CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 4 (2013) 708–710

Contents lists available at SciVerse ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Clinical challenges in drug induced pancreatitis: Presentation of two cases and review of the literature

Fatih Yanar*, Orhan Agcaoglu, Inanc S. Sarici, Beyza Ozcinar, Ali F.K. Gok, Kayıhan Gunay, Cemalettin Ertekin

Department of General Surgery, Trauma & Emergency Surgery Service, Istanbul University, Istanbul Medical Faculty, Turkey

ARTICLE INFO

Article history:
Received 31 October 2012
Received in revised form 2 January 2013
Accepted 28 February 2013
Available online 17 April 2013

Keywords:
Drug induced acute pancreatitis
Folinic acid
Corticosteroid
Anti-neoplastic agents
Transverse myelitis

ABSTRACT

INTRODUCTION: A wide variety of drugs have been reported to cause pancreatitis. Although the incidence of drug induced acute pancreatitis is low, the disease is associated with substantial morbidity and mortality, which makes timely identification of the causative agent important.
PRESENTATION OF CASE: Herein, we report two patients with clinical, biochemical, and radiological evidence of acute pancreatitis. There were no etiologic factors except their prescribed drugs.
DISCUSSION: The majority of patients with acute pancreatitis recover uneventfully, but there remains an uncontrollable risk of mortality. It is prudent to withdraw a medication with a known association with acute pancreatitis. Necessity of multi-drug regimens especially in oncological patients however, presents a challenge.
CONCLUSION: Corticosteroid pulse therapy was easily detectable as the causative agent in our first case, but combined anti-neoplastic drug therapy and additional multi-drug regimen presented great difficulties in identifying single causative agent in our second patient.
© 2013 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Acute pancreatitis (AP) results from premature activation of proteolytic enzymes within the pancreas. The spectrum of the disease varies from mild, which is usually self-limiting, to severe, which correlates with the degree of pancreatic involvement and complications.[1] Bile duct stones and alcohol abuse together account for about 80% of AP; other causes of AP are various toxins, drugs, obstructive lesions of the bile duct system (other than stones), metabolic abnormalities, trauma, ischemia, infections, and autoimmune diseases.[2] Occult biliary microlithiasis may be the cause of two-thirds of the 'idiopathic' cases which account for 10% of AP.[2]

The pancreas is capable of biotransforming drugs and other chemicals and is subject to toxic injury by the resulting reactive metabolites.[3] The proportion of drug induced pancreatitis is estimated at 1.4%[4] to 2%[5] in the general population, with much higher proportions in specific subpopulations, such as children (approximately 13%)[6] and patients who are HIV positive.[5]

2. Case 1

A 58-year-old woman was consulted to our Emergency Surgery Unit from the Neurology Department of our hospital. She had complained of severe abdominal pain lasting for the last 24 h. Physical examination revealed a predominantly epigastric pain which radiates to the back. There was no guarding or rebound, but tenderness, and the bowel sounds were frequent. There was no history of alcohol or tobacco use or abdominal trauma. She had essential hypertension for 15 years, hypothyroidism for two years and was receiving 100 mg Lysinopril and 100 μg L-thyroxine daily. Serum and urine amylase levels were elevated at 298 U/L (three times normal) and 768 U/L (seven times normal), respectively. Serum lipase level was elevated to 2800 U/L (14 times normal). Liver function tests were normal: GGT: 70 U/L (5–85 U/L), AST: 17 U/L (5–42 U/L), ALT: 38 U/L (5–45 U/L). LDH was elevated at 547 U/L (240–480 U/L). Other causes of AP such as hyperlipidemia and hypercalcemia were excluded. The white blood cell (WBC) count was significantly elevated at 17,630/mm^3 (4000–10,000/mm^3). C-reactive protein was significantly elevated at 38.2 mmol/L (normal: <0.5 mmol/L). Abdominal ultrasound (US) examination and computerized tomography (CT) scan revealed a normal liver and biliary tract. CT scan also revealed the expansion of the head of the pancreas and hyperdense mesenterium surrounding, both of which were evidence of pancreatitis. The follow-up diagnosis was transverse myelitis on the second day of pulse corticosteroid therapy. After steroid therapy, elevated blood glucose levels were taken under control by regular insulin injections. We did not perform endoscopic retrograde cholangiopancreaticography (ERCP) because of the normal liver function tests and biliary tract imaging. Corticosteroid therapy was stopped after lowering the doses gradually in three days. The patient quickly improved and was painless after six days. Conservative treatment resulted with

* Corresponding author at: Istanbul University, Istanbul Medical Faculty, Department of General Surgery, 34093 Capa, Istanbul, Turkey. Tel.: +90 533 564 3432.
E-mail address: yanar_fatih@yahoo.com (F. Yanar).

2210-2612/$ – see front matter © 2013 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijscr.2013.02.025

success. Control CT scan which was performed after 1 month was normal.

3. Case 2

A 50-year-old woman was admitted to our Emergency Surgery Unit with 4 days of severe abdominal pain, loss of appetite, nausea, and vomiting. There was no history of alcohol or tobacco use. She underwent right hemicolectomy and ileotransversostomy two months ago, because of a right sided colonic adenocarcinoma. The fourth dose of combination chemotherapy was given six days ago consisting of Camptotesin (Irinotecan) (125 mg/m^2), 5-Fluorourasil (500 mg/m^2) and Folinic acid (20 mg/m^2). She was also given Dexamethasone (16 mg/day, i.v.) and Ondansetron (8 mg/day, i.v.) for prevention of emesis, Codeine (60 mg/day, p.o.) and NSAID (Piroxicam 20 mg tablets/day) for pain relief and Omeprasole (40 mg/day) tablets for gastric ulcer prophylaxis.

Serum and urine amylase levels were elevated at 284 U/L (three times normal), and 1988 U/L (19 times normal), respectively. Serum lipase level was elevated at 3600 U/L (18 times normal). Liver function tests were within normal limits: ALP 82 U/L, GGT 80 U/L, AST 32 U/L, and ALT 45 U/L. There was neither hyperlipidemia nor hypercalcemia. C-reactive protein was significantly elevated at 15.9 mmol/L (normal: <0.5 mmol/L). Abdominal US and CT scan was revealed a normal biliary tract but the CT scan revealed multiple milimetrical metastatic lesions in the left lobe of the liver and evidence of edematous pancreatitis. ERCP was not performed. All medications were withdrawn and conservative management was begun. Symptoms relieved and oral nutrition was started 36 h later, specifically with improvement in both clinical and biochemical findings.

4. Discussion

Regarding their certainty of causing AP, medications can be classified as Definite/Probable/Possible association.[1,7] A 'definite' association implies a total relationship of drug administration with abdominal pain and hyperamylasemia or a positive response to rechallenge with the causative agent.[1,7]

The pathogenesis of drug induced pancreatitis does not appear to differ from other causes of AP as discussed in several studies in the literature.[8–10] Exactly how medications induce AP is unknown, but postulated mechanisms include immune-mediated inflammatory response, direct cellular toxicity, pancreatic ductal constriction, arteriolar thrombosis, and metabolic effects.[1,7]

Most of the 'evidence' supporting associations between drugs and AP are based on anecdotal case reports.[11] Relatively large volumes of case-based evidence exist about drug induced pancreatitis, but little is known about the epidemiology and mechanisms of this entity.

Yashizawa and co-workers reported a case and a prospective study in 1999 and stated that corticosteroid pulse therapy, using very high doses, may cause pancreatitis that is unexpected and may sometimes be fatal.[12] On the other hand, there are many experimental studies reporting that steroids could have a protective effect in acute phase of pancreatitis when they are administered by intravenous or intraductal route.[13,14] These studies conclude that steroid pulse therapy inhibits the development of AP by inhibition of leukocyte activation and the release of cytokines such as IL-1 beta and IL-6. These are the cytokines highly responsible for the inflammatory process during the pathophysiological course of AP.[14]

In our first case, there was a close relationship between drug administration and the onset of clinical symptoms (approximately 8 h) and other causes of AP were easily excluded. As a definite proof, it is needed to see the recurrence of pancreatitis upon readministration of the drug, but for ethical reasons rechallenge with the suspected drug can only be done if the drug is necessary to treat a serious condition,[15] but such a necessity did not exist in our case.

Our second case had many confounding pharmacological factors, but still confirmed a diagnosis of AP. To the best of our knowledge, Folinic acid was not previously reported as a causative agent in AP, but codein,[16] NSAID's,[11] omeprasole[3] have all been reported to have such a relationship. Combination therapy with several medications related with AP has also been reported,[1] but management algorithms for such a challenging situation are lacking in the literature. This forced us to report on this patient to clarify that there may be such challenging situations where demonstrating a causal relationship between a single drug and AP may sometimes be impossible. In one of the recent reviews, Nische et al. reported an algorithm for the diagnosis and management of acute pancreatitis.[10] However, trying to detect only one drug or implicating all the medications as causative agents is a question to be answered. Identification of a single drug of the patient's treatment and additive effects of several drugs associated with AP is needed for establishing treatment strategies in the near future. To hear about experiences of authors who had such cases would honor and help us with our further patients. We also agree with the authors who did not recall evidence because of ethical reasons, consistent statistical data, or evidence from experimental studies on a possible mechanism to treat and to prohibit drawing definitive conclusions about the drugs.[5]

The majority of patients with AP recover uneventfully, but there remains an uncontrollable risk of mortality. It is prudent to withdraw a medication with a known association with acute pancreatitis. Necessity of multi-drug regimens especially in oncological patients however, presents a challenge. More studies are needed to establish the risk profiles and to form therapeutic algorithms in the field of drug induced acute pancreatitis.

Conflict of interest statement

None.

Funding

None.

Consent

Written consent obtained.

Author contributions

Drafting of manuscript was done by Fatih Yanar, Orhan Agcaoglu. Acqusition of data was done by Inanc S Sarici. Study conception and design was done by Beyza Ozcinar. Analysis and interpretation of the data was done by Ali FK Gok. Critical revision of the manuscript was done by Kayihan Gunay, Cemalettin Ertekin.

References

1. Berardi RR, Montgomery P. Pancreatitis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. McGraw-Hill; 2002. p. 701–16.
2. Sakorafas GH, Tsiotou AG. Etiology and pathogenesis of acute pancreatitis: current concepts. *Journal of Clinical Gastroenterology* 2000;**30**:343–56.
3. Scarpelli DG. Toxicology of the pancreas. *Toxicology and Applied Pharmacology* 1989;**101**:543–54.

4. Lankisch PG, Droge M, Gottesleben F. Drug induced pancreatitis: incidence and severity. *Gut* 1995;**37**:565–7.
5. Wilmink T, Frick TW. Drug induced pancreatitis. *Drug Safety* 1996;**14**:406–23.
6. Mader TJ, McHugh TP. Acute pancreatitis in children. *Pediatric Emergency Care* 1992;**8**:157–61.
7. Underwood TW, Frye CB. Drug induced pancreatitis. *Clinical Pharmacy* 1993;**12**:440–8.
8. Muniraj T, Gajendran M, Thiruvengadam S, Raghuram K, Rao S, Devaraj P. Acute pancreatitis. *Disease-a-Month* 2012;**58**(March (3)):98–144, http://dx.doi.org/10.1016/j.disamonth.2012.01.005.
9. Ksiądzyna D. Drug-induced acute pancreatitis related to medications commonly used in gastroenterology. *European Journal of Internal Medicine* 2011;**22**(February (1)):20–5, http://dx.doi.org/10.1016/j.ejim.2010.09.004.
10. Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. *Best Practice and Research Clinical Gastroenterology* 2010;**24**(April (2)):143–55, http://dx.doi.org/10.1016/j.bpg.2010.02.002.
11. Eland IA, Puijenbroek EP, Sturkenboom MJ, Wilson JH, Stricker BH. Drug associated acute pancreatitis: twenty one years of spontaneous reporting in the Netherlands. *American Journal of Gastroenterology* 1999;**94**:2417–22.
12. Yoshizawa Y, Ogasa S, Izaki S, Kitamura K. Corticosteroid induced pancreatitis in patients with autoimmune bullous disease: case report and prospective study. *Dermatology* 1999;**98**:304–6.
13. Kerekes L, Sipka Jr S, Dezsö B, Furka A, Petö K, Bráth E, et al. Effect of intravenous and intraductal glucocorticosteroids in experimental acute pancreatitis in dogs. *Magyar Sebeszet* 2002;**55**:225–8.
14. Takaoka K, Kataoka K, Sakagami J. The effect of steroid pulse therapy on the development of acute pancreatitis induced by closed duodenal loop in rats. *Journal of Gastroenterology* 2002;**37**:537–42.
15. McArthur KE. Review article: drug induced pancreatitis. *Alimentary Pharmacology and Therapeutics* 1996;**10**:23–8.
16. Hastier P, Buckley M, Peten EP, Demuth N, Dumas R, Demarquay JF, et al. A new source of drug induced acute pancreatitis: codeine. *American Journal of Gastroenterology* 2000;**95**:3295–8.

Open Access
This article is published Open Access at sciencedirect.com. It is distributed under the IJSCR Supplemental terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.