Valproic acid 사용과 관련된 급성췌장염에 합병된 출혈성 가성낭종 1예

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A Large Hemorrhagic Pseudocyst in Patient with Valproic Acid-Induced Severe Acute Pancreatitis: A Case Report

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The occurrence of valporic acid (VPA)-induced pancreatitis is a rare condition, predominantly observed in adolescent. Also, the occurrence of VPA-associated with hemorrhagic pseudocyst is extremely rare. We report the case of a 54-year-old man who had been taking VPA for uncontrolled seizures. He was admitted to our hospital with complaints of abdominal pain and diagnosed with acute on chronic pancreatitis. There were no other causes explaining pancreatitis, and it was thought to be due to VPA therapy. Despite of cessation of VPA, there was ongoing severe abdominal pain with fever. The patient underwent follow-up CT, which revealed a large loculated fluid collection that was observed with intra-cystic hemorrhage. After treatment with percutaneous catheter drainage, he was discharged with regression of the pancreatic pseudocyst. VPA-associated pancreatitis with hemorrhagic pseudocyst is rare but possible. Therefore, this possibility should be considered in the cause of hemorrhagic pseudocyst in a patient taking VPA.

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INTRODUCTION

Valproic acid (VPA) is an important anti-epileptic drug with a broad spectrum of anti-epileptic activity. It is used in a variety of disorders, including idiopathic and symptomatic generalized epilepsies and, in some cases, symptomatic focal epilepsies, as well as in trigeminal neuralgia, migraines, and bipolar disorder.¹ Despite its many uses, it has serious ad-

verse effects such as hepatotoxicity, hyperammonemic encephalopathy, coagulation disorders, and pancreatitis. Among these, the incidence of VPA-associated pancreatitis has been estimated to be 1:40,000.^{2,3} The toxic effects it provokes can be dose-dependent or idiosyncratic. Idiosyncratic reactions to VPA are adverse effects not directly related to the pharmacodynamic mechanisms of the drug, and they can take place in an unpredictable way via abnormal inter-

Fig. 1. (A & B) Portal phase-enhanced computed tomography (CT) initially performed in the emergency department showed multifocal peripancreatic fat infiltration, large amounts of fluid collection in the right pericolic area, and heterogeneous enhancing parenchyma in the pancreatic head with multiple tiny calcifications (C & D) Endoscopic ultrasonography (EUS) showed hypoechoic pancreatic parenchyma with scattered high-echo spots and multiple tiny calcifications in the pancreatic head without gallstones or bile duct stones.

actions between the drug and the organism. Such interactions are usually mediated by immunologic or cytotoxic effects triggered by the drug or its metabolites.⁴ The occurrence of a pancreatic pseudocyst as a complication of VPA-induced pancreatitis was first reported in 1984.⁵ Since then, seven more cases have been described,³ and seven of these eight patients were under the age of 20. In the cases found in the literature, the development of pancreatic pseudocysts occurred during both early and late treatment and was independent of VPA dose and titer. Conservative treatment of the cyst was administered in seven of eight cases; in

one patient the pseudocyst was primarily treated surgically. To date, there is no literature reporting a VPA-associated pancreatic hemorrhagic pseudocyst as a severe complication of treatment.

We herein report a case of an acute, large hemorrhagic pseudocyst in a patient with pancreatitis after exposure to VPA who responded successfully and dramatically to percutaneous catheter drainage as the sole therapeutic management. A literature review of pancreatitis after VPA treatment revealed a small number of patients with pancreatic pseudocysts and a few cases involving hemorrhagic pseudocysts.

Fig. 2. (A - D) Portal phase-enhanced CT preformed on the fourth hospital day showed a large loculated fluid collection (maximal diameter: 17 cm) with intracystic hemorrhage compatible with a large hemorrhagic pseudocyst.

CASE REPORT

A fifty-four year-old man previously treated in our hospital's neurosurgery department was admitted to the emergency department with complaints of abdominal pain radiating to the back starting two days prior to presentation. He had been taking oral VPA (25 mg/kg/d) for approximately one year for uncontrolled seizures after craniotomy for intra-cerebral hemorrhage. He did not smoke or consume alcohol, and he was not obese (body mass index: 27 kg/m²). Sixth months earlier, he had received treatment for acute pancreatitis of unknown etiology and recovered after con-

servative treatment. On physical examination, he was febrile with a pulse rate of 92 beats/minute and a blood pressure of 154/84 mmHg. Abdominal physical examination revealed epigastric tenderness with guarding. Laboratory tests showed the following results: white blood cell (WBC) count, 18,640/uL; hemoglobin (Hb) level, 15.3 g/dL; serum amylase, 551 IU/L (reference range: 54-168 IU/L); serum lipase, 598 U/L (reference range: 13-60 U/L); and total bilirubin, 1.64 mg/dL. Other biochemistry parameters, including liver function tests, serum calcium, and serum triglycerides, were normal. Multi-detector computed tomography (MDCT) showed multifocal peripancreatic fat infiltration, a large flu-

id collection in the right pericolic area, and heterogeneous enhancing parenchyma in the pancreatic head with multiple tiny calcifications, which was compatible with acute on chronic pancreatitis (Fig. 1, A & B). Endoscopic ultrasonography demonstrated hypoechoic pancreatic parenchyma with scattered high-echo spots and multiple tiny calcifications in the pancreatic head without gallstones or bile duct stones (Fig. 1, C & D). A serum VPA level was 54.3 ug/mL (therapeutic range, 50-100 ug/mL). His oral VPA was discontinued immediately and he was started on levetiracetam after consultation. On the fourth day of the patient's hospital stay, his abdomen was diffusely and severely tender to palpation, he was breathing inefficiently with mild dyspnea and an oxygen saturation level below 90% on room air, and he had a high fever. The patient underwent follow-up MDCT imaging on hospital day 4, which revealed a large loculated fluid collection (maximal diameter: 17 cm) that was observed with intracystic hemorrhage. Considering the appearance of the lesion with internal hemorrhage, radiologists suggested the possibility of a large hemorrhagic pseudocyst (Figure 2). Laboratory data were as follows: WBC count, 14,900/uL; Hb level, 8.4g/dL; platelets, 89,000/uL; total bilirubin, 2.18 mg/dL; alanine aminotransferase, 53 IU/L; aspartate aminotransferase, 143 IU/L; and C-reactive protein, 20.41 mg/dL. Pancreatic enzyme testing revealed that serum lipase had decreased to 80 U/L and amylase was found to be 99 IU/L. We started meropenem and an aminoglycoside for possible severe sepsis. There was no evidence of current hemorrhage or pseudoaneurysm on angiography of the superior mesenteric artery and celiac trunk. On the sixth hospital day, he was treated with percutaneous catheter drainage for the large hemorrhagic pseudocyst after current hemorrhage or pseudoaneurysm was ruled out. He showed a relatively acceptable post-procedure clinical course with regression of the pancreatic pseudocyst in subsequent follow-up MDCT, and he was discharged from the hospital 21 days after intervention. On follow-up testing three month post-discharge, including clinical examination, routine laboratory tests, and MDCT, our patient was healthy and asymptomatic.

DISCUSSION

We herein describe an extremely rare case of VPA associated with hemorrhagic pseudocyst. VPA is the most widely used first-generation antiepileptic drug, and is prescribed predominantly in epilepsy and psychiatric disorders. VPA has good efficacy and pharmaco-economic profiles, as well as a relatively favorable safety profile;⁶ however, adverse drug reactions have been reported in relation to VPA use, either in monotherapy or polytherapy with other antiepileptic drugs. In particular, it is likely the most frequent cause of drug-induced acute pancreatitis.⁷⁻¹⁰ The association between acute pancreatitis and VPA therapy was first described in 1979 by Batalden et al.¹¹ and Camfield et al.⁷ Since 1979, several single-case reports or case series have been reported. Among these, the study of Sinclair et al.¹² showed that the dose of VPA, duration of treatment, serum VPA level, generic preparation, and the presence of concomitant antiepileptic drugs did not seem to be risk factors for acute pancreatitis. These findings suggested that the mechanism of toxicity likely involves metabolic idiosyncrasy, which is mediated by aberrant VPA metabolism.² In general, the development of drug-induced pancreatitis has been linked to more than 55 different drugs. Specifically, drug-induced pancreatitis is possibly caused by azathioprine, furosemide, tetracycline, metronidazole, isoniazid, rifampicin, VPA, sulphonamides, cyclosporine, and some antineoplastic drugs. In our case, there were no other causes (infection, trauma, obstruction, hypercalcemia, hypertriglyceridemia, or use of other medications) explaining acute pancreatitis, and it was thought to be due to VPA therapy.

The largest study¹³ investigating the risk factors for VPA-induced pancreatitis demonstrated that pancreatitis was found to be more frequent in young patients with polytherapy and that pancreatitis occurred primarily during the first year after initiation of VPA therapy. This study is not in concordance with our case, which pertained to a patient was not in the most-affected age group. In addition, the patient was using VPA monotherapy at the appropriate dose (25 mg/kg/day), with an appropriate serum level (54.3 mg/dL),

reinforcing the idiosyncratic nature of this adverse reaction.⁴ Unique to our case, our patient was initially examined because of abdominal pain, and he was diagnosed with uncomplicated acute pancreatitis associated with VPA therapy. Owing to ongoing severe abdominal pain with fever, follow up MDCT was done, which revealed a large hemorrhagic pseudocyst, indicating severe complicated pancreatitis. Its etiology indicated that it may have been primarily related to VPA. Other examination results for the etiology of acute pancreatitis were negative, including a lack of trauma history, no infectious cause, no use of other medication, and normal lipid levels. After cessation of VPA and the application of percutaneous catheter drainage, the patient recovered both clinically and radiologically. Consequently, the patient was discharged with complete resolution. In conclusion, acute pancreatitis is a rare, severe adverse reaction to VPA therapy, although the safety of VPA has been proven in several clinical trials. If a patient who is receiving VPA develops abdominal pain, VPA-associated pancreatitis must be considered. If there is persistent abdominal pain, radiologic screening must be planned to exclude complicated pseudocyst with acute pancreatitis, as occurred in our case. Because early detection and prompt discontinuation of VPA may prevent long-term complications, physicians must be very cautious about the complications associated with VPA and recognize their occurrence as soon as possible. Another point that we considered was that a large hemorrhagic pseudocyst, which developed in our patient, is extremely rare in respect to the use of VPA. In this situation, the patient might be treated successfully with prompt discontinuation of the drug and insertion of percutaneous catheter drainage.

요약

발프로산은 가장 보편적으로 사용되는 항간질제로서 약제 유발성 췌장염의 흔한가능한 원인으로 잘 알려져 있다. 그러나 발프로산 유발성 췌장염의 유해사례로서 발프로산 유발성 췌장염의 국소 합병증으로서 췌장 가성낭종은 매우 드물며 주로 소아청소년기에 호발한다고 알려져 있다. 또한 이

로 인한 발프로산 유발성 췌장염에 병발된 출혈성 가성낭종은 보고된 증례가 없을 정도로 드물다. 이에 본 저자들은 발프로산을 복용한 후 발생한 급성 출혈성 췌장 가성낭종을 경피적 배액술로 성공적으로 치료한 증례를 보고하고자 한다.

국문 색인: Valproic acid, 출혈, 췌장 가성낭종, 췌장염

Conflicts of Interest

The author has no conflicts to disclose.

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