



Occurrence of autoimmune pancreatitis after chronic immune thrombocytopenia in a Caucasian adolescent

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Abstract

Autoimmune pancreatitis is a rare, distinct and increasingly recognized form of chronic inflammatory pancreatic disease secondary to an underlying autoimmune mechanism. We report on a 14-year-old boy who developed autoimmune pancreatitis, while he was under treatment with eltrombopag for chronic immune thrombocytopenia. Therapy with corticosteroids resulted in complete remission of both. This is the first report on the co-occurrence of autoimmune pancreatitis and chronic immune thrombocytopenia in childhood, and clinicians should be aware of this rare association, because early diagnosis and therapy of autoimmune pancreatitis may prevent severe complications.

Keywords Autoimmune pancreatitis · Immune thrombocytopenia · Pancreas · Hematology · Immunology

Introduction

Immune thrombocytopenia (ITP) is an acquired bleeding disorder, caused by autoimmune-mediated destruction of platelets and megakaryocytes [1]. In pediatrics, ITP generally has a good prognosis and is spontaneously resolving in 70–80% of patients. However, in some patients, severe bleedings and a chronic course can occur [1]. In addition, ITP can be complicated by the co-occurrence of other autoimmune diseases, such as autoimmune thyroiditis, celiac disease, systemic lupus erythematosus, autoimmune hepatitis, and other autoimmune cytopenias [2–5].

Within the spectrum of autoimmune diseases, autoimmune pancreatitis (AIP) is increasingly recognized as a distinct entity. AIP is characterized by abdominal pain, obstructive jaundice, pancreatic parenchymal changes caused by lymphoplasmacytic infiltration, and a prompt clinical response to steroid therapy [6, 7]. AIP is extremely rare in children, with only about 50 patients described so far [6, 8]. Of note, ~27% of these have been reported to additionally suffer from other autoimmune diseases [6, 7]. However, the co-occurrence of ITP and AIP in childhood has not been reported before.

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Case report

ITP first manifested in the Caucasian male patient at the age of 11 years. He was admitted due to signs of bleeding and laboratory tests revealed severe isolated thrombocytopenia (platelet count $3 \times 10^9/L$). Pertinent diagnostic data are provided in Table 1. Except for elevated anti-nuclear antibodies (ANA 1:640, normal negative), no abnormalities were found, and a diagnosis of ITP was made. While repetitive treatments with IVIG (0.8 g/kg) and a short course of corticosteroids resulted in transiently increased platelet counts ($> 100 \times 10^9/L$), he failed, however, in achieving a stable remission. During each relapse, platelet count was $< 10 \times 10^9/L$ with the presence of cutaneous and/or

Table 1 Diagnostic work-up and results for chronic immune thrombocytopenia (cITP) and autoimmune pancreatitis (AIP)

Diagnostics	Results (normal values)
Chronic immune thrombocytopenia	
Humoral (auto-)immunity	
<i>Anti-platelet antibodies</i>	Negative
<i>Nuclear antibodies: ANA, DNA, SM, RNP, RO, LA, SCL, JO, HIST, NUC, ACENA</i>	ANA 1:640 (negative), all others negative
<i>Antiphospholipid antibodies: CARG, CARA, B2GPG, B2GPA, B2GPM</i>	Negative
<i>Mannan binding lectin, complement analyses (C3, C4)</i>	Normal
<i>Immunoglobulins: IgG, IgM, IgA, IgG1, IgG2, IgG3, IgG4</i>	Normal
Cellular immunity (flow cytometry)	
<i>T-cells: CD3, CD4/3, CD8/3, CD4/8, HLA-D3, CD25/3, Ta/b, Tg/d, 45RA/45R0, 45R0/45RA, 4/45RA, 4/45R0, 8/45RA, 8/45R0, 45RA/62L/8, 3/127, 3/132, 3/154, DNT</i>	T cells and subtypes: normal
<i>B-cells: CD19, IgD+/CD27+, IgD-/CD27+, CD21</i>	B cells and subtypes: normal
<i>NK-cells: CD56/3</i>	NK-cells: normal
<i>Lymphocyte function testing: CD3, SEA and TT induced proliferation</i>	Normal
Bone marrow failure or myelodysplasia/leukemia	
<i>Cytogenetics, diepoxybutan testing</i>	46, XY[10], normal
<i>FLOW</i>	No leukemic cells detectable
<i>FISH-MDS (monosomy 7, trisomy 8, monosomy 5, deletion 5q, deletion 7q)</i>	No MDS typical chromosomal anomalies detectable
<i>Bone marrow analysis (Giemsa staining)</i>	Normal cellularity except for increased number of megakaryocytes, compatible with ITP
Infection diseases	
<i>Virus nucleic acid testing via PCR in bone marrow/plasma: CMV, PVB19, AdV A/B/C/D/E/F/G, EBV</i>	Negative
<i>Helicobacter pylori (PCR stool)</i>	Negative
<i>HIV serology</i>	Negative
<i>Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc IgG, anti-HBc IgM</i>	All negative except for anti-HAV IgG 4 IU/l (negative) and anti-HBsAg > 1000 IU/l
Other autoimmune diseases	
<i>Thyroid hormones (TSH, fT4)</i>	Normal
<i>Celiac disease serology</i>	Normal
Autoimmune pancreatitis	
<i>Pancreas function testing: serum or stool analyses</i>	Amylase 395 U/L (28–100 U/L), lipase 1262 U/L (7–39 U/L), HbA1c 5,4% (4–6%), OGTT normal, elastase < 50 µg/g stool
<i>Liver function testing: serum analyses</i>	GGT 773 U/L (< 52 U/L), ALT 453 U/L (0–31 U/L), AST 247 U/L (0–34 U/L), ALP 947 U/L (< 390 U/L), TBIL 3.1 mg/dl (0–1 mg/dl), BC 2,76 mg/dl (0–0.25 mg/dl), TP 58,7 g/L (60–80 g/L), PRALB 19 mg/dl (12–42 mg/dl)
Tumor marker: Serum analyses	
<i>Immunology testing: immunoglobulins: IgG, IgM, IgA, IgG1, IgG2, IgG3, IgG4</i>	IgG 548 mg/dl (698–1194 mg/dl), all others normal
<i>Autoantibodies: ANA, DNA, NUC, ENA subsets (RO, LA, SCL-70, SM, RNP, Jo-1, centromer B, c-ANCA, p-ANCA, X-ANCA, smooth muscle, mitochondria, parietal cells, LKM, CARG, CARA, B2GPG, B2GPA, B2GPM, AMA-M2, SP-100, GP210, LC1, SLA</i>	ANA 1:160 (negative), all others negative
<i>Imaging: abdominal ultrasonography</i>	Slightly enlarged liver with normal tissue echogenicity, dilatation of the intra- and extra-hepatobiliary ducts, and a hypoechoic and enlarged pancreatic head
<i>Magnetic resonance cholangiopancreatography</i>	Abrupt termination of the dilated common bile and pancreatic ducts caused by a pancreatic ‘head mass’

Table 1 (continued)

Diagnosics	Results (normal values)
Endoscopic ultrasound (EUS)-guided core biopsy-histopathology: HE and immunological staining	Marked fibrosis, lymphoplasmacytic infiltration, and destruction of pancreatic ducts without an increased number of IgG4-positive plasma cells

ACENA anti-centromere antibodies, AdV adenovirus, ALP alkaline phosphatase, ALT alanin-aminotransferase, AMA-M2: anti-mitochondrial antibodies M2, ANA anti-nuclear antibodies, ANCA anti-neutrophil cytoplasmic antibodies, anti-HAV anti-hepatitis A virus antibodies, anti-HBc anti-hepatitis B core antigen antibodies, AST aspartate transaminase, BC conjugated bilirubin, B2GPA beta-2-glycoprotein-1 IgA antibodies, B2GPG beta-2-glycoprotein-1 IgG antibodies, B2GPM beta-2-glycoprotein-1 IgM antibodies, c-ANCA cytoplasmic ANCA, CARA: anti-cardiolipin IgA antibodies, CARG anti-cardiolipin IgG antibodies, CA19-9 cancer antigen 19–9, CD3 CD3 positive T-lymphocytes, CD4/3 CD4 positive T-cell subsets, CD4/8 CD4/CD8 ratio, CD8/3 CD8 positive T-cell subsets, CD19 B-lymphocytes, CD21 CD21 positive B-cell subsets, CD25/3 activated CD25 positive T-cell subsets, CD56/3 CD56 positive CD3 negative NK-cell subsets, CEA carcinoembryonic antigen, CMV cytomegalovirus, DNT TCR alpha/beta positive CD4 negative CD8 negative T-lymphocytes, DNA native/double-stranded deoxyribonucleic acid antibodies, EBV Epstein–Barr virus, ENA extractable nuclear antigens, FISH-MDS fluorescence in situ hybridization-myelodysplastic syndrome, FLOW flow cytometry, ft4 free thyroxine, GGT gamma-glutamyl transpeptidase, GP210 anti-glycoprotein-210 antibodies, Hba1c hemoglobin A1c, HBsAg hepatitis B surface antigen, HE hematoxylin and eosin, HLA-D3 activated HLA-D positive T-cell subsets, HIST anti-histone antibodies, HIV human immunodeficiency virus, IgD+/CD27+ IgD positive CD27 positive memory B-cell subsets, IgD-/CD27+ IgD negative CD27 positive memory B-cell subsets, JO anti Jo-1 antibodies, LA anti-La antibodies, LC1 anti-liver cytosol antibodies type 1, LKM anti–liver-kidney microsomal antibodies, NUC anti-nucleosome antibodies, NSE neuron specific enolase, OGTT oral glucose tolerance test, p-ANCA perinuclear ANCA, PCR polymerase chain reaction, PRALB prealbumin, PVB19 parvovirus B19, RNP anti-nuclear ribonucleoprotein antibodies, RO anti-Ro-antibodies, SCL anti-Scl-70 antibodies, SEA staphylococcus enterotoxin a, SLA anti-soluble liver antigen antibodies, SM anti-Smith antibodies, SP-100 anti-sp100 antibodies, Ta/b TCR alpha/beta positive T-lymphocytes, TBIL total bilirubin, Tg/d TCR gamma/delta positive T-lymphocytes, TP total protein, TSH thyroid stimulating hormone, TT tetanus toxoid, X-ANCA atypical ANCA, 3/127 IL-7R alpha-chain positive T-lymphocytes, 3/132 common gamma-chain positive T-lymphocytes, 3/154 CD40L positive T-lymphocytes, 4/45RA CD4 positive naive T-cell subsets, 4/45R0 CD4 positive memory T-cell subsets, 8/45RA CD8 positive naive T-cell subsets, 8/45R0 CD8 positive memory T-cell subsets, 45RA/45R0 CD45RA positive naive T-lymphocytes, 45RA/62L/8 CD45RA positive CD62L positive CD8 positive naive T-lymphocytes, 45R0/45RA CD45R0 positive memory T-lymphocytes

mucous bleedings. 17 months after diagnosis, treatment with eltrombopag was started at a dosage of 50 mg/day. An initial increase of the platelet count to $144 \times 10^9/L$ within 3 weeks led to subsequent dose reductions to a final dose of 25 mg/every second day, which resulted in stable platelet counts ranging between $77 \times 10^9/L$ and $128 \times 10^9/L$ (median $99 \times 10^9/L$).

After 25 months on eltrombopag, routine laboratory tests showed elevated transaminases (Table 1). Despite discontinuing eltrombopag treatment, transaminases further increased and he developed icterus and complained of itching and a mild intermittent abdominal pain. Platelet count remained stable after discontinuation of eltrombopag. Further laboratory tests revealed cholestasis and elevated pancreatic enzymes as well as an impaired exocrine pancreas function, whereas endocrine pancreas function remained normal. Pertinent details on further investigations are provided in Table 1. Abdominal ultrasound evaluations revealed dilatation of the intra- and extra-hepatobiliary ducts and a hypoechoic and enlarged pancreatic head. A capsule-like rim surrounding a pancreatic head mass was seen on magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) revealed abrupt termination of the dilated common bile and pancreatic ducts caused by the pancreatic head mass (Fig. 1e, f). These findings were suggestive of AIP and endoscopic ultrasound (EUS)-guided core biopsy of the mass with a 22-gauge needle (EZ Shot 3 Plus, Olympus) revealed

marked fibrosis, granulocytic infiltration of duct walls, and, in some sections, a dense infiltrate of predominantly lymphocytes and plasma cells encasing pancreatic ducts (Fig. 1a–d), findings characteristic for AIP in childhood [6, 7]. An additional immunohistochemical staining with anti-IgG4 antibody showed scant IgG4-positive plasma cells with one “hot spot” region with 5 IgG4-positive cells/high power field (HPF) and apart from that 0–1 IgG4-positive cells/HPF. Given the adolescent age, the normal serum level of IgG4 (46 mg/dl, reference value 4.9–198.6 mg/dl), and the characteristic histologic findings with granulocyte infiltration of duct walls and only scant IgG4-positive cells, a diagnosis of type 2 AIP was established according to the international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis [9]. After thorough immunological investigations including an NGS-based immunology panel screen to rule out a genetically defined immune defect [10], treatment with oral prednisone (1 mg/kg/day) was initiated and tapered slowly over 4 months. Within 1 month, transaminases, pancreatic enzymes, and cholestasis parameters normalized as well as the follow-up MRCP 2 months after diagnosis. Platelet counts remained stable within the normal range since start of AIP therapy. Regular follow-up investigations are performed (currently every 4 months), and complete remission of AIP and cITP was documented 30 months after discontinuation of steroid therapy.

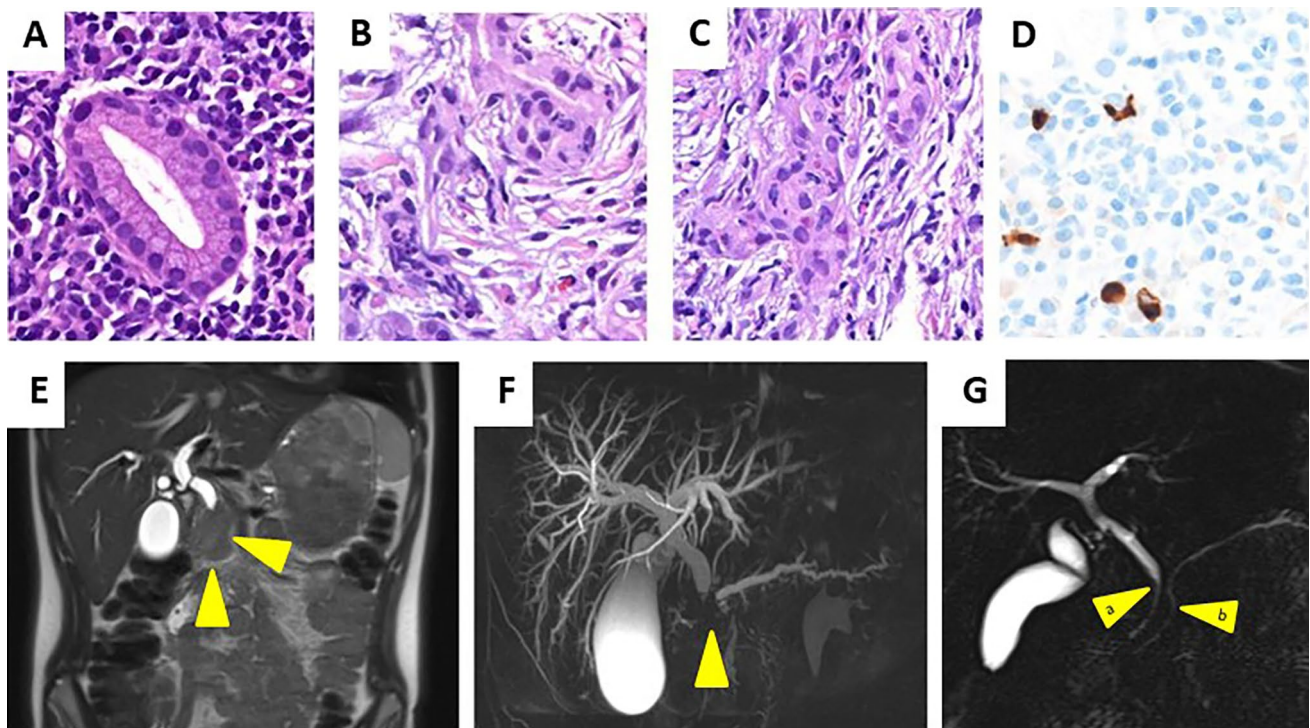


Fig. 1 Histopathologic characteristics and imaging findings of autoimmune pancreatitis in a Caucasian adolescent. Depicted are results from pancreas histopathology (a–d), magnetic resonance imaging (MRI, e), and magnetic resonance cholangiopancreatography (MRCP, f, g). Dense infiltrate of predominantly lymphocytes and plasma cells encases pancreatic ducts (a, hematoxylin and eosin (H&E) staining, $\times 40$). Infiltration of the ducts and duct walls by neutrophilic and eosinophilic granulocytes (b, c, H&E, $\times 40$). Only very occasional

in solitary areas IgG4-positive plasma cells (d, IgG4 immunostaining, $\times 40$). Frontal T2-weighted abdominal MRI showed enlargement of the pancreatic head (arrow) (e). MRCP revealed abrupt termination of the dilated common bile duct (9 mm) and the main pancreatic duct (4.5 mm) caused by a pancreatic head mass (arrow) (f). The common bile duct (arrow a) and the main pancreatic duct (arrow b) regained its normal caliber within 2 months of steroid therapy (g)

Discussion

Herein, we report for the first time the occurrence of AIP after cITP in childhood. Until now, such an association was reported only in 10 Japanese adults (median age of disease onset 68.5 years, range: 61–80 years) [11]. In these Asian adults, AIP and ITP occurred concurrently in two patients; in the other patients, ITP always arose after the onset of AIP [median 4 months (range: 10 days to 4 years)]. AIP was recognized to be IgG4-related in all adults where it was measured. IgG4-related disease is a rare immune-mediated disorder characterized by tissue infiltration by IgG4-positive plasma cells and elevated serum IgG4 [11, 12]. In contrast, our Caucasian patient developed AIP at the age of 14 years and neither had an elevated serum IgG4 level, nor an increased number of IgG4-positive plasma cells in the pancreatic biopsy specimen. This is in line with the previous reports, stating that pediatric AIP (p-AIP) is uncommon as part of IgG4-related disease and that children more commonly follow the disease presentation of type 2 AIP [6–8]. According to the ICDC for autoimmune pancreatitis [9], diagnosis of definitive type 2 AIP in our patient was

based on the characteristic histology of idiopathic duct-centric pancreatitis in combination with imaging findings of focal enlargement of the pancreatic head with delayed enhancement and a prompt response to a therapy with corticosteroids. P-AIP, however, is commonly associated with other autoimmune/inflammatory diseases, including Crohn's disease, ulcerative colitis, glomerulonephritis, and hemolytic anemia; our observation extends the spectrum to cITP [6, 7]. Routine immunological testing (Table 1) including a NGS-based immunology panel screen [10] did not reveal obvious pathologies in our patient's immune system except for elevated ANAs and a transient mild decrease of IgG. In patients with p-AIP tested for ANAs, up to 40% had detectable antibodies [6–8]. Clearly, further investigations and a thorough follow-up for other potential autoimmune manifestations including systemic lupus erythematoses are required in our patient [13].

CITP was successfully treated with eltrombopag, which is an approved cITP medication [14]. Elevations in liver enzymes or bilirubin are known adverse drug effects (ADRs) of eltrombopag [15]. Thus, monitoring of AST, ALT, and bilirubin is mandatory during therapy. In our patient, the

first signs of AIP were elevated transaminases, which further increased after stop of eltrombopag. Therefore, it is unlikely that eltrombopag was the cause of AIP. However, occurrence of pancreatitis has been reported during eltrombopag treatment in at least two adult patients with cITP [16, 17]. The type of pancreatitis was not specified, but careful post-marketing surveillance for the ADR pancreatitis in patients treated with eltrombopag is mandatory.

Complications of p-AIP include failure of exocrine (16% of patients) and endocrine (11% of patients) pancreas function [6, 7]. In our patient, exocrine pancreas insufficiency was fully reversible, and early diagnosis and therapy as reported herein may have contributed to this favorable outcome.

Clinicians should be aware of the co-occurrence of cITP and p-AIP. Abdominal pain and obstructive jaundice are suggestive for p-AIP. Imaging studies and laboratory investigations can help to quickly establish the diagnosis, and therapy with steroids typically induces remission.

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Author contributions HK, WN, and LK designed the study and wrote the manuscript; AV, CZ, and WDH performed gastroenterology diagnostics and therapy and manuscript editing; WK & KL performed radiological diagnostics and manuscript editing; KW and JS performed histopathology and manuscript editing; KB performed immunological panel screen diagnostics and manuscript editing.

Declarations

Conflict of interest Leo Kager received advisory board expenses from Bayer, Novartis and Amgen. Hubert Kogler, Wolfgang Novak, Andreas Vécsei, Christina Zachbauer, Wolf-Dietrich Huber, Wolfgang Krizmanich, Karoly Lakatos, Katharina Woeran, Judith Stift and Kaan Boztug declare that they have no conflict of interest.

Human Rights This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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