


## CASE REPORT

# Arsenic toxicity manifesting as profuse watery diarrhea during induction therapy for acute promyelocytic leukemia

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## Abstract

Arsenic trioxide (ATO) is generally well tolerated for treatment of APL. We present a patient with severe watery diarrhea and pancreatitis thought to be due to ATO toxicity in the setting of obesity and acute kidney injury. Future studies evaluating ATO levels in patients experiencing toxicities may help guide dose modifications.

## KEYWORDS

APL, APLM, arsenic, diarrhea, obesity, renal insufficiency

## 1 | INTRODUCTION

The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), with or without cytotoxic chemotherapy, has dramatically improved treatment outcomes for patients with acute promyelocytic leukemia (APL), leading to high rates of cure.<sup>1,2</sup> Within the context of APL therapy, both ATRA and ATO are generally well-tolerated, and side effects are typically not barriers to therapy. Common adverse events (AEs) from ATRA include headaches, rashes, hypercholesterolemia, hypertriglyceridemia, transaminitis, and less commonly, pseudotumor cerebri and pancreatitis. Potentially

severe but treatable complications include hyperleukocytosis and differentiation syndrome.<sup>1</sup> Common side effects of ATO include nausea, vomiting, and mild diarrhea. More serious ATO toxicities include cardiac AEs, such as QTc prolongation or arrhythmias, neurologic AEs, such as peripheral neuropathy, varicella-zoster reactivation, risk of secondary malignancies, and rarely pancreatitis.<sup>3,4</sup>

While severe diarrhea is a known presenting side effect of acute arsenic poisoning from environmental exposure,<sup>5</sup> to our knowledge, profuse watery diarrhea has not been described in APL patients receiving ATO at treatment doses. Here, we report a patient with low-risk APL treated with standard-dose

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ATRA and ATO, whose treatment course was complicated by 3–6 liter large-volume diarrhea and pancreatitis. She was found to have a high urine concentration of inorganic arsenic. Symptoms resolved promptly with therapy discontinuation, suggestive of acute ATO toxicity.

## 2 | CASE REPORT

A 72-year-old woman with a history of obesity (BMI 42) was admitted to the hospital with fatigue, nose bleeds, and easy bruising. Blood counts were notable for a white blood cell count of 5.34 K/ $\mu$ L, platelet count of 13 K/ $\mu$ L, and hemoglobin of 12.4 g/dL. A blood smear revealed 19% promyelocytes and 9% granulated blasts with auer rods. Coagulation studies were significant for a PT/INR of 18.3 seconds/1.5, PTT 30.2 seconds, d-dimer 8115 ng/mL, and fibrinogen of 77 ng/mL. Chemistries were notable for a creatinine of 0.8 mg/dL (baseline 0.5–0.8 mg/dL). Cytogenetic studies returned with  $t(15;17)(q24;q21)$  and trisomy 8 with PCR confirming a *PML-RARA* fusion, diagnostic for APL. She was promptly started on standard-dose ATRA 45 mg/m<sup>2</sup> split as an oral twice daily dose on admission with the addition of ATO 0.15 mg/kg IV daily starting day 5 upon confirmation of diagnostic studies using her actual body weight (ABW) of 103 kg.

On day 8, she was noted to have dyspnea, headache, lower extremity edema, and a new oxygen requirement, concerning for differentiation syndrome. She was started dexamethasone 10 mg IV twice daily with resolution of her symptoms. Between day 19 and 26, dexamethasone was slowly tapered from 10 mg daily to 1 mg daily and discontinued on day 27. She also developed intermittent loose stools, and by day 30, she developed a fever to 102F°. Broad-spectrum antibiotics were started and a comprehensive infectious workup was pursued. Blood cultures, SARS-CoV-2 nasopharyngeal PCR, and stool studies for bacterial culture, *Clostridium difficile*, ova/parasite, adenovirus, rotavirus, and norovirus were all negative. Antibiotics were discontinued after a brief 6-day course.

By day 32, the frequency and volume of her stools significantly increased. Stool volumes ranged between 3 and 6 liters per day and were nonbloody with a rice-water appearance. Fasting had no impact on stool volume. She reported generalized and crampy abdominal pain without nausea or vomiting. CT abdomen and pelvis demonstrated findings consistent with ileus. Given the patient's persistent diarrhea, the gastroenterology service was consulted for further evaluation and management.

A colonoscopy on day 34 revealed endoscopically normal-appearing colonic mucosa. Random biopsies were collected. Histopathologic evaluation revealed evidence of surface injury, atrophic crypts, and scattered neutrophilic

crypt microabscesses (Figure 1A). Stains for cytomegalovirus were negative. The pathologic differential diagnosis included ischemic-type injury, drug injury, and infection.

Around the same time, the patient began reporting epigastric tenderness with nausea. Workup revealed an elevated lipase at 428 U/L (ULN 60 U/L) with abdominal CT scan notable for acute edematous pancreatitis. She was started on aggressive fluid resuscitation with improvement of her symptoms within 2–3 days.

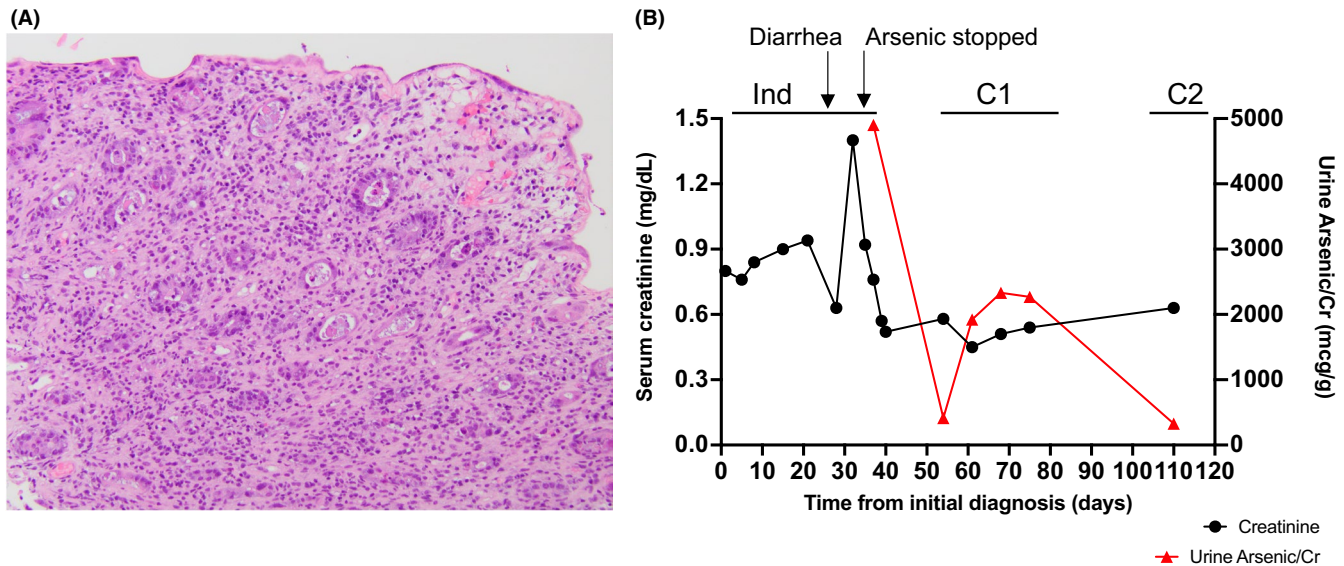
Given the patient's negative infectious workup and absence of hemodynamic instability that would predispose to ischemic injury, drug effect was thought to be the most likely cause of the patient's symptoms. On reviewing the patient's medications and temporal clinical course, the large-volume rice-water diarrhea and the acute pancreatitis were felt to be most consistent with classic symptoms of acute arsenic toxicity. No other medications were clear culprits that could explain the patient's presentation. Given the concerns for drug toxicity and as her absolute neutrophil count and platelet count recovered to >1000/ $\mu$ L and >100 K/ $\mu$ L, respectively, both ATRA and ATO were stopped on day 35. A random urine sample was sent for arsenic level testing on day 37 and was notable for elevated inorganic arsenic (>5000 mcg/L) with an arsenic to creatinine (Cr) ratio of >4902 mcg/g Cr. Around 4 days after stopping therapy, the patient started having formed stools.

Three weeks postdischarge, urine was retested prior to starting ATRA/ATO consolidation therapy; arsenic levels remained elevated but decreasing (Figure 1B) with an inorganic arsenic level of 482 mcg/L and arsenic to creatinine ratio of 413 mcg/g Cr. Given concerns for prior severe toxicity, arsenic was dose reduced by 50% to 0.075 mg/kg ABW for consolidation cycle 1, which she tolerated well without further episodes of diarrhea.

## 3 | DISCUSSION

Arsenic is a naturally occurring metalloid found in water, soil, and air. It is found as both an organic and an inorganic compound and can exist in several different oxidation states in nature, the trivalent form being the most toxic given its ability to react with and inhibit various sulfur-containing enzymes, thus inhibiting several essential metabolic systems.<sup>5</sup> Environmental exposure to arsenic compounds can lead to gastrointestinal toxicities including nausea, vomiting, hemorrhage, and large-volume watery diarrhea.<sup>5–7</sup> Other acute toxicities can include anemia, peripheral neuropathy, hyperpigmentation, and fatal arrhythmias.<sup>5–7</sup> Chronic exposures have resulted in cancers of the skin, bladder, kidney, and lung.<sup>7</sup>

While the toxicity of arsenic has long been established, the beneficial role of ATO as a highly effective differentiating



**FIGURE 1** A, Hematoxylin and eosin stain of random colon biopsy demonstrating atrophic crypts and scattered neutrophilic crypt micro-abscesses. B, Serum creatinine levels (black circles) and spot urine arsenic to creatinine (Cr) ratio (mcg/g Cr) (red triangles) shown during induction (Ind), consolidation 1 (C1) and start of consolidation course 2 (C2). Diarrhea started around day 28 and resolved around day 39. Arsenic was stopped on day 35 during induction

therapy of APL was only more recently identified. Arsenic trioxide functions by binding to the promyelocytic leukemia protein (PML) moiety of the PML-RARA oncoprotein, leading to its degradation and the induction of apoptosis of leukemic promyelocytes.<sup>1,2,4</sup> Its synergy with ATRA has led to remission rates of up to 95% and cure rates exceeding 80%, when used in combination.

Arsenic trioxide is quickly cleared from the plasma and distributed predominately to the liver, kidney, muscle, and skin.<sup>5</sup> Most ingested inorganic arsenic is hepatically metabolized through oxidative methylation, creating monomethylarsinic acid (MMA), and dimethylarsinic acid (DMA), reaching maximum serum levels between 16-24 and 24-48 hours, with a half-life of 32 and 72 hours, respectively. Inorganic arsenic along with MMA and DMA are eliminated in the urine.<sup>3</sup> Since there are other forms of arsenic and several metabolites of varying toxicities, including relatively nontoxic forms from fish and other foods (arsenobetaine, arseno sugars), speciation of urine arsenic samples is recommended where possible rather than measurement of total urine arsenic alone. Variations in susceptibility to ATO toxicity and the rate of ATO metabolism have been observed between populations, which may be due to polymorphisms of multiple methylation genes<sup>7</sup> and differences in gut microbiome.<sup>8</sup>

Within the context of APL therapy, underlying comorbidities may also potentially contribute to an increased risk of ATO toxicity. In one retrospective study of low-to-intermediate risk APL patients receiving ATO, obese patients with a BMI  $\geq 35$  kg/m<sup>2</sup> were found to have a higher rate of dose holding or modifications due to AEs compared to patients with BMI  $<35$  kg/m<sup>2</sup>,<sup>9</sup> highlighting the need for additional studies

of dosing in this population since ATO is currently dosed based on ABW. In addition, patients with mild to severe acute kidney injury (AKI) have demonstrated decreased urinary excretion of ATO and its metabolites, with 1.4- to eightfold increased exposure after a multidose administration.<sup>10</sup>

In the case of our patient, pancreatitis and profuse large-volume diarrhea were two serious complications encountered approximately 4 weeks after the initiation of ATRA and ATO. The patient's urine arsenic levels 2 days after cessation of treatment were much higher than the detectable limit, and in a range reported in individuals with arsenic poisoning. Since monitoring of serum or urine arsenic levels is not currently routinely performed during APL therapy, levels are difficult to interpret given the lack of data on expected levels during therapy. However, our comprehensive workup along with the brisk clinical recovery after stopping ATO suggests that ATO toxicity led to the severe diarrhea. Potential contributing factors may have been underlying obesity and AKI during her induction course (Figure 1B). This case highlights the need to be vigilant for acute ATO toxicity in APL patients with potential predisposing comorbidities including obesity and renal impairment. Additional studies evaluating dosing in patients with comorbidities and evaluating the utility of urine arsenic monitoring in patients experiencing toxicities may be helpful to guide potential dose reduction strategies for toxicity mitigation.

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## CONFLICT OF INTEREST

Author and coauthors have no conflicts of interest to disclose.

## AUTHOR CONTRIBUTIONS

AO and VV: wrote the initial draft of the manuscript. TRB and RN: reviewed and edited the manuscript. RG: reviewed the manuscript. SS: contributed images and interpretation of pathology slides. DAV, PA, SM, AB, and ATF: reviewed the manuscript and managed the clinical care of the patient. All authors: approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## ETHICAL APPROVAL

The patient has given her informed consent to publish her case.

## DATA AVAILABILITY STATEMENT

Patient's data are available from the corresponding author upon reasonable request.

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