1-1-2022

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Leukemia Research Reports 18 (2022) 100353

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Management of acute promyelocytic leukemia in the setting of acute COVID-19 infection

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ARTICLE INFO

Keywords:
Acute promyelocytic leuekemia
COVID-19
Arsenic trioxide
Differentiation syndrome

ABSTRACT

Acute promyelocytic leukemia (APL) often presents with significant coagulopathy which may result in both hemorrhagic and thrombotic complications. The emergence of the COVID-19 pandemic has complicated the initial treatment and diagnosis of APL owing to the viral infection's own associated coagulopathy. Here we report two cases of APL newly diagnosed in the setting of COVID-19 infection and considerations in their management. Included is a discussion of strategies for the dosing of arsenic trioxide in patients with significant obesity and renal insufficiency.

The case series submitted does not represent a study on patients and thus no specific informed consents or permissions were required. All images included in our manuscript have been deidentified and all authors certify that personal details that could potentially be used to identify the patients in the cases described have been removed. The corresponding author has personally confirmed that both patients included in this study have given verbal permission to present their cases in the de-identified manner as described above.

1. Introduction

The initial presentation of acute promyelocytic leukemia (APL) carries an extremely high risk for complications of coagulopathy. Early treatment of APL is critical, as hemorrhagic events can occur rapidly and be potentially lethal at rates as high as 50% in untreated patients. The early treatment period also requires close monitoring for symptoms of differentiation syndrome, characterized in part by symptoms of respiratory failure, fever, volume overload, acute renal failure, and hypotension. Differentiation syndrome occurs following initiation of treatment for APL with differentiating agents and is felt to be mediated by systemic release of cytokines from differentiating blasts. Hematologic laboratory findings associated with APL coagulopathy are generally consistent with disseminated intravascular coagulation (DIC), including elevated D-dimer, downstream hyperfibrinolysis, and severe thrombocytopenia [1]. Careful management of the potential complications of APL is especially salient given the excellent clinical outcomes that can be achieved thanks to well-defined treatment protocols with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) [2].

Concurrent acute nSARS-COV2 (COVID-19) infection presents a particular challenge in the management of newly diagnosed APL by also contributing to respiratory failure and coagulopathy. While studies examining the role for prophylactic-intensity or therapeutic-intensity anti-coagulation during moderate or severe COVID-19 infection are underway, the individual risk assessment for thrombosis and bleeding remains the primary consideration pending final results. Furthermore, patients with obesity and immunocompromise have been noted to have poor outcomes with COVID-19 pneumonia and are at significantly increased risk for more severe infection [3,4]. These unique considerations for both APL and COVID-19 require careful and frequent monitoring.

Here we describe two patients hospitalized for acute COVID-19 infection and new diagnosis of APL requiring management for respiratory failure, coagulopathy, and differentiation syndrome. In the second case, renal failure further complicated the management of concurrent COVID-19 and APL, necessitating hemodialysis and dose adjustment of arsenic trioxide. Both patients described here were unvaccinated at the time of presentation.

2. Case 1

An otherwise healthy 37-year-old female noticed progressively

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https://doi.org/10.1016/j.lrr.2022.100353
Received 5 January 2022; Received in revised form 13 September 2022; Accepted 14 October 2022
Available online 19 October 2022

worsening shortness of breath, cough, fever, malaise, bruising, and loss of taste and smell. Physical exam at initial presentation was significant for scattered large bruises of the bilateral lower extremities and no frank bleeding. The patient was found to have COVID-19 infection by PCR assay and was admitted for fever and hypoxia requiring supplemental oxygen by nasal cannula. The patient's complete blood count at admission included hemoglobin 7.7 g/dL, platelet count 23 $\times$ 10^9/L, leukocyte count 7.7 $\times$ 10^9/L, and absolute neutrophil count (ANC) 220/mm^3. Dexamethasone 6 mg daily for COVID-19 treatment and empiric broad spectrum antibiotics for neutropenic fever were initiated, as well as PRBC and platelet transfusions. Peripheral blood smear and peripheral blood flow cytometry raised concern for APL six days after admission, and the patient was transferred for additional evaluation and management. Treatment for presumptive APL diagnosis was initiated with ATRA, 45 mg/m^2/day divided in two doses. Peripheral blood FISH for PML/RARA rearrangement was confirmed, and ATO 0.15 mg/kg infusion daily was initiated. At the time of treatment, the patient's blood counts were hemoglobin 5.7 g/dL, platelet count 6 $\times$ 10^9/L, and ANC 100/mm^3. The patient's coagulation studies revealed prolonged PT 20.5s (ref. 8.6 –13 s), decreased fibrinogen 160 (ref. 236–516 mg/dL), and elevated D-dimer of 58,691 ng/mL (ref. <=499). During the initiation of treatment, the patient developed leukocytosis, increasing oxygen requirement, increased pulmonary infiltrates on chest radiographs, tachycardia, and persistent fevers concerning for differentiation syndrome superimposed on viral pneumonia. The patient's steroid dosing was increased to methylprednisolone 1 mg/kg BID, a course of hydroxyurea was initiated for leukocytosis, and one dose of ATRA was held. Bone marrow biopsy confirmed APL with PML/RARA rearrangement by FISH and FLT3 internal tandem duplication (ITD) by next generation sequencing.

This patient's induction therapy was relatively unremarkable until approximately two weeks after starting treatment when the patient noted blurry vision and multiple retinal hemorrhages were found on ophthalmologic evaluation (Fig. 1). There was no evidence of DIC on laboratory monitoring. Platelet counts at the time these symptoms were noted ranged between 46 and 50 $\times$ 10^9/L and in previous days had been between 26 and 70 $\times$ 10^9/L requiring regular transfusions to maintain counts above 50 $\times$ 10^9/L. MR imaging demonstrated several additional small bilateral supratentorial hemorrhages. The platelet transfusion threshold was increased with resolution of visual symptoms without further intervention.

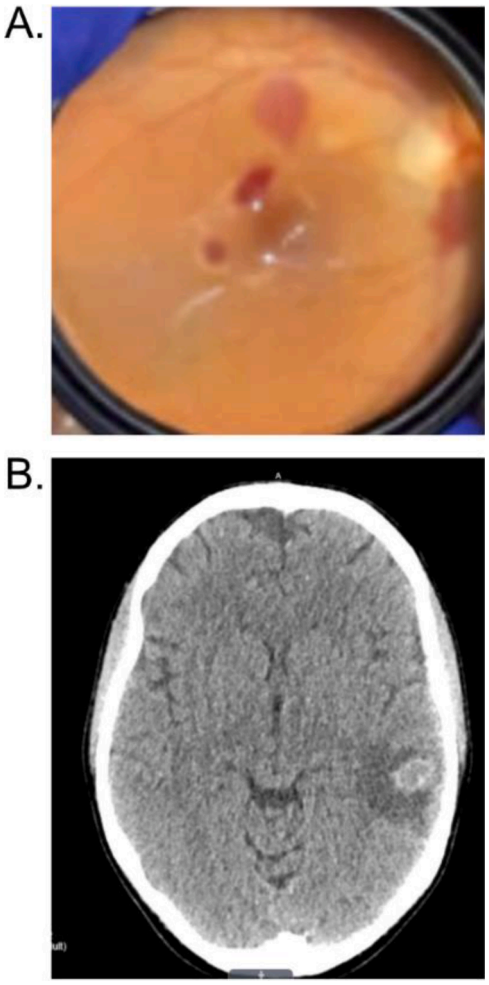

Fig. 1. Bedside retinal exam (A) and non-contrasted head CT (B) demonstrating retinal hemorrhages and hemorrhagic lesion with surrounding edema in the temporal lobe of the patient described in case 1. This patient did not experience any residual visual or neurological deficits following their treatment course.

3. Case 2

A 60-year-old female with a history of seronegative rheumatoid arthritis with underlying suspected interstitial lung disease on chronic 2L home oxygen and severe obesity (BMI > 50) presented with fever, progressive dyspnea, hypoxia, and positive COVID-19 PCR assay. There were no physical exam findings of bleeding or bruising. Laboratory testing demonstrated pancytopenia with hemoglobin 9.5 g/dL, platelet count 64 $\times$ 10^9/L, leukocyte count 0.4 $\times$ 10^9/L, ANC 100/mm^3, as well as PT elevated to 17.2 s, fibrinogen 87 mg/dL, and D-dimer >80,000 ng/mL. The patient was initially treated with dexamethasone for COVID-19 and broad-spectrum antibiotics for neutropenic fever. Peripheral blood smear demonstrated atypical promyelocytes, and peripheral blood flow cytometry was suspicious for APL. Treatment was initiated with ATRA, 45 mg/m^2/day divided in two doses, and hospital transfer was arranged for further leukemia management. Peripheral blood FISH confirmed the presence of PML/RARA rearrangement, bone marrow biopsy demonstrated immature promyelocytes, and NGS demonstrated FLT3-ITD mutations.

Shortly following initiation of ATRA, the patient developed obtunded mental status, respiratory failure, and oliguric renal failure felt to be attributable to differentiation syndrome in retrospect. Since our initial differential included both differentiation syndrome and progressive COVID manifestations, all possible reversible causes were addressed during acute management. Endotracheal intubation was performed, and continuous venovenous hemofiltration (CVVH) initiated. A non-contrast head CT demonstrated no acute abnormalities. Bronchoscopy demonstrated diffuse alveolar hemorrhage and removed a large blood clot from a mainstem bronchus. Shortly thereafter, treatment with arsenic trioxide was initiated with a dose reduction from standard dose 0.15 mg/kg to 0.075 mg/kg actual body weight infusion delivered over two hours daily during pauses in CVVH. Hydroxyurea and methylprednisolone 1 mg/kg were initiated for management of leukocytosis and hypoxia. The patient was eventually extubated and transitioned to intermittent hemodialysis. Their urine output gradually improved and dialysis was successfully discontinued. The patient's subsequent induction course was also notable for visual disturbances of altered color perception and the sensation of objects moving, which gradually resolved after transitioning to intermittent hemodialysis.

4. Discussion

These cases illustrate the challenges of managing the overlapping disease processes of COVID-19 and APL concurrently and the need for close clinical monitoring during the duration of induction therapy for a broad range of frequent complications. Furthermore, our cases highlight some clinical features of hyperinflammatory coagulopathic states and the need to further understand the physiologic mechanisms driving them. Our experience mirrors the challenges reported in other published

case reports regarding COVID-19 and APL: one reporting a severe thrombotic stroke and all highlighting complex decision-making for managing multiple diagnoses driving abnormal coagulation [5–7].

Each case presented highlights the challenge in navigating the competing pro-thrombotic state caused by COVID-19 and hemorrhagic state induced by APL. Emerging data suggests that the underlying physiological processes driving COVID-19 associated coagulopathy (CAC) include systemic inflammation and vascular endothelial dysfunction, manifesting as both macro- and microthrombotic complications. The propensity for clot formation may be a function of illness severity and the highly inflammatory response to infection rather than an inherent property of the virus itself [8]. On the other hand, the early treatment course for APL is often focused on the prevention of severe coagulopathy associated life-threatening hemorrhagic complications. There are data to suggest that leukemic blasts contribute to a systemic hyperinflammatory state and directly express antigens that drive aberrant activation of the clotting cascade [9]. The available evidence, supported by these cases, suggests that immunomodulatory therapies at the right time in disease course may be of benefit in those patients with concurrent APL and COVID-19. Based on available data, no single clinical approach to the coagulopathies induced by these conditions is universally applicable. We believe the cases presented here continue to emphasize current mainstays of clinical practice including frequent intensive monitoring during therapy induction, supportive care with cryoprecipitate/platelet transfusions, and prompt treatment of APL.

The second case highlights the treatment dilemma associated with the potentially overlapping symptoms of COVID-19 and differentiation syndrome. The differential for this patient's acute hypoxic respiratory failure included worsening COVID-19 pneumonia, superimposed bacterial or fungal pneumonia in a relatively immunocompromised host, or pulmonary embolism. Early suspicion for hematologic malignancy and rapid acquisition of relevant diagnostic studies were key to narrow this differential and begin appropriate treatment.

The second case also highlights a clinical challenge of dosing ATO in obese and renally impaired patients diagnosed with APL. In major trials it has typically been dosed as a 0.15 mg/kg infusion once daily based on absolute body weight [2]. ATO is excreted through the urine and has significant potential toxicity including transaminitis and prolongation of the QTc interval. There are few resources guiding dosing in patients with obesity and impaired renal function. This presents a challenge especially given pharmacokinetic data demonstrating the renal clearance and wide tissue distribution of ATO [2,10].

There are currently no consensus guidelines on dosing of ATO for obese patients or for patients with impaired renal function. Recommendations issued by ASCO specifically do not call for any dose reduction or modification to actual body weight dosing [11]. Two retrospective case series examining this issue arrived at differing results, with one group noting a statistically significant increase in dose holding or modification in obese patients that was not found by the other group [12,13]. A small number of cases and pharmacokinetic studies are available in the literature describing safe treatment with strategies involving dosing around dialysis sessions and dose reduction [14,15].

Based on institutional experience, a 50% dose reduction for renal failure was administered based on actual body weight with dosing once daily as a two-hour infusion during an interruption in continuous dialysis for the patient in Case 2. We have also used this dose reduction for severely obese patients before. After initial disease control and clinical improvement with transition to an intermittent hemodialysis schedule, the ATO dose interval was adjusted to three times weekly after hemodialysis sessions. Our patient in Case 2 tolerated this dosing well, with the visual disturbances noted above as the only ATO-associated toxicity observed in either case.

At the time of this writing, both patients have completed consolidation with ATRA and ATO, and remain in complete morphologic and molecular remission.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Kevin G Shim: Conceptualization, Writing – original draft, Writing – review & editing. **Mallory Crain:** Conceptualization, Writing – original draft, Writing – review & editing. **Kristan Augustin:** Conceptualization, Writing – original draft, Writing – review & editing. **Karolyn A Oetjen:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None

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