Severe Wernicke encephalopathy and acute pancreatitis due to all-trans-retinoic acid and arsenic trioxide during treatment of acute promyelocytic leukaemia: a case report

Yan Jiang¹ and Linhua Ji²

Abstract
A 55-year-old woman developed acute promyelocytic leukaemia during treatment with all-trans-retinoic acid and arsenic trioxide. Initially, she presented with symptoms of epigastric pain, vomiting, and nausea, and she developed acute pancreatitis. She was treated with parenteral nutritional supplementation for 20 days. However, the patient continued to develop refractory hyponatraemia, hypotension, and apathy. Finally, the patient was diagnosed with Wernicke encephalopathy (WE) using head magnetic resonance imaging. The patient underwent high-dose intravenous thiamine administration, and her symptoms were alleviated. WE is a rare adverse event during acute pancreatitis therapy. Acute pancreatitis that is caused by all-trans-retinoic acid and arsenic trioxide is a rare complication of acute promyelocytic leukaemia during chemotherapy. Further study is essential to improve our comprehension of the risk factors for complications in patients with acute promyelocytic leukaemia, considering that the associated complications were potentially caused by multiple etiological factors. A better understanding of these risk factors may help to improve the prognosis of patients with acute promyelocytic leukaemia at an early stage.
**Keywords**
Acute promyelocytic leukaemia, arsenic trioxide, acute pancreatitis, all-trans-retinoic acid, Wernicke encephalopathy, prognosis, chemotherapy

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**Introduction**
Acute promyelocytic leukaemia (APL) is an idiopathic subtype of acute myeloid leukaemia (AML), which accounts for 10% to 15% of all adult AML cases. APL is considered to be a treatable illness with a cure rate of 80% and a complete remission rate of 90%, which is attributed to treatment with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO). Early-stage APL may be correlated with more than one complication, including bleeding, disseminated intravascular coagulation (DIC), hyperleukocytosis, and infections. Complications arising from infections and DIC are the leading causes of death in patients with APL. Acute pancreatitis (AP) is a rare complication of APL that has been previously studied. Some cases reported that the occurrence of AP was related to the application of arsenic, and some cases were associated with the administration of retinoic acid, which was secondary to hypertriglyceridemia or differentiation syndrome. Wernicke encephalopathy (WE) is caused by thiamine deficiency and is strongly related to malnutrition, which may result from chronic alcohol abuse, gastrointestinal surgery, prolonged vomiting, or chemotherapy. WE, which is regarded as an acute and severe neuropsychiatric syndrome, is characterised by symptoms of confusion, ophthalmoplegia, and gait ataxia. If it is not diagnosed early, WE is associated with a high mortality rate (>20%).

Here, we present a typical case of a 55-year-old woman with APL who developed WE during treatment for AP after therapy with ATO and ATRA. Some previous cases have reported that WE is induced by AP and that AP was induced by treatment with ATO and ATRA in patients with APL. However, no reports have described a case of a patient with WE and APL after treatment with ATO and ATRA, or examined whether the administration of ATO and ATRA could induce WE in patients with AP.

**Case presentation**
An obese 55-year-old female patient was transferred to our hospital in August 2019 because of gingival bleeding for 7 days along with low-grade fever and cough for 3 days. She was pale, with multiple purpuras over the body, wet purpura in the buccal mucosa, no icterus, no hepatosplenomegaly, and no lymphadenopathy. Her initial peripheral blood panel results were as follows: white blood cell (WBC) count, 57.87 × 10^9/L; haemoglobin (Hb), 101 g/L; platelet count (PLT), 26 × 10^9/L; prothrombin time, 12.7 s; activated partial thromboplastin time, 27.6 s; fibrinogen, 0.501 g/L; D2 polymer, 20.3 mg/L; and triglyceride, 3.48 mmol/L. No obvious abnormalities were observed on computed tomography (CT) imaging of the brain, chest, or abdomen. Peripheral blood cell morphology showed the presence of abnormal promyelocytes. Bone marrow immunophenotyping and cytogenetic analysis suggested APL. Polymerase chain reaction results for
promyelocytic leukaemia-retinoic acid receptor-α (PML-RARA) were positive. The bone marrow aspirate results are shown in Figure 1.

Immunophenotyping was performed, and the abnormal cell population (94% of tested cells) was positive for CD9, CD13, CD33, CD38, CD58, CD64, CD117, CD123, and myeloperoxidase (MPO). A chromosome analysis applying GTG-banding was conducted in accordance with standard procedures before treatment with ATRA, displaying a karyotype of 46 XX, add(5)(q33), add(6)(q21), add(11) (p11), t(15;17)(q22;q21). The patient scored more than 6 points and had a WBC count >10,000/μL, and in accordance with the World Health Organization classification, the National Comprehensive Cancer Network (NCCN), and the Chinese DIC scoring system, she was diagnosed with APL. She was considered to be at high risk because of her WBC count combined with DIC. Therefore, the patient was treated with ATRA (45 mg/m²), idabycin (IDA, 8 mg/m² for days 1–3), and ATO (0.15 mg/kg) in accordance with NCCN guidelines. Supplemental fibrinogen and platelets were administered, and the patient was monitored for DIC and differentiation syndrome. The patient’s initial DIC parameters showed some improvement within 5 days of starting ATRA. Unfortunately, on day 12 of ATRA and ATO therapy, the patient complained of epigastric pain, nausea, and vomiting. Peripheral blood test results revealed a WBC count of \(2.57 \times 10^9/L\), Hb of 101 g/L, PLT of \(23 \times 10^9/L\), and C-reactive protein of 27.30 mg/L, and physical examination results revealed tenderness in the epigastric pancreas. Abdominal colour Doppler ultrasound suggested cholecystitis, and an antibiotic was immediately administered, but the patient’s pain did not subside. Serum enzyme results showed lipase at 484.2 U/L (normal range, 0–60 U/L) and amylase at 216 U/L (normal range, 35–135 U/L). These biochemical parameters were suggestive of AP, and contrast-enhanced CT of the abdomen (Figure 2) revealed bulky oedematous pancreatitis without any necrotic areas.

Lipase and amylase were restored to their normal ranges after 8 days of hydration and analgesia. However, the patient still felt intermittent abdominal pain and discomfort, resulting in a further decrease in her appetite. During 14-day parenteral nutrition supplementation, the patient developed hypotension and apathy. Her blood pressure dropped to 95/60 mmHg and was maintained at that level. The patient also developed refractory hyponatraemia, despite continuous administration of the appropriate sodium supplement for
7 days, and she still had apathy and confusion after 20 days of parenteral nutrition supplementation. In addition, she had developed a reduced range of motion, dysarthria, generalised muscle weakness, and vertical nystagmus. Neurological examination of the patient demonstrated slower pupillary reaction to light as well as more evident signs of nystagmus with paralysis of the bilateral abduction nerves. During this period, we performed a lumbar puncture. The patient’s intracranial pressure was within the normal range, and her brain CT was normal when she was admitted to the hospital. Finally, the patient was diagnosed with WE, which was confirmed using magnetic resonance imaging (MRI). The MRI showed symmetrical lesions in T2-weighted imaging and high fluid-attenuated inversion recovery signal intensity in the periaqueduct, third ventricle, and around the nipple body (Figure 3). High-dose intravenous thiamine administration was administered to the patient, and her symptoms resolved. Despite these efforts, the patient eventually stopped treatment due to financial concerns.

Discussion

The two most common causes of AP in the general population are alcohol abuse and common bile duct obstruction by gallstones. However, this patient had no history of alcohol consumption or gallstones and had a normal abdominal CT upon admission to hospital. However, she was obese and had hypertriglyceridemia. On day 14 of ATRA and ATO therapy, the patient was diagnosed with AP. After eliminating other possible factors, we highly suspected that AP was related to the administration of ATRA and ATO. AP in APL is a rare complication and the exact etiopathogenesis of AP remains unknown. Furthermore, both ATRA and ATO rarely cause AP. The common mechanism of AP with ATRA and ATO is derived from the development of hypertriglyceridemia. The presence of high triglyceride levels in this patient before treatment is consistent with the disease characteristics. Studies have found that ATO may play a role in direct islet cell injury in the pancreas, especially pancreatic islet endocrine cellular components in APL.13

While some of the patient’s indicators of AP improved after multiple treatments, the patient unfortunately presented with neurological symptoms and developed WE as a consequence of severe vomiting and poor oral intake, both of which may be predisposing factors. WE results from thiamine deficiency and features an acute or subacute onset of ataxia, acute mental confusion, and ophthalmoparesis. Thiamine plays a

Figure 2. Contrast computed tomography of the abdomen showing a bulky oedematous pancreatitis.
vital role in cerebral fuel utilisation and thiamine deficiency can lead to initially reversible nervous system damage resulting from the overproduction of reactive oxygen species along with blood-brain barrier destruction.

WE is, unfortunately, associated with a high mortality rate, which can be as high as 20%. Patients in whom a diagnosis is missed will fail to be sufficiently treated. Because of the high rate of missed WE diagnoses, it is suggested that WE should be considered an usual differential diagnosis for patients with changing mental status as well as other relevant symptoms. This is particularly true for patients with a history of malnutrition, gastrointestinal surgery, and alcohol consumption. For patients who are strongly suspected to have WE, it is proposed that parenteral therapy with

Figure 3. MRI showed unusual symmetric cortical abnormalities in the frontal and parietal lobes, as well as typical lesions surrounding the third ventricle and aqueduct. This is consistent with Wernicke encephalopathy.
thiamine should be considered. In addition, MRI should be conducted to confirm a WE diagnosis provided that this modality is available. A diagnosis of WE can be confirmed through typical clinical manifestations and MRI reports.

AP is a rare complication of APL during chemotherapy, and multiple etiological factors can trigger AP in these patients. Among these factors, drug-induced AP is the most common, and WE is a rare adverse event in the treatment of AP. There have been many reports about ATO- and ATRA-induced AP and AP-induced WE, but this is the first report of a patient with WE due to APL during treatment with ATO and ATRA. It is unusual that, while this patient did not completely fast and her AP was effectively controlled, she still developed WE, and occurrence of adverse events may be related to the use of ATRA and ATO.

It can be concluded from this case report that physicians need to pay more attention to some issues that may otherwise be ignored to avoid rare adverse events.

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The authors declare that there is no conflict of interest.

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Ethics statements and consent
All patient details have been de-identified such that the patient’s identity remains anonymous, and we obtained verbal consent from the patient to publish the case report and attached images.

ORCID iD
Yan Jiang https://orcid.org/0000-0001-9633-8900

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