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Etanercept: A Rare Cause of Acute Pancreatitis

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Abstract

A 65-year-old female patient with a history of rheumatoid arthritis who was recently started on etanercept therapy, presented with abdominal pain. She denied a history of alcohol use, trauma, or gallstones and workup yielded a lipase of 1012U/L with normal remaining lab work. Imaging would not indicate evidence of biliary obstruction. The patient was medically managed for pancreatitis, suspected in the setting of etanercept use. She was managed medically with fluid resuscitation and diet advanced as tolerated. She was advised to refrain from etanercept and is symptom-free at one year follow up. The lack of extensive prior trials and studies has prevented consensus guidelines on drug-induced pancreatitis. It is vital to rule out common etiologies such as obstruction, trauma, alcohol use and lab abnormalities. A high index of suspicion is vital for management and preventing recurrence. Etanercept is being increasingly used for a variety of autoimmune conditions and its association with acute pancreatitis is not well known. Further studies are needed to clarify this adverse effect.

Keywords: Acute pancreatitis etanercept • Drug effect • Gastroenterology • Abdominal pain

Introduction

The pancreas is a peritoneal abdominal organ sitting adjacent to the stomach, duodenum and spleen, which plays a significant role in both exocrine and endocrine functions within the human body. The organ functions in an exocrine manner to synthesize and secrete various digestive enzymes *via* the Sphincter of Oddi that is crucial to the breakdown and absorption of substances within the intestines [1]. Acute pancreatitis involves pancreatic acinar injury with a systemic and local inflammatory response. This results from premature activation of trypsinogen within the pancreas, which leads to inflammation, edema and sometimes necrosis of the pancreatic gland. Various underlying mechanisms contribute to the progression of the disease, the development of symptoms and the manifestation of complications. Ischemia-reperfusion injury plays a significant role, as evidenced by the importance of early fluid resuscitation. Changes in the microvasculature contribute to permeability, fluid leakage, edema, hemorrhage and even pancreatic necrosis [2].

Prompt diagnosis is essential, as while mild pancreatitis has a reported mortality of less than 1%, severe pancreatitis mortality has been reported as high as 30%. The 2012 revised Atlanta Classification required two of three: Characteristic epigastric abdominal pain suggestive of pancreatitis, serum amylase or lipase elevation greater than or equal to three times the upper limit of normal and characteristic Computed Tomography (CT) findings of acute pancreatitis. Patients are classified as interstitial edematous acute pancreatitis or acute necrotizing pancreatitis, with the former being much more common than the latter. The presence or absence of organ failure and systemic symptoms further stratifies patients into levels of severity [1].

Upon preliminary diagnosis of acute pancreatitis, the next steps in the workup involve the evaluation of common etiologies. History should focus on a thorough evaluation of ongoing or prior alcohol abuse and a history of gallstones, trauma, or recent Endoscopic-Retrograde Cholangiopancreatography (ERCP). Laboratory workup should entail serum amylase/lipase levels and a lipid panel to evaluate for hypertriglyceridemia. Elevated pancreatic amylase or lipase levels to three times the upper limit of normal support the diagnosis of acute pancreatitis but is not pathognomonic. The diagnostic utility of these tests decreases over time after the onset of symptoms. Therefore, depending on the timing of the presentation, levels may not be high enough to be diagnostic and a high clinical index of suspicion is needed to proceed with preliminary diagnosis and treatment. A basic metabolic panel should be ordered to evaluate for evidence of hypovolemia and end-organ dysfunction and rule out hypercalcemia as a potential etiology. Liver function tests can help clarify jaundice and biliary obstruction evidence [1,2].

Imaging plays a vital role in the workup of acute pancreatitis. Due to its cost and bedside nature, trans-abdominal ultrasound is the preferred initial imaging modality. Sensitivity in detecting acute pancreatitis is up to 75%, but over 25-30% of patients' examination is limited due to overlying gas. In addition, it assists in evaluating potential etiologies of gallstones and biliary obstruction. Although CT is often done at admission, it is not recommended to be performed within the first 48 hours of admission because it is associated with increased length of stay, offers a slight improvement in patient outcomes and is often done too early to estimate pancreatic complications. Exceptions include when there is diagnostic uncertainty or a high index of suspicion or pancreatic complications such as necrosis, abscess, or vascular complications such as thrombosis or hemorrhage [2].

As previously mentioned, the hemodynamic and vascular complications of acute pancreatitis revolving around increased permeability and subsequent third-spacing of fluid and hypovolemia contribute to the progression of the disease and development of complications. Therefore, fluid resuscitation is the mainstay of initial treatment, regardless of etiology. Depending on the underlying cause of acute pancreatitis, individualized treatment modalities can be adopted, such as ERCP for obstructive jaundice, cholecystectomy for gallstone pancreatitis and insulin or plasmapheresis for hypertriglyceridemia. Other critical management aspects include prompt reinitiation of enteral nutrition as tolerated by the patient and pain control [2]. The specifics regarding the treatment of the etiologies mentioned above are beyond the scope of this paper.

For the vast majority of cases of acute pancreatitis, the previously mentioned workup algorithm will adequately identify the underlying etiology and lead to the appropriate treatment algorithm. Drug-induced pancreatitis is generally a known and documented cause and tends to be often

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overlooked. Despite causing less than 3% and as low as 0.1% of cases of acute pancreatitis, DIP is a growing and notable cause of acute pancreatitis [1,3]. Diagnosis is challenging, as most data comes from case reports, case series, or case-control studies. Definitive studies or trials are overall lacking. In addition, definitive causation and correlation are established in less than 10% of suspected DIP. Inherent bias exists and due to a lack of mandatory drug reporting mechanisms, cases often go unreported. Although not financially appropriate nor feasible on a population-based model, further studies such as ERCP and Endoscopic Ultrasound (EUS) are only sometimes done if clinically indicated to evaluate for less common causes of pancreatitis, such as biliary microlithiasis. It is also established that to definitively diagnose DIP, a latency period with the reintroduction of the possible offending agent associated with the resumption of pancreatitis symptoms is needed. However, this is only sometimes feasible due to the risk of disastrous complications [3].

Case Presentation

Our patient is a 65-year-old African American female with a past medical history of rheumatoid arthritis who presented to our hospital, endorsing three to four days of sharp, epigastric abdominal pain. The pain was sudden in onset with radiation around the flanks, not associated with eating and with concurrent nausea. She also denied a prior history of pancreatitis, gallstones, alcohol use, recent trauma, or endoscopic retrograde cholangiopancreatography. Her past medical history was only notable for rheumatoid arthritis, for which she was started on etanercept therapy around one week prior. She otherwise denied being on any other medications, both prescription and over-the-counter medications, nor herbal or vitamin supplementation.

The patient's vitals were stable on presentation. Preliminary blood work was notable for a white blood cell count of 11.4 K/uL, normal liver function tests, calcium of 10.1 mg/dl, lipase 1012 U/L, Blood Urea Nitrogren (BUN) of 29 mg/dl, creatinine 1.02 mg/dl and triglycerides of 187 mg/dl. CT Abdomen/Pelvis with Intravenous (IV) contrast obtained in the emergency department had evidence of hepatic steatosis, with no findings of acute pancreatitis or gallbladder stone disease (Figure 1). Subsequent transabdominal ultrasound confirmed the findings on the CT scan, manifesting a gallbladder with no gallstones, distention, or pericholecystic fluid (Figure 2). An endoscopic ultrasound would rule out microlithiasis, pancreas divisum, malignancy and autoimmune processes. The patient was started on intravenous fluids and the diet advanced as tolerated.

The patient would have gradual mitigation of abdominal pain and nausea. Vitals would remain stable. Infection was deemed unlikely with no worsening leukocytosis, fevers, evidence of infection on chest x-ray nor abdominal imaging, or growth noted on blood cultures. Further workup would return negative, including Antinuclear Antibody (ANA), immunoglobulin G4 (IgG4) and hereditary genetic panel (CFRT, SPINK and PRSS1 mutations). After multidisciplinary discussion, the recent initiation of etanercept administration coinciding with the development of pancreatitis was considered to be suspicious. The patient was advised to stop etanercept therapy and follow up with gastroenterology and rheumatology outpatient. Repeat abdominal ultrasound within a few weeks of discharge indicated resolving pancreatitis. Since stopping etanercept, the patient has been symptom free at 6 months since discharge.

Results and Discussion

DIP was first reported in the 1950s, with case reports depicting cases in the setting of cortisone and chlorthalidone use [4]. Since then, the World Health Organization has reported over 500 culprit medications associated with acute pancreatitis, with data primarily stemming from case reports and series, making interpretation and diagnosis challenging. It is generally seen as a diagnosis of exclusion, with more common etiologies of alcohol abuse, gallstone disease and other metabolic derangements having to be ruled out. Alcohol abuse and gallstone disease account for most cases of acute pancreatitis, with data reporting them being the cause of 40-70% and 25-35%, respectively. The remaining causes include metabolic derangements such as hypertriglyceridemia, hypo and hypercalcemia, trauma, recent ERCP, malignancy and autoimmune disease [3].

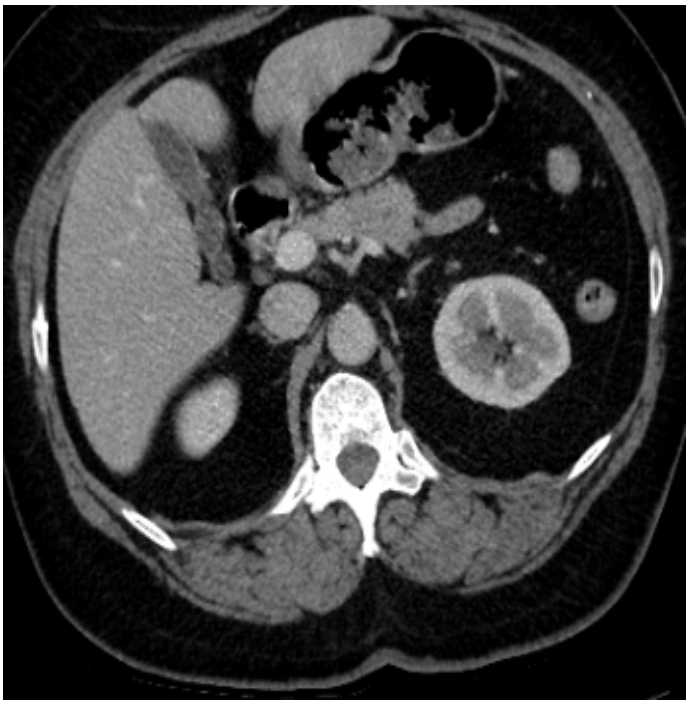

Figure 1. CT Scan of Abdomen with evidence of hepatic steatosis and no evidence of acute pancreatitis.

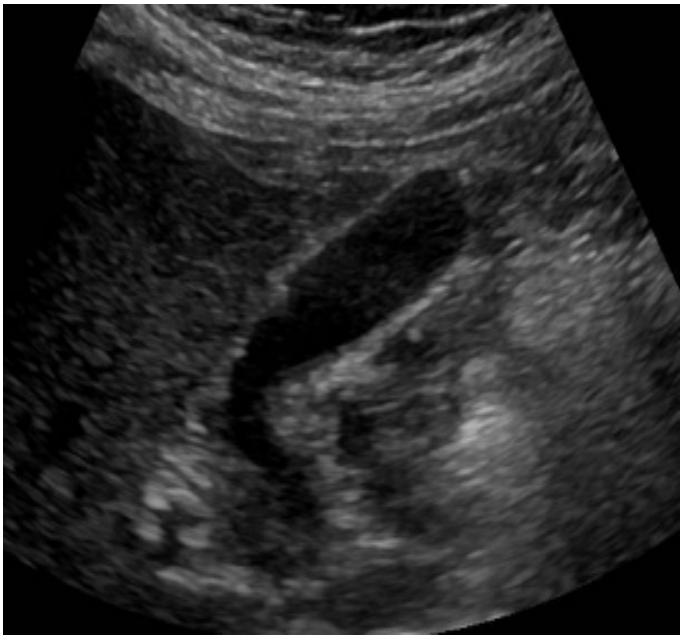

Figure 2. Transverse positioning indicating nondistended gallbladder, no pericholecystic fluid, nor any gallstones. Sonographic Murphy's sign was right upper quadrant ultrasound in left lateral decubitus negative.

Our patient did not endorse a history of alcohol abuse, trauma, or recent ERCP, with a workup coming up negative for significant metabolic derangements or gallbladder disease. Preliminary workup for autoimmune pancreatitis was not convincing, with negative biomarkers and no concurrent autoimmune disease. A genetic etiology was not considered due to the patient's first presentation at an elderly age and lack of notable family history. An argument could be made to consider malignancy as a potential etiology in a patient presenting with a first episode of acute pancreatitis at an elderly age. However, due to a lack of concurrent risk factors such as tobacco use, no

Table 1. Proposed diagnostic algorithm for drug induced pancreatitis by Weissman S, et al. [3] >9: Highly probable 6-8: Probable 3-5: Possible ≤2: Doubtful MRCP: Magnetic resonance cholangiopancreatography.

Question
1. Are there published reports of the drug causing acute pancreatitis?
2. Was there short latency (<7days) between initiation of the drug and diagnosis of acute pancreatitis?
3. Was there a temporal relationship (<1month) between initiation of the drug and onset of acute pancreatitis symptoms?
4. Did the acute pancreatitis resolve following discontinuation of the drug?
5. If a drug re-challenge was performed, did acute pancreatitis recur?
6. Were all commonly recognized causes of acute pancreatitis ruled out? (e.g. gallstones/choledocholithiasis, alcohol, hypertriglyceridemia, hypercalcemia, ERCP, trauma)
7. Was a serum IgG4 level checked? (to rule out autoimmune pancreatitis)
8. Does the patient have or was the patient recently diagnosed with an infection (bacterial, fungal, or viral) which could cause pancreatitis?
9. Was an EUS and/or MRCP performed? (e.g. to rule out occult microlithiasis, pancreatic malignancy, and pancreatic divisum)
10. Was genetic testing (SPINK-1, CFTR, and PRSS-1) performed to rule out hereditary pancreatitis? (In patients less than 30 years of age)
Summative score

endorsed history of chronic weight loss or changes in bowel function, nor any evidence of apparent suspicious mass on initial imaging, malignancy was not considered during this episode.

This highlights the importance of ruling out other etiologies and underscores the diagnosis of the exclusion component in the workup of DIP. Azathioprine/mercaptopurine and didanosine have been attributed to up to 5% and 23% of cases of DIP, respectively. A variety of diagnostic mechanisms have been proposed. A core diagnostic algorithm involves initially diagnosing acute pancreatitis in a suspected patient presenting to the hospital. Common etiologies should be investigated and appropriately ruled out through thorough history taking and workup. After this, the differential should be broadened to consider less common etiologies, such as autoimmune pancreatitis, genetic causes and DIP. A comprehensive review of medications, including prescription and non-prescription medications, should be taken, noting any over-the-counter medications, herbal supplements and vitamins. A high index of suspicion should be utilized to consider culprit medications, which should be promptly held. The difficulty in many proposed diagnostic algorithms is that ideally, a medication re-challenge is noted as being the gold standard, with the recurrence of symptoms upon re-administration of the offending agent being needed to establish causation [3].

Trivedi CD and CSP proposed an initial diagnostic algorithm in the 1980s, classifying patients into three Class tiers. Class I medications were deemed to have the most robust causative evidence, having at least one documented report of a positive re-challenge and at least 20 reported case reports. Class II and III had less convincing evidence, with Class II having with or without re-challenge evidence and 10-20 case reports and Class III with all reported drugs and less than 10 case reports. They reviewed the top 100 prescribed medications in the United States, with 44 falling under Class III and 14 under Class I and II, respectively [5].

A subsequent proposed diagnostic algorithm by Weissman S, et al. is a modified enhancement on the Naranjo scale (itself assessing the probability of adverse drug reactions) to be more pancreatic-specific. It is based on an aggregate score from a series of 10 questions (Table 1). Through this scoring mechanism, our patient scores a 5, indicating possible DIP. Unfortunately, no studies assess the diagnostic accuracy of this proposed algorithm [3].

As previously discussed, hundreds of reports of various drugs associated with pancreatitis have been reported. The most commonly reported medications include but are not limited to statins, 5-Aminosalicylic Acid (5-ASA) agents, antibiotics such as metronidazole and tetracyclines, steroids and anti-inflammatory drugs (NSAIDs), immunotherapy, Angiotensin-Converting-Enzyme Inhibitors (ACE-I) and Angiotensin-Receptor-Antagonists (ARBs), diuretics, antacids, Highly Active Antiretroviral Therapy (HAART), anti-seizure medications and herbal supplements. Through discussion with the patient and a thorough medication-claim review, the patient was not on any of the above medications [3].

Tumor Necrosis Factor-α (TNF-α) inhibitors play a crucial role in inhibiting the inflammatory response that plays the central role in the development and pathogenesis of various auto-immune conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis and inflammatory bowel disease. Due to their underlying mechanism of action, infection is seen as the most common side effect. Overall, acute pancreatitis is not commonly associated with these agents. Most prior case reports, although limited, commonly attribute pancreatitis to infliximab and adalimumab use. To our knowledge, there are only two prior case reports of acute pancreatitis in the setting of recent etanercept initiation. Although one case resulted in fatal fulminant necrotizing pancreatitis, the second case noted the resolution of symptoms with cessation of etanercept [6].

A variety of mechanisms for DIP have been proposed. These include pancreatic/biliary duct constriction, direct cytotoxic effects, metabolic effects and accumulation of potentially toxic metabolites [3]. Etanercept, quite interestingly in animal trials, has been associated with potentially protective and therapeutic effects on pancreatic cell function. However, there are no human studies regarding this topic and with definitive data lacking, its potential associated with acute pancreatitis should not be overlooked, particularly with one case resulting in death. Outside of the potential explanations for DIP outlined above, there are no apparent mechanisms for the role of TNF-α inhibitors and how they contribute to acute pancreatitis [6].

We ruled out more common and other causes of pancreatitis in our patient, including gallstone obstruction, alcohol use, trauma, hypertriglyceridemia, trauma and hereditary etiologies. The patient was managed medically and advised to stop the etanercept. The patient on outpatient follow up had no recurrent symptoms or evidence of pancreatitis.

Conclusion

DIP is a diagnostic dilemma, with hundreds of reported medication affiliations and no consensus diagnostic algorithm. Despite the etiology, prompt fluid resuscitation and workup for common etiologies remain essential to every case of acute pancreatitis. After common etiologies are excluded, the differential should be broadened to include DIP with a thorough evaluation of every prescription and non-prescription medication the patient has taken. A drug rechallenge with the return of symptoms is seen as crucial to diagnosis. However, this is quite challenging to do due to the inherent risk of worsening outcomes and complications. TNF-α inhibitors and, of note, etanercept are not well reported as being associated with acute pancreatitis. With one of two prior reports reporting a fatality, a high index of suspicion should be utilized in patients on etanercept presenting with acute pancreatitis. We acknowledge that further studies are needed to assess this relationship appropriately.

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