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Research Article

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A Storm Within Remission: Multisystem Complications of All-Trans Retinoic Acid-Arsenic Trioxide Therapy in Acute Promyelocytic Leukemia

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Abstract

Background

Acute promyelocytic leukemia (APML) is a hematologic emergency with high curative potential when treated with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). However, early-phase induction therapy may be complicated by serious adverse events requiring rapid recognition and management.

Case Presentation

We report the case of a 22 years old woman with newly diagnosed APML who developed multiple life-threatening complications during induction therapy with ATRA and ATO. These included significant QT interval prolongation, severe electrolyte disturbances, focal seizures, pseudo-ischemic chest pain likely due to coronary vasospasm, and dural venous sinus thrombosis (DVST). Temporary discontinuation of therapy, aggressive supportive care, and coordinated multidisciplinary management enabled full recovery and resumption of curative treatment.

Conclusion

This case underscores the importance of close monitoring and individualized, dynamic treatment strategies during ATRA-ATO induction in APML. Clinicians should maintain a high index of suspicion for both common and rare complications such as DVST and ATO-induced vasospasm. Early intervention and multidisciplinary collaboration are essential to safely navigate toxicity while preserving therapeutic efficacy.

Keywords: Acute Promyelocytic Leukemia, Differentiation Syndrome, Arsenic Trioxide, QT Prolongation, Dural Venous Sinus Thrombosis, Premature Ventricular Contractions (PVCs

1. Introduction

Acute promyelocytic leukemia (APML) is a distinct and highly curable subtype of acute myeloid leukemia (AML), characterized cytogenetically by the balanced reciprocal translocation t (15;17) (q24;q21), which results in the formation of the PML-RARA fusion gene [1,2]. This translocation leads to a block in myeloid differentiation at the promyelocyte stage, resulting in the accumulation of abnormal promyelocytes in the bone marrow and peripheral blood [1,3]. Clinically, APML presents with a unique coagulopathy profile-most notably disseminated intravascular coagulation (DIC) and hyperfibrinolysis-which historically contributed to high early mortality rates, particularly from intracerebral or pulmonary hemorrhage if diagnosis and treatment were delayed [2,4,10,16].

The introduction of all-trans retinoic acid (ATRA) in the 1990s represented a paradigm shift in APML management by promoting differentiation of leukemic promyelocytes into mature granulocytes [2,5]. Subsequent studies revealed the synergistic benefit of combining ATRA with arsenic trioxide (ATO), which induces PML-RARA degradation and apoptosis [3,5,9]. This chemotherapy-free regimen has now become the standard of care for low- and intermediate-risk APML, achieving complete remission rates exceeding 90% and long-term event-free survival approaching 85–90% [6,10,15].

Nevertheless, induction therapy with ATRA and ATO is not without complications. ATRA can induce differentiation syndrome (DS), a potentially fatal cytokine storm marked by fever, weight gain, pulmonary infiltrates, and organ dysfunction [5,10]. ATO is associated with dose-dependent cardiotoxicity, especially QT interval prolongation, which increases the risk of life-threatening arrhythmias [5,11,13]. Both agents also predispose patients to electrolyte abnormalities-such as hypokalemia, hypomagnesemia, and hypocalcemia-which may exacerbate cardiac risks and trigger neurological manifestations [5,11,13]. In addition, thrombotic events, although less common than hemorrhagic complications, are now increasingly reported during induction and consolidation phases [7,8,14,17]. One such rare but serious complication is dural venous sinus thrombosis (DVST), which can present with seizures, focal neurological deficits, and signs of increased intracranial pressure [4,12,14].

Thus, early induction in APML represents a high-risk window during which patients are vulnerable to overlapping toxicities that can rapidly escalate without timely intervention. This calls for a multidisciplinary approach encompassing vigilant cardiac, neurologic, and hematologic monitoring [9,16,17]. In this case report, we describe a young woman with newly diagnosed APML who developed multiple systemic complications during ATRA-ATO induction therapy-including QT prolongation, seizures, chest pain, and DVST-underscoring the importance of proactive surveillance and individualized care during this critical phase of treatment.

2.Case Presentation

A 22-year-old previously healthy woman presented to the emergency department with a one-week history of worsening fatigue, spontaneous gum bleeding, and diffuse petechiae. She also reported intermittent mild headaches and recent bruising after minor trauma. There was no history of fever, weight loss, night sweats, or recent infections. Her medical history was unremarkable, and she was not taking any medications, herbal supplements, or contraceptives. She denied smoking, alcohol, or illicit drug use.

On physical examination, the patient appeared pale and fatigued but was hemodynamically stable. Petechiae were evident on the lower limbs and buccal mucosa. There was no lymphadenopathy, hepatosplenomegaly, or signs of active infection. Cardiopulmonary and abdominal examinations were unremarkable.

2.1 Differential Diagnosis:

The initial differential diagnosis included:

• Other subtypes of acute myeloid leukemia (AML) such as monocytic or myelomonocytic variants

• Idiopathic thrombocytopenic purpura (ITP) due to isolated thrombocytopenia and bleeding

• Thrombotic thrombocytopenic purpura (TTP) due to petechiae and low platelets

• Severe systemic infection or sepsis-related DIC

However, the presence of abnormal promyelocytes, DIC features, and molecular confirmation rapidly narrowed the diagnosis to APML.

2.2 laboratory Investigations

Initial laboratory investigations showed WBC count of 2.1 × 10^9/L, hemoglobin of 8.7 g/dL, and platelet count of 19 × 10^9/L, consistent with pancytopenia. Coagulation studies revealed INR 1.6, markedly elevated D-dimers, and low fibrinogen, raising suspicion for early disseminated intravascular coagulation (DIC). Liver and renal function tests were normal. Peripheral smear showed circulating promyelocytes with prominent Auer rods, prompting urgent hematology consultation. A bone marrow biopsy confirmed 80–90% hypergranular promyeloblasts, and reverse transcription-polymerase chain reaction (RT-PCR) detected the PML-RARA fusion gene, establishing the diagnosis of APML.

The sagittal section clearly delineates the midline anatomical structures. The white arrow points to an abnormally hyperintense (bright) area within the superior sagittal sinus, which normally should appear as a flow void (dark due to fast-flowing blood). This hyperintensity suggests the presence of a thrombus occluding the lumen of the superior sagittal sinus, consistent with DVST. No signs of parenchymal infarction or herniation are visible (Figure 1). The axial image further supports the diagnosis. The white arrow highlights a filling defect or altered signal intensity in the region of the superior sagittal sinus, suggesting thrombus formation. The lack of the usual flow void and the presence of high signal intensity is characteristic of thrombosed venous sinus in subacute stages on T1-weighted imaging. The surrounding brain parenchyma shows no signs of edema or hemorrhagic conversion (Figure 2).

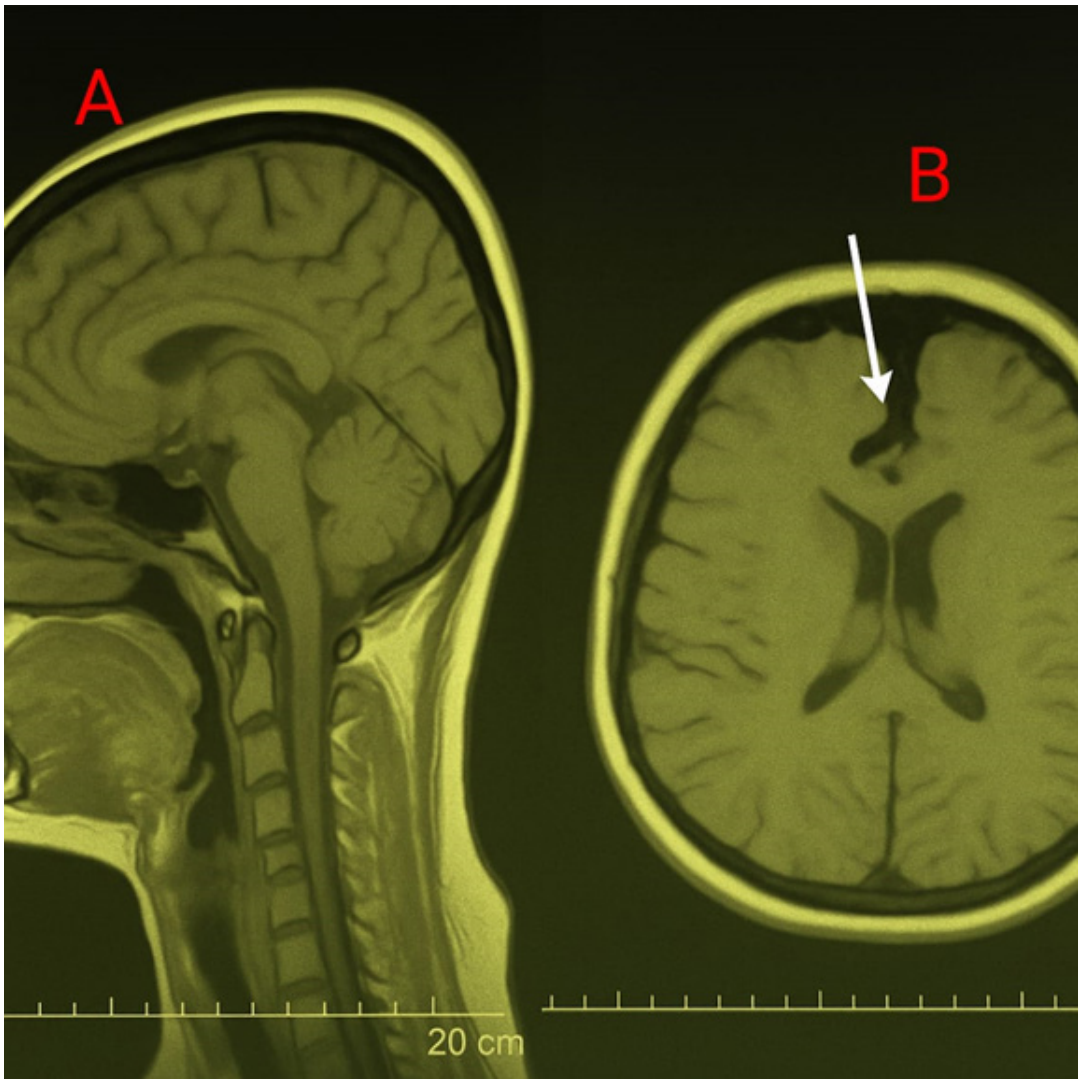

Figure A (Sagittal T1-weighted MRI):

Legend
MRI showing hyperintensity in the superior sagittal sinus, consistent with Dural venous sinus thrombosis (DVST). No signs of infarction, hemorrhage, or herniation are noted.

Figure 2 (Axial T1-weighted MRI):
Legend
Axial T1-weighted image depicting a filling defect (white arrow) in the superior sagittal sinus. Loss of flow void and hyperintensity indicate subacute thrombus formation.
The figure C demonstrates a subacute dural venous sinus thrombosis (DVST). A white arrow indicates the thrombus within the superior sagittal sinus, visualized as an area of abnormal hyperintensity along the midline. This radiologic appearance is typical of the subacute phase of thrombosis, during which the clot contains intracellular methemoglobin, resulting in increased signal on T2-weighted images. No associated hemorrhage, infarction, or mass effect is observed. The remaining cerebral structures appear within normal limits (Figure 3).

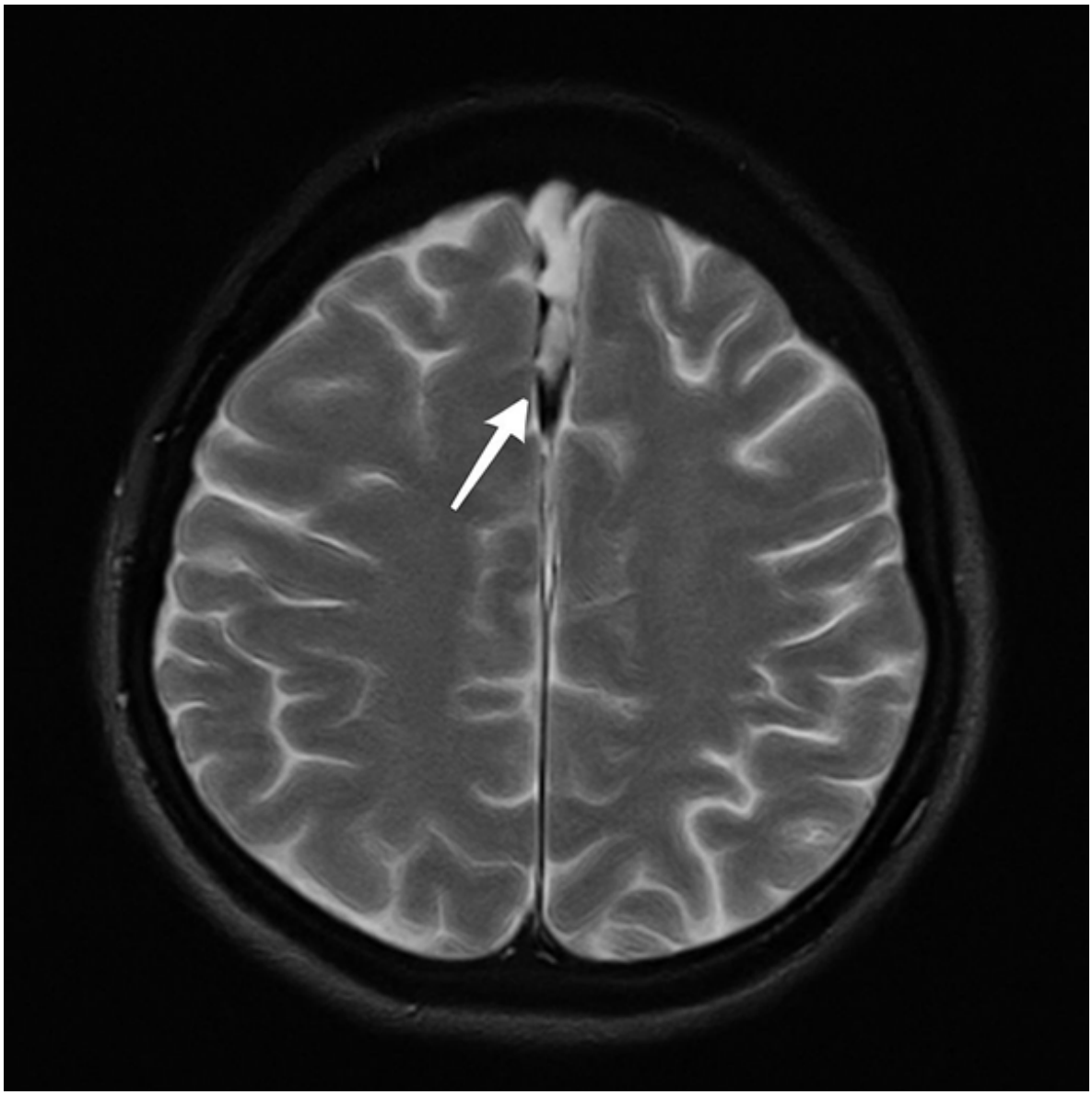

Figure 3: Axial T2-Weighted Magnetic Resonance Imaging (MRI) of the Brain

Legend:
T2-weighted image showing abnormal midline hyperintensity in the superior sagittal sinus (white arrow). Appearance is typical of subacute DVST with no mass effect or parenchymal injury.

2.3 Management and Complications

Given the emergent risk of hemorrhage due to DIC, ATRA was promptly initiated at a dose of 45 mg/m²/day. Plans were made to add ATO; however, baseline electrocardiogram (ECG) revealed prolonged QTc >500 ms, delaying its initiation. Electrolyte supplementation (potassium, magnesium, and calcium) was started immediately to mitigate the risk of torsades de pointes.

On Day 6 of induction, the patient developed diffuse myalgias and a focal seizure involving the left upper limb. Repeat ECG showed frequent premature ventricular complexes (PVCs) with persistently prolonged QTc. ATRA was temporarily withheld, and aggressive electrolyte repletion was undertaken. No abnormalities were found on brain MRI at that stage, and an autoimmune panel was negative.

By Day 10, ECG changes had improved, and ATRA was restarted cautiously along with ATO. However, on Day 12, she developed sudden-onset chest discomfort, associated with palpitations and mild dyspnea. ECG revealed ST-segment depressions, but troponin levels were negative and cardiac enzymes only mildly ele-

vated. Echocardiography demonstrated a normal ejection fraction (EF) with no wall motion abnormalities. A coronary angiogram ruled out obstructive coronary disease. The episode was attributed to drug-related vasospasm or transient ATO-related cardiotoxicity.

On Day 15, the clinical course worsened when the patient developed sudden lower limb weakness progressing to complete paraplegia. Neurologic exam confirmed flaccid paralysis with reduced reflexes in both lower extremities, and sensory level at T10. An urgent spine MRI ruled out compressive myelopathy. A repeat brain MRI was unremarkable, but magnetic resonance venography (MRV) of the brain showed extensive DVST involving the superior sagittal and transverse sinuses. This was considered a thrombotic complication related to APML and ATRA. Induction therapy was paused, and therapeutic low-molecular-weight heparin (LMWH) was initiated under close hematologic and neurologic supervision.

Over the next two weeks, the patient showed gradual neurological improvement, regaining partial strength in her lower limbs. Repeat MRV showed partial recanalization of the thrombosed venous sinuses. Following stabilization, ATRA and ATO were reinitiated cautiously, with frequent ECG monitoring and electrolyte correction. No further seizures or cardiac symptoms occurred during the remainder of therapy.

Throughout hospitalization, the patient required frequent platelet and cryoprecipitate transfusions to manage her DIC and prevent hemorrhagic complications. Supportive care included neuroprotective measures, analgesia for myalgias, and psychiatric support to address anxiety and mood disturbances during prolonged hospitalization.

2.4 Outcome and Follow-up

By the end of induction, the patient had achieved hematologic and molecular remission. Neurologically, she had mild residual weakness in her lower limbs, but was able to walk with support. She was discharged on Low Molecular Weight Heparin (LMWH) and planned for continued ATO-based consolidation therapy. At her 6-month follow-up, the patient remained in remission, with marked neurological recovery, stable cardiac status, and no recurrence of thrombotic or seizure events.

2. Clinical Discussion

This case illustrates the unpredictable and potentially life-threatening complications that can arise during the induction phase of ATRA-ATO therapy in APML. While this therapeutic combination has revolutionized outcomes-achieving remission rates of >90% in low- to intermediate-risk patients [6,10,15]-it demands vigilant supportive care due to its narrow therapeutic window and toxicities. Our patient experienced a rare convergence of complications, including cardiac arrhythmia, neurological dysfunction, and venous thrombosis, despite being otherwise healthy.

QT prolongation was among the earliest and most dangerous manifestations. Arsenic trioxide blocks hERG potassium channels, disrupting ventricular repolarization and increasing arrhythmia risk [11,13]. In our case, the QTc exceeded 500 ms, accompanied by premature ventricular contractions (PVCs) and a seizure episode (Figure D). Although initial MRI was unremarkable, and seizures may suggest leukemic CNS involvement or thrombosis, the temporal association with QTc changes and correction with electrolyte supplementation suggests a metabolic or drug-induced encephalopathy [5,13].

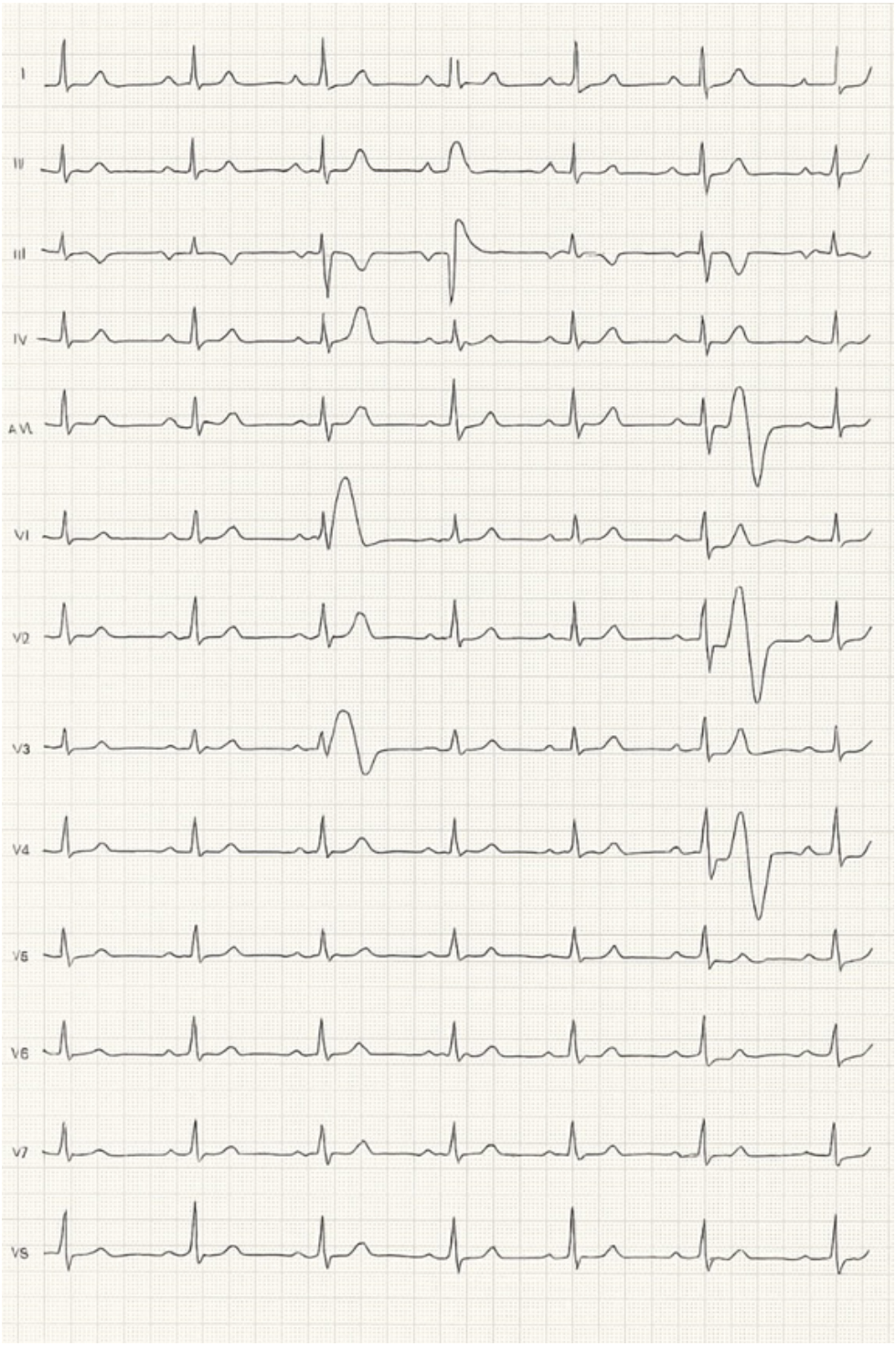

Figure 4: Twelve-lead electrocardiogram (ECG) showing QTc prolongation and frequent premature ventricular contractions (PVCs). Legend

The ECG demonstrates sinus rhythm with a prolonged corrected QT interval (QTc >500 ms). Frequent monomorphic PVCs are observed in leads II and V2–V5. The T-wave morphology appears broad and notched in several precordial leads, consistent with repolarization abnormalities. No ST-segment elevations are present.

Electrolyte imbalances are a well-documented toxicity during induction, contributing to both neurological and cardiac complications [5,11,13]. Close monitoring and replacement of potassium, calcium, and magnesium are essential, especially in patients receiving QT-prolonging agents such as ATO and ATRA. Our patient required intensive electrolyte repletion and temporary cessation of therapy, which ultimately prevented torsades de pointes or progression to ventricular fibrillation.

The transient chest pain and ECG changes further complicated the clinical course. Despite negative troponins and normal angiography, the presentation was consistent with drug-induced coronary vasospasm or myopericarditis-a known but rare ATO-related toxicity [5,9,13]. This pseudo-ischemic syndrome can closely mimic acute coronary events and requires a high index of suspicion and cardiology input for accurate diagnosis and supportive care.

Most notably, the patient developed paraplegia due to extensive dural venous sinus thrombosis (DVST)-a rare but increasingly recognized thrombotic event in APML patients, even those classified as low-risk [7,8,14]. Although hemorrhagic complications remain more common, venous thromboembolism-including cerebral vein thrombosis-has emerged as a serious risk during ATRA-ATO therapy [4,12,14,17]. Anticoagulation in the setting of thrombocytopenia and DIC poses a major clinical dilemma; however, as this case demonstrates, with adequate transfusion support and close neurologic monitoring, LMWH can be administered safely and effectively [12,14,16].

What makes this case particularly instructive is the co-occurrence of multiple high-risk events during the same induction window-QTc prolongation, seizure-like activity, chest pain with ECG changes, and DVST-all in a young, low-risk APML patient. While each of these has been described in isolation, their simultaneous presentation is exceptionally rare. Moreover, this case exemplifies the importance of not hesitating to temporarily halt therapy during toxicity, as treatment interruptions-when medically justified-do not necessarily compromise remission outcomes [6,10,17].

Multidisciplinary management, including hematology, neurology, cardiology, and supportive care teams, was key to ensuring survival and recovery. This underscores that even in the era of chemotherapy-free regimens, APML induction therapy remains a high-stakes period requiring proactive planning, real-time clinical decision-making, and comprehensive monitoring protocols [9,15,17].

3. Conclusion

This case highlights the complexity of managing APML during ATRA-ATO induction therapy. Early-phase complications such as seizures, cardiac symptoms, electrolyte imbalances, and thrombotic events like DVST necessitate proactive surveillance, rapid intervention, and individualized treatment strategies. Despite encountering several potentially fatal toxicities, our patient completed induction successfully due to timely multidisciplinary care and therapy modification. As ATRA-ATO becomes the standard of care, awareness of its toxicities and readiness to manage them is crucial for achieving optimal outcomes.

5. Consent: Written informed consent was obtained from the patient for participation in this case study and for the publication of related clinical details and images. The patient was assured of confidentiality, and all identifying information was anonymized to protect their privacy.

Aknowledgmnets: None

Ethical Considerations

Our institution does not require ethical approval for reporting individual cases or case series.

Consent for Publication

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Langdon, K., Cosentino, S., & Wawryk, O. (2024). Superiority of anthracycline-free treatment in standard-risk acute promyelocytic leukemia: A systematic review and comparative epidemiological analysis. *Cancer Reports, 7*(3), e2035.
2. Odetola, O., & Tallman, M. S. (2023). How to avoid early mortality in acute promyelocytic leukemia. *Hematology, 2023*(1), 248-253.
3. Autore, F., Chiusolo, P., Laurenti, L., Pagano, L., Bacigalupo, A., De Stefano, V., & Sica, S. (2023). Coagulopathy in patients with low/intermediate risk acute promyelocytic leukemia treated with first line arsenic trioxide in combination with all-trans retinoic acid: a monocentric experience. *Mediterranean Journal of Hematology and Infectious Diseases, 15*(1), e2023009.
4. ElHaddad A, Williams M, Abedalthagafi M. Cerebral vein thrombosis as the initial presentation of acute promyelocytic leukemia. J Rare Dis Res Treat. 2024;9(1):14-9.
5. Ghiaur, A., Doran, C., Gaman, M. A., Ionescu, B., Tatic, A., Cirstea, M., ... & Coriu, D. (2024). Acute promyelocytic leukemia: Review of complications related to all-trans retinoic acid and arsenic trioxide therapy. *Cancers, 16*(6), 1160.
6. Mistry AR, Rotz SJ, Telis ER, Montesinos P, Lo-Coco F, Tallman MS, et al. Characteristics and outcome of patients

with low/intermediate-risk APL treated with arsenic trioxide: an international collaborative study. Haematologica. 2021;106(8):2092–7.
7. Zhang Y, Liu X, Wang L, Fang X, Li H, Lu Y, et al. Thromboembolism in adult patients with APL: clinical characteristics, risk factors, and a predictive nomogram. Ann Hematol. 2025;104(3):345–56.
8. Ghiaur G, Hambley B, Tomuleasa C. The coagulopathy of APL: update on pathophysiology, risk stratification, and clinical management. Blood Rev. 2023;56:100945.
9. Iriyama N, Miyawaki S, Chibana K, et al. Updated treatment strategies for acute promyelocytic leukemia in the ATRA-ATO era. Int J Hematol. 2023;117(2):201–10.
10. Cicconi L, Lo-Coco F. Current management of newly diagnosed acute promyelocytic leukemia. Ann Oncol. 2021;32(9):1047–56.
11. Kanduri M, Sharma A, Upadhyay V, et al. QT prolongation with arsenic trioxide: risk factors and management. J Oncol Pharm Pract. 2023;29(1):32–8.
12. Rana V, Sood S, Gupta A, et al. A case of cerebral venous thrombosis in APML during induction: diagnostic challenges. Case Rep Hematol. 2022;2022:8354109.
13. Chen Y, Xu X, Zhou J, et al. Electrolyte disturbances in APL patients during ATRA-ATO therapy: clinical correlations and outcomes. Support Care Cancer. 2021;29(11):6375–83.
14. Nasr R, Al-Dabbous M, Abou Dalle I, et al. Thrombosis in acute promyelocytic leukemia: a comprehensive review. Clin Lymphoma Myeloma Leuk. 2024;24(3):e197–204.
15. Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2024;22(5):481–522.
16. de la Serna J, Montesinos P, Vellenga E, et al. Causes and management of early death in APL. Blood Rev. 2022;46:100754.
17. De la Fuente A, Gómez-Millán J, Requena MJ, et al. Multidisciplinary approach in the management of acute promyelocytic leukemia. Hematol Transfus Cell Ther. 2023;45(1):43–51.