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COMPREHENSIVE MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APML) COMPLICATED WITH INTRACRANIAL HAEMORRHAGE AND DIFFERENTIATION SYNDROME: A MULTIDISCIPLINARY CASE REPORT

Oncology

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ABSTRACT

Acute Promyelocytic Leukemia (APML) is a unique subtype of acute myeloid leukemia characterized by the RARA and PML gene abnormality. This case study details the management of a 33-year-old male with APML, who developed intracranial hemorrhage during treatment. Initial therapy with Arsenic Trioxide (ARCENIC) and All-Trans Retinoic Acid (ATRA), along with supportive care including RBC and platelet transfusions, was employed. A brain MRI revealed multiple intraparenchymal hemorrhages, complicating the treatment. Around the 9th day, the patient developed differentiation syndrome, with additional complications such as nausea, chest pain, and hemoptysis. A multidisciplinary team of hematology, neurology, critical care, and oncology specialists adjusted the treatment plan, preventing further complications and respiratory failure, which necessitated intensive care. The patient eventually improved and was discharged with ongoing chemotherapy. This case underscores the importance of close monitoring and a collaborative approach in managing complex APML cases.

KEYWORDS

Acute Promyelocytic Leukemia, ATRA, Arsenic, Neurological Complications, differentiation syndrome, Hematologic Malignancy

INTRODUCTION:

Acute Promyelocytic Leukemia (APML) is a subgenre of Acute Myeloid Leukemia (AML) and shows t (15,17) translocation product which is responsible for the PML-RARA fusion gene. This genetic (mutational) anomaly leads to a blockage in normal myeloid cell differentiation which results in an increased amount of promyelocytes. APML therapy usually involves the addition of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) that function as differentiation-inducing agents. These drugs are meant to re-establish the correct progression of cell development, and this is relevant for sustained interaction with the illness[1,4]. While this therapeutic approach seems promising as a possible resource for certain patient populations, it is not free of risks, the most common being intracranial hemorrhages and differentiation syndrome (DS), which was formerly called retinoic acid syndrome. DS in APML is a potentially life-threatening complication characterized by a systemic inflammatory response activated by cytokine release during the differentiation of undeveloped and immature cells. This syndrome expresses symptoms such as shortness of breath, unexplained fever, hypotension, and renal failure. Intracranial hemorrhages are often attributed to several factors, including disseminated intravascular coagulation (DIC), hypercoagulability, fibrinolysis, proteolysis, and thrombocytopenia. These factors contribute to an increased risk of bleeding events, particularly in the central nervous system. Preventing intracranial hemorrhage before achieving remission is critical for improving patient outcomes[1,2,3].

Case Presentation

A 33-year-old male with a known condition of acute promyelocytic leukemia (APML), presented with bleeding gums, fever, and Pancytopenia. Additionally, he reported a 15-day history of occipital headache without nausea or vomiting. The initial hematological assessments conducted on the same day revealed significant abnormalities, with a platelet count of 33,000 cells/cumm, a hemoglobin level of 6.7g/dl, WBC of 11050 cells/cumm, and plasma fibrinogen level of 112. Peripheral smear showed features of acute leukemia, suggestive of the AML M3-FAB category. Recognizing the severity of these findings, therapeutic interventions were promptly initiated. An inclusive approach included a 2-pint platelet transfusion, aiming to address the thrombocytopenia and a 2-pint fresh frozen plasma transfusion to address coagulation factors.

The neurological assessment revealed findings suggestive of chloroma on a CT scan. This prompted the recommendation for an MRI of the brain with contrast. The MRI revealed multiple well-defined t1 iso-hyperintense, t2 hypointense lesions with blooming on GRE, indicative of intraparenchymal hemorrhages. These lesions were distributed in bilateral temporal lobes, bilateral frontal lobes, right parietal lobes, right insular cortex, and right cerebellum. The largest lesion, measuring 2.4x2.3cm, was noted in the right cerebellum. Some lesions exhibited mild perilesional vasogenic edema. The basal ganglia, thalami, midbrain, pons, medulla, sellar, and suprasellar regions appeared normal (figure 1). Given the patient's known APML and the new finding of intraparenchymal hemorrhages, a comprehensive treatment plan was initiated. This plan included the administration of intravenous (IV) Meropenem 1gm , Dexa 8mg , Mannitol 100ml, Ondansetron 4mg IV TID and Levetiracetam 500mg BD. The patient received their first Arsenic and ATRA (All-Trans Retinoic Acid) treatment on November 28th, 2023. He also had IV Ranitidine 50mg + Pheniramine 25mg for gastric protection. The arsenic was given as Arsenic 7mg in 500cc 5% dextrose IV over 2 hours. Additionally, he continued taking Cap. ATRA 10MG three times a day (TID), which started on November 24th, 2023 These treatment regimens aimed to manage the intraparenchymal

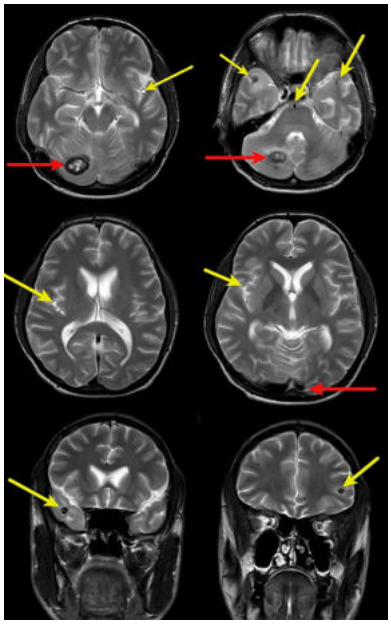

figure 1: Multiple well-defined T1 iso-hyperintense, T2 hypointense lesions showing blooming on GRE- s/o hemorrhages noted in bilateral temporal lobes, bilateral frontal, right parietal lobes, right insular cortex and right cerebellum, largest in right cerebellum measures 2.4x2.3cm. (yellow arrows) , Bleeding (red arrows) hemorrhages and provide supportive care for the patient's APML condition.

On the 8th day, chest pain prompted the administration of Tab paracetamol 650 bd alongside the continuation of ATRA and Arsenic, with arsenic 7mg IV given over 2 hours. Chemotherapy resumed on the 9th day with Arsenic 7mg in 500ml 5% dextrose iv, which the patient tolerated. However, on the 11th day of chemotherapy, the patient reported troubling symptoms of breathlessness, fever, and blood-streaked sputum, necessitating aggressive treatment with IV Piperacillin+Tazobactam 4.5gm, clindamycin 600mg, Tab Sulfamethoxazole+Trimethoprim, and Tab voriconazole 300mg were initiated. (figure 2) Chest x-ray scan showed bilaterally scattered inhomogeneous opacities noted in the right middle and lower zone and left middle

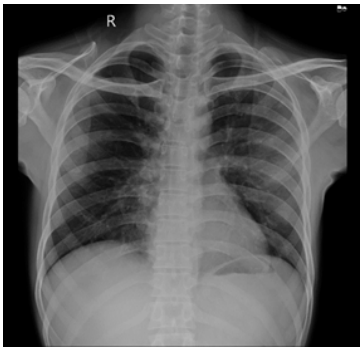

Figure 2: . Chest x-ray scan showing bilaterally scattered inhomogenous opacities noted in the right middle and lower zone and left middle zone.

On the 12th day, the patient presented with symptoms indicative of type I respiratory failure, possibly due to differentiation syndrome. This included tachypnea, increased work of breathing, low oxygen saturation (spo2 83%), and irregular pleural lining observed on lung imaging. The medical team initiated a treatment plan involving dexamethasone 10 mg, Tab Sulfamethoxazole+Trimethoprim 2-2-1, and hydrocortisone 100 mg IV stat. To monitor progress, CRP, procalcitonin, and Nt pro BNP levels were to be checked, and foley catheterization for hourly urine output was advised. The patient was put on BiPAP (bilevel positive airway pressure) to assist with breathing, with plans for ABG (arterial blood gas) analysis after 2 hours. Intubation was considered if necessary, and a 2D echo was planned. The treatment also included IV fluids at 60 ml/hr to maintain hydration, and the patient was kept nil per oral (NPO) to restrict intake. The team also discussed the possibility of increasing antibiotics if the PCT (procalcitonin) showed an upward trend, with a plan to follow up on blood reports. On December 15th, 2023, the patient continued to receive management on BiPAP for respiratory support, showing improvement as reported better, maintaining saturation with 30% oxygen. Treatment during this period included a platelet transfusion and plans to wean off from BiPAP, indicating progress in the respiratory condition. The medical team, closely monitored the patient's progress, made adjustments to medications such as IV Piperacillin+Tazobactam 4.5gm, clindamycin 600mg, and Tab Sulfamethoxazole+Trimethoprim, and continued supportive care. Showed signs of improvement as they were able to tolerate being off non-invasive ventilation (NIV) for 24 hours with adequate urine output. Dexamethasone was gradually tapered down and stopped. During this time, the patient was reassessed and found comfortable on nasal prongs, indicating respiratory improvement. The patient underwent day 23 chemotherapy with Inj. arsenic 7mg in 500ml 5%dextrose over 2hrs, connected through a 22g cannula. They were also given Tab Tramadol SOS due to chest pain and crepts.

The patient underwent consecutive chemotherapy sessions from day 24 to day 30th with arsenic and Tab ATRA 10mg 3-0-3, no new complaints were noted, prompting to advise continuing arsenic depending on normal ECG and QTc results. The following days showed symptomatic improvement and was advised to continue chemotherapy and was subsequently administered Tab. Voriconazole, Tab. ATRA, and Tab. Levetiracetam as the general condition of the patient was improved he was advised for discharge with Tab ATRA 10mg for 3-0-3 for 2 days, Tab Sulfamethoxazole+Trimethoprim 0-1-0 m/w/f, Tab pan 40mg SOS, Tab Levetiracetam 500mg 1-0-1 with stable vitals.

DISCUSSION:

In many induction therapy protocols for APML, patients with high white blood cell counts are advised to undergo a combination of chemotherapy and All-trans retinoic acid (ATRA) treatment, with a focus on preventing ATRA syndrome. However, the risk of fatal intracranial hemorrhage (FICH) is not typically addressed in these regimens. To mitigate this risk, a strategy involving an initial single administration of ATRA followed by concurrent chemotherapy after addressing Disseminated intravascular coagulation (DIC) may be beneficial for high-risk patients. This approach aims to reduce the likelihood of FICH while still effectively treating APL and managing potential complications such as ATRA syndrome. Such tailored treatment strategies could improve outcomes for APL patients with elevated white blood cell counts and mitigate the risk of life-threatening intracranial hemorrhage during induction therapy[1]. A previously healthy 22-year-old male with seizures was diagnosed with APML and intracranial hemorrhage. He underwent emergent decompressive hemicraniectomy and ATRA but developed refractory elevated intracranial pressure, pancytopenia, and ischemic infarcts. Due to the risks, a frontal lobectomy was not performed, and an external ventricular drain was placed for hydrocephalus. Despite these measures, his condition worsened, leading to the need for dialysis, and eventually multisystem organ failure. Care was withdrawn on postoperative day 3. [7] such a case emphasizes the complexities of managing APML with intracranial complications, where treatment decisions must balance aggressive intervention with the patient's overall condition and disease aggressiveness.

Diagnosing DS in APML is challenging due to the lack of specific criteria and biomarkers. Symptoms overlap with common APML abnormalities like leukocytosis, anemia, and coagulopathy, and DS can mimic conditions such as infections, heart failure, anaphylaxis, and thromboembolism, requiring a thorough differential diagnosis. Clinical identification of DS relies on recognizing associated signs including dyspnea with interstitial pulmonary infiltrates, Acute kidney injury (AKI), pleuropericardial effusion, hypotension, peripheral edema, hyperbilirubinemia, and musculoskeletal pain. DS often presents in two peaks, typically occurring around week 1 and then again around week 3 of treatment. Vigilance for these clinical features is crucial for timely identification[3]. As per the treatment guidelines for emergency treatment, the plan is to Initiate empiric treatment with steroids promptly upon suspicion of APL Differentiation Syndrome, as it poses a life-threatening risk, and starting steroids for a limited duration carries no significant risk. Simultaneously, perform thorough evaluations to rule out bacterial and fungal infections, bacteremia, sepsis, pneumonia, Diffuse alveolar hemorrhage (DAH), and alternative etiologies for renal and heart failure [2,3,5]. similarly in this case management of this patient with APML and DS aligns closely with the provided guidelines. The team followed recommendations for prompt initiation of steroid treatment, aggressive infection management, and supportive care for respiratory distress and fluid overload. The approach to monitoring for complications and adjusting treatment based on clinical indicators demonstrates adherence to best practices in APML-DS management.

CONCLUSION:

This case underscores the necessity for a personalized, multidisciplinary strategy in managing APML, especially when complicated by intracranial hemorrhage and respiratory failure. The successful outcome highlights the critical role of continuous evaluation, timely adjustments in medication, and the collaborative efforts of specialized teams.

REFERENCES :

1. Tamai H, Yamanaka S, Yamaguchi H, Nakayama K, Inokuchi K. Effective management of acute promyelocytic leukemia with high risk of fatal intracranial hemorrhage. Biol Med (Aligarh). 2015;8(262):2.
2. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. British journal of haematology. 2019 Oct;187(2):157-62.
3. Khizer U, Annam B, Akhtar A, Dhaliwal JS, Yang C. Fatal Differentiation Syndrome Complicating Acute Promyelocytic Leukemia Treatment: A Case Report. Cureus. 2024 Feb 19;16(2).
4. Lo-Coco F, Ammatuna E, Montesinos P, Sanz MA. Acute promyelocytic leukemia: recent advances in diagnosis and management. InSeminars in oncology 2008 Aug 1 (Vol. 35, No. 4, pp. 401-409). WB Saunders.

5. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. Journal of oncology pharmacy practice. 2012 Mar;18(1):109-14.
6. Arbuthnot C, Wilde JT. Haemostatic problems in acute promyelocytic leukaemia. Blood reviews. 2006 Nov 1;20(6):289-97.
7. Smith EC, Stevens EA. Fatal intracranial hemorrhage as the presenting sign of acute promyelocytic leukemia: A case report. Radiology Case Reports. 2022 Jun 1;17(6):2123-8.