

Case Report

Multifaceted Management of Severe Pancytopenia in a Diabetic Patient: A Case of MRSE-Induced Bone Marrow Suppression

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Severe pancytopenia presents a multifactorial clinical challenge, particularly in patients with complex comorbidities such as diabetes mellitus (DM) and systemic infections. This case report discusses the management of a 42-year-old male with uncontrolled type 2 DM who developed severe pancytopenia secondary to methicillin-resistant *Staphylococcus epidermidis* (MRSE)-induced bone marrow suppression. The patient presented with high-grade fever, pancytopenia, and systemic infection, exacerbated by poor glycemic control. Initial management included broad-spectrum antibiotics, blood transfusions, and supportive care. Blood cultures revealed MRSE, prompting targeted antimicrobial therapy with linezolid, which led to significant clinical improvement. Persistent pancytopenia required the use of thrombopoietin receptor agonist eltrombopag, which successfully stimulated platelet production and improved hematopoiesis. Bone marrow biopsy findings confirmed marked hypocellularity with serous atrophy and reactive fibrosis, consistent with chronic inflammatory and infectious processes.

The patient's course highlighted the critical role of hyperglycemia in exacerbating immune dysfunction and the complexities of managing severe infections in diabetic patients. MRSE-induced biofilm formation and immune evasion further contributed to the prolonged inflammatory state and bone marrow suppression. This case underscores the importance of a multidisciplinary approach, involving antimicrobial therapy, supportive care, and novel agents like eltrombopag, in addressing pancytopenia in the setting of chronic infection and comorbidities. It highlights the need for early and accurate diagnostic workup, tailored therapy, and vigilant monitoring to optimize outcomes in critically ill patients with severe pancytopenia.

Introduction

Pancytopenia is defined as the simultaneous reduction in all three major blood cell lines that include red blood cells, white blood cells, and platelets^[1]. The condition can be caused by variety of etiologies, including bone marrow failure, hematologic malignancies, or peripheral destruction of blood cells^[2]. The management of pancytopenia includes significant challenges, especially in the context of patients with complex comorbidities such as uncontrolled diabetes mellitus (DM) and co-existing infections^[3]. The bone marrow, as the primary site of hematopoiesis, is highly vulnerable to systemic insults such as infection, inflammation, and metabolic disturbances^[4]. Infections, particularly those involving multidrug-resistant organisms, can lead to bone marrow suppression through various mechanisms, including direct microbial invasion, immune-mediated destruction, and cytokine-induced apoptosis^[5].

Methicillin-resistant *Staphylococcus epidermidis* (MRSE), a common pathogen in immunocompromised patients, has gained increasing recognition for its ability to cause severe sepsis and bacteremia, contributing to bone marrow dysfunction^[6]. This organism's ability to form biofilms and evade host immune responses further complicates management, often leading to prolonged infections and persistent pancytopenia^[7].

Diabetes mellitus, particularly when poorly controlled, is an important risk factor for both infection and hematologic dysfunction^[8]. Hyperglycemia impairs immune function by affecting neutrophil chemotaxis, macrophage activation, and T-cell responses, thereby increasing susceptibility to infections^[8]. Moreover, the chronic inflammatory state associated with diabetes may exacerbate the bone marrow suppression observed in infections, contributing to severe pancytopenia^[9].

The management of pancytopenia in this context requires a multifaceted approach, including antimicrobial therapy, blood product transfusions, and supportive care^[10]. Recent advances in the use of thrombopoietin receptor agonists, such as eltrombopag, have offered addressing thrombocytopenia in patients with bone marrow failure secondary to infectious processes^[11]. This case report describes the clinical course and management of a 42-year-old male with uncontrolled type 2 diabetes who presented with severe pancytopenia secondary to MRSE-induced bone marrow suppression. The report highlights the complexities of diagnosing and managing pancytopenia in critically ill patients with multiple comorbidities, and the role of targeted therapy and supportive measures in improving patient outcomes.

Case Presentation

A 42-year-old male with a known history of uncontrolled type 2 diabetes mellitus (DM) presented to the emergency department on July 25th, 2024, with complaints of high-grade fever accompanied by chills for the past four days. The patient reported that the fever had started three weeks ago as a low-grade fever, which progressively increased in intensity. Initially, he took treatment at a local clinic, where there was some symptomatic improvement. However, the medication prescribed (details unknown) led to the development of oral ulcers and decreased appetite, leading the patient to discontinue the treatment. Subsequently, the fever worsened, and the patient began experiencing generalized body aches and myalgias.

On admission, the patient's vital signs were as follows: blood pressure 130/80 mmHg, heart rate 84 beats per minute, respiratory rate 18 breaths per minute, oxygen saturation 98% on room air, and temperature 101°F. His blood sugar level was significantly elevated at 347 mg/dL, consistent with his history of poorly controlled DM. A general physical examination (GPE) revealed that the patient was pale and appeared anemic but showed no signs of jaundice, cyanosis, clubbing, edema, rash, or palpable lymphadenopathy. Notably, the patient had mild cellulitis in his left hand, which developed five days earlier following intravenous (IV) line insertion at a local clinic. Systemic examination revealed clear lung fields, a soft and non-tender abdomen without signs of organomegaly, and a normal cardiovascular examination. Neurologically, the patient was fully oriented with a Glasgow Coma Scale (GCS) score of 15/15.

Initial Investigations and Management

Initial laboratory investigations revealed significant pancytopenia: hemoglobin (Hb) level of 5.2 g/dL, platelet count of 10,000/ μ L, and white blood cell (WBC) count of 1,120/ μ L. An electrocardiogram (ECG) performed at admission showed normal sinus rhythm. Blood cultures were obtained before initiating empirical antibiotic therapy, and an ultrasound (USG) of the abdomen was performed, which showed mild splenomegaly (12.3 cm) and mild fatty hepatomegaly, with no other significant findings.

The patient was immediately admitted to the intensive care unit (ICU) for close monitoring and management. Empirical broad-spectrum antibiotic therapy with meropenem (1 g every 8 hours) was initiated, alongside paracetamol (1 g every 12 hours) for fever management and an insulin infusion at 2 units per hour to control hyperglycemia. Two hours after admission, the patient developed tachycardia. A repeat ECG revealed supraventricular tachycardia (SVT), which was managed with intravenous verapamil

(2.5 mg) and magnesium sulfate (2 g). A cardiology consultation was obtained, and the patient was started on oral verapamil (40 mg twice daily). An echocardiogram (ECHO) showed an ejection fraction (EF) of 60%, with a normal-sized left ventricle and good systolic and diastolic function. Given the severity of pancytopenia, the patient received multiple blood product transfusions, including 6 units of fresh frozen plasma (FFP), 6 units of platelets, and 1 unit of red cell concentrate (RCC). Despite these interventions, the patient continued to experience high-grade fever spikes, which were managed conservatively.

On the second day of admission, laboratory tests revealed no clinical improvement; the patient's Hb dropped further to 4.9 g/dL, WBC count to 550/ μ L, and platelet count to 62,000/ μ L post-transfusion. Table 1 shows details of further investigations.

| Lab Investigation | Value |
|--|------------------|
| Urea | 41 mg/dL |
| Creatinine | 0.9 mg/dL |
| Sodium | 133 mmol/L |
| Potassium | 3.2 mmol/L |
| Chloride | 99 mmol/L |
| Uric Acid | 11.0 mg/dL |
| Thyroid-Stimulating Hormone (TSH) | 1.03 μ IU/mL |
| Free T4 | 1.77 ng/dL |
| D-dimer | 983 ng/mL |
| Activated Partial Thromboplastin Time (aPTT) | 44 seconds |
| Prothrombin Time (PT) | 21 seconds |
| International Normalized Ratio (INR) | 1.9 |
| Direct Coombs Test | Negative |
| Indirect Coombs Test | Negative |
| HIV | Negative |
| Triglycerides | 116 mg/dL |
| Ferritin | 1563 ng/mL |

On the third day of admission, Crimean-Congo hemorrhagic fever (CCHF) serology was sent due to the presence of melena and hematuria. However, CCHF came to be negative. The patient's Hb was 5.7 g/dL, platelet count 38,000/ μ L, and WBC count 510/ μ L. As a result, the patient received further transfusions, including 1 unit of RCC, 4 units of FFP, and 4 units of platelets. Intravenous omeprazole infusion at 8 mg/hour was initiated to manage the gastrointestinal bleeding, which settled after two days of treatment. Hematuria also settled after two days. The patient became afebrile after six days, however, meropenem was continued till day fourteen.

On the fourth day, additional blood product transfusions were required, with pre-transfusion Hb at 7.5 g/dL, platelet count at 18,000/ μ L, and WBC count at 580/ μ L. The patient received 1 unit of RCC, 4 units of FFP, and 4 units of platelets. On the fifth day, a bone marrow biopsy was attempted, but it failed due to technical difficulties. The patient continued to receive transfusions as his clinical condition remained critical. On the sixth day, the patient experienced another episode of SVT, which was managed with intravenous metoprolol. A repeat cardiology consultation did not reveal any significant underlying cardiac pathology. Despite ongoing transfusions, the patient's platelet count dropped significantly to 3,000/ μ L on the seventh day, but no obvious bleeding was noted. The patient received an additional 4 units of FFP and 6 units of platelets. On the seventh day, *Staphylococcus epidermidis* was isolated from the blood culture, and based on the sensitivity report, oral linezolid 600 mg twice daily was initiated. The patient was also started on eltrombopag (Revolade) 50 mg daily to stimulate platelet production, and this was continued for eight days.

On the eighth, ninth, and tenth days of admission, the patient's platelet count remained critically low, necessitating further transfusions. Another blood culture reported on the tenth day revealed methicillin-resistant *Staphylococcus epidermidis*, which was sensitive to linezolid. As a result, linezolid 600 mg twice daily was continued, leading to further stabilization of the patient's condition. By day 11, the patient's platelet count began to show a marked improvement, initially rising to 24,000/ μ L. Subsequently, the platelet levels increased progressively to 30,000/ μ L, then to 40,000/ μ L, followed by 53,000/ μ L, 79,000/ μ L, 106,000/ μ L, and eventually reaching 195,000/ μ L over the following days.

On the fourteenth day of admission, a surgical consultation was obtained due to persistent cellulitis in the patient's left hand, which had not improved despite ongoing antibiotic therapy. An incision and drainage (I&D) procedure were performed on the fifteenth day, and meropenem was discontinued. The patient was hospitalized for an additional five days, during which his condition remained stable. His wound showed signs of improvement, and laboratory results demonstrated significant progress. Consequently, he was discharged with a prescription for oral medication and advised to attend regular follow-up appointments.

Histopathological and Bone Marrow Findings

A bone marrow biopsy was successfully performed on the tenth day of admission, and the histopathological examination revealed significant findings:

The bone marrow trephine biopsy specimen consisted of a tan-brown, thick linear core measuring 1.5 cm in length. The bone marrow was markedly hypocellular with an overall cellularity of approximately 10%.

The marrow primarily exhibited serous atrophy, characterized by atrophied fat cells and eosinophilic granular material, all embedded within a reactive fibroblastic network. A small, residual area of native hematopoietic tissue was present. Immunohistochemistry was conducted to further characterize the cellular components within the bone marrow. The staining revealed that CD20 was positive in B-lymphocytes, indicating the presence of B-cell populations. Conversely, CD34 staining was negative, suggesting an absence of progenitor cells. Additionally, CD3 staining was positive in T-lymphocytes, confirming the presence of T-cell populations. Special staining techniques, including the Reticulin stain, highlighted grade-2 generalized fibrosis and grade-3 focal fibrosis within the marrow, which is indicative of significant reticulin fiber deposition.

Final Diagnosis and Clinical Implications

The bone marrow biopsy demonstrated gross serous atrophy and reactive fibrosis with marked hypocellularity. There was no evidence of granuloma formation or malignancy in the examined sections. Given the degree of hypocellularity and fibrosis, the findings strongly suggested bone marrow suppression secondary to chronic inflammatory or infectious processes, rather than a primary hematological malignancy. This finding was consistent with the patient's clinical presentation of pancytopenia, high-grade fever, and splenomegaly. The chronic inflammatory process likely led to serous atrophy of the bone marrow, contributing to the severe pancytopenia observed. The absence of progenitor cells (as indicated by the negative CD34 staining) suggested a depletion or suppression of the bone marrow's ability to regenerate blood cells. The reticulin staining, which showed significant fibrosis, also pointed to a chronic process, potentially exacerbated by the patient's underlying uncontrolled diabetes mellitus and ongoing sepsis caused by methicillin-resistant *Staphylococcus epidermidis*. The presence of reactive fibrosis within the marrow further supported the diagnosis of a secondary bone marrow failure syndrome, likely due to the severe and prolonged inflammatory state.

Given the findings from the bone marrow biopsy and the patient's clinical course, it was recommended to rule out potential chronic infections, inflammatory conditions, nutritional deficiencies, or drug-induced causes contributing to the serous atrophy and fibrosis. Continued management with antibiotics, blood product transfusions, and supportive care was advised, along with close monitoring of peripheral blood counts. A follow-up bone marrow biopsy in 8-12 weeks was recommended to assess the progression of marrow recovery and the effectiveness of ongoing.

Treatment

The patient's treatment plan began with empirical broad-spectrum antibiotic therapy using meropenem, later adjusted to linezolid after methicillin-resistant *Staphylococcus epidermidis* (MRSE) was identified in blood cultures. To address his severe pancytopenia, the patient received a total of 6 units of red cell concentrate (RCC), 22 units of platelets, and 16 units of fresh frozen plasma (FFP) throughout his hospital stay. Eltrombopag was initiated on day seven and continued for eight days, resulting in a gradual improvement in platelet levels. Filgrastim was also administered from the second day at a dosage of 300 mcg twice daily for five days to stimulate white blood cell production. Fever was managed with paracetamol, and an incision and drainage procedure was performed on day fifteen to treat left-hand cellulitis. Episodes of supraventricular tachycardia (SVT) were managed with verapamil and metoprolol. Insulin therapy was used to control elevated blood glucose levels, and supportive care, including nutritional support and management of gastrointestinal bleeding, was provided to stabilize the patient's overall condition.

Discussion

This case highlights the management of severe pancytopenia in a diabetic patient, complicated by a methicillin-resistant *Staphylococcus epidermidis* (MRSE) infection, with resultant bone marrow suppression. The patient's clinical course underscores the complexities in diagnosing and managing pancytopenia, especially in the context of chronic uncontrolled diabetes and an ongoing systemic infection. The report discusses several critical aspects of the case, including the pathophysiology of pancytopenia in the context of infection and diabetes, the challenges in diagnosing bone marrow suppression, the management strategies employed, and the role of MRSE in this clinical scenario.

Pathophysiology of Pancytopenia in the Context of Infection and Diabetes

Pancytopenia can arise from various etiologies, including bone marrow failure, peripheral destruction of blood cells, and sequestration in organs such as the spleen^[12]. In this patient, pancytopenia was most likely secondary to bone marrow suppression induced by a prolonged infectious process, intensified by the patient's uncontrolled diabetes.

DM, particularly when poorly controlled, is known to impair immune function by impairing neutrophil function, reducing T-cell activation, and disrupting cytokine production. Chronic hyperglycemia can also

exacerbate inflammation and contribute to the progression of infections^[13]. In this case, the patient's elevated blood glucose levels of 347 mg/dL likely contributed to both the severity and persistence of the MRSE infection, potentially leading to prolonged sepsis and exacerbating the bone marrow suppression. Chronic hyperglycemia has been implicated in an increased risk of infections due to impaired neutrophil chemotaxis and reduced bacterial killing capacity^[14]. As such, this patient's underlying diabetes may have significantly contributed to the progression of pancytopenia.

Bone Marrow Suppression and Infectious Etiologies

The patient's bone marrow biopsy findings were consistent with bone marrow suppression, marked by hypocellularity, serous atrophy, and fibrosis. These findings suggest a chronic inflammatory process, likely exacerbated by the MRSE infection. Infection-induced bone marrow suppression, especially in patients with systemic inflammation, is not uncommon^[15]. Sepsis and chronic infections can lead to bone marrow dysfunction via direct suppression of hematopoietic stem cells, cytokine-induced apoptosis, and altered immune responses^[15]. The presence of reactive fibrosis, identified on the bone marrow biopsy, further supports the hypothesis of a long-standing inflammatory process affecting hematopoiesis^[16]. This is in line with previous studies that have demonstrated that bone marrow fibrosis can be a sequela of chronic infections and systemic inflammation^[17].

The relationship between infection and bone marrow suppression is complex, and although the precise mechanisms remain an area of ongoing research, it is well established that cytokines such as TNF- α , IL-6, and IL-1 play a pivotal role in the suppression of bone marrow progenitors^[17]. The patient's febrile episodes, persistent pancytopenia, and evidence of systemic infection likely contributed to this dysregulated hematopoiesis, leading to the observed findings of hypocellular marrow with reactive fibrosis.

Role of Methicillin-Resistant Staphylococcus epidermidis

MRSE is a common pathogen in healthcare-associated infections, particularly in immunocompromised patients^[18]. In this case, the patient developed cellulitis following intravenous line insertion, which progressed to bacteremia. MRSE's propensity to form biofilms and its ability to evade the immune system make it particularly difficult to eradicate in such patients^[7]. This patient's persistence of fever, pancytopenia, and worsening clinical status in the absence of an appropriate antimicrobial therapy underscores the importance of obtaining early and accurate microbiological cultures to guide treatment.

Interestingly, the patient's clinical course highlights the significance of using linezolid for MRSE. Although MRSE is resistant to methicillin and other β -lactam antibiotics, linezolid, a synthetic oxazolidinone antibiotic, remains effective due to its unique mechanism of action (Hashemian et al., 2018). By inhibiting bacterial protein synthesis through binding to the 23S ribosomal RNA of the 50S subunit, linezolid is effective against Gram-positive organisms, including MRSE (Kosecka-Strojek et al., 2020). The patient's subsequent improvement following initiation of linezolid is consistent with the established effectiveness of this drug against resistant strains like MRSE.

Platelet Management and the Role of Eltrombopag

The management of severe thrombocytopenia in this case was a critical aspect of the patient's treatment. The patient's platelet count remained critically low despite multiple transfusions, reflecting the underlying bone marrow suppression. The administration of eltrombopag, a thrombopoietin receptor agonist, was initiated on day 7 to stimulate platelet production. Eltrombopag, which acts by binding to the thrombopoietin receptor, was instrumental in the gradual improvement in the patient's platelet count, from 3,000/ μ L on day 7 to 195,000/ μ L by day 14.

The use of eltrombopag in the setting of pancytopenia induced by sepsis or chronic inflammation has been increasingly reported in the literature (Gonzalez-Porras & Bastida, 2018). Studies have demonstrated that thrombopoietin mimetics like eltrombopag can effectively stimulate platelet production in patients with chemotherapy-induced thrombocytopenia, idiopathic thrombocytopenic purpura (ITP), and, as seen here, secondary bone marrow failure^[19]. This approach is especially valuable in critically ill patients, where platelet transfusions alone may not be sufficient to restore normal platelet counts or prevent bleeding complications.

Challenges in Diagnosis and Management

This case also highlights the challenges in diagnosing the underlying cause of pancytopenia in a critically ill patient. Bone marrow biopsy failure on day 5 due to technical issues delayed a definitive diagnosis, which could have guided more tailored therapy earlier. The suspicion of an underlying hematological malignancy, such as leukemia, was appropriately ruled out through histopathological examination, and the findings instead pointed to marrow suppression due to chronic inflammatory or infectious processes. The presence of splenomegaly and elevated ferritin also pointed to a reactive process rather than a primary hematologic disorder. While the initial diagnostic approach was

comprehensive, the delayed biopsy highlights the importance of early intervention in such complex cases.

Moreover, the management of the patient's fever, sepsis, and pancytopenia required a multifaceted approach, involving not only antibiotics and transfusions but also careful management of blood glucose levels, arrhythmias, and complications such as gastrointestinal bleeding. This multidisciplinary approach is essential in managing critically ill patients, particularly those with underlying comorbidities such as diabetes.

Conclusion

This case underscores the complex interplay between infection, diabetes, and bone marrow suppression, particularly in the setting of a methicillin-resistant *Staphylococcus epidermidis* infection. The patient's clinical course highlights the importance of a thorough diagnostic workup, timely antimicrobial therapy, and supportive care, including blood product transfusions and the use of thrombopoietin receptor agonists like eltrombopag. Furthermore, it emphasizes the need for close monitoring of blood counts, glucose levels, and organ function in critically ill patients. Early intervention, coupled with a multidisciplinary approach, is critical to improving outcomes in patients with severe pancytopenia secondary to infection.

Ethical Consideration

The ethical approval for this study was obtained from the Institutional Review Board (IRB) of Alkhidmat Raazi Hospital, Rawalpindi, Pakistan (Reference Number: IRB/A/CR/01/24). Informed consent was obtained from the patient prior to participation. No identifiable patient information is included in this case report to ensure confidentiality. All treatment procedures were conducted in accordance with the hospital's established protocols, and appropriate consents were secured throughout the process.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.