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CASE REPORT

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Effective management of pediatric septic shock: a case study utilizing continuous renal replacement therapy with cytosorb and citrate in a leukemic patient with hyper-interleukin (IL)-6-naemia and severe thrombocytopenia

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Abstract

Background Sepsis is a critical condition characterized by a dysregulated immune response to infection, often resulting in organ dysfunction. Interleukin-6 (IL-6) is a key proinflammatory cytokine associated with sepsis and its complications. This case study explored the use of Continuous Renal Replacement Therapy (CRRT) combined with Cytosorb in managing pediatric patients with leukemia, severe thrombocytopenia, and elevated IL-6 levels.

Case presentation A 10-year-old boy with Fanconi anemia presented with pancytopenia, fever, and necrotic lesions, indicative of mucormycosis. Following the diagnosis of acute myeloid leukemia (AML), the patient experienced severe complications, including septic shock. Despite appropriate treatment, inflammatory markers, such as C-reactive protein (CRP), procalcitonin (PCT), and IL-6, were significantly elevated. CRRT with Cytosorb was initiated to manage hypercytokinemia and improve the patient's clinical status.

Intervention The CRRT procedure utilizes citrate as an anticoagulant because of severe thrombocytopenia. The treatment lasted for 20 h, during which the inflammatory biomarkers were monitored. The post-treatment results indicated a significant reduction in IL-6 levels within 24 h and a decrease in PCT levels at 8 h. CRP levels gradually declined over 40 h.

Outcome The patient exhibited marked clinical improvement, with significant healing of cutaneous lesions and stabilization of inflammatory markers, allowing transfer to the ward for continued chemotherapy.

Conclusion This case suggests that CRRT combined with cytosorb may be a valuable adjunctive therapy for managing complex cases of septic shock. The observed reduction in inflammatory markers, particularly IL-6,

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warrants further investigation. Concurrent antimicrobial, antifungal, and dexamethasone treatments for IRIS may have influenced the observed outcomes in this single case. Controlled studies are needed to evaluate the specific contribution of Cytosorb-CRRT and assess its long-term efficacy and safety in similar patient populations, particularly in resource-limited settings.

Clinical trial number Not applicable.

Keywords Sepsis, Continuous renal replacement therapy (CRRT), Cytosorb, Interleukin-6 (IL-6), Pediatric leukemia

Introduction

Sepsis is a life-threatening condition caused by a dysregulated host response to an infection that results in organ dysfunction. Interleukin 6 (IL-6) is a pro-inflammatory cytokine that plays a significant role in the body's immune response, particularly during systemic inflammatory conditions such as sepsis, it also exhibits anti-inflammatory properties with multifunctional nature. Interleukin-6 is a pleiotropic cytokine with a molecular weight of approximately 21 kDa that belongs to the IL-6 superfamily of cytokines. It is composed of 185 amino acids, including a 28amino acid signal peptide. IL-6 signals through a receptor complex consisting of IL-6 receptor alpha (IL-6Rα, CD126) and the signal-transducing beta-receptor component gp130 (CD130). The half-life of IL-6 in circulation is relatively short, typically ranging from minutes to a few hours, owing to rapid clearance via receptor-mediated endocytosis and degradation [1, 2]. It is synthesized by various cells and plays a vital role in the immune response, induction of fever, production of acute-phase proteins, and maturation of B cells [3]. It is consistently upregulated in critically ill patients with sepsis [4, 5]. In addition, increased IL-6 levels are correlated with mortality [6]. Increased IL-6 levels are also associated with cardiac, liver, and renal damage [7]. Moreover, it plays a crucial role in cancer biology, including cancer cell invasiveness and metastasis formation [8]; thus, decreasing the level of IL-6 plays a crucial role in improving survival in these patients [9].

We focused on IL-6 because it is a well-established key mediator in the pathogenesis of sepsis, with elevated levels correlating with disease severity, organ dysfunction, and mortality. Although other inflammatory markers are also relevant in sepsis, IL-6 has been extensively studied and is often used as a target for therapeutic interventions aimed at modulating the inflammatory response. Furthermore, in the context of this specific case, the patient presented with markedly elevated IL-6 levels (> 1000 pg/mL), making it a primary target for intervention [1, 2].

Cytosorb, when used alongside Continuous Renal Replacement Therapy (CRRT), is an extracorporeal blood purification technique capable of removing inflammatory mediators and promoting immune stability. This combination has been recognized as a potential treatment approach for patients with severe sepsis and intense inflammatory response [10]. Cytosorb has shown the ability to significantly reduce various inflammatory biomarkers, including IL-6, IL-8, IL-10, C-reactive protein (CRP), and Tumor Necrosis Factor-α (TNF-α) [11, 12]. However, there remains a lack of consensus regarding its overall effectiveness in clinical settings [13].

Although Cytosorb has not been associated with reported complications, the use of anticoagulants such as heparin during CRRT poses significant challenges, particularly in patients with thrombocytopenia or coagulation disorders. We present the case of a pediatric patient with leukemia complicated by thrombocytopenia and sepsis who exhibited markedly elevated serum IL-6 levels. Continuous Renal Replacement Therapy combined with cytosorb was successfully utilized to achieve a significant reduction in IL-6 levels. To the best of our knowledge, this case represents the successful management of a pediatric cancer patient using CRRT with Cytosorb and citrate, despite the presence of thrombocytopenia. Notably, the use of citrate in pediatric patients has not been previously reported in Iran.

Case presentation

A 10-year-old boy with a known history of Fanconi anemia was admitted to our tertiary oncology teaching hospital with pancytopenia, fever, and necrotic cutaneous lesions on the left forearm surrounded by nodular lesions located just below the cubital fossa (Fig. 1). A definitive diagnosis of mucormycosis was established through potassium hydroxide (KOH) preparation and fungal culture (Figs. 2a and b). Treatment was promptly initiated with intravenous liposomal amphotericin at a dosage of 5 mg/kg/day in combination with broad-spectrum antibiotic therapy that included meropenem (20 mg/kg every 6 h) and vancomycin (15 mg/kg every 6 h). Despite receiving appropriate antibiotic and antifungal treatment, the patient continued to exhibit persistent pancytopenia with a white blood cell (WBC) count of less than 500 cells/mm^3. This led to suspicion of a secondary malignancy. Bone marrow aspiration and biopsy confirmed the diagnosis of acute myeloid leukemia (AML). A few hours after the initiation of chemotherapy using the BFM (Berlin-Frankfurt-Münster) protocol, which included Cytosar, Etoposide, and Idarubicin, the patient developed high-grade fever, tachypnea, hypoxia, and cough.

Fig. 1 Soft tissue cellulitis, measuring 3 × 3 cm with central necrosis, was located below the left cubital fossa. Surrounding the primary lesion is a multiple nodular lesion indicative of localized inflammation or secondary involvement. This area demonstrated features consistent with invasive cutaneous fungal infections

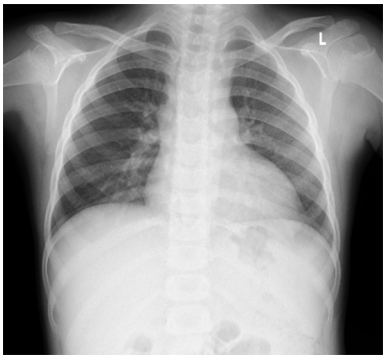

Fig. 3 Chest radiography (CXR) shows normal findings. All radiographic markers were within normal limits, indicating no evidence of pulmonary pathology, pleural effusion, or other abnormalities

Consequently, chemotherapy was discontinued and a thorough workup for sepsis was performed. Laboratory tests included complete blood count (CBC) with differential coagulation studies (PT, aPTT, INR, fibrinogen), blood cultures, procalcitonin (PCT), CRP, IL-6 levels, lactate, and blood gas analysis. Imaging studies consisted of a chest X-ray (CXR) and computed tomography (CT) scan of the chest, abdomen, and pelvis to identify potential infection sources, such as abscesses or organ involvement. Multiple classic pulmonary nodules with halo signs were identified in both lungs despite no detectable abnormalities on chest radiography (Figs. 3 and 4a-d). Consequently, the patient was scheduled for diagnostic bronchoscopy and bronchoalveolar lavage (BAL) for further evaluation. Although KOH and fungal cultures were negative, the BAL galactomannan level was strongly positive (GM index value: 7.5). Antifungal treatment was intensified by incorporating posaconazole and caspofungin into the patient's antifungal regimen. The patient subsequently developed immune reconstitution inflammatory syndrome (IRIS), manifesting as a paradoxical worsening of clinical symptoms. This included increased hypoxia, exacerbation of cough and dyspnea, and the presence of lung crackles and wheezing upon physical examination. These findings were accompanied by an increase in white blood cell count, as detailed in our case series [14]. Dexamethasone was administered intravenously at a dosage of 0.15 mg/kg every 8 h, resulting in significant clinical improvement within eight days. The patient's clinical condition deteriorated after one week, necessitating transfer to the Pediatric Intensive Care Unit (PICU) with a suspected diagnosis of septic shock. Inflammatory biomarkers exhibited significant elevation, with CRP and procalcitonin (PCT) levels recorded at 488.9 mg/L and 4.2 ng/mL, respectively, while IL-6 levels exceeded 1000 pg/ml. Upon arrival in the PICU, the patient required immediate respiratory support with a high-flow nasal cannula (HFNC) oxygen therapy due to worsening hypoxia. Given the persistent hypotension despite initial fluid resuscitation, he was also started on a low-dose dopamine infusion (5 µg/kg/min) for inotropic support. Linezolid was initiated, considering the patient's condition, which included aplastic anemia and secondary AML, both of which limited the use of Granulocyte Colony-Stimulating Factor (G-CSF). Continuous Renal Replacement Therapy (CRRT) with Cytosorb was deemed necessary to manage hypercytokinemia following consultation with a pediatric intensivist. The Cytosorb device was integrated with CRRT in continuous venovenous hemodialysis (CVVHD) mode, with a total treatment duration of 20 h. Interleukin-6, CRP, and PCT

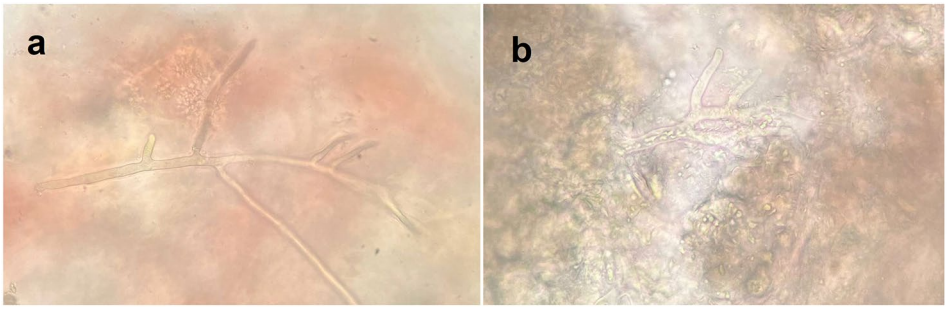

Fig. 2 Microscopic examination using potassium hydroxide (KOH) revealed broad, non-septate hyphae with rectangular branching patterns. These morphological characteristics indicate a diagnosis of mucormycosis

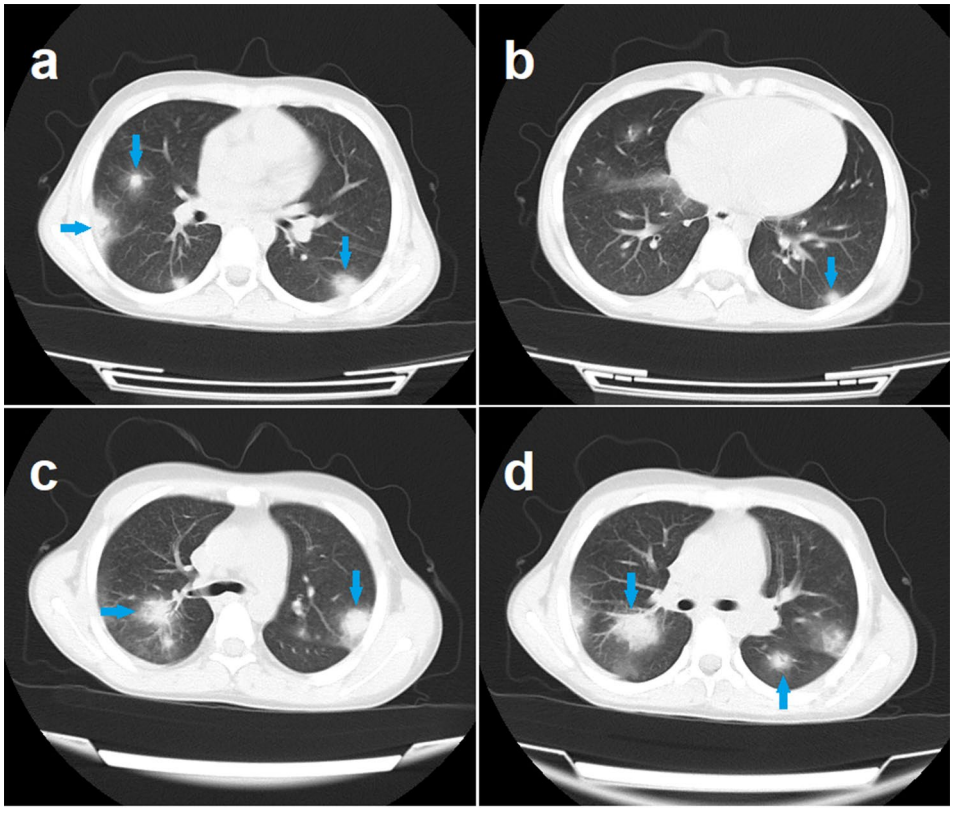

Fig. 4 **a**-**d** Chest spiral computed tomography (CT) without contrast demonstrated multiple bilateral nodules of varying sizes, each surrounded by a halo sign. This radiological finding is highly suggestive of an infectious process, most likely an invasive fungal infection

levels were monitored every eight hours following the initiation of CRRT. This decision was particularly challenging because of the patient's severe thrombocytopenia, with platelet counts falling below 60,000 cells/mm³ (Fig. 5), which precluded the use of heparin as an anticoagulant. Based on the machine's data, including pre-filter pressure, trans-filter pressure, and trans-membrane pressure, citrate was considered an alternative anticoagulant during the CRRT procedure. Notably, CRRT was conducted without anticoagulants during certain periods, contingent on the machine's readings. The procedure was completed over 20 h without any complications. The decision regarding treatment duration was influenced by the high cost of cytosorb in our country.

Inflammatory biomarkers exhibited a progressive decline, accompanied by significant improvement in the patient's overall clinical status. The lowest level of IL-6 was recorded 24 h after the initiation of treatment (Fig. 6), whereas PCT levels decreased at 8 h post-treatment (Fig. 7). A gradual decline in CRP concentration was noted over the 40-hour period following the initiation of CRRT (Fig. 8). The patient's cutaneous lesions showed significant improvement, leading to their transfer to the ward for continuation of chemotherapy (Fig. 9a-c).

Discussion

The management of pediatric patients with septic shock, particularly those with underlying conditions, such as aplastic anemia and AML, presents unique challenges. The case presented highlights a 10-year-old boy whose clinical condition deteriorated, necessitating transfer to the PICU due to suspected septic shock. Sepsis with associated organ failure has a mortality rate of up to 50% [9].

In this case, inflammatory biomarkers were significantly elevated, with CRP levels > 480 mg/L, PCT > 4 ng/mL, and IL-6 > 1000 pg/ml. Elevated levels of inflammatory biomarkers are indicative of severe systemic inflammation and are associated with poor outcomes in patients with sepsis. Specifically, IL-6 has been shown to correlate with mortality in sepsis and is involved in the pathogenesis of organ dysfunction during septic states [3]. Although timely and appropriate antibiotic therapy remains the cornerstone of treatment, modulation or removal of inflammatory cytokines may play a pivotal role in reducing sepsis-related mortality [6, 15]. The progressive decline of these markers following treatment with CRRT combined with cytosorb suggests a therapeutic benefit in managing hypercytokinemia, a common complication of severe sepsis. Although adjunctive

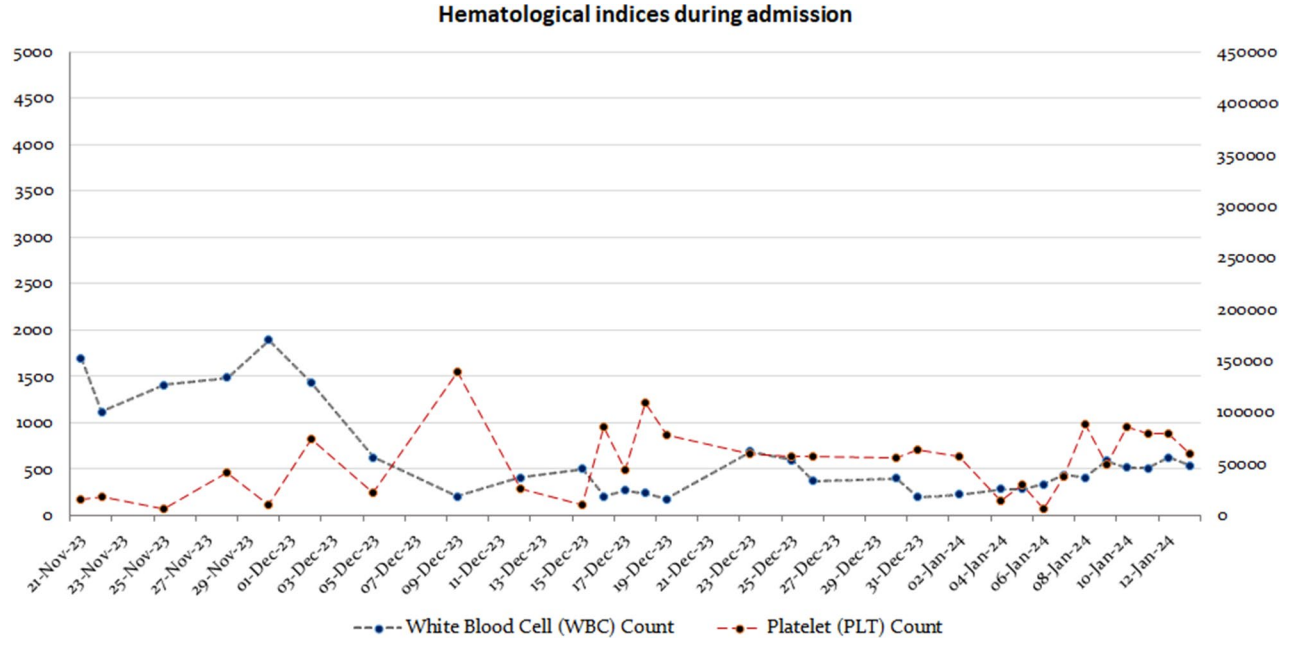

Fig. 5 Hematological indices on admission indicated severe thrombocytopenia and neutropenia

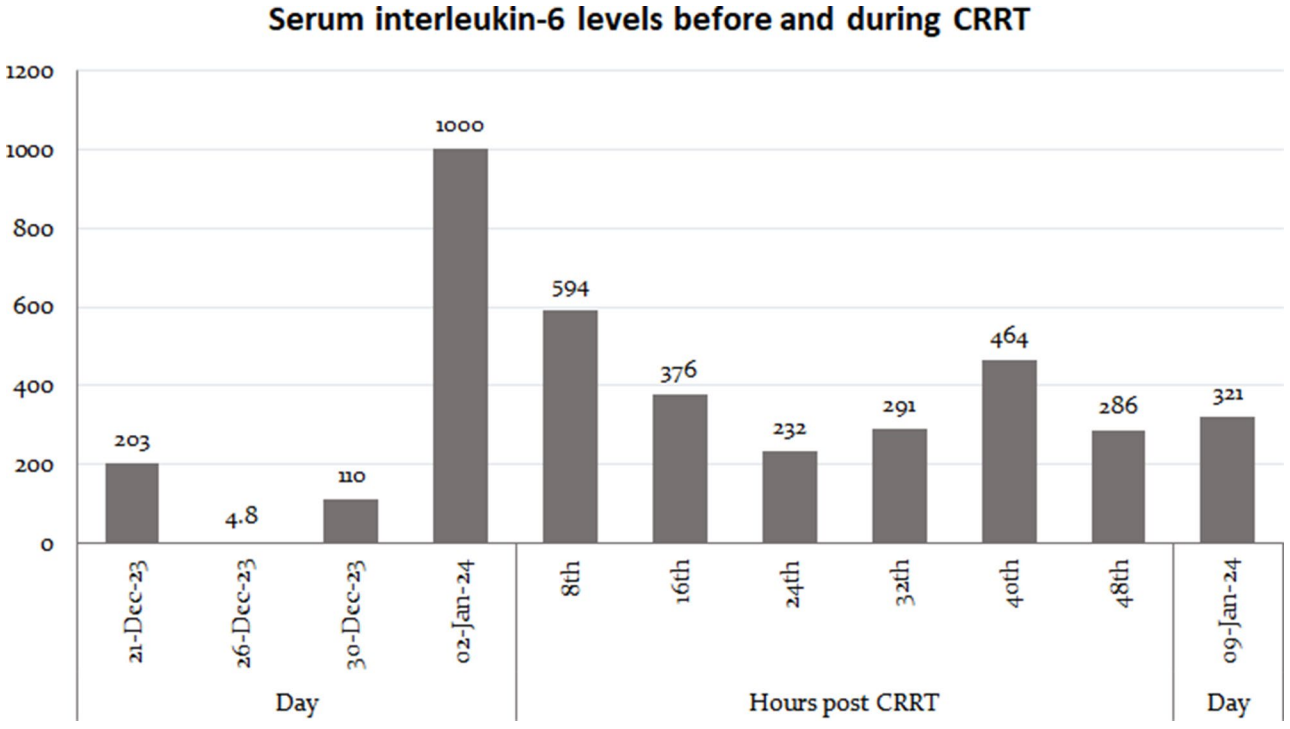

Fig. 6 Serum interleukin-6 levels were measured before and during continuous renal replacement therapy (CRRT). The data illustrated the dynamic changes in IL-6 concentrations, highlighting the inflammatory response associated with the patient's condition throughout the treatment period

therapies targeting cytokine reduction, such as hemadsorption using devices like Cytosorb, have demonstrated potential in mitigating hyperinflammatory states in critically ill patients, their impact on improving survival outcomes remains uncertain. Recent systematic reviews and meta-analyses have highlighted the lack of consensus regarding their overall clinical efficacy despite the reduction in inflammatory markers such as IL-6 and TNF-α observed in some studies [9, 13].

In pediatric sepsis, traditional inflammatory markers, such as albumin, lactate, CRP, and PCT, are commonly used for initial assessment and monitoring because of

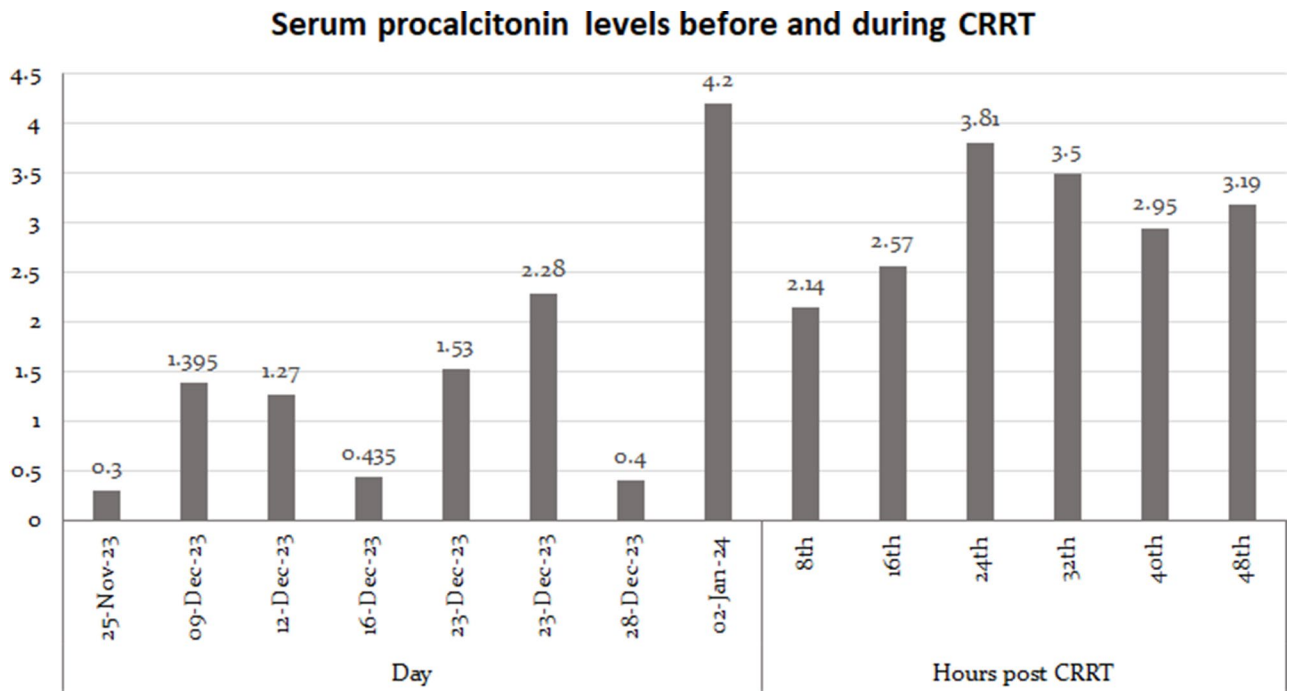

Fig. 7 Serum procalcitonin levels before and during continuous renal replacement therapy (CRRT). The results demonstrated a significant decrease in procalcitonin concentration, with levels reduced by half within 8 h after the initiation of CRRT. These findings highlight the potential impact of CRRT on the clearance of inflammatory biomarkers

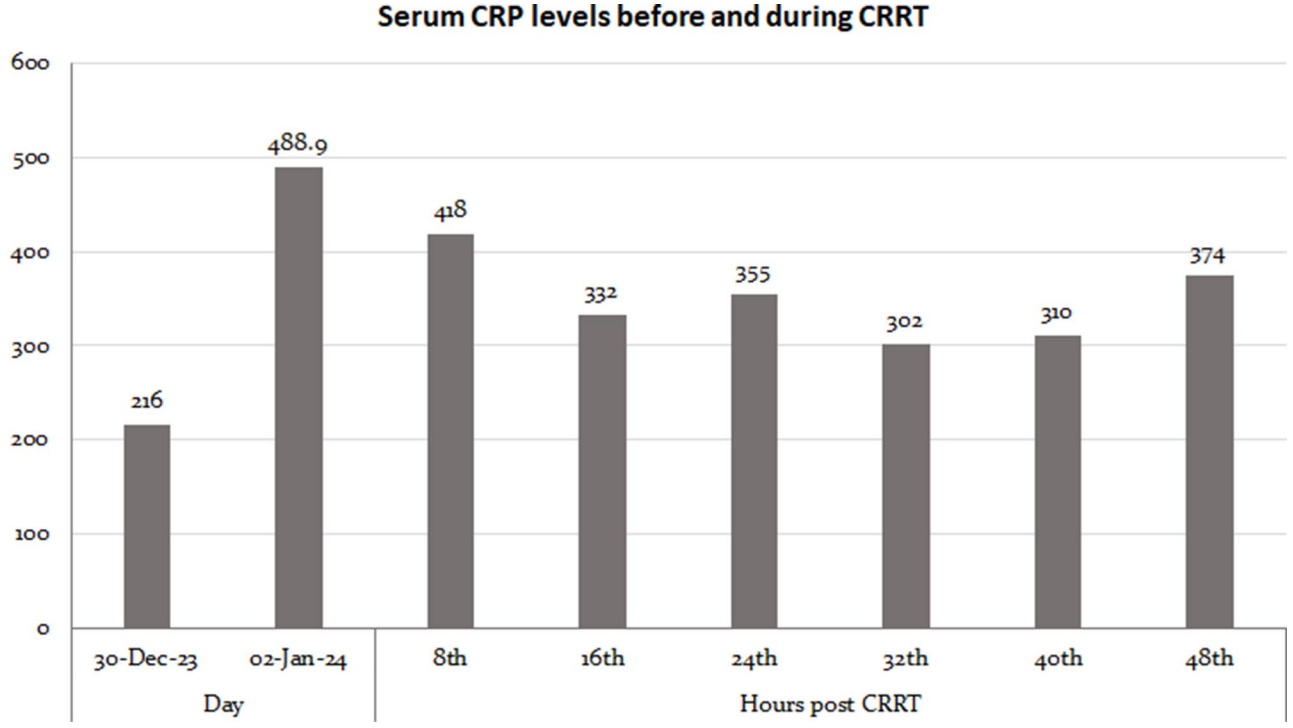

Fig. 8 Serum C-reactive protein (CRP) levels were measured before and during continuous renal replacement therapy (CRRT). The data demonstrated a gradual decrease in CRP concentrations over the course of 40 h following the initiation of CRRT, indicating a reduction in the inflammatory response during treatment

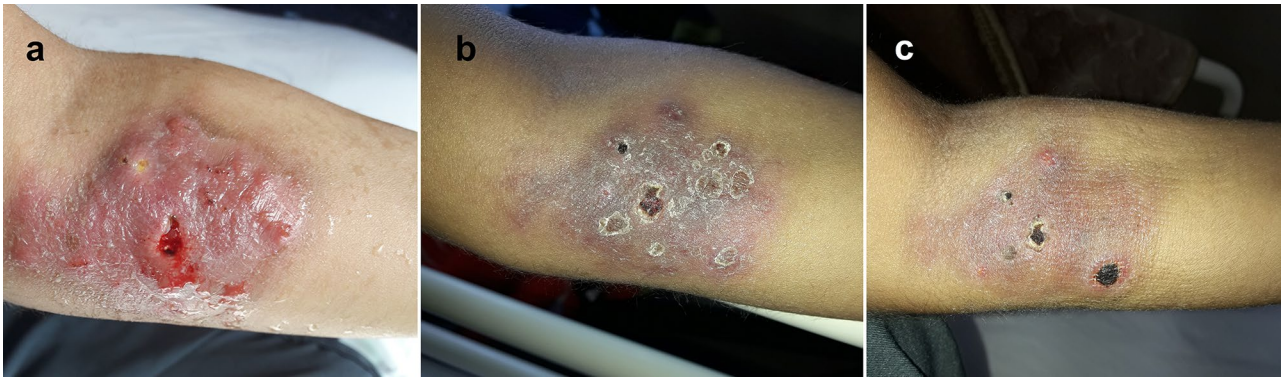

Fig. 9 **a**-**c**. The patient's cutaneous lesions demonstrated significant improvement during treatment, which consisted of a combination of antifungal therapy and supportive care, including continuous renal replacement therapy (CRRT)

their widespread availability and rapid turnaround times. Albumin levels can reflect the severity of illness and capillary leak, whereas lactate serves as an indicator of tissue hypoperfusion. CRP and PCT are acute-phase reactants that indicate the presence of inflammation and infection. However, these markers may lack specificity and can be influenced by various noninfectious conditions [16, 17]. Interleukin-6 (IL-6), which is more complex and often requires specialized assays, provides a more direct assessment of the cytokine storm associated with severe sepsis and has been shown to correlate with disease severity and mortality [18].

In this case, while we monitored traditional markers, such as CRP and PCT, the markedly elevated IL-6 levels (> 1000 pg/mL) prompted the use of CRRT to manage the hyperinflammatory state. The decline in IL-6 levels following treatment, along with clinical improvement, supported the decision to continue extracorporeal therapy. Furthermore, IL-6 levels, in conjunction with other clinical parameters, play a role in determining the patient's readiness for transfer from the PICU to the ward, indicating stabilization of the inflammatory response and a decreased risk of further complications [19].

Liu et al. reported successful reductions in inflammatory factors in patients with pancreatitis complicated by acute renal failure [10], while Bottari et al. demonstrated significant decreases in IL-6 and IL-10 levels in patients with septic shock treated with cytosorb [20]. Bottari et al. reported a significant reduction in interleukin-6 and interleukin-10 levels in eight patients with septic shock following cytosorb treatment [20]. In other studies, there have been successful reductions in IL-6 levels and associated decreases in mortality rates [21–23].

In our country, heparin is commonly used as the anticoagulant of choice for CRRT in pediatric patients despite existing evidence supporting the use of citrate as a safer alternative. The decision to use citrate as an anticoagulant during CRRT was particularly crucial because of the patient's thrombocytopenia, which posed the risk of exacerbated bleeding with heparin use. Citrate acts as a regional anticoagulant by chelating calcium, which is essential in the coagulation cascade. By specifically binding calcium within the extracorporeal circuit of the CRRT machine, citrate prevents systemic anticoagulation and reduces the risk of bleeding, particularly in patients with thrombocytopenia. However, citrate metabolism can lead to systemic hypocalcemia if not monitored carefully. Therefore, frequent monitoring of ionized calcium (iCa) levels, both pre-and post-filter, is crucial to ensure adequate anticoagulation within the circuit and to prevent systemic calcium imbalances, which can have adverse effects on cardiac function and overall patient stability [19, 24, 25].

In resource-limited settings, such as in many Low- and Middle-Income Countries (LMICs), the high cost of treatments such as Cytosorb can significantly impact clinical decision-making. This case underscores the importance of carefully considering both clinical efficacy and economic factors when determining the treatment duration and modality. Despite these challenges, the successful administration of CRRT without complications illustrates the potential for effective management strategies, even in resource-constrained environments.

Another treatment option for patients with thrombocytopenia-associated sepsis (TAMOF) is plasmapheresis. While plasmapheresis can remove a broad range of inflammatory mediators and has a role in certain sepsis-related conditions, we favored cytosorb combined with CRRT in this particular case for several reasons. First, the mechanism of action of Cytosorb focuses on adsorbing hydrophobic cytokines such as IL-6, which is the dominant cytokine in this patient's presentation (IL-6 > 1000 pg/mL). Plasmapheresis, while effective at removing a wider array of substances, may also remove beneficial proteins and clotting factors, potentially exacerbating the risk of bleeding in a patient already severely thrombocytopenic [26]. Second, CRRT provides continuous renal support, which is crucial in managing fluid overload and

electrolyte imbalances frequently seen in septic shock, offering an advantage over intermittent plasmapheresis. Finally, in our specific setting and based on available resources, we considered Cytosorb + CRRT to be a more readily available and logistically feasible option for rapid cytokine reduction and continuous organ support than plasmapheresis, particularly given the need for specialized equipment and personnel for plasmapheresis. However, we acknowledge that plasmapheresis remains a valuable therapeutic modality in selected cases of sepsis, and the optimal approach should be individualized based on the patient's clinical presentation, underlying conditions, and available resources.

The patient demonstrated significant clinical improvement following treatment, as evidenced by the decreased levels of IL-6 and PCT. However, CRP levels remained stable, suggesting that while certain inflammatory responses were effectively managed, others persisted. This observation is consistent with the existing literature, indicating that CRP may not always correlate directly with clinical improvement in sepsis management. The incorporation of innovative therapies, such as Cytosorb, into standard care protocols for pediatric patients with septic shock has the potential to enhance clinical outcomes. Future research should focus on the long-term effects of these treatments across diverse populations, particularly in LMICs, where healthcare resources are often limited.

Conclusion

This case highlights the challenges of managing pediatric septic shock complicated by underlying conditions like leukemia, severe thrombocytopenia, and invasive fungal infections, particularly when treatment options are limited by resource constraints. This emphasizes the importance of monitoring inflammatory biomarkers and adapting appropriate treatment strategies. The successful use of CRRT with Cytosorb in this patient underscores its potential role as an adjunctive therapy in severe sepsis management.

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Author contributions
Study concept and design: AA and AS; Acquisition of data: AA, AS, and HJ; Analysis and interpretation of data: AA, AS, and HJ; Drafting of the manuscript: AA, AS, and HJ, Critical revision of the manuscript for important intellectual content: AA, and, AS; Study supervision: AA and AS. All authors corrected and approved the final manuscript.

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Data availability
The dataset used and analyzed during the current study will be available from the corresponding author upon reasonable request.

Declarations

Ethics and consent to participate
The current study was conducted in accordance with the Declaration of Helsinki and pertinent national standards and regulations governing medical research. This study was approved by the local institutional review board. The patient and his parents were duly informed about the study, and written informed consent was obtained for the child's participation and anonymized utilization of his clinical data in the research.

Consent for publication
Written informed consent for publication was obtained from patients and their parents.

Competing interests
The authors declare no competing interests.

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