Acute Pancreatitis During All-trans-retinoic Acid Treatment for Acute Promyelocytic Leukemia in a Patient Without Overt Hypertriglyceridemia

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All-trans-retinoic acid (ATRA) has been successfully used in the treatment of acute promyelocytic leukemia (APL). One of its adverse effects is acute pancreatitis. In the literature, a proposed cause of acute pancreatitis is hypertriglyceridemia. Here, we present the case of a 45-year-old male with APL, treated with ATRA combined with induction chemotherapy (cytarabine and idarubicin), who developed acute pancreatitis without overt hypertriglyceridemia. This finding suggests that hypertriglyceridemia might not be the sole contributing factor in the pathogenesis of ATRA-induced acute pancreatitis and that attention should be paid to the possibility that ATRA treatment causes acute pancreatitis in the absence of overt hypertriglyceridemia.

Key words: acute promyelocytic leukemia – acute pancreatitis – all-trans-retinoic acid – hypertriglyceridemia

INTRODUCTION

All-trans-retinoic acid (ATRA) has been successfully used in the treatment of acute promyelocytic leukemia (APL) (1,2). Reported adverse effects vary from dry skin to retinoic acid syndrome (3). Acute pancreatitis is a rare adverse event which is purported in the literature to be due to hypertriglyceridemia during ATRA treatment (4–6). Herein, we report the case of an APL patient, treated with ATRA, who developed acute pancreatitis in the absence of significant hypertriglyceridemia.

CASE REPORT

A 45-year-old Chinese male patient with APL developed easy-gum bleeding initially and his complete blood count (CBC) showed a white blood cell count (WBC) of 4890/mm³, red blood cell count (RBC) of 4.20 × 10⁶/mm³, platelet count of 44 000/mm³ and 4% blasts. He had no prior history of hypertension, diabetes mellitus, hyperlipidemia, gallstones or alcoholism that could precipitate acute pancreatitis. Bone marrow cytology revealed abnormal cellularity indicating APL, and the cytogenetic study showed the presence of t(15,17) (q22;q12). The initial serum biochemistry data were normal. The patient received ATRA (45 mg/m²/day, until remission) on day 1 and induction chemotherapy on day 3 with cytarabine (200 mg/m²/day for 7 days) and idarubicin (10 mg/m²/day for 3 days) initially. He suffered from epigastric pain 2 weeks after ATRA treatment. The biochemistry profile, except for an elevated amylase level of 241 U/l (normal range <190 U/l) and lipase level of 961 U/l (normal range <190 U/l), was normal. Computed tomography (CT) of the abdomen revealed no gallstones but did find a swollen pancreas, compatible with acute pancreatitis. [At this time, Ranson’s score was 1, serum lactic dehydrogenase was 371 U/l, WBC was 3900/mm³ (neutrophil 95.3%), RBC was 3.70 × 10⁶/mm³, and platelet count was 23 000/mm³ (Fig. 1).] The peak level of triglyceride was only 343 mg/dl (range: 98–343 mg/dl, normal value = 200 mg/dl) throughout the whole course, and the lipase level remained elevated. At the same time, the serum level of cholesterol did not exceed 200 mg/dl (normal value = 240 mg/dl). Because complete remission was achieved, ATRA was discontinued after 6 weeks. Follow-up evaluation revealed that the serum lipase level decreased from 678 to 525 U/l. Later, the patient received ATRA as a maintenance treatment. However, the lipase level increased again from 525 to 808 U/l 8 days after the reinstitution of ATRA treatment, prompting discontinuation of the ATRA. Two weeks later, the levels of lipase and amylase were normal without further treatment (Fig. 2).

DISCUSSION

The rare adverse events of ATRA include acute pancreatitis, hypercalcemia, male infertility, bone marrow fibrosis, bone marrow necrosis, thromboembolic events and Sweet’s syndrome (3). To the best of our knowledge, only three cases of
ATRA-related acute pancreatitis have been previously reported in the English literature (4–6). All three patients had a triglyceride level of >500 mg/dl (range, 687–1425 mg/dl) (7). The hypertriglyceridemia was the putative cause of acute pancreatitis after ATRA in these cases. In the literature, hyperlipidemic acute pancreatitis has been reported, with triglycerol levels reaching 1000–2000 mg/dl (8). ATRA-induced pancreatitis (National Cancer Institute Common Toxicity Criteria Grade 3) was suspected in our patient because of the concordance of elevated lipase level and ATRA treatment, and its occurrence seemed less likely to be related to the triglyceride level. Therefore, hypertriglyceridemia might not be the sole contributing factor in the pathogenesis of the ATRA-induced acute pancreatitis. Later treatment with consolidation chemotherapy with cytarabine (200 mg/m²/day for 5 days) and idarubicin (10 mg/m²/day for 2 days) did not lead to acute pancreatitis. Therefore, the acute pancreatitis was not dependent on cytarabine and idarubicin. The pathogenesis of acute pancreatitis has remained poorly understood. The disturbance of cellular metabolism in pancreatic acinar cells was presumed to be due to injury initiated by an inappropriate, premature activation of proteolytic and lipolytic zymogens, but this mechanism has not been demonstrated (9). After pancreatic acinar cell injury, cytokines, such as pro-inflammatory mediators [platelet activating factor, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-2, IL-6, nitric oxidase, reactive oxygen radicals, and arachidonic acid metabolites] and chemokines [IL-8 and monocyte chemoattractant protein-1 (secreted from normal T cells)], could worsen the acute pancreatitis (10). Interestingly, the cytokines produced by APL cells after ATRA-induced differentiation also include the IL-1β, IL-8, and TNF-α that may play a role in the pathogenesis of ATRA-related pancreatitis (11,12).

This case should alert physicians to the possibility that acute pancreatitis may arise during ATRA treatment, even in the absence of overt hypertriglyceridemia.

Figure 1. Focal mild swelling of the head of the pancreas (arrows). Balthazar grade B pancreatitis was indicated.

Figure 2. The time course of change of amylase, lipase, triglyceride (TG) and cholesterol (CHOL) during all-trans-retinoic acid (ATRA) treatment. The patient was treated with ATRA between July 24 and September 12, 2003, and again between September 23 and 30, 2003.
References


