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Case Report

Peripheral blood smear diagnosis of invasive candidiasis in a patient of myelodysplastic syndrome/myeloproliferative neoplasm treated with hypomethylating agent: A case report

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ABSTRACT

Patients with haematological malignancies undergoing treatment with hypomethylating agents are predisposed to opportunistic infections, including Candidiasis. We present the case of a 73-year-old female patient diagnosed with Myelodysplastic/Myeloproliferative neoplasms who was receiving a hypomethylating agent as part of her treatment regimen. During the course of her treatment, peripheral blood smear examination revealed the presence of budding yeast cells, consistent with Candida species. Subsequent culture confirmed the diagnosis of Candidiasis.

The development of Candidiasis in patients with haematological malignancies receiving hypomethylating agents poses a significant clinical challenge due to overlapping symptoms with other infections and chemotherapy-induced myelosuppression. Peripheral smear examination serves as a rapid and cost-effective adjunctive diagnostic tool for the early detection of Candidiasis in these patients. Timely detection of Candidiasis in this population is critical for appropriate management and improved outcomes.

1. Introduction

In patients with hematological malignancies like AML (Acute myeloid leukemia) and MDS (Myelodysplastic syndrome), invasive Candidiasis poses a severe threat with a 40% mortality rate. Despite newer antifungal agents, mortality remains high.[1]

Those ineligible for intensive chemotherapy often undergo hypomethylating agent (HMA) treatment, including azacitidine (AZA) and decitabine (DAC). HMA-treated AML or MDS patients may face extended neutropenia, exceeding 10 days, heightening IFIs (invasive fungal infections) risk.[2]

Establishing a definite diagnosis of IFIs in immunocompromised patients is particularly challenging and time-consuming, but delayed initiation of antifungal treatment increases mortality. Timely diagnosis of candidemia has proven to be difficult as blood cultures often require 2 to 3 days of incubation.[3]

The diagnosis of candidemia from peripheral blood smears has not been widely reported. Although the sensitivity of peripheral smear review for Candida infection is low, in this case, the peripheral blood smear led to the diagnosis of a blood-borne Candida infection before cultures became positive.

This demonstrates the importance of utilizing peripheral blood smear examination as a diagnostic methods to detect opportunistic infections, especially in patients with compromised immune systems, especially when

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conventional diagnostic techniques may be inconclusive or time-consuming.

2. Case Report

This report details the case of a 73-year-old female presenting with persistent thrombocytopenia incidentally discovered during a complete blood count (CBC). Chief complaints included generalized weakness, loss of appetite, and chronic constipation. A CT scan of the chest revealed small sub centimeter-sized level II/III lymph nodes. A positive infectious mononucleosis panel indicated Epstein-Barr virus (EBV) infection. Bone marrow biopsy showed hypercellularity with increased megakaryocytes, dyserythropoiesis, and grade 3 reticulin condensation. Laboratory studies on admission showed a white blood cell count (WBC) of 5700/cmm, hemoglobin level of 9.80 g/dl, and platelet count of 31,000/cmm. The patient received symptomatic treatment and platelet infusions. Leukocytosis (total leukocyte count [TLC] 70,000/cmm) with persistent thrombocytopenia prompted BCR-ABL1 and JAK2 mutation tests, which were negative. Next-generation sequencing (NGS) identified an SRSF2 mutation, leading to a diagnosis of Myelodysplastic/Myeloproliferative neoplasms. Azacitidine (hypomethylating agent) therapy was initiated. Post-chemotherapy, the patient developed dry, itchy, and scaly rashes on her back. Laboratory studies showed a WBC of 8900/cmm, hemoglobin level of 9.00 g/dl, and platelet count of 11,000/cmm. Peripheral smear revealed a left shift with neutrophils showing intracellular yeast forms of Candida species. Urine routine examination revealed the presence of yeast and pseudohyphae. A catheter tip culture confirmed the growth of Candida species. Elevated (1, 3)-β-D Glucan levels at 338.93 pg/ml supported the diagnosis of invasive fungal infection. Treatment with fluconazole and amphotericin B was initiated. Unfortunately, the patient succumbed to various complications a few days later.

3. Discussion

The estimated annual incidence rate of candidaemia is 3.88 per 1 lakh inhabitants, with reported rates ranging from 1.0 to 10.4.[4] Candida species, opportunistic fungi, commonly cause candidiasis, with C. albicans being the most prevalent, followed by C. glabrata, C. parapsilosis, C. tropicalis, C. krusei, and C. kefyr. In recent decades, candidiasis has emerged as a significant concern in immunosuppressed patients with hematologic malignancies. Patients with prolonged neutropenia (≤500/μL for ≥7 days), like those undergoing remission-induction chemotherapy (RIC) for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS), or severe aplastic anaemia, are at the highest risk of invasive fungal infections (IFI).[5] Factors contributing to increased risk include defects in immunity,

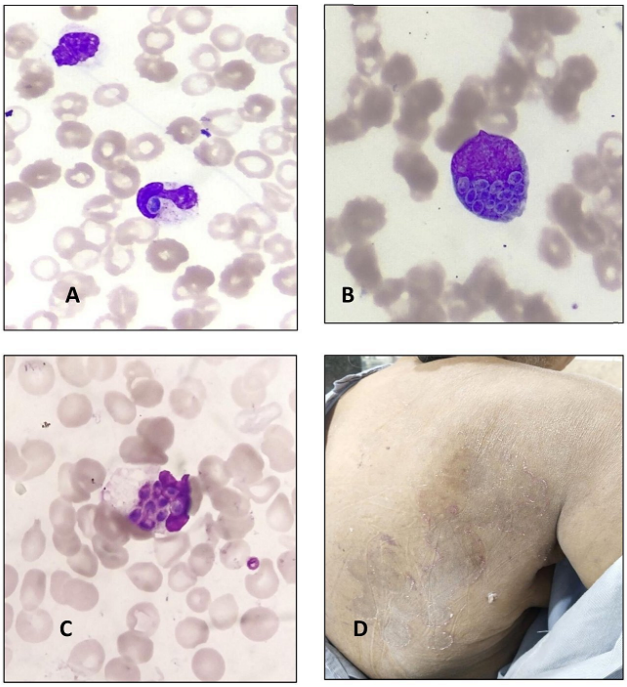

Figure 1: (A, B, C) : Peripheral blood smear showing neutrophils with intracellular yeast. (100× oil. Wright's stain). **(D):** Dry scaly and itchy rash over the back

cytotoxic chemotherapies, targeted immunotherapies, prolonged hospital stays, broad-spectrum antibiotics, and immunosuppressive treatments for organ transplants.[6,7]

Hypomethylating agent regimens, associated with a higher risk of neutropenia and thrombocytopenia, increase the susceptibility to fungal infections in patients, with reported IFI percentages ranging from 1.6% to 12.5% in AML/MDS populations receiving HMA-containing regimens.[8,9]

Peripheral blood smears rarely show Candida spp., as demonstrated in a study by Yera et al. published in 2004, which included only a few cases of disseminated candidiasis diagnosed from peripheral blood smears. Interestingly, the majority of these cases were caused by Candida albicans. The majority of patients described in such cases had hematological malignancies, AIDS, or intestinal obstruction, with a subsequent high mortality rate of 62%. In 26 of the 52 reported cases of disseminated yeast infection, Histoplasma capsulatum was implicated, notably with 13 cases occurring in AIDS patients. As the second most common cause of fungemia, Candida spp. predominated, especially in patients with hematological malignancies or intestinal diseases.[10]

The presence of candida on peripheral blood smear typically requires a high concentration of fungal elements in the peripheral blood. For instance, John A. Branda et al. demonstrated in their report that yeasts need to be present at a concentration of at least 5 x 10^5CFU/mL before they

can be visualized in the peripheral blood. This degree of fungemia is unusual; therefore, detection of candidemia by blood smear review will not be possible in most cases. In diagnosing true fungemia, it is essential for fungi to be phagocytosed, either by neutrophils in the case of Candida species and P. marneffei, or by monocytes in the case of Histoplasma species and Cryptococcus species. The presence of yeast forms inside neutrophils and monocytes serves as evidence of true fungemia, distinguishing it from specimen contamination after collection. The similar findings were present in our case.[3]

However, this case report does not discuss potential confounding factors or external influences that could have impacted the patient's outcomes, such as comorbidities, concurrent medications, or environmental exposures. Understanding these factors is essential for interpreting the case's findings accurately. The findings may not be applicable to all patients with similar conditions or treatment regimens. Variability in patient characteristics, disease biology, and healthcare settings can affect the generalizability of the findings to other clinical contexts.

4. Conclusion

Peripheral smear examination is a valuable adjunctive tool for the early detection of candidiasis in patients with haematological malignancies and those receiving chemotherapy. Integration of peripheral smear examination into routine clinical practice can aid in prompt diagnosis and initiation of appropriate antifungal therapy, ultimately improving patient outcomes in this high-risk population.

5. Key Takeaway

This case underscores the importance of vigilance for opportunistic infections, like candidiasis, in patients receiving hypomethylating agents for hematological malignancies. Despite diagnostic challenges due to overlapping symptoms and treatment effects, peripheral blood smear examination emerges as a valuable tool for early detection.

6. Key Points

Clinical challenge: Patients with hematological malignancies undergoing hypomethylating agent therapy face increased susceptibility to opportunistic infections, complicating diagnosis and management.

Diagnostic utility of peripheral blood smear: Despite its limited sensitivity, peripheral blood smear examination serves as a crucial adjunctive diagnostic tool. Its integration into routine clinical practice aids in the early detection of candidiasis, facilitating prompt initiation of appropriate antifungal therapy.

Importance of early recognition: Timely diagnosis and treatment are essential for optimizing patient outcomes and reducing morbidity and mortality in this vulnerable patient population.

7. Conflict of Interest

None.

References

1. Sipsas NV, Lewis RE, Tarrand J, Hachem R, Rolston KV, Raad II, et al. Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001-2007):stable incidence but changing epidemiology of a still frequently lethal infection. *Cancer*. 2009;115(20):4745–52.
2. Gao C, Wang J, Li Y, Zhao H, Li R, Hou L, et al. Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(34):11860.
3. Ansari IA, Eswari V, Prakash G, Bhat S, Tania RP. Diagnosis of Systemic Candidiasis on Peripheral Blood Smear: A Rare Case Report. *Res Rev J Med Health Sci*. 2014;3(1):27–30.
4. Koehler P, Stecher M, Cornely OA, Koehler D, Vehreschild MG, Bohlius J, et al. Morbidity and mortality of candidaemia inEurope: An epidemiologic meta-analysis. *Clin Microbiol Infect*. 2019;25(10):1200–12.
5. Pagano L, Busca A, Candoni A, Cattaneo C, Cesaro S. Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. *Blood Rev*. 2017;31(2):17–29.
6. Pagano L, Akova M, Dimopoulos G, Dimopoulos G, Herbrecht R, Drgona L, et al. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *J Antimicrob Chemother*. 2011;66:i5–14.
7. Lewis RE, Cahyame-Zuniga L, Leventakos K, Chamilos G, Ben-Ami R, Tamboli P, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with hematological malignancies: A 20-year autopsy study. *Mycoses*. 2013;56(6):638–45.
8. Marodi L, and RBJ. Invasive Candida species disease in infants and children: occurrence, risk factors, management, and innate host defense mechanisms. *Curr Opin Pediatr*. 2007;19(6):693–7.
9. Gao C, Wang J, Li Y, Zhao H, Li R, Hou L, et al. Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia: A systematic review and meta-analysis. Med (Baltimore). 2018;97(34):e11860.
10. Yera H, Poulain D, Lefebvre A, Camus D, Sendid B. Polymicrobial candidaemia revealed by peripheral blood smear and chromogenic medium. *J Clin Pathol*. 2004;57(2):196–204.

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