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Adalimumab-Induced Acute Pancreatitis in a Patient with Ulcerative Colitis: An Unusual Case

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Abstract

Background: Drug-induced acute pancreatitis is a rare but well-recognized entity, accounting for less than 5% of all cases of acute pancreatitis. Numerous medications have been implicated, with varying levels of evidence. Tumor necrosis factor-alpha (TNF-*α*) inhibitors, widely used in inflammatory bowel disease, are only exceptionally reported as a cause of acute pancreatitis, mainly through isolated case reports in the literature. **Case Presentation:** We report the case of a 28-year-old woman with extensive ulcerative colitis (pancolitis), initially treated with azathioprine for five years with insufficient efficacy. Therapy with adalimumab was initiated according to the standard induction regimen. Ten weeks after treatment initiation, the patient developed epigastric pain associated with a serum lipase level exceeding six times the upper limit of normal, leading to the diagnosis of acute pancreatitis without severity criteria. Abdominal imaging confirmed mild edematous acute pancreatitis (Balthazar stage C). Etiological workup did not identify any alternative cause, including biliary, alcoholic, metabolic, or autoimmune origins. Discontinuation of adalimumab, combined with supportive management, resulted in a favorable outcome. Pharmacological assessment using the French method of causality evaluation concluded that the pancreatitis was probably drug-induced and attributable to adalimumab (imputability score I3B4). Treatment was subsequently switched to ustekinumab. **Conclusion:** Acute pancreatitis is a rare but possible complication of adalimumab therapy. This diagnosis should be considered in any patient receiving TNF-*α* inhibitors who presents with acute pancreatitis after exclusion of more common etiologies. Early recognition of this cause allows for appropriate management and the initiation of an alternative therapeutic strategy to prevent recurrence.

Keywords

Adalimumab, TNF-α Inhibitors, Drug-Induced Acute Pancreatitis, Ulcerative Colitis, Pharmacovigilance

1. Introduction

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas that may extend to peripancreatic tissues, both locally and at distant sites. In the United States, the annual incidence of AP is approximately 17 cases per 100,000 population. According to previous studies [1], acute pancreatitis accounts for around 100,000 hospitalizations per year. On average, approximately 2000 patients die annually due to complications related to AP.

Although gallstones and alcohol are responsible for more than 90% of cases in adults, drugs are recognized as a potential cause of AP [2]. Drug-induced pancreatitis is a rare entity but is increasingly reported, with an incidence that appears to be rising. Since the first case reported with chlorthalidone and cortisone in the 1950s [3], hundreds of commonly prescribed medications from various therapeutic classes have been implicated in pancreatic injury.

More than 500 agents are currently listed as potentially causative; however, only azathioprine and didanosine have strong supporting evidence, making the true burden of drug-induced acute pancreatitis uncertain [4]. TNF-α inhibitors, widely used in chronic inflammatory diseases, are only rarely associated with acute pancreatitis, based on a limited number of isolated case reports in the literature.

We report the case of a patient treated with adalimumab for extensive ulcerative colitis (pancolitis) who developed acute pancreatitis.

2. Case Presentation

A 28-year-old woman with a history of extensive ulcerative colitis (pancolitis) had initially been treated with azathioprine at a dose of 2 mg/kg/day for five years. The clinical course was marked by persistent gastrointestinal symptoms, with recurrent flares and rectal syndrome. Measurement of azathioprine metabolites revealed subtherapeutic levels (6-MMP and 6-TGN < 50).

Azathioprine was discontinued before initiation of adalimumab because of persistent disease activity and lack of therapeutic efficacy. Therefore, no overlap occurred between the two therapies.

Following multidisciplinary discussion, treatment with adalimumab was initiated according to the standard induction regimen: 160 mg, followed by 80 mg, then 40 mg every two weeks.

Ten weeks later, the patient presented with epigastric pain associated with an elevated serum lipase level of 424 IU/L, exceeding six times the upper limit of normal, leading to the diagnosis of acute pancreatitis without severity criteria. An abdominal computed tomography scan (**Figure 1**), performed between day 3 and

day 5, confirmed mild edematous acute pancreatitis, classified as Balthazar stage C, with a CT severity index (CTSI) of 2.

Table 1. Laboratory findings.

Setting	Value	Normal range	Units
Lipase	424	<70	U/L
Calcium	2.36	2.2 - 2.6	mmol/L
Triglycérides	0.8	<1.7	Mmol/L
IgG4	0.8	0.04 - 0.87	g/L
Liver enzymes (ASAT/ALAT)	19/21	0 - 35	U/L

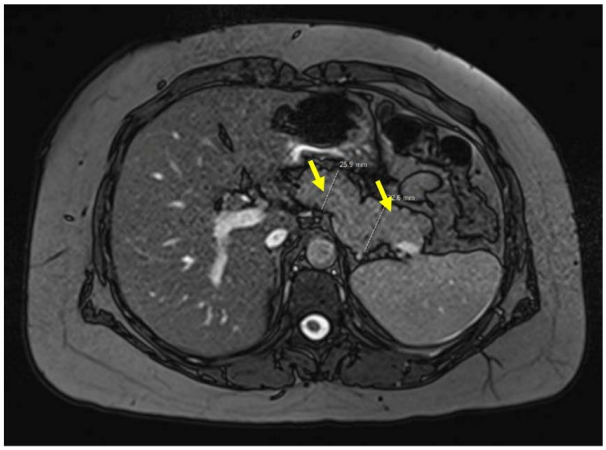

Figure 1. Axial computed tomography (CT) images showing edematous pancreatitis.

Axial abdominal CT scan demonstrating interstitial edematous pancreatitis. The pancreas appears enlarged and hypoattenuating with ill-defined margins, associated with peripancreatic fat stranding and peripancreatic fluid collections. These imaging findings are consistent with Balthazar grade C acute pancreatitis.

The etiological assessment did not identify any predisposing factors. The patient reported no alcohol or tobacco use. Hepatobiliary ultrasound performed 24 hours after diagnosis, as well as magnetic resonance cholangiopancreatography (MRCP) conducted one week later, revealed no evidence of biliary lithiasis (**Figure 2**) nor any findings suggestive of autoimmune pancreatitis (**Figure 1**). Liver function tests (transaminases, alkaline phosphatase, gamma-glutamyl transferase, and bilirubin) were within normal ranges. The triglyceride levels, and serum IgG4 (0.8 g/L; normal range: 0.04 - 0.87 g/L) were also within normal limits.

Total serum calcium was mildly decreased (2.0 mmol/L); however, corrected serum calcium was within the normal range after adjustment for albumin and therefore hypercalcemia was excluded (**Table 1**).

The patient had no family history of pancreatitis or pancreatic disorders, no recent viral infection, no history of abdominal trauma, no recent endoscopic pro-

cedure (including ERCP), and was not pregnant.

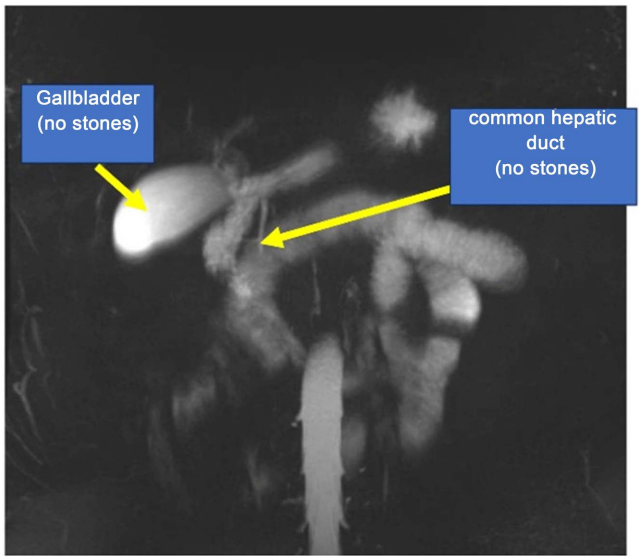

Figure 2. Magnetic resonance imaging (MRI) showing the absence of biliary lithiasis.

Management consisted of temporary bowel rest, appropriate fluid resuscitation, analgesic therapy, and discontinuation of adalimumab.

The causal role of adalimumab was considered based on the temporal relationship and the absence of any alternative diagnosis.

At the time of pancreatitis, the patient was not receiving azathioprine, mesalamine, systemic corticosteroids, oral contraceptives, herbal medications, or nutritional supplements. No other concomitant medication known to induce pancreatitis was identified.

Pharmacovigilance assessment concluded that this was a probable case of drug-induced acute pancreatitis attributable to adalimumab (imputability score I3B4 = likely) (**Table 2**). This led to the permanent discontinuation of TNF-α inhibitors and a therapeutic switch to ustekinumab.

Table 2. Intrinsic imputability score.

	Chronology score C0-C3	Semiological score S1-S3	Intrinsic score I0-I6
ADALIMUMAB	Compatible time frame Suggestive evolution: R0 = C2	Semiology not suggestive of a pharmacological role Etiological assessment: L0 = S2	C2S2 = I3

The clinical course was favorable, marked by resolution of pain, improvement in overall condition, and no recurrence of pancreatitis after six weeks of follow-up.

Chronologically, the patient had been treated with azathioprine for five years, which was discontinued because of persistent disease activity and inadequate ther-

apeutic response. Adalimumab was then initiated according to the standard induction regimen (160 mg at week 0, 80 mg at week 2, followed by 40 mg every two weeks). Ten weeks after treatment initiation, she developed acute epigastric pain associated with a serum lipase level of 424 U/L, leading to the diagnosis of mild acute pancreatitis. Contrast-enhanced abdominal CT confirmed Balthazar stage C edematous pancreatitis, while subsequent MRCP excluded biliary or pancreatic duct abnormalities. Adalimumab was immediately discontinued, supportive treatment was initiated, and the patient experienced complete clinical recovery without recurrence during the six-week follow-up. Treatment was subsequently switched to ustekinumab.

3. Discussion

Acute pancreatitis (AP) is one of the most common causes of hospitalization for acute gastrointestinal disease worldwide. Globally, its annual incidence is estimated to range between 13 and 45 cases per 100,000 population, with an overall increasing trend over recent decades [5] [6].

According to the international consensus (revised Atlanta classification) [7], the diagnosis of AP is established when at least two of the following three criteria are present: characteristic abdominal pain, serum lipase or amylase levels at least three times the upper limit of normal, and imaging findings consistent with AP on cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]). These diagnostic criteria are endorsed by all national and international societies [1] [7].

Identifying the etiology of AP is essential for appropriate and timely management, efficient use of healthcare resources, and prevention of recurrence. A thorough clinical history may provide valuable clues, including prior episodes of AP, known gallstone disease or biliary colic, alcohol consumption, smoking, metabolic syndrome, hypertriglyceridemia, recent drug exposure, family history of pancreatic disease, recent abdominal trauma, or recent procedures such as endoscopic retrograde cholangiopancreatography (ERCP).

Drug-induced acute pancreatitis (DIAP) is a rare but well-recognized cause of AP, accounting for less than 5% of cases in the general population. However, this incidence is likely underestimated due to diagnostic challenges and the frequent coexistence of other risk factors [8].

A large number of drugs have been implicated, with varying levels of evidence. Among them, didanosine, asparaginase, azathioprine, valproic acid, 6-mercaptopurine, and mesalamine appear to have the strongest association with the risk of AP [9].

In most cases, the pathogenesis of pancreatic toxicity remains unclear. Two main mechanisms have been proposed. The first involves a direct toxic effect of the drug or one of its metabolites, either through intrinsic toxicity or an immunoallergic reaction. The second involves indirect mechanisms related to drug-induced adverse effects, such as hypertriglyceridemia, hypercalcemia (thiazides), lo-

calized angioedema (ACE inhibitors), sphincter of Oddi spasm (opioids), ischemia (diuretics, azathioprine), intravascular thrombosis (estrogens), or increased viscosity of pancreatic secretions (diuretics, corticosteroids) [10].

Establishing drug causality in DIAP is a key but often challenging step in the diagnostic process. In the absence of a specific biomarker, it relies on a systematic assessment combining clinical, chronological, biological, and bibliographic criteria. The French drug imputability method (Bégaud method), widely used in pharmacovigilance, allows evaluation of the causal relationship between a drug and an adverse event [11]. This method distinguishes intrinsic imputability (based on chronological and clinical criteria) from extrinsic imputability (based on literature data).

In our case, the 1985 French imputability method [11] was applied. The evaluation showed a suggestive chronological score (C2) associated with a suggestive clinical score (S2). The overall intrinsic imputability score was estimated at I3, considered "likely."

TNF-α inhibitors have only exceptionally been reported as triggers of acute pancreatitis. In our case, common causes such as alcohol use, smoking, biliary disease, autoimmune disorders, and metabolic factors were excluded. The resolution of AP following discontinuation of adalimumab, the absence of recurrence after its permanent withdrawal, and an imputability score of I3B4 provide strong evidence supporting adalimumab as the causative agent.

Our case is consistent with a report published in *American College of Gastroenterology Case Reports*, describing acute pancreatitis occurring after two doses of adalimumab (40 mg), with exclusion of biliary, alcoholic, and metabolic causes, and resolution after treatment discontinuation [12].

El Ouardi *et al.* also reported a case of adalimumab-induced acute pancreatitis, with recurrence upon drug reintroduction (**Table 3**), further strengthening the causal association [13].

This report has several limitations. First, causality assessment remains probabilistic because adalimumab was not reintroduced for ethical reasons. Second, the observation concerns a single patient and therefore cannot establish a definitive causal relationship. Finally, the follow-up period was relatively short, although no recurrence of pancreatitis occurred after drug withdrawal and treatment switch.

Table 3. Reported cases of adalimumab-induced acute pancreatitis.

Author	Disease	Delay	Severity	Rechallenge	Outcome
Badalov [12]	Crohn	2 weeks	Mild	No	Recovery
El Ouardi [13]	Crohn	Few weeks	Mild	Yes	Recurrence
Our case	Ulcerative colitis	10 weeks	Mild	No	Recovery

4. Conclusion

This case strongly suggests a diagnosis of adalimumab-induced drug-related acute pancreatitis (imputability score: I3B4 = likely). Reintroduction of the drug is

strictly contraindicated due to the risk of recurrence, which may be more severe than the initial episode. Therefore, alternative therapeutic options should be considered.

Author Contributions

All authors contributed substantially to the conception, drafting, revision, and final approval of the manuscript. All authors reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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