Immunoglobulin G4 related disease and pancreatic malignancy - an association or two independent processes?

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Abstract

Immunoglobulin G4 related disease (IgG4-RD) is a rare multisystem inflammatory disease, in which one of the main gastrointestinal manifestations is autoimmune pancreatitis (AIP) type 1. AIP type 1 is correlated with a clinical presentation of obstructive jaundice, increased serum levels of IgG4 and suggestive pancreatic findings on radiologic imaging. Histo-pathology (HP) and immune-histochemistry (IHC) examinations obtained by biopsy are the gold standard for establishing the diagnosis. Several theories tried to elucidate the correlation between IgG4-RD and pancreatic or other extra-pancreatic malignancies. There are controversial opinions whether AIP type 1 serves as a premalignant state, or whether these two conditions are coexistent. We present a patient who had clinical, laboratory, radiologic and histologic findings that were consistent with a pancreatic space occupying lesion (SOL). As a result, he underwent a Whipple operation, but the IHC findings were compatible with AIP type 1. After 1 year of remission, the patient presented with a new pancreatic SOL that was diagnosed as adenocarcinoma.

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ABSTRACT

Immunoglobulin G4 related disease (IgG4-RD) is a rare multisystem inflammatory disease, in which one of the main gastrointestinal manifestations is autoimmune pancreatitis (AIP) type 1. AIP type 1 is correlated with a clinical presentation of obstructive jaundice, increased serum levels of IgG4 and suggestive pancreatic findings on radiologic imaging. Histo-pathology (HP) and immune-histochemistry (IHC) examinations obtained by biopsy are the gold standard for establishing the diagnosis.

Several theories tried to elucidate the correlation between IgG4-RD and pancreatic or other extra-pancreatic malignancies. There are controversial opinions whether AIP type 1 serves as a premalignant state, or whether these two conditions are coexistent.

We present a patient who had clinical, laboratory, radiologic and histologic findings that were consistent with a pancreatic space occupying lesion (SOL). As a result, he underwent a Whipple operation, but the IHC findings were compatible with AIP type 1. After 1 year of remission, the patient presented with a new pancreatic SOL that was diagnosed as adenocarcinoma.

Key words: autoimmune pancreatitis (AIP) type 1, pancreatic malignancy, Immunoglobulin G4 related disease (IgG4-RD)

CASE REPORT

A 74 years old male had previously presented to a different hospital with a painless jaundice and weight loss of 10kg without additional symptoms. The patient had a medical history of heavy smoking, hypertension, hyperlipidaemia, insulin dependent diabetes mellitus and a simultaneous carcinoma of the bladder and prostate followed by prostatectomy and cystectomy with urinary bladder reconstruction 15 years ago. His family history was notable for a brother who died of an acute leukaemia at the age of 9 years, a brother with lung cancer at the age of 60 and a father with an adenocarcinoma of the prostate at the age of 75. On physical examination, the patient was thin, with apparent jaundice but without lymphadenopathy or organomegaly. In the laboratory blood tests, an increased tumour marker CA 19-9 (757 U/ml, normal reference 0-37 U/ml) was present. A whole body computer tomography (CT) scan revealed a space occupying lesion (SOL) in the head of the pancreas with a regional lymphadenopathy.

The patient underwent a Whipple procedure. Histo-pathology (HP) and immune-histochemistry (IHC) examinations from the SOL biopsy revealed a chronic lympho-plasmocytic infiltrate with a storiform pattern and a fibrotic inflammatory infiltrate prominent with eosinophils and plasma cells with an immune-stain positive for IgG4. No evidence of malignancy was found. A repeated revision of the biopsy that was performed at a different medical center has confirmed these findings. After the operation, serum IgG4 and CA-19-9 levels were within the normal limits. The diagnosis of autoimmune pancreatitis (AIP) type 1was established.

Eight months after the procedure, the patient was referred to our hospital for a routine follow-up. Physical examination was unremarkable. Blood tests showed normal levels of IgG4 and CA-19-9, and liver enzymes

levels were slightly elevated but similar to the levels that were detected before the development of jaundice (Table 1). He underwent a positron emission tomography (PET-FDG) scan that found no signs of disease. One year after the operation, a routine abdominal magnetic resonance imaging (MRI) has displayed a SOL with cystic component of 20 mm in the tail of the pancreas with a contrast enhancement (Figure 1A). The patient underwent an endoscopic ultrasound (EUS) followed by a biopsy utilizing a fine needle aspiration (FNA) from the SOL which was not conclusive. A surgical removal of the tail of the pancreas was recommended, but the patient refused further investigation. Three months later, the patient reported a gradual weight loss of 5kg without additional complaints. A follow-up PET-FDG scan showed a hypermetabolic consolidation in the tail of the pancreas, and an increase of the SOL to 24 mm was seen on additional MRI (Table 1). Since the patient did not consent to additional procedures and the differential diagnosis included recurrence of IgG4-RD or malignancy, empiric treatment with prednisone at a dosage of 0.5 mg/kg/day was started. At this time point, CA-19-9 and IgG4 in serum were still within the normal limits. A month later, he had a MRI which detected an increase in the size of the known SOL to 29 mm and several new consolidations in the liver suspected to be liver metastases, that were confirmed by PET-FDG (Figure 1B, Figure 2). Steroid treatment was discontinued. HP of the biopsy from the liver lesions revealed a chronic inflammation without evidence of malignancy. IgG4 immuno-stain was negative. For the first time, increased CA 19-9 levels were documented (Table 1). An additional EUS of the tail of the pancreas with FNA has revealed poorly differentiated adenocarcinoma. The patient refused further treatment with chemotherapy and immunotherapy and followed a conservative management. Afterwards, he was lost to follow-up.

Discussion

We present a patient with an AIP type 1 that underwent a Whipple procedure due to a high suspicion for PM, had a full recovery, and presented a year later with a true PM. The differential diagnosis included recurrence of AIP type 1 or a pancreatic tumor *de novo*in the remaining part of the pancreas. It should be noted that at this time point, both serum IgG4 levels and tumor marker CA-19-9 levels were normal and the elevation of CA-19-9 has been noted concurrently with the appearance of the liver metastases. Neither MRI nor PET-FDG could differentiate between the two possible diagnoses during the evaluation, and only repeated EUS with FNA revealed adenocarcinoma of the pancreas.

IgG4-RD is a rare systemic fibro-inflammatory disease. The disease affects mainly the pancreas, an entity known as autoimmune pancreatitis (AIP) type 1. Middle-aged males are more prone to IgG4-RD and AIP type 1 (1). One cohort study described a higher prevalence of IgG4-RD in plumbers and construction workers, suggesting that chronic exposure to occupational antigens such as pigments, oils, solvents and industrial dusts may be related to the underlying pathogenesis of the IgG4-RD in these patients (2). Most commonly, the clinical presentation is sub-acute. AIP type 1 presents as a painless jaundice (74% of cases) or as an abdominal pain (37% of cases). In 60-90% of the cases, AIP type 1 is accompanied by damage to other organs or by a malignancy, which may result in organ failure and increased morbidity and mortality. There are reports of combined IgG4-related sclerosing cholangitis (IgG4-SC) disease in 56% of patients with AIP type 1 (3,4). Rarely, an overlap of IgG4-RD and ANCA-associated vasculitis have been seen (5,6).

AIP type 1 and pancreatic malignancy (PM) have similar clinical and radiologic presentations (7,8). Therefore, in order to establish the appropriate treatment approach, it is essential to differentiate between both entities. According to the International Consensus Diagnostic Criteria (ICDC), IgG4-RD is confirmed by the combination of clinical presentation, biochemical laboratory tests, radiologic findings and IHC findings (9). In particular, the diagnosis of AIP type 1 is determined by the following: an appropriate clinical presentation which often includes obstructive jaundice; increased levels of IgG4 in serum (>1.35 g/L); and typical findings in radiologic imaging (CT or MRI), which include diffuse enlargement of the pancreas with multiple strictures, lack of upstream dilatation and late contrast enhancement. The histologic findings from pancreatic biopsy obtained by endoscopic ultrasound (EUS) consist of lympho-plasmacytic infiltrate (often associated with eosinophil infiltrate) (10,11), 10-50% IgG4+ plasma cells per high-power field, an IgG4/Ig4 cell *ratio* of more than 40%, fibrosis arranged in a storiform pattern and obliterative phlebitis. A favorable

response to steroid treatment also supports the diagnosis (12-14).

The association of AIP type 1 and increased risk for PM is controversial, and data on this subject are limited. Nevertheless, several findings have been described regarding the appearance of malignancy in patients with AIP type 1.

Firstly, AIP type 1 has been associated with a high incidence rate of PM, especially within 1 year of AIP type 1 diagnosis (15-17). In addition, several studies showed a higher risk of predominant lung, gastric and prostate malignancies (18), and a general increased incidence rate for all type cancers compared with the general population (3,19). In contrast, different studies which included 95 and 116 patients with AIP type 1 showed no significant increase in the incidence rate of PM (20,21).

Secondly, several studies have described a coexistence between AIP type and PM (22). Thus, elevated serum levels of IgG4 has been reported in 14 patients with established diagnosis of PM, and in 2 of these patients, the levels were twice the upper limit of normal. In these patients, further IHC examination of the surgical pancreatic biopsy revealed IgG4 lympho-plasmacytic infiltrate (22).

Increased serum levels of IgG4 (70%-80% of cases) may possibly aid to distinguish between AIP type 1 and PM, although it is known that high serum levels of IgG4 are sensitive but not specific for IgG4-RD (23). A retrospective study tested different serological markers including IgG4, anti-plasminogen binding peptide (a-PBP) and anti-carbonic anhydrase-II (a-CA-II) in order to find new serological markers which would help to differentiate AIP type 1 from PM. This study concluded that IgG4 was the most useful marker in this regard (24). When differentiating between PM and AIP type 1, CA-19-9 elevation over 150 U/ml is associated with increased risk for PM, whereas levels of CA-19-9 that are less than 85 U/ml, combined with a high IgG4 serum level (over twice the upper limit of normal) support the diagnosis of AIP type 1 (22,25).

In conclusion, we present an interesting case of a patient with AIP type 1 who consequently developed metastatic PM in the remaining part of the pancreas after 1 year of disease remission. Physicians should be aware of the possibility of PM in a patient that was previously diagnosed with AIP type 1.

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Figure 1. I.V. contrast enhanced T1 FS axial MRI at the level of the pancreas, showing a hypointense mass (curser) in the pancreatic tail, 12 months (A) and 18 months (B) after the Whipple procedure, which increased in size.

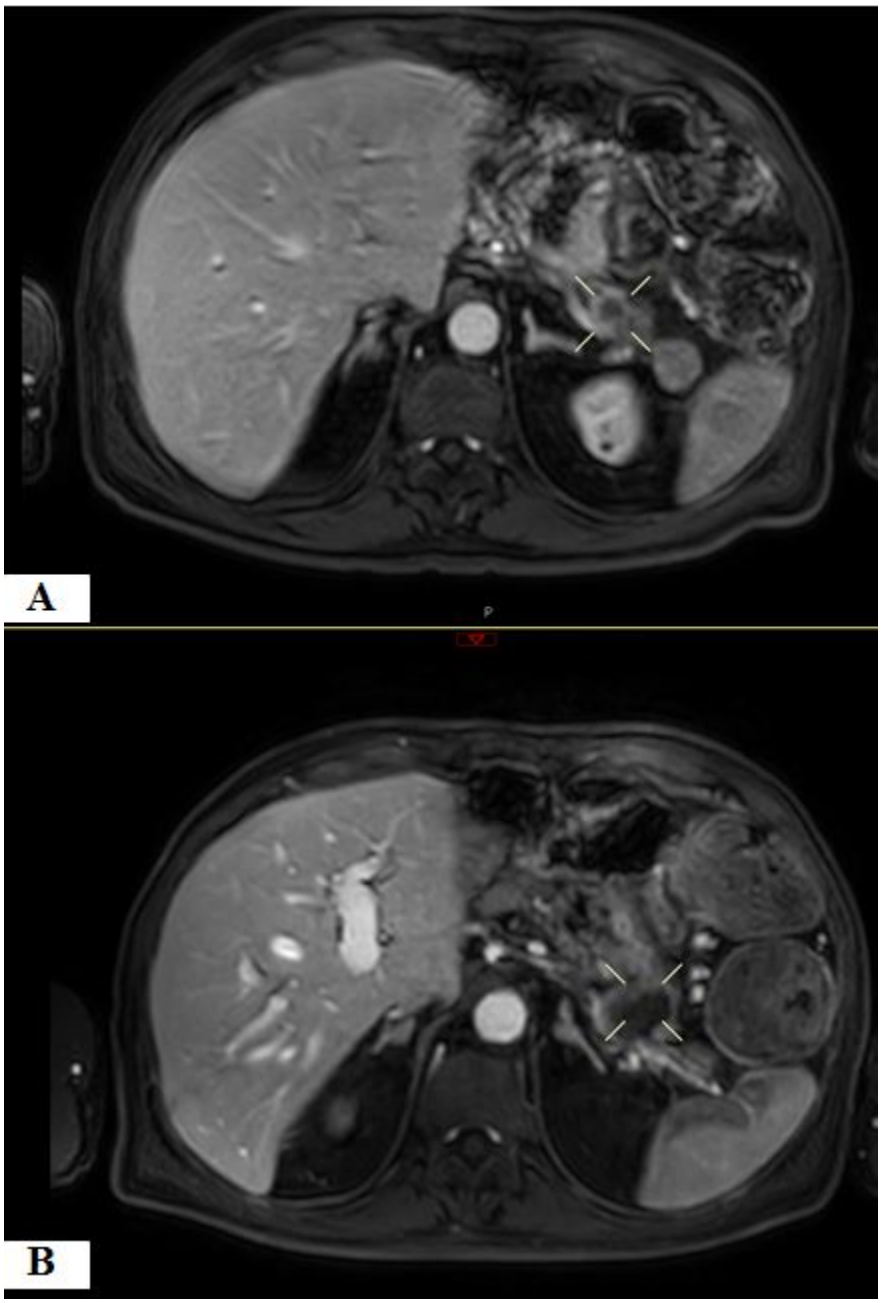
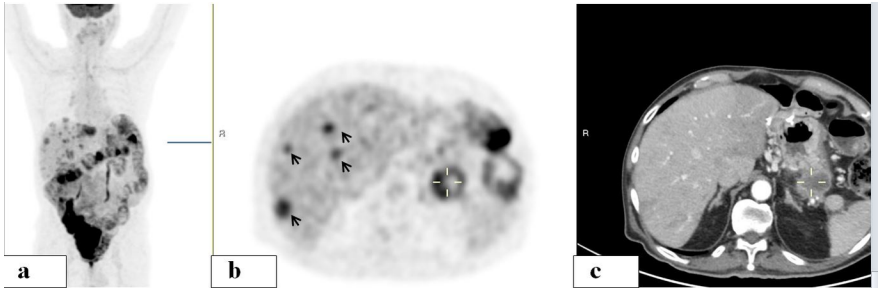
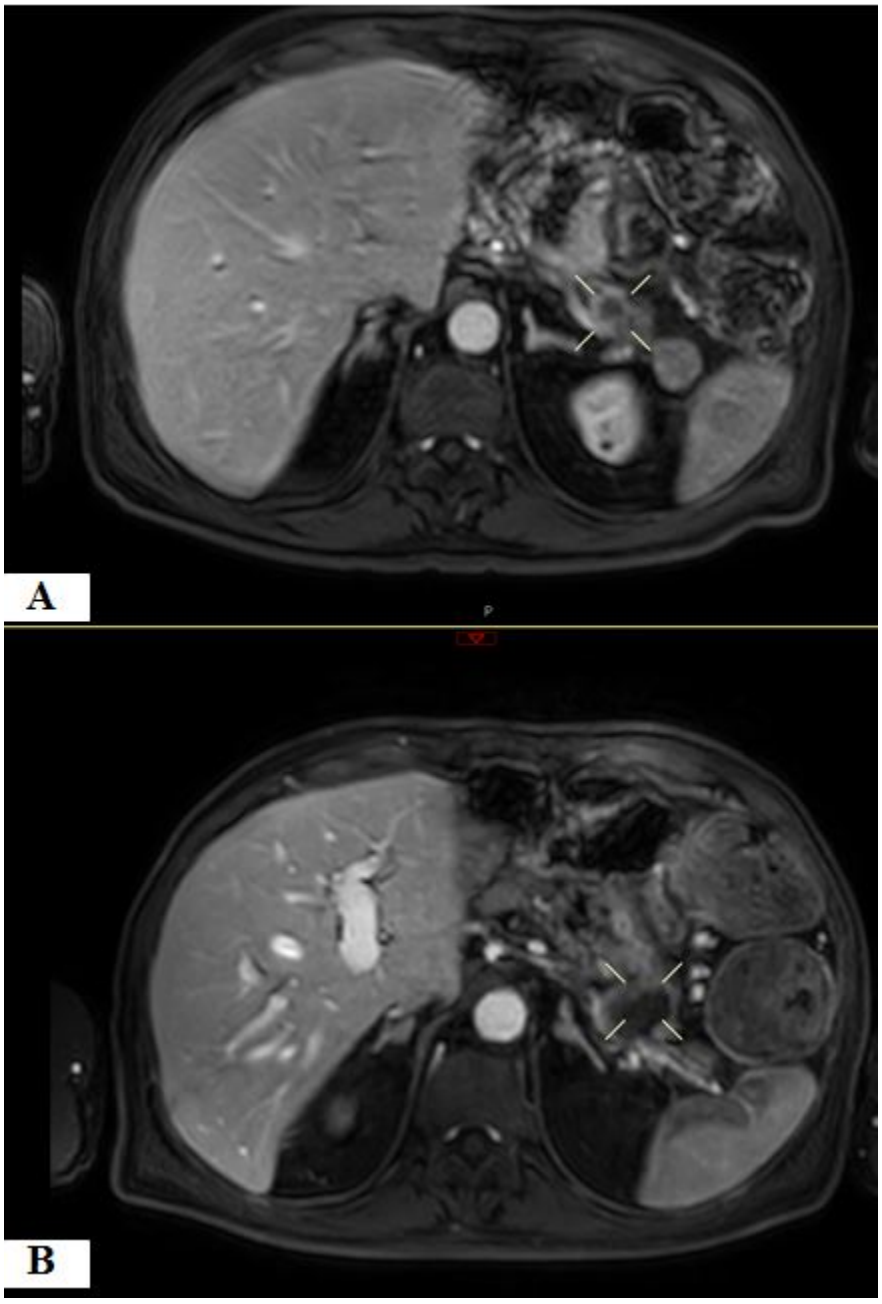
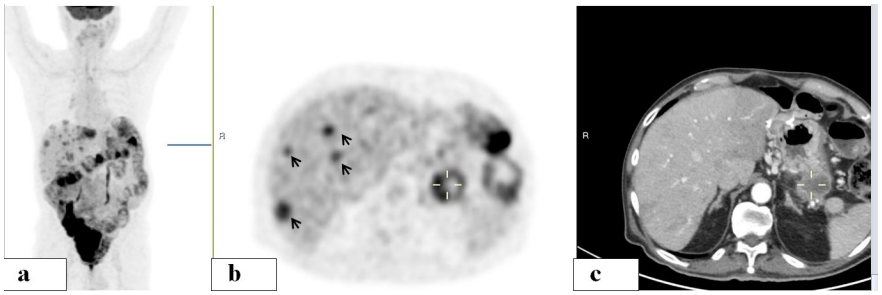


Figure 2. A 74-year old male, 19 months post Whipple procedure. 18 Fludeoxyglucose (FDG)-PET/CT images: Maximum intensity projection (MIP) (a) and representative PET (b) and CT (c) axial slices. The PET-CT scan demonstrated a FDG-avid non-homogeneous soft tissue lesion in the pancreatic tail (white cursor) consistent with a space occupying mass and multiple liver hypermetabolic findings in the liver (black arrows) consistent with metastases.







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