Clinical Case Report

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Acute pancreatitis induced by etoposide–lobaplatin combination chemotherapy used for the treatment of lung cancer

A case report and literature review

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Abstract

Rationale: Drug-induced pancreatitis (DIP) is a rare type of pancreatitis that is not usually observed in the clinical practice. It is generally difficult to distinguish from acute pancreatitis (AP) induced by other causes.

Patient concerns: Here, we report a 62-year-old Chinese female patient with "small cell lung cancer" as the initial presentation. Because the patient could not bear the surgical treatment, the chemotherapy composed of lobaplatin and etoposide was performed. Three days later, the patient displayed sudden abdominal pain, distension, nausea, and vomiting without obvious inducements. Laboratory tests showed that the levels of serum and urine amylase were enhanced; abdominal computed tomography (CT) result showed the enlargement of the pancreas, peripancreatic effusion, and a rough edge, which suggested the diagnosis of AP. The patient had no history of biliary tract disease, alcoholism, binge overeating, hyperlipidemia, and hereditary pancreatitis.

Diagnoses: The patient was diagnosed with DIP.

Interventions: The chemotherapy was stopped at once and we performed fluid resuscitation, pain alleviation, prophylactic antibiotics, and nutritional support, etc on the patient. Later, the patient's clinical symptoms were obviously relieved, and she recovered successfully.

Outcomes: The chemotherapy was continued, but later, the patient showed abdominal pain, distension, nausea, and vomiting again. The levels of serum amylase and urine amylase were enhanced again. Further imaging examination strongly indicated the recurrence of AP.

Lessons: We should raise awareness of the clinicians regarding DIP, thereby enabling its timely diagnosis and accurate treatment, as well as promoting the rational and safe use of drugs.

Abbreviations: ALT = alanine aminotransferase, AP = acute pancreatitis, AST = aspartate aminotransferase, Ca = calcium ion, DIP = drug-induced pancreatitis, MRCP = magnetic retrograde cholangiopancreatography, TBIL = total bilirubin, TG = triglyceride, WBC = white blood cell.

Keywords: acute pancreatitis, chemotherapy, drug-induced pancreatitis, etoposide, lobaplatin

1. Introduction

Acute pancreatitis (AP) is a commonly clinical acute abdominal disease that has a potentially fatal disease course and is difficult to treat. AP is often induced by biliary tract disease, alcoholism, excessive eating and drinking, and trauma, etc.[1,2] Recently, the clinical incidence of drug-induced pancreatitis (DIP) has gradually increased owing to the extensive use of medications. DIP, a rare type of pancreatitis, is not commonly observed in the clinical practice.[3] It usually presents as AP rather than chronic pancreatitis, with a rapid onset and a short course. Clinically, it is generally similar to AP induced by other causes, and has no specific markers. Therefore, in clinical diagnosis, DIP is difficult to distinguish from AP induced by other causes,[4,5] and can even be mistaken for idiopathic pancreatitis. The incidence of DIP is approximately 0.1% to 5.3%,[6–9] wherein the elderly, children, and women are considered high-risk populations. Studies have shown that DIP mostly occurs in single cases and there are relatively few relevant prospective studies and research reports. In addition, DIP is commonly mistaken for AP induced by gallstone disease or alcohol consumption; hence, its reported incidence is lower than the actual value.[10] Currently, relatively few case reports of DIP are available, which may be because of the lack of

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understanding of or attention to DIP by clinicians. This study reported, for the first time, a case of AP induced by etoposide–-lobaplatin combination chemotherapy used for treatment of lung cancer, and a literature review was conducted. Our aim was to raise awareness of the clinicians regarding DIP, thereby enabling its timely diagnosis and accurate treatment, as well as promoting the rational and safe use of drugs.

2. Case presentation

This case report was approved by the Institutional Review Board of the first affiliated hospital of Harbin Medical University and the patient was also informed and agreed to participate in our research. A 62-year-old Chinese female patient of the Han nationality was referred to the Department of Thoracic Surgery of the first affiliated hospital of Harbin Medical University, 2015-10-22, presenting with "cough and chest pain of forty days duration." The patient had no fever or fatigue. Laboratory examination results after admission: alanine aminotransferase (ALT) 23 U/L, aspartate aminotransferase (AST) 26.60 U/L, total bilirubin (TBIL) 11.30 mmol/L, calcium ion (Ca) 2.11 mmol/L, triglyceride (TG) 1.64 mmol/L, white blood cell (WBC) 7.9×10^9/L. The lung computed tomography (CT) scan showed the occupying lesion of the left lung (Fig. 1), accompanied by mediastinal and hilar lymph node enlargement. Therefore, bronchoscopy and histopathological biopsy were performed to reveal the diagnosis of small cell lung cancer. Because of the severely obstructive pulmonary ventilation dysfunction, surgical treatment could not be implemented. After a detailed communication with the family members, the chemotherapy composed of lobaplatin and etoposide (etoposide: 100 mg/m^2, d_{1-3} ivgtt; lobaplatin: 30 mg/m^2, d_1 ivgtt) was performed. Three days after the onset of chemotherapy, the patient developed sudden abdominal pain, distension, nausea, and vomiting without obvious inducements. Physical examination of the patient showed acute facial appearance in a poor state. Abdominal swelling, tenderness, and rebound tenderness were positive, while shifting dullness was negative with weak bowel sounds.

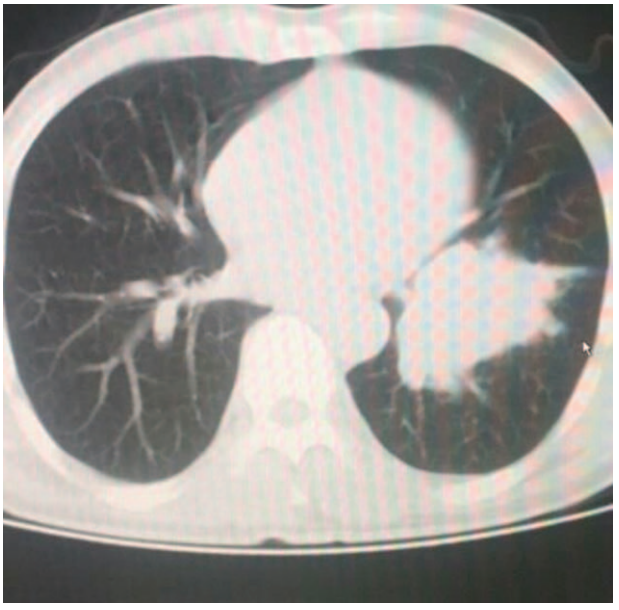

Figure 1. Lung CT result showed the occupying lesion of the left lung.

Table 1

Laboratory test results of the patient.

Items	On admission	Onset of AP	Scope	Unit
ALT	23.00	24.01	5.00–40.00	U/L
AST	26.60	25.63	8.00–40.00	U/L
TBIL	11.30	14.51	3.40–21.00	mmol/L
TG	1.64	1.72	0.48–2.25	mmol/L
Ca	2.11	1.91	2.08–2.60	mmol/L
WBC	7.9	14.1	3.97–9.15	10^9/L
Serum amylase	—	1600	0–95	U/L
Urine amylase	—	13450	32–641	U/L

ALT = alanine aminotransferase, AP = acute pancreatitis, AST = aspartate aminotransferase, Ca = calcium ion, TBIL = total bilirubi, TG = triglyceride, WBC = white blood cell.

Laboratory tests and imaging examinations showed ALT 24.01 U/L, AST 25.63 U/L, TBIL 14.51 mmol/L, Ca 1.91 mmol/L, TG 1.72 mmol/L, WBC 14.1×10^9/L, serum amylase 1600 U/L, urine amylase 13,450 U/L (Table 1). Magnetic retrograde cholangiopancreatography (MRCP) showed no obvious expansion or irregular shape of the cystic duct, intrahepatic bile duct, left and right hepatic ducts, common hepatic duct, and common bile duct. The gall bladder was not large and its wall was not thick (Fig. 2). Abdominal ultrasound displayed that the gall bladder had a normal size and shape, and the wall was smooth and not thick without stone and polyp in it. There was no obvious expansion of the bile duct, while the pancreas was enlarged with a rough edge and a small amount of effusion around it could also be found. Abdominal CT result showed the enlargement of the pancreas, peripancreatic effusion, and a rough edge, which suggested the diagnosis of AP (Fig. 3). We stopped the chemotherapy at once

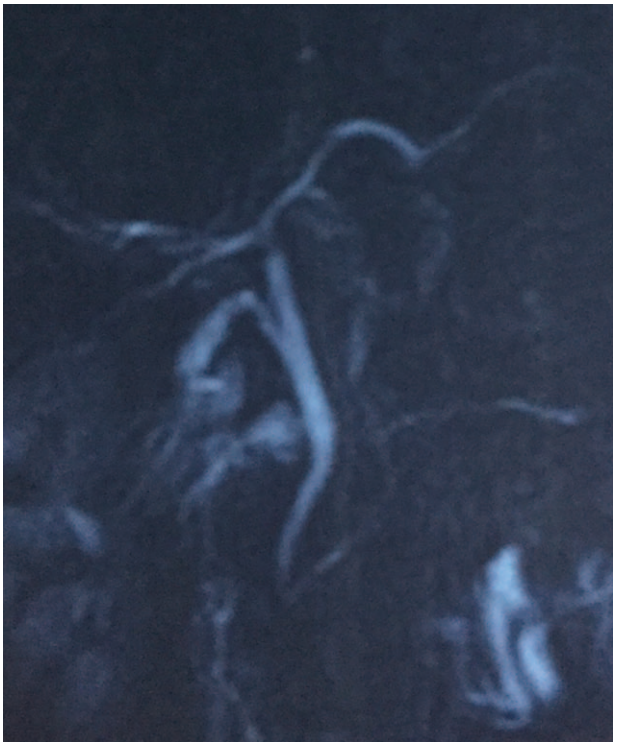

Figure 2. MRCP result showed no obvious expansion and irregular shape of the cystic duct, intrahepatic bile duct, left and right hepatic ducts, common hepatic duct, and common bile duct. The gall bladder was not large and its wall was not thick.

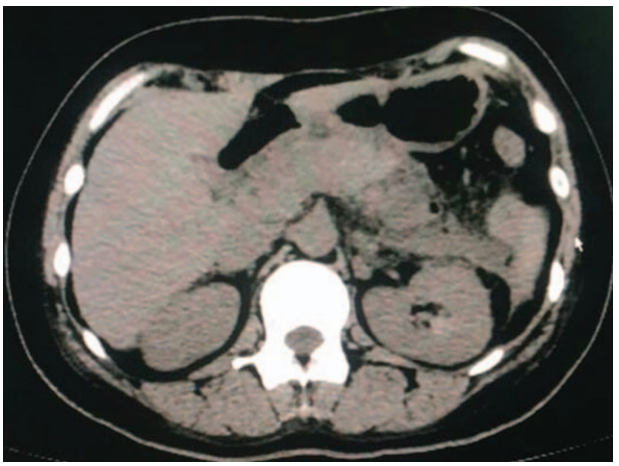

Figure 3. Abdominal CT result showed the enlargement of the pancreas, peripancreatic effusion, and a rough edge, which suggested the diagnosis of AP.

and performed fluid resuscitation, pain alleviation, prophylactic antibiotics, and nutritional support, etc on the patient. Two weeks later, the patient's clinical symptoms were obviously relieved, and she recovered successfully. The chemotherapy was continued after the patient took the liquid diet showing no obvious discomfort. Two days after resuming the chemotherapy, the patient showed abdominal pain, distension, nausea, and vomiting again. The levels of serum amylase and urine amylase were 970 and 12978 U/L, respectively. Further imaging examination strongly indicated the recurrence of AP. In a word, the patient had no history of biliary tract disease, alcoholism, binge overeating, hyperlipidemia and hereditary pancreatitis, and the restoration of chemotherapy led to the recurrence of AP that confirmed the final diagnosis of drugs-induced AP.

3. Discussion

DIP was first described by Mallory and Kern in 1980.[11] Currently, the understanding of the pathogenesis of DIP is primarily based on theories and other data collected from case reports, controlled studies, and animal experiments; however, the specific pathogenesis is still not completely known. Moreover, the mechanisms by which different drugs induce DIP are different, and the mechanisms of the same drug may differ in different individuals. Studies have shown that the pathogenesis of DIP may involve: direct toxicity of the drug, wherein many cases of DIP result from the use of cytotoxic drugs, such as L-asparaginase, which may have toxic effects on the major organs that synthesize proteins such as the pancreas and liver that result in inhibition of protein synthesis. In addition, these cytotoxic effects can lead to coagulative necrosis and hemolysis of the pancreatic parenchyma, dysfunction of pancreatic differentiation, and necrosis of the adipose tissue. Allergic reaction, of which the representative drug is azathioprine, which can induce AP in 6% of the patients.[12] Its latency period is relatively short, generally 2 to 3 weeks, and the symptoms occur within a few hours. Furthermore, its onset is often unrelated to the dose of drug. In addition, azathioprine and other drugs can lead to secondary pancreatic microcirculatory dysfunction, pancreatic duct obstruction, and toxic metabolite accumulation. This can result in pancreatic congestion and edema, which, in turn, induces the release of histamine and other inflammatory mediators to activate trypsin and lead to DIP. Between 1972 and 1977, Paloyan et al[13] reported 6 cases of AP induced by azathioprine. Repeated drug tests were conducted for 5 of these cases, where the drugs suspected of being responsible for AP were administered again to induce AP recurrence. This experiment confirmed that azathioprine is the key drug responsible for induction of AP. Idiosyncratic reactions showed that a few patients are particularly sensitive to certain drugs, which can induce DIP. Sphincter of Oddi contraction or biliary tract obstruction, where certain drugs, such as codeine and octreotide, can increase the pressure in the biliary tract to exceed the internal pressure of the pancreatic duct resulting in reflux of the bile into the pancreatic duct, thereby activating trypsin and leading to DIP. In addition, biliary disease and hyperlipidemia secondary to drugs may be closely related to development of DIP. It is noteworthy that only a few individuals will develop DIP after using these drugs. Therefore, clinicians should consider the effect of genetics, age, sex, comorbidities, and other individual factors that influence the development of DIP.

Approximately 2% of the cases of AP in adults are drug-induced,[14,15] and most cases of AP are mild or moderate with good prognosis.[16] On the basis of the degree of correlation between drug use and induction of pancreatitis, drugs can be classified into 3 categories: definitively correlated, probably correlated, or possibly correlated.[17] It was found that 160 drugs could lead to DIP,[18] of which the drugs clearly correlated with pancreatitis include azathioprine, tetracycline, diuretics, sulfonamides, nonsteroidal anti-inflammatory drugs, calcium, antacids, and immunomodulators, etc (Table 2).[19–21] In addition,

Table 2

The drugs associated with AP [18–21].

Classification	Name	Mechanism
Immunomodulator	5-aminosalicylic acid, mesalazine, sulfasalazine	Induce AP by causing the pancreas hyperemia' edema and releasing the histamine that activates the pancreatic enzyme
Anti-inflammatory drug	Macrolides antibiotics, erythrocin, metronidazole, ceftriaxone, acheomycin	Induce AP through promoting kinetic effect and the role of Oddi sphincter spasm leading to the elevation of main pancreatic duct pressure; promote cholestasis and formation of the gallstone; interfere with the hepatic protein synthesis in the cell
Diuretic	Thiarizonaide	Direct toxic effect pancreatic; microcirculation dysfunction; hyperlipidaemia
Antiretroviral drug	Proteinase inhibitor, nucleoside reverse transcriptase inhibitor	Drugs infection; cause the body metabolic disorder including insulin resistance and blood sugar elevation
Antineoplastic drug	l-asparaginase, azathioprine	Direct toxic effect leads to pancreatic parenchymal's coagulation necrosis and hemolysis
Statin	Simvastatin	Direct toxic effect of the pancreas and toxic metabolite accumulation; drug-induced rhabdomyolysis or via the metabolism of CYP3A4
ACEI	Captopril, benazepril quinapril, ramipril	Restrictive edema of pancreatic duct or angioedema
Contraceptive	Progestin, estrogen	Aggravate the degree of hyperlipidemia and hypercoagulable state of patients

ACEI = angiotensin-converting enzyme inhibitors, AP = acute pancreatitis.

drugs that may induce AP in patients undergoing chemotherapy include paclitaxel, ifosfamide, vinorelbine, cisplatin, cytarabine, retinoic acid, and L-asparaginase. Badalov et al[4] classified the drugs that can induce DIP into 4 categories (Classes I-IV), with Class I further divided into Ia and Ib. Class Ia drugs are those with at least 1 case report of positive challenge test, where other causes, such as ethanol, hypertriglyceridemia, and gallstone disease, are ruled out. Class Ib drugs are those with at least 1 case report of positive challenge test; however, other causes could not be ruled out. Class II drugs are those with at least 4 case reports in the literature with consistent latency (≥75% consistency among the cases). Class III drugs are those with at least 2 case reports in the literature without consistency in latency or without positive challenge test. Class IV drugs are those with only 1 case report and no positive challenge test. In our study, lobaplatin–etoposide combination treatment has not been previously reported to induce DIP; thus, this combination therapy was classified as a Class Ia drug.

Many drugs can cause DIP; in addition, the time between the first drug use and the appearance of pancreatitis symptoms is inconsistent; thus, early and accurate diagnosis of AP is difficult. Similar to the diagnosis of drug-induced liver injury (DILI), the diagnostic criteria of DIP include meeting the diagnostic criteria of AP[22]; AP onset during the period of drug administration; ruling out other common causes of AP; alleviation or disappearance of AP symptoms after withdrawal of the causative drug; and reappearance of AP symptoms after readministration of the suspected drug (positive challenge test). Similar to the conventional diagnosis of AP, the diagnosis of DIP depends on conducting a comprehensive analysis of the clinical manifestations, laboratory examination, and radiographic examination.[9,19,23,24] It is worth noting that another characteristic that differentiates DIP from AP is that the patient's condition should improve or recover completely after cessation of drug administration, whereas continuous administration of the same drug will lead to recurrence of AP.[25]

Prevention of DIP requires identification of the common causative drugs, particularly Class I and II drugs that have a high level of evidence. In addition, high-risk groups, such as children, women, elderly, patients with advanced acquired immune deficiency syndrome (AIDS), patients with inflammatory bowel disease, and cancer patients receiving chemotherapy, should be identified.[16] In-depth understanding of the pathogenesis of DIP helps to prevent the occurrence of related adverse effects. Once diagnosis of DIP is confirmed, the causative drug should be immediately discontinued to prevent ongoing damage to the pancreas. In addition, the other relevant treatment regimens are the same as those used for conventional treatment of AP.

DIP provides insights into the potential importance of metabolism in AP. Here, we first reported a case of a lung cancer patient who developed sudden abdominal pain, bloating, nausea, and vomiting while undergoing chemotherapy with a combination of etoposide and lobaplatin. Moreover, both radiographic and laboratory data indicated AP. There are currently no clinical reports of AP induced by etoposide and lobaplatin. The patient did not have a history of common causes of AP, such as biliary tract disease, alcoholism, excessive eating and drinking, hyperlipidemia, and hereditary AP. Furthermore, discontinuation of chemotherapy and administration of AP-targeted treatment for 2 weeks resulted in a significant improvement of the symptoms, whereas resuming chemotherapy led to AP relapse. Therefore, we concluded that these chemotherapeutic agents could induce AP. We believe that these results can improve the understanding of the adverse effects of chemotherapeutic drugs. If cancer patients undergoing chemotherapy experience sudden, unexplained symptoms in the upper abdomen, the clinician should be aware of the possibility of AP, other than considering the side effects of chemotherapy on the gastrointestinal tract. The patient should be observed closely, and appropriate measures should be taken rapidly to identify the possible drugs that may induce AP. In addition, AP-targeted treatment should be considered to avoid more serious complications. In addition, the patient and his/her family should be informed of the name of the specific drug responsible for AP to avoid AP relapse because of readministration, thereby reducing patient suffering and unnecessary treatment costs.

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