable condition at the time of discharge. Serum IgG4 levels performed two days prior to discharge were elevated at 2220 mg/L (39.2-864). Patient follow up CT scan abdomen after one year was unremarkable. Serum IgG4 levels were 1470 mg/L.

Case 2

A 52-year-old male patient, known case of hypertension and diabetes presented to our radiology department as outside referral with the indication of "hepatic steatorrhea and left parapelvic cyst" (**Figure 2**).

Case 3

A 35-year-old male with no known co-morbids, presented with the complaints of epigastric pain for 2 days. On examination the abdomen was mildly tender in the epigastric region otherwise soft and without rebound tenderness. The rest of the examination was unremarkable. Early laboratory investigations including complete blood count, lipase, amylase, and liver function tests were within the normal range (Serum amylase was at the upper limit of normal). CT abdomen with contrast showed a mildly enhancing soft tissue density mass involving the head and uncinate process of the pancreas completely encasing the superior mesenteric artery. Mild peripancreatic fat stranding and inflammatory changes extending into the mesentery along with prominent peripancreatic lymph nodes were also noted. Scan was concluded as acute on chronic pancreatitis. The possibility of intraductal papillary mucinous tumor was also raised. His serum CA19-9 (non-detectable to 39 U/mL) and CEA (0-3.0 ng/mL healthy subjects) were 162 and 2.25 respectively. Endoscopic retrograde cholangiopancreatography (ERCP) showed filling defects in the distal common bile duct (CBD) consistent with sludge. CBD was cleared from the sludge with repeat cholangiogram showing no filling defect. Pancreatic duct could not be cannulated. The patient was discharged in a stable condition. CT abdomen performed 4 years later redemonstrated the same findings with interval progression. This time the infiltrating lesion was seen encasing the portal vein and hepatic artery (**Figure 3**). The conclusion of the scan was neoplastic lesion with remote possibility of IgG4 related disease. CT guided transhepatic core biopsy of the pancreatic lesion was performed. Histopathology reported linear cores of fibrocollagenous tissue exhibiting dense mixed

inflammation with small abscesses and no evidence of malignancy (**Figure 4**). Serum IgG-4 level was 2960 mg/L. Patient has not paid a follow up visit after this.

Case 4

A 77-year-old male with known retroperitoneal fibrosis resulting in bilateral ureteric strictures (status post DJ stenting) was admitted for replacement of bilateral DJ stents. PET-CT was performed during the hospital stay to rule out neoplastic disease. PET-CT showed an interval hypermetabolic hypodense lesion in the head of pancreas. Besides that, there was redemonstration of soft tissue retroperitoneal fibrotic mass encasing the lower abdominal aorta with mild FDG avidity without interval change. CT abdomen and pelvis with contrast reported focal hypodense area at the junction of the pancreatic head and neck of corresponding to the hypermetabolic area identified on PET/CT (**Figure 5**). Findings were reported as neoplastic disease. His serum CA19-9 (non-detectable to 39 U/mL) and CEA (0-3.0 ng/mL healthy subjects) were 304 and 4.27 respectively. At follow up visit after one month his serum IgG-4 level was also requested which was measuring 11100 mg/L. Based on the imaging features and IgG-4 levels diagnosis of IgG-4 disease was made. The patient was started on oral steroids. Serum IgG-4 level repeated after two months was measuring 5440 mg/L. Follow up CT did not show any focal lesion in the pancreas.

Discussion

Pancreatic malignancy is the seventh most important cause of cancer morbidities globally. In 2018, 459,000 new patients reported with this disease [11]. In future, it is predicted to outstrip breast cancer in European countries as the third fore-most cause of cancer mortality [12]. Frequent etiological factors include obesity, nicotine exposure and elevated blood glucose levels [13,14]. It is perturbing for the patients diagnosed with pancreatic mass and they are mostly worried about the type of lesion which makes it essential to counsel appropriately and conduct rapid medical examination to conclude the final diagnosis.

Inflammatory pseudotumor is a title devised by Umiker and Iverson in 1954 due to overlapping symptomatic and radiological findings with pancreatic malignancy [15]. It is a benign, unusual entity which tends to involve all locations in the body but most frequently present in orbit and the lung. Inflammatory pseudotumors may be solitary or multitudinous with a blend of neutrophils and lymphocytes along with an uneven extent of fibrosis, myofibroblastic spindles, necrosis, and formation of granulomas [16-18].

ITP is known to be associated with autoimmune diseases, trauma and fibrosarcoma [19-21]. Other conditions such as IgG4 associated sclerosing disease where T-cell and IgG4 positive plasma cells attack multiple tissues. The manifestations include autoimmune pancreatitis, cholecystitis, tubulointerstitial nephritis, IPT, prostatitis, interstitial pneumonia and sclerosing cholangitis along with lymphadenopathy. Few patients have reported IgG4-related IPTs in the absence of autoimmune pancreatitis [22, 23].

IgG4-related disease presents as a tumor like swelling involving the organs it affects. The type 1 form of IgG4-related disease depicts a type of autoimmune pancreatitis. Patients frequently show up with an acutely developing mass, painless obstructive jaundice, and diffuse organomegaly. Such a presentation can be misunderstood for pancreatic cancer [24]. IgG4-related disease has a criteria of a serum IgG4 level $>$ 135 mg/dL with around 40% of IgG+ plasma cells being IgG4+ ($>$10 cells/high-power field of biopsy sample). The following criterion is valuable, yet not adequately sensitive to diagnose type 1 IgG4-related autoimmune pancreatitis [25].

An international agreement was set up by the International Association of Pancreatology regarding the differential diagnosis of the two particular types of autoimmune pancreatitis (types 1 and 2). This can be differentiated on the basis of 5 criteria: (1) imaging changes in the pancreatic parenchyma and duct; (2) serology (for IgG4 and IgG antinuclear antibodies); (3) extrapancreatic involvement; (4) histology; and (5) response to corticosteroid therapy [26]. Radiological evaluation plays a crucial role in closely studying and identifying these lesions. However, the histopathological review is thought to be a much-needed step in landing on a definitive diagnosis [27]. CT scans might show a variable appearance of such inflammatory tumors, from hypoattenuated to isoattenuated depending on the muscle and few calcifications might be there

in the liver, pancreas, or stomach pseudotumors. MRI images can likely differ; after the introduction of the contrast heterogeneous enhancement is seen. However, this still cannot differentiate these lesions from a true pancreatic carcinoma [19].

The definitive diagnosis of these lesions depends on the histopathological outcomes; with some specimens being attained post-surgical resection. This accounts for around 5–10% of the pancreatectomies. Surgical resection of the tumor is believed to be therapeutic despite the chances of possible morbidity and post-surgical complications. Some data indicate corticosteroids, nonsteroidal anti-inflammatory drugs, and thalidomide to have curative role and curtail the tumor burden [27, 21]. Recurrence rate is calculated to be around 18–40% [27]. Such recurrent lesions can be associated with local invasion. Resection of such lesions is indicated since they might possess a malignant transformation potential [21]. Literature suggests few occurrences of spontaneous regression [27,21].

IPTs are a rarity and a frequent incidental finding during routine radiological examination. They can also be encountered while investigating for non-specific clinical features or a detected mass from an unknown source. Definite diagnosis depends on the radiological and histological assessment that can be attained post-surgical resection or biopsy. Surgical resection is the first line of treatment if the diagnosis is not clear or was not previously done and it is curative in most cases. Surgical resection is the first line of treatment in case the diagnosis is unclear or wasn't done in the first place. Surgical resection is curative in most cases.

Conclusion

Pancreatic pseudo tumors, often present as a subsidiary discovery during an evaluation of some inconsistent symptoms or an unusual finding during usual radiological scans. Determining this rare entity is an exigent task and can only be done through biopsy after surgical extraction. Therefore, in case of an ambiguous or missed diagnosis, surgical resection is the recommended treatment of choice which can be restorative in most cases.

Thorough assessment of the medical symptoms and evaluation of radiological findings may condense the differentials and aid in curtailing any redundant invasive procedures. This can further reduce infections, complications and in turn mortality rates. On the contrary, misdiagnosing pancreatic pseudo tumors can be fatal. Although imaging is the substantial source of detecting the tumor, biopsy is the ultimate expedient for the definitive diagnosis.

References

1. Patlas M, Deitel W, Taylor B, Gallinger S, Wilson SR (2007) Focal chronic pancreatitis mimicking pancreatic head carcinoma: are there suggestive features on ultrasound? Can Assoc Radiol J = Journal l'Association canadienne des radiologistes 58(1):15–21

2. Ichikawa T, Federle MP, Ohba S, et al. (2000) Atypical exocrine and endocrine pancreatic tumors (anaplastic, small cell, and giant cell types): CT and pathologic features in 14 patients. Abdom Imaging 25(4):409–419

3. Kalra MK, Maher MM, Mueller PR, Saini S (2003) State-of-the- art imaging of pancreatic neoplasms. Br J Radiol 76(912):857–865

4. Coakley FV, Hanley-Knutson K, Mongan J, et al. (2012) Pancreatic imaging mimics: part 1, imaging mimics of pancreatic adenocarcinoma. AJR Am J Roentgenol 199(2):301–308. doi:10.2214/

AJR.11.7907

5. Proctor RD, Rofe CJ, Bryant TJ, Hacking CN, Stedman B (2013) Autoimmune pancreatitis: an illustrated guide to diagnosis. Clin Radiol 68(4):422–432. doi:10.1016/j.crad.2012.08.016

6. Shah S, Mortele KJ (2007) Uncommon solid pancreatic neoplasms: ultrasound, computed tomography, and magnetic resonance imaging features. Semin Ultrasound CT MR 28(5):357–370

7. Lalwani N, Mannelli L, Ganeshan DM, Shanbhogue AK, Dighe MK, Tiwari HA, et al. Uncommon pancreatic tumors and pseudotumors. Abdom Imaging. 2015 Jan;40(1):167–80.

8. Adsay NV, Basturk O, Klimstra DS, Klöppel G. Pancreatic pseudotumors: non-neoplastic solid lesions of the pancreas that clinically mimic pancreas cancer. Semin Diagn Pathol. 2004 Nov;21(4):260–7.

9. Sun MH, Tsai HM, Yu CY, Chen CY, Lin PW. "Mimics" of pancreatic carcinoma: pseudotumors of the pancreatic head. Zhonghua Fang She Xue Za Zhi. 2005;30:47–53.

10. Baião JM, Martins RM, Correia JG, et al. Inflammatory Pseudotumor of the Pancreas Mimicking a Pancreatic Neoplasm. Case Rep Gastroenterol. 2019;13(2):245-252. Published 2019 Jun 13. doi:10.1159/000501064

11. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.

12. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol. 2016 Sep - Oct;55(9-10):1158–60.

13. Qiu D, Kurosawa M, Lin Y, et al. Overview of the epidemiology of pancreatic cancer focusing on the JACC Study. J Epidemiol 2005;15:S157–67.

14. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007;132:2208–25.

15. Umiker WO, Iverson L. Postinflammatory tumors of the lung; report of four cases simulating xanthoma, fibroma, or plasma cell tumor. J Thorac Surg 1954; 28:55–63. [Medline] [Google Scholar]

16. Hedlund GL, Navoy JF, Galliani CA, Johnson WH. Aggressive manifestations of inflammatory pulmonary pseudotumor in children. Pediatr Radiol 1999; 29:112–116.

17. Safran D, Welch J, Rezuke W. Inflammatory pseudotumors of the spleen. Arch Surg 1991; 126:904–908

18. Scott L, Blair G, Taylor G, Dimmick J, Fraser G. Inflammatory pseudotumors in children. J Pediatr Surg 1988; 23:755–758.

19. Narla LD, Newman B, Spottswood SS, Narla S, Kolli R. Inflammatory pseudotumor. RadioGraphics 2003; 23:719–729.

20. Maves CK, Johnson JF, Bove K, Malott RL. Gastric inflammatory pseudotumor in children. Radiology 1989; 173:381–383

21. Sanders BM, West KW, Gingalewski C, Engum S, Davis M, Grosfe]ld JL. Inflammatory pseudotumor of the alimentary tract: clinical and surgical experience. J Pediatr Surg 2001; 36:169–173.

22. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010; 7:401–409.

23. Notohara K, Arimoto M, Wani Y, Fujisawa M. Autoimmune pancreatitis: pancreatic manifestation of IgG4-related disease. Pathol Case Rev 2010; 15:219–224.

24. Moutsopoulos HM, Fragoulis GF, Stone JH. Pathogenesis and clinical manifestations of IgG4-related disease. UpToDate. 2019. Available from: https://www.uptodate.com/contents/overview-of-igg4-related-disease

25. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012 Feb;22(1):21–30. 26. Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al.; Research Committee of Intractable Diseases

of the Pancreas. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol. 2006 Jul;41(7):626–31.

27. Patnana M, Sevrukov AB, Elsayes KM, Viswanathan C, Lubner M, Menias CO. Inflammatory pseudotumor: the great mimicker. AJR Am J Roentgenol. 2012 Mar;198(3):W217–27.

Hosted file

`Figures File.docx` available at https://authorea.com/users/603482/articles/633792-igg4-related-inflammatory-pancreatic-head-pseudotumor-mirror-pancreatic-carcinoma-a-novel-case-series-with-a-review-of-the-literature