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Necrotizing pancreatitis, microangiopathic hemolytic anemia and thrombocytopenia following the second dose of Pfizer/BioNTech COVID-19 mRNA vaccine

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Summary Implementing vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major asset in slowing down the coronavirus disease 2019 (COVID-19) pandemic. For mRNA vaccines, the main severe adverse events reported in pharmacovigilance systems and post-authorization studies were anaphylaxis and myocarditis. Pancreatitis after Pfizer/BioNTech COVID-19 vaccination has been reported only in 10 patients.
We report a 31-year-old female with a history of borderline personality disorder, intravenous drug abuse, allergic asthma, eating disorder, psoriatic arthritis treated with tofacitinib, neurogenic bladder disturbance, cholecystectomy, recurrent thoracic herpes zoster, vaginal candida infections and urinary tract infections, who developed pancreatitis associated with thrombotic microangiopathy and hemolytic-uremic syndrome 10 days after the second vaccination, whereas the first has been well tolerated. She was treated by plasma exchange, and eventually by transgastric drainage with implantation of a plastic stent to remove fluid abdominal retentions. She was discharged after 19 days. Since then her condition has improved continuously. Computed tomography after 12 months did not reveal retentions anymore.
As other causes of pancreatitis have been excluded, this case of acute pancreatitis, microangiopathic hemolytic anemia and thrombocytopenia, temporally associated with the Pfizer-BioNTech COVID-19 vaccine, suggests a causal link.

Keywords Adverse effect · Necrosis · Renal failure · Hemolytic anemia · COVID-19 vaccine · Adverse effect · Renal failure

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Introduction

Different types of vaccines against coronavirus disease 2019 (COVID-19) have been developed: mRNA vaccines, viral vector, inactivated, and protein-based vaccines. For mRNA vaccines, severe adverse events reported in pharmacovigilance systems and postauthorization studies were anaphylaxis and myocarditis [1]. Pancreatitis after Pfizer/BioNTech COVID-19 vaccination has been reported in only 10 patients [2–11]. Thrombotic microangiopathy and hemolytic-uremic syndrome after Pfizer/BioNTech COVID-19 vaccination has been reported in two cases [12, 13]. For all these reports, it is not possible to decide unequivocally whether there is a causal connection or just a random confluence of the events.

The coincidence of pancreatitis with thrombotic microangiopathy and hemolytic-uremic syndrome, has not yet been reported following the Pfizer/BioNTech COVID-19 vaccination. The present case was reported to the Austrian Pharmacovigilance Center, and the patient consented to publication.

Case report

A 31-year-old female negative for human immunodeficiency virus (HIV) was admitted to a municipal hospital because of sudden onset of abdominal pain and nausea starting 2 days after the second Pfizer-BioNTech COVID-19 mRNA vaccination. She had a history of borderline personality disorder, intravenous drug abuse and allergic asthma since childhood, eating disorder with anorexia and binge eating since the age of 12 years. At age of 18 years she started to suffer from psoriatic arthritis with only minimal cutaneous manifestations, and repeated synovectomy on both knees were carried out. Additionally, she suffered from urinary incontinence due to neurogenic bladder disturbance since the age of 22 years, and she received a vesical pacemaker at age of 25 years. At the age of 29 years she underwent cholecystectomy because of cholecystolithiasis. Additionally, she suffered from recurrent thoracic herpes zoster, vaginal candida infections and urinary tract infections. She was on a chronic medication with levomethadone 45 mg/day, tizanidine 4 mg/day, zolpidem 10 mg/day, mirtazapine 40 mg/day and tofacitinib 5 mg/day. The pharmacotherapy had remained unchanged for 9 months and was not interrupted or modified because of the vaccinations. The patient denied any alcohol intake, which her family confirmed. The family history did not disclose any cases of pancreatitis.

Blood tests showed leukocytosis (12.6 G/L, normal range 4.0.–10.0 G/L), elevated alpha-amylase (418 U/L, normal range 28–100 U/L) and lipase (1162 U/L, normal range 13–60 U/L), thus indicating pancreatitis. Abdominal ultrasound revealed slight splenomegaly and a nondilated common bile duct. Because of psychiatric problems, she left the hospital after 2 days

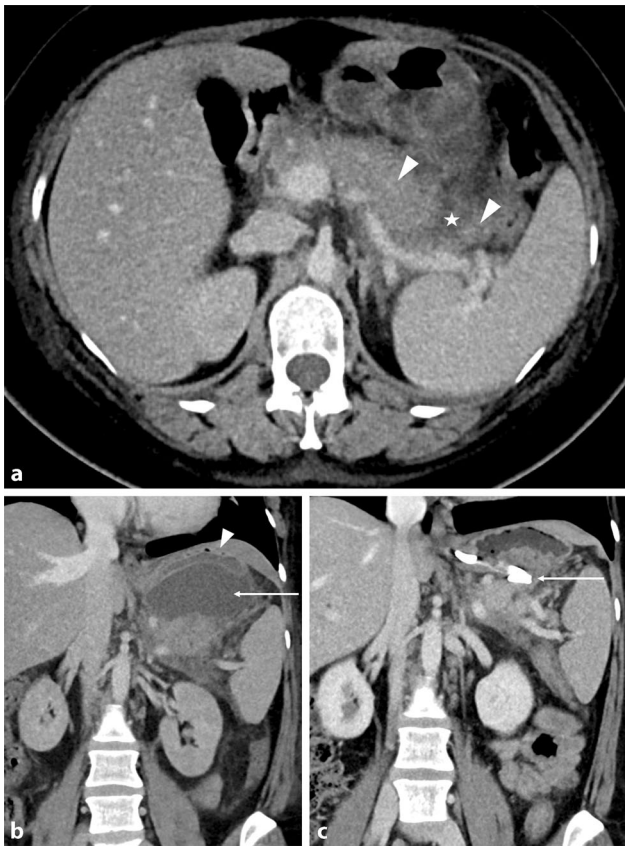

Fig. 1 Axial contrast-enhanced abdominal computed tomography (CT) on the day of admission (**a**) shows a necrotizing pancreatitis with enlarged edematous pancreas (*arrowheads*) and nonenhancing areas in the cauda pancreatis, indicating parenchymal necrosis (*asterisk*). Coronal contrast-enhanced CT image after 10 days shows a large acute necrotic collection (*arrow*) in the lesser sac (*arrowhead*: stomach) (**b**). Postprocedural coronal contrast-enhanced CT image shows successful decompression (*arrow*) of the collection after transgastric drainage (**c**)

against medical advice but 4 days later she was readmitted to another hospital due to vomiting, severe abdominal pain and deterioration of her general condition. On clinical examination the entire abdomen was tender. A periumbilical hematoma and multiple bruises on the lower limbs were noted. Based on laboratory results (alpha-amylase 268 U/L, lipase 393 U/L, thrombocytopenia 34 G/L, normal range 150–370 G/L, elevated C-reactive protein, CRP 26.15 mg/dl, normal range < 0.5 mg/dl) and computed tomography (CT) of the abdomen, necrotizing pancreatitis with fluid retention was diagnosed (Fig. 1). The CT showed neither dilatation of the biliary duct nor choledocholithiasis.

The immunosuppressive therapy with tofacitinib for psoriatic arthritis was terminated and an empirical antibiotic treatment with cefotaxime was initiated. In view of the severe anemia (erythrocytes 2.5 T/L, normal range 3.8–5.2 T/L) she received 4 units of packed red blood cells. Laboratory tests revealed 30‰ red blood cell schistocytes, elevated serum creatinine (1.37 mg/dl, normal range 0.5–0.9 mg/dl)

and lactate dehydrogenase (599 IU/L, normal range <250 IU/L), thus suggesting thrombotic microangiopathy. Blood was obtained for measurement of CH50 antibodies, Coombs test, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS-13) activity, C3/C4, quantitative immunoglobulins, bacterial and fungal PCR, haptoglobin and hemopexin. Then, plasma exchange with 4000 ml fresh frozen plasma was started and repeated on the following day. As ADAMTS-13 activity was 70% (normal range 40–130%) and no signs of bacterial or viral infection were detected, thrombotic thrombocytopenic purpura (TTP) was excluded, and an atypical hemolytic-uremic syndrome was diagnosed. Microangiopathic hemolytic anemia was considered as a differential diagnosis. The CH50 level was 53.8 U/mL (normal range 31.6–57.6 U/mL), C3/C4 94.6/23.5 mg/dL (normal range 60–180 mg/dL/10–40 mg/dL), IgG 792.0 mg/dL (normal range 700–1600 mg/dL), IgA 98.7 mg/dl (normal range 70–400 mg/dL), IgM 81.6 mg/dL (normal range 40–230 mg/dL), haptoglobin 151.0 mg/dL (normal range 30–200 mg/dL) and hemopexin 36.1 mg/dL (normal range 50–115 mg/dL). Bacterial and fungal PCR, as well as Coombs test, were negative. As folic acid levels were 1.7 nmol/L (normal range 9.53–44.9 nmol/L), folic acid was substituted intravenously.

Over the next days, the patient's condition improved steadily. As the CT scan of the abdomen performed after 10 days still showed fluid retentions between the greater gastric curvature and the spleen, a transgastric drainage with implantation of a plastic stent was carried out (Fig. 1). The patient was discharged after 19 days. Since then, her condition has improved continuously. A CT scan 12 months after onset did not reveal retentions anymore; however, after cessation of tofacitinib, an aggravation of psoriatic arthritis was noted. Restarting treatment with a conventional and subsequently, if needed, escalation with a biological disease-modifying antirheumatic drug is considered.

Discussion

Pancreatitis may have various causes. Gallstones and alcohol abuse, the most frequent causes of acute pancreatitis, have been excluded in the presented patient based on history, clinical and radiological findings [14]. Further causes for pancreatitis, such as a history of endoscopic retrograde cholangiopancreatography, hypercalcemia, hypertriglyceridemia, infections, genetics, autoimmune diseases, and trauma were not present in the patient. In addition, many drugs are reported to induce pancreatic damage [15]; however, pancreatitis associated with intake of tizanidine. zolpidem and mirtazapine occurred either shortly after initiation of the drugs [16] or with concomitant precipitating disorders, such as alcohol abuse or hypertriglyceridemia [17, 18]. In the presented patient, drug-induced pancreatitis is rather unlikely as the chronic medication was unchanged during the 6 months prior to admission and neither hypertriglyceridemia nor alcohol abuse was present. Most probably, pancreatitis and subsequent thrombotic microangiopathy were related to the COVID-19 vaccine, and possibly, the comedication and comorbidities may have made her more susceptible or may have aggravated the disease [19].

Acute pancreatitis attributed to COVID-19 infection has been described [20]. As SARS-CoV-2 (the causative agent of COVID-19) receptors are expressed in the pancreas and endothelial damage can occur, this association is plausible; however, this hypothesis has many biases and needs further investigation [21].

Vaccine-induced pancreatitis has been described as an uncommon adverse reaction after viral vaccines, such as measles, mumps, rubella, hepatitis A, hepatitis B, and human papillomavirus [3]. The mechanism responsible for vaccine-induced pancreatitis remains unclear. Still, molecular mimicry is the most probable hypothesis proposed, in which structural similarities between the virus and self-antigens can result in an autoimmune reaction against pancreatic acinar cells. Other hypotheses discussed include polyclonal activation of lymphocytes, bystander activation of self-reactive lymphocytes, somatic mutations of immunoglobulin variable genes, vaccine-induced vasculitis, and vaccine-triggered release of histamine and leukotrienes [3].

Worldwide, several mRNA vaccines, viral vector vaccines, inactivated vaccines and protein-based vaccines are used against COVID-19 [1]; however, pancreatitis after COVID-19 vaccination has only been reported in the literature in relation to Pfizer/BioNTech vaccine. We do not have an explanation for this finding.

Pancreatitis after COVID-19 vaccination has been reported from 6 female and 4 male patients with an age range from 14 to 96 years [2–11]. In 6 reported cases, pancreatitis occurred after the first vaccination [2, 4, 6–9], in 3 patients after the second vaccination [3, 5, 11] and in 1 patient after the third vaccination [10]. The interval between vaccination and onset of symptoms ranged from few hours [10] to 2 months [11]. Three patients were without comorbidities [2, 6, 11], and one was pregnant in the 31st gestational week [9]. The remaining patients suffered from obesity [3], hypertension and stroke [4], asthma with a history of alcohol-precipitated pancreatitis 10 years previously [5], heart failure and hypothyroidism [7], allergic rhinitis [8] coronary artery disease, prostate cancer, hypothyroidism and gastroesophageal reflux disease [10]. Of the 10 patients 9 had a relatively benign clinical course and were treated with intravenous fluids and symptomatic therapy [3, 4, 6–11]. Necrotizing pancreatitis necessitating drainage or surgery, was only reported from one patient after the second

vaccination, whereas the first vaccination was well tolerated as in our patient [5]. This is in accordance with findings from a cohort study which found that adverse events, except local pain, were more common after the second Pfizer/BioNTech vaccine dose compared with the first vaccine dose [22].

From 2 of the reported 10 cases, an association of pancreatitis with further immunological reactions was reported [2, 11]. A previously healthy female started to suffer from abdominal symptoms simultaneously with vasculitic rashes on the extremities 7 days after the first Pfizer/BioNTech vaccine dose [2]. Laboratory tests revealed leukopenia, hemolytic anemia, thrombocytopenia, positive immunological tests including ANA and anti-dsDNA [2]. Systemic lupus erythematosus was diagnosed, and she was treated with glucocorticoids, azathioprine and hydroxychloroquine. According to the authors' hypothesis, the pathogenesis suggests an autoimmune response rather than a pre-existing systemic lupus erythematosus flare-up [2]. A further previously healthy male patient started to suffer from fever, erythematous rash and abdominal pain 2 months after the second Pfizer/BioNTech vaccine dose [11]. A diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, a delayed T cell-mediated reaction including drug allergy and viral reactivation, was established and he was treated with glucocorticoids and ceftriaxone [11]. Pathogenetic hypotheses, provided by the authors, comprised a contribution of the m-RNA viral antigens in the vaccine to the disease's induction, or a reaction to the adjuvants in the Pfizer-BioNTech vaccine, such as lipid nanoparticles of polyethylene glycol, which can activate drug-specific T cells [11].

Thrombotic microangiopathy, which occurred in our patient, is an event-triggered disorder due to the overactivation of the alternative complement pathway. Thrombotic microangiopathy has been reported after Pfizer/BioNTech [12, 13], ChAdOx1 nCoV-19 [23], and mRNA-1273 COVID-19 vaccination [24]. Thrombotic microangiopathy preceded by acute pancreatitis has been rarely described, but not after vaccinations [25]. Although the exact relationship between these two conditions is unclear, it is thought that cytokines, such as interleukin-1 and tumor necrosis factor-alpha are released during acute pancreatitis, which cause vascular endothelial damage [25]. Of interest, thrombotic microangiopathy preceded by acute pancreatitis has been reported in a kidney transplant recipient with COVID-19 infection [26].

At present, it is unclear whether the comedication has contributed to pancreatitis, microangiopathic hemolytic anemia and thrombocytopenia. Adverse events of COVID-19 vaccine associated with simultaneous intake of levomethadone, tizanidine, zolpidem or mirtazapine have not been reported. Additionally, because of psoriatic arthritis the patient received the Janus kinase (JAK) inhibitor tofacitinib, which was not interrupted during both COVID-19 vaccinations. Only later, in August 2021, was the recommendation published to withhold JAK inhibitors for 1 week after each vaccine dose, based on concerns related to the effects of this medication class on interferon signalling that may result in diminished vaccine response [27].

This case of acute pancreatitis, microangiopathic hemolytic anemia and thrombocytopenia was temporally associated with the Pfizer-BioNTech COVID-19 vaccine suggesting a causal link.

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Conflict of interest C. Stöllberger, K. Kastrati, C. Dejaco, M. Scharitzer, J. Finsterer, P. Bugingo, M. Melichart-Kotik and A. Wilfing declare that they have no competing interests.

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