

CASE REPORT



Etanercept – A culprit agent in acute pancreatitis?

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ABSTRACT

Drugs are responsible for 3%–5% of acute pancreatitis cases. There are a lot of medications that are known to cause acute pancreatitis, however only one case has been reported so far on Etanercept.

This is a case about 62-year old female with history of Rheumatoid arthritis (RA) was started on Etanercept to control her severe RA symptoms. Three weeks later, she presented with abdominal pain, nausea, vomiting and found to have acute pancreatitis based on clinical symptoms and elevated pancreatic enzymes. A thorough workup for the cause of pancreatitis was done and all were unrevealing. There was no history of alcohol use, abdominal trauma or any gastroenterology procedures. Ultrasound and CT abdomen ruled out hepatobiliary abnormalities. Lipid profile and electrolytes including calcium were also found to be normal. As all the workup was unremarkable, it was thought that drug-induced acute pancreatitis was likely the case. Etanercept was the only medication that was started recently, which made it the likely culprit and therefore it was stopped. Patient continued to improve and was discharged after medical stabilization. Her rheumatologist started her on Abatacept and she has remained symptom-free since then.

Our case is interesting as it is the second case of etanercept induced acute pancreatitis. Furthermore, recent animal trials have demonstrated that etanercept potentially has a protective and/or therapeutic role in acute pancreatitis. However, no human studies regarding this topic have been performed. Due to limited data, a clear explanation behind these paradoxical actions of etanercept is still lacking.

ARTICLE HISTORY

Received 20 December 2018

Accepted 7 March 2019

KEYWORDS

Pancreatitis; drug-induced; etanercept; TNF-alpha inhibitors

1. Introduction

Acute pancreatitis is a rapid-onset inflammatory process of the pancreas with devastating consequences. Drugs are responsible for 3%–5% of acute pancreatitis cases. There are a lot of medications that are known to cause acute pancreatitis; however only few cases have been reported on TNF-alpha inhibitor induced acute pancreatitis. It is important to further analyze this association between TNF-alpha inhibitors and acute pancreatitis due to wide-spread use of these agents for treatment of various rheumatological conditions.

We report a case where etanercept was suspected to cause acute pancreatitis. The challenges regarding diagnosis and management of this clinical condition are also discussed in context of the recent medical evidence.

2. Case description

A 62-year old female with a history of asthma, hypertension and hypothyroidism was started on etanercept for control of severe rheumatoid arthritis by her rheumatologist. Three weeks later, she presented to the emergency department with complaints of sudden-onset nausea, vomiting and abdominal pain. Her examination showed tachycardia, signs of dehydration and epigastric tenderness. Initial blood workup which included complete

blood count, metabolic profile, liver profile and urinalysis was normal. Electrocardiogram, chest x-ray, and cardiac enzymes were also normal. However, she was found to have an amylase level of 430 IU/L and lipase level of 274 IU/L. Although, her US abdomen and CT scan abdomen showed no evidence of gallstone, cholecystitis and pancreatitis, patient was diagnosed with acute pancreatitis as she met 2 out of 3 criterias which were abdominal pain and serum amylase and/or lipase more than 3 times upper limit of normal.

She was admitted and treated with intravenous fluids plus analgesics which led to rapid improvement in her condition. Meanwhile, a thorough workup for the cause of pancreatitis was initiated. There was no history of alcohol use, abdominal trauma or any gastroenterology procedures. Extensive abdominal imaging such as ultrasound and CT abdomen ruled out any hepatobiliary abnormalities. Lipid profile and electrolytes such as calcium were also found to be normal.

As all the workup was unremarkable, it was thought that it was likely drug-induced acute pancreatitis. Etanercept was the only medication that had been started recently which made it the likely culprit. Therefore, it was stopped after the case was discussed with patient's rheumatologist. The patient continued to improve and was discharged after

medical stabilization. Her rheumatologist started her on abatacept and she has remained symptom-free since then.

3. Discussion

Acute pancreatitis is characterized by rapid-onset inflammation of the pancreas secondary to parenchymal and/or peripancreatic necrosis. It can be either in the form of interstitial edematous or necrotizing pancreatitis with variable severity. This clinical condition should be suspected in any patient presenting with acute-onset abdominal pain and needs prompt diagnosis as severe pancreatitis can lead to devastating medical consequences with mortality rates as high as 30%.

Leading causes of acute pancreatitis include gallstones and alcohol while drugs are responsible for only 3%-5% of cases [1–3]. Although not clearly understood, drug-induced pancreatitis (DIP) is mainly postulated to occur due to either direct cytotoxic tissue injury or indirect metabolic effects such as hypercalcemia and hypertriglyceridemia. Other possible mechanisms include idiosyncratic and hypersensitivity reactions. Various medications are known to have acute pancreatitis as a well-known side-effect and are categorized accordingly (Table 1) [3,4].

An extensive workup for an underlying etiology leading to acute pancreatitis in our patient was

unrevealing. Therefore, DIP was considered as a possibility. Patient was on hydrochlorothiazide but it was thought not to be the culprit agent as it was being used for a long-time by the patient. In addition, hypercalcemia and/or hypertriglyceridemia secondary to thiazides is thought to cause pancreatic injury which did not fit in our case as the calcium and triglyceride levels were normal.

Tumor necrosis factor (TNF) inhibitors, used to treat various autoimmune conditions such as rheumatoid arthritis, psoriasis and ankylosing spondylitis, are only known to cause DIP in exceptionally rare instances. Although the true incidence of TNF inhibitor-induced pancreatitis is not clearly estimated, most of those cases are documented to have occurred in patients who were on infliximab and adalimumab [5]. Our patient had been recently started on etanercept which is also a TNF-alpha inhibitor although with a different mechanism of action. As the patient had developed acute pancreatitis shortly afterwards, etanercept-induced DIP was considered as the most likely diagnosis.

This makes our case intriguing as etanercept is not known to be injurious to pancreas. The FDA has not documented pancreatitis as a possible or even a rare adverse effect of etanercept while only one case of DIP secondary to etanercept use has been reported so far in the medical literature [6]. On the other hand, recent animal trials have demonstrated etanercept to have a potentially protective and/or therapeutic role in acute pancreatitis [7–9]. However, no human studies regarding this topic have been performed. Due to limited data, a clear explanation behind these paradoxical actions of etanercept is still lacking.

As a medical team, the most difficult aspect of this case was confirming the suspected diagnosis. This is because definitive diagnosis of any suspected DIP can only be made when re-introduction of the same drug results in recurrence of the symptoms [2]. Despite being performed in closely-monitored settings, this 're-challenge' testing can run an unpredictable course leading to catastrophic complications; which is why it is usually deferred in most cases. Due to the presence of multiple comorbidities in our patient, it was decided not to perform this procedure after a multidisciplinary discussion involving the rheumatology team. Withdrawal of etanercept along with supportive management led to resolution of symptoms and the patient has continued to remain symptom-free until the last rheumatology clinic visit.

One can argue that given patient's history of RA, this episode could have been due to autoimmune pancreatitis (AIP) especially since IgG4 levels were not checked. However, the following points go against AIP in this case: (1) Clinical improvement within 48 hours without any corticosteroid treatment. (2) Imaging did not show features suggestive of AIP.

Table 1. Classification of drugs associated with acute pancreatitis [3,4].

Class	Criteria	Drugs
Ia	Class Ia drugs At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs	Codeine, cytarabine, dapson, enalapril, furosemide, isoniazid, mesalamine, metronidazole, pentamidine, pravastatin, procainamide, simvastatin, sulfamethoxazole, sulindac, tetracycline, valproic acid
Ib	At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out	Amiodarone, azathioprine, dexamethasone, ifosfaide, lamivudine, losartan, 6-MP, premarin, TMP-SMZ
II	At least 4 cases in the literature Consistent latency (75% of cases)	Acetaminophen, Clozapine, DDI, erythromycin, estrogen, l-asparaginase, propofol, tamoxifen
III	At least 2 cases in the literature No consistent latency among cases No rechallenge	Alendronate, carbamazepine, ceftriaxone, clarithromycin, cyclosporin, hydrochlorothiazide, interferone/ribavirin, metformin, minocycline, naproxen, paclitaxel, prednisone, prednisolone
IV	Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge	Ampicillin, cisplatin, colchicine, cyclophosphamide, diclofenac, doxorubicin, interleukin-2, octreotide, propoxyphene, rifampin, risperidone, sertaline, tacrolimus, vincristine

4. Conclusion

Our case demonstrates many important points for the clinicians:

- (1) A thorough medication history to identify common culprit drugs and any recent use of a new medication should be considered an integral part of investigation in all patients with acute pancreatitis. Failure to withdraw a culprit drug can lead to poor outcomes due to ongoing pancreatic injury.
- (2) TNF-alpha inhibitors have done wonders for patients with various rheumatological and hematological conditions. However, over time new side-effects associated with TNF-alpha inhibitors are being identified such as our case which we believe is the second documented incidence of etanercept induced DIP. Therefore, patients using these medications need to be followed more closely and with extra caution so that prompt evaluation of any unexpected or unexplained symptoms can be done.
- (3) Current medical data is lacking regarding pancreatic effects of etanercept. While research is being executed to prove etanercept as a beneficial agent for patients with acute pancreatitis, it is crucial that we do not overlook the possibility of this drug being toxic to the pancreas.

Disclosure statement

No potential conflict of interest was reported by the authors.

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