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CASE REPORT

Prolonged Acute Kidney Injury and Symmetrical Peripheral Gangrene: A Rare Case Report of Acute Promyelocytic Leukemia

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Abstract: Acute kidney injury (AKI) is a serious complication of acute promyelocytic leukemia (APL). However, symmetric peripheral gangrene (SPG) and AKI have rarely been reported in this disease. Here we present the case of a patient who developed life-threatening APL complicated by AKI and SPG. Laboratory investigations revealed disseminated intravascular coagulation (DIC), respiratory failure, renal insufficiency, hepatic insufficiency, cardiac failure, and infection with multiple pathogens, including: novel coronavirus disease (COVID-19), candida monda, saccharomyces capitis, aspergillus fumigatus, candida lusitaniae, aspergillus flavus. One month later, the patient was off the ventilator, but his renal function needed hemodialysis. He also developed SPG, particularly the fingers of the hands and feet. After two months, the patient was discharged from hospital with normal liver and heart function. Four months after discharge, the patient's APL was on the mend, but some of the gangrenous sites had undergone autoamputation. Therefore, AKI and SPG are complex clinical complications in APL that pose significant challenges to clinicians. In addition to coagulopathy, the presence of COVID-19 and DIC worsened the clinical outcomes. At the same time, we extensively reviewed the literature to provide a comprehensive analysis of the pathogenesis and management strategies of these complications.

Keywords: acute kidney injury, acute promyelocytic leukemia, symmetrical peripheral gangrene, disseminated intravascular coagulation, case report

Introduction

Acute promyelocytic leukemia(APL), also referred to as M3 leukemia, accounts for approximately 15% of acute myelogenous leukemia (AML) and is distinguished by the occurrence of abnormal leukemia, thrombocytopenia, and coagulation dysfunction.[1] Drugs such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have significantly improved outcomes for patients with APL, which is now considered curable.[2] However, these chemotherapeutic agents also increase the risk of acute kidney injury (AKI), which has been reported to occur in up to 40% of newly diagnosed APL patients.[2,3] AKI refers to the sudden or rapid loss of kidney function that results in a large reduction in urine output, leading to the retention of harmful urea, creatinine, and other waste products that are normally eliminated by the kidneys. In severe cases, patients even require renal replacement therapy. AKI also can be fatal and is particularly difficult to treat in the setting of APL and critical illness.[4]

The specific coagulopathy often poses a threat to the lives of APL patients. Although bleeding symptoms are well-known and well-described in these patients, the thrombosis associated with APL has not received sufficient attention. There is a scarcity of data on this complication, and its incidence varies.[5] Local ischemia caused by thrombosis can lead to gangrene if it reaches a certain intensity and duration. In the early stages of gangrene in a limb, symptoms such as pain or pallor may be overlooked until irreversible necrosis occurs.Gangrene is a devastating and dreaded condition in APL than in diabetes and peripheral arterial disease or systemic lupus erythematosus (SLE).[6] When gangrene occurs predominantly in the extremities

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and bilaterally in two or more sites in the absence of major vascular occlusive disease, it is often referred to as "symmetric peripheral gangrene" (SPG).[7] SPG is a disabling complication that occurs mainly in critically ill patients and affects their survival.[8] However, there is a paucity of research on APL complicated by AKI and SPG. We report a case of AKI with SPG secondary to APL complicated by severe infection, DIC and intracranial hemorrhage. A multidisciplinary approach resulted in a life-saving outcome.

Case Report

Clinical Presentation

A 58-year-old man presented with a 3-week history of fever, cough, dyspnea, and oliguria. A bone marrow biopsy revealed acute promyelocytic leukemia (M3 type), and he was treated with retinoic acid and arsenic trioxide (ATO) in combination with cytarabine chemotherapy. Due to a sharp increase in white blood cells, the arsenic trioxide was changed to hydroxyurea.

Investigations

Laboratory tests indicated disseminated intravascular coagulation (DIC), respiratory failure, renal insufficienent, hepatic insufficiency, cardiac failure, and infection with multiple pathogens, such as nasal swabs: novel coronavirus disease (COVID-19), candida monda; alveolar lavage fluid: saccharomyces capitis, aspergillus fumigatus, Candida lusitaniae, aspergillus flavus. The laboratory test results are presented in Table 1. Notably, each organism was isolated from sterile sites, and they were true pathogens. CT showed exudation of both lungs, subarachnoid hemorrhage and cerebellar hemorrhage.

Hospital Course

The patient was admitted to the intensive care unit (ICU) and received mechanical ventilation, anti-infection, anticoagulation, continuous renal replacement therapy (CRRT), bilirubin adsorption, plasma exchange and other organ support treatments.

Table 1 Dynamic Changes of Laboratory Test Results

Laboratory Test Results (Normal Range)	Time 0	1 Week	1 Month	2 Months	6 Months	1 Years
Blood tests						
White blood cells,× 10^9/L (4.0–10.0)	13.08	28.4	11.82	10.9	8	6.8
Hemoglobin,g/L (130–175)	64	58	62	86	108	110
Platelets,×10^9/L (100–300)	225	120	45	83	90	101
Albumin,g/L (40–55)	27.7	29.6	31.2	30.0	32	35
CHO,mmol/l,(2.3–5.2)	3.44	2.99	2.20	1.70	1.88	2.11
Triglyceride, mmol/L,(0.56–1.7)	3.14	4.37	3.11	3.92	3.49	3.01
CRP,mg/L,(<10)	267.86	151.84	170.14	44.90	17.75	9.86
Blood urea nitrogen, mmol/L, (3.1–8)	27.14	15.34	27.89	30.23	9.42	8.79
Creatinine,μmol/L, (57–97)	550.1	485.5	433.1	468.1	410.4	388.2
ALT,U/L,(9–50)	410	360	154	126	49	28
AST,U/L,(15–40)	303	136	97	89	40	30
D-dimer, ug/mL,(<0.5)	1.94	1.79	1.91	1.56	2.04	1.98
APTT,s,(25.4–38.4)	33.4	82.3	40.3	49.6	38.3	33.1
NT-proBNP,pg/mL,(<125)	35,000	9214	11,571	27,057	2388	1178
PCT,ng/mL,(0–0.046)	1.12	0.796	0.598	0.629	0.799	0.668
Covid-19 (−)	+	+	−	−	−	−
Urine tests						
Protein (−)	1+	2+	1+			
Bld (−)	±	−	−			
RBC (0–7/ul)	26	0	6			
pH (4.5–8)	6.0	5.5	7.0			

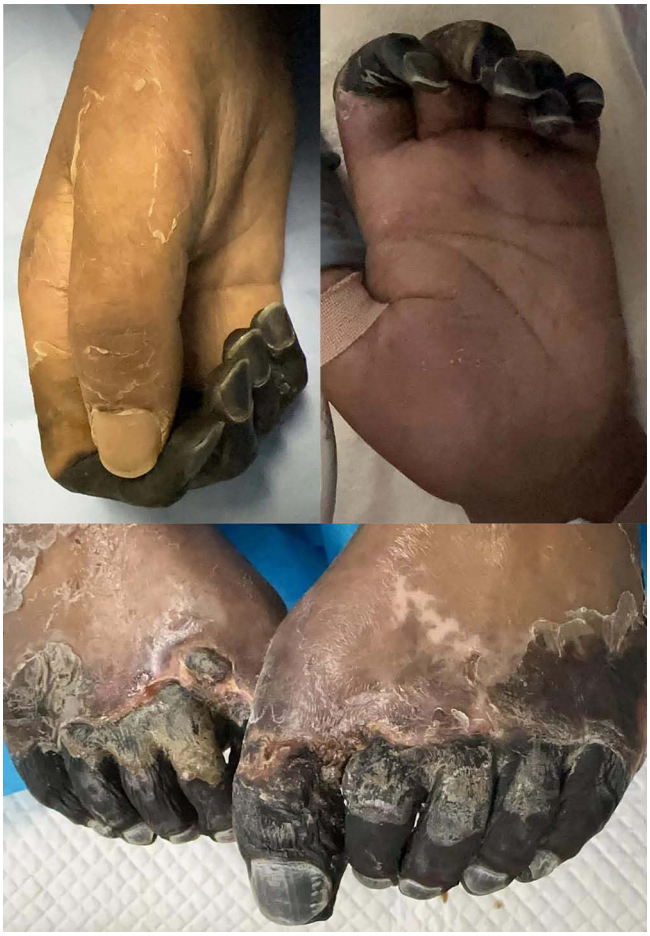

Figure 1 Presentation with severe gangrene of fingers and toes.

One month later, the tracheal catheter was removed and the brain hemorrhage had stopped. Unfortunately, the patient still had anuria, hepatic, renal and cardiac dysfunction, as well as intermittent low fever. Notably, he developed dry gangrene of the fingers (toes) at the extremities (Figure 1). Repeat sputum culture showed aspergillus, acinetobacter baumannii, staphylococcus aureus, etc. Anti-infective drugs such as minocycline, voriconazole, and vancomycin were administered sequentially. In addition to CRRT, the patient received immunoglobulin, human serum albumin, red blood cells and nutritional solutions.

After two months, the patient's liver and heart functioned normally, infections had been successfully treated. However, there was a persistent oliguria and a creatinine level in excess of 400 μmol/L (Table 1). There was no improvement in SPG and despite recommendations for amputation, the patient declined and was discharged.

Outcome

Four months after discharge, the patient was on long-term hemodialysis and had undergone partial autoamputation of some gangrenous fingers (Figure 2). Fortunately, the patient's APL remained stable One year later, the patient's vital signs are stable and he is undergoing regular hemodialysis.

Discussion

This case report details a patient suffering from APL, AKI, SPG, COVID-19, cerebral hemorrhage, and multiple organ dysfunction (MODS). After active treatment, the patient made a smooth transition to regular hemodialysis, resulting in a life-saving outcome, which to our knowledge has not been described before.

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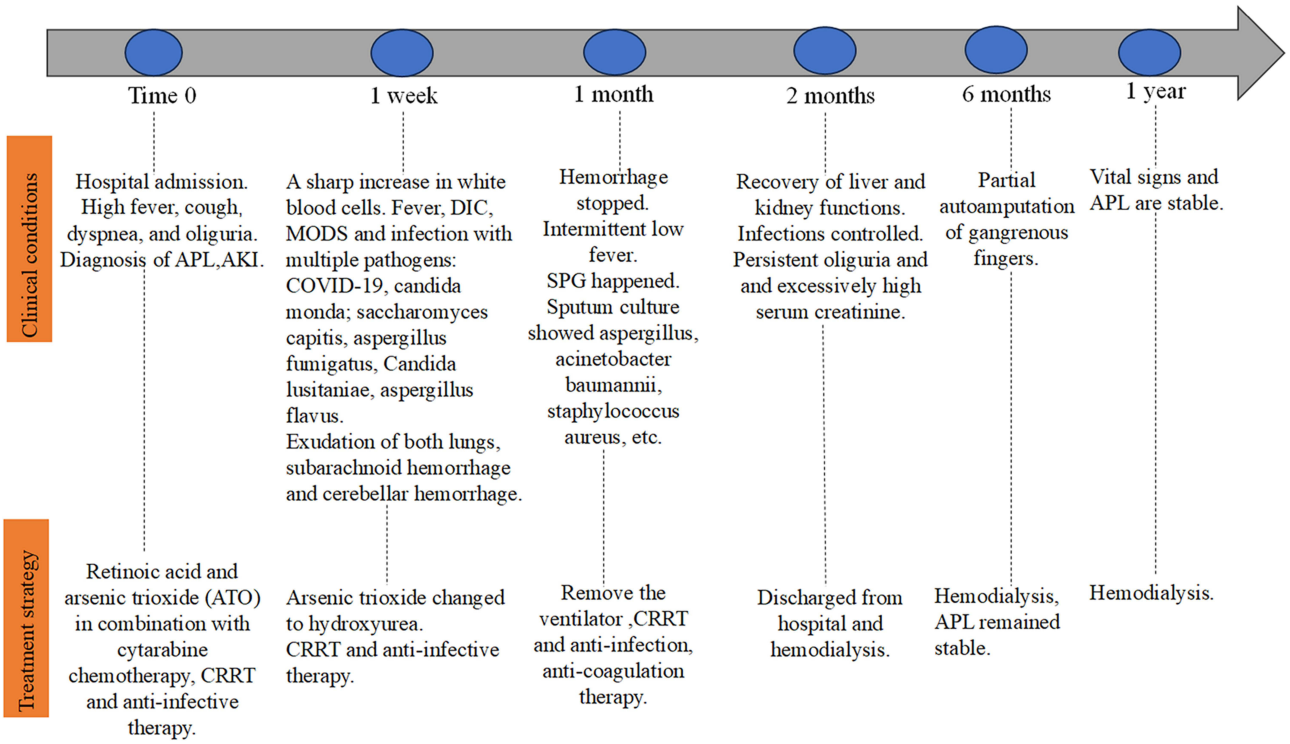

Figure 2 The time line of major events including onset of AKI, initiation of CRRT, onset of gangrene etc.

The pathogenesis of AKI in APL may be related to infection, DIC, administration of chemotherapy drugs, and disturbance of water and electrolytes. High doses of ATO may lead to severe nephrotoxicity and AKI. In order to reduce the occurrence of AKI, JEN and colleagues suggest setting an upper dose of ATO.[9] DIC is a serious complication of APL, with a higher incidence than other types of AML.[10] It is the leading cause of treatment failure in APL.[11] DIC can lead to microvascular thrombosis of the kidneys, affecting blood flow and possibly causing AKI.

Patients suffering from APL are predisposed to a high risk of coagulopathy. It is noteworthy that nearly 90% of APL patients exhibit signs of hemorrhage.[12] Severe hemorrhage, particularly intracranial hemorrhage, is significantly linked to treatment failure and early mortality in APL.[11] It has been documented that the incidence of hemorrhage in APL is higher than that of thrombus, with the former reaching 38% and the latter only 3%.[13] The presence of both hemorrhage and thrombosis underscores the intricacy of APL coagulopathy and the heterogeneity of their presentations. Consequently, in cases of APL, it is imperative to closely monitor hemorrhage while maintaining vigilance for thrombotic events.

SPG is a form of acquired acral limb ischemia syndrome, indicating a severe disturbance of the procoagulant-anticoagulant balance in the vulnerable tissue.[7] The causes of thrombosis associated SPG in APL are complex and may be related to genetic susceptibility, DIC, ATRA treatment and the biological characteristics of tumor cells. Currently, the pathogenesis mainly focuses on three aspects: (a) circulatory shock, (b) DIC and (c) natural anticoagulant failure.[8] Molos etal[14] identified DIC as the most common underlying condition associated with SPG, affecting 90% of patients, with sepsis being the main type and cardiac shock accounting for the rest. Protein C, protein S and antithrombin are the three natural anticoagulant factors, acute liver dysfunction helps account for severe depletion of natural anticoagulants in patients who develop SPG. In a study by Safdar et al[15] silencing the antithrombin and protein C genes in mice resulted in acute coagulopathy, characterized by fibrin deposition and the subsequent necrosis of the hind legs. In addition, vasopressors and antiphospholipid syndrome (APS) are other possible causes of SPG.This patient did not use vasopressors and the antiphospholipid antibody was normal. Therefore, these two reasons were not taken into consideration.

The case in our report was also complicated by severe infections with multiple pathogens, including COVID-19. APL patients have immune dysfunction following chemotherapy or immunotherapy, with a marked reduction in resistance to pathogens. Perianal infection, subcutaneous necrosis, Fournier's gangrene and ATRA-associated gangrenous cheilitis

have been reported in APL patients.[16] Since its emergence in 2019, COVID-19 has turned the world topsy-turvy. As shown in the study by Jenner et al[17] 56.3% of patients with COVID-19 experienced thrombotic events.This is associated with an increased risk of mortality and morbidity.[17,18] NOVARA et al[19] reported a case showing the rapid development of dried gangrene in a non-vasculopathic patient following COVID-19 coagulopathy and DIC. Histological examination of the postmortem tissues from COVID-19 patients revealed signs of microvascular thrombosis in their skin and lungs, which further proves the connection between microvascular inflammation and thrombosis, and highlights the prothrombotic and immunosuppressive effects of COVID-19.[20] The mortality of COVID-19 complicated by gangrene was very high, and all patients reported in the literature died within 2 weeks.[18,19] All patients with gangrene require surgical amputation, or the affected area of gangrene will eventually be lost.[6]

Hematological diseases are frequently associated with genetic defects.The pathogenesis of APL is mainly the translocation of chromosomes 15 and 17, resulting in the formation of the fusion gene PML-RARα. There are also APL-like leukemias that do not show PML-RARα fusion but have MYC amplification or cytogenetic abnormalities, and EZH2 alterations associated with RAR gene dysregulation may cause APL-like morphology in AML.[21] The detection of whole genome exons is helpful for early diagnosis and guiding treatment strategies of gene-related diseases.

In summary, to the best of our knowledge, there were no prior cases of APL with SPG and AKI occurring concurrently. This case demonstrates the irreversible progression of prolonged AKI and rapid development of SPG due to the susceptibility of APL to DIC, as well as coagulopathy in patients with COVID-19. Early recognition, multidisciplinary management, and the emerging therapies such as anticoagulation, antifungal strategies, immunomodulation can prevent the life-threatening consequences. In the future work, we should be more alert to the critical complications of APL, strengthen multidisciplinary collaboration and improve the curability of APL.

Ethics Approval and Consent to Participate

No ethics approval was required as this is a case study. Lanzhou University Second Hospital approved to publish the case details. Written and verbal consent was obtained from the patient.

Consent to Publish Declaration

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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