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Dr. Hemant Gupta
Professor, Head of the Department of Internal Medicine, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Dr. Adhvik Jagath
Intern, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Dr. Akash Parab
Assistant Professor, Department of Internal Medicine, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Dr. Harshal Bisen
Assistant Professor, Department of Internal Medicine, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Dr. Samyuktha Sainath Nair
Intern, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Corresponding Author:
Dr. Hemant Gupta
Professor, Head of the Department of Internal Medicine, MGM Medical College, Hospital and Research Centre, Vashi, Navi Mumbai, Maharashtra, India

Breakthrough fungal pneumonia in Multiple myeloma post-immunosuppressive therapy with polypharmacy, complications, and outcome in elderly patient

Hemant Gupta, Adhvik Jagath, Akash Parab, Harshal Bisen and Samyuktha Sainath Nair

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Abstract
Background: Clonal proliferation of plasma cells in the bone marrow is a hallmark of Multiple myeloma (MM), a malignant neoplasm associated with severe immunological dysregulation. While novel agents have improved survival, they have also altered the infectious risk profile, making invasive fungal infections (IFIs) a growing threat in non-neutropenic elderly patients.
Case: We describe a 78-year-old female with MM undergoing Lenalidomide maintenance who experienced severe breakthrough pneumonia subsequent to hip surgery. Initially resistant to broad-spectrum antibiotics, her condition was complicated by sepsis, atrial fibrillation, and acute heart failure. Advanced diagnostics revealed a dual infection comprising MRSA and probable invasive fungal disease, indicated by positive serum Galactomannan and Beta-D-Glucan. The patient was effectively treated with Voriconazole, Linezolid, and cardiac optimisation.
Conclusion: This case highlights the significant risk posed by mixed infections in elderly immunocompromised patients. It underscores the essential role of early fungal biomarker testing and the management of complex polypharmacy when conventional treatment does not prevent clinical decline.

Keywords: Multiple myeloma, invasive fungal pneumonia, galactomannan, MRSA, polypharmacy, elderly care, voriconazole

Introduction

The haematologic malignancy known as Multiple myeloma (MM) is marked by the growth of clonal plasma cells, which causes severe immunological dysregulation. The treatment of MM in older patients requires a careful balancing act because the disease itself impairs humoral immunity (hypogammaglobulinemia), and life-prolonging treatments like proteasome inhibitors and immunomodulatory medications (e.g., Lenalidomide) further reduce cellular immunity. Patients are extremely vulnerable to infections, which continue to be a major cause of morbidity and death due to this "double hit" to the immune system.

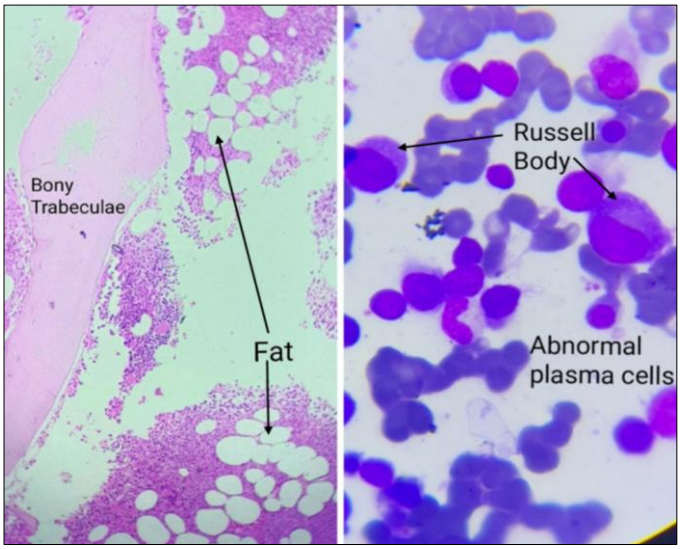
Whilst novel drugs have increased longevity, they have also changed the infectious landscape. Although bacterial pathogens are prevalent, invasive fungal infections (IFIs) are becoming serious complications, especially in patients with structural lung disease, extended hospital stays, or recent exposure to broad-spectrum antibiotics. Fungal pneumonia in non-neutropenic patients is a notoriously challenging diagnosis that frequently necessitates a high index of suspicion and reliance on biomarkers like beta-D-glucan and galactomannan.

This case examines the clinical course of an elderly woman receiving maintenance chemotherapy who experienced acute cardiac failure, sepsis, and severe breakthrough fungal pneumonia complicated by bacterial co-infection (MRSA). Unlike existing reports, this case explicitly highlights the utility of biomarker-driven decision-making in a non-neutropenic patient on post-CYBORD, lenalidomide maintenance who presents with complex cardiac overlap. It draws attention to the difficulties associated with polypharmacy and the need for interdisciplinary care to achieve a successful result. Modern regimens create a unique vulnerability in contrast to the clear-cut immunosuppression observed in the era of traditional chemotherapy; recent observations suggest that invasive fungal diseases are now a critical, evolving threat in this particular patient population.

Case Report

We describe the case of a 78-year-old woman who has a history of Type II Diabetes Mellitus and hypertension. In February of 2024, she was experiencing Persistent Lower Back Pain which was not subsiding even after being prescribed Bisphosphonates Injections since 4 weeks. So, an MRI was done on 3rd March 2024, which showed an impression of Extensive patchy marrow signal intensity lesions scattered within the cervico-dorsal-lumbosacral spine as well as pelvic bones which were suspicious for metastases with Multiple myeloma as the differential. On 11th March 2024, Bone marrow biopsy was performed and on Histopathology her Multiple myeloma diagnosis was confirmed.

Post-diagnosis, 16 cycles of chemotherapy under the CYBORD regimen (Cyclophosphamide, Bortezomib, and Dexamethasone) were part of her oncological management; the final cycle was given in October 2024. After that, starting since November 2024, she was put on maintenance oral chemotherapy with Lenalidomide.



On Left: Bone Marrow Trephine biopsy (H&E stain), Date:13/03/2024 - Section demonstrates preserved bony trabeculae and the intertrabecular areas are replaced mainly by adipose tissue due to senile ageing. Hypercellular for age showing interstitial excess of plasma cells with focal areas of preserved trilineage hematopoiesis seen.

On Right: Bone Marrow Aspirate Smear (Giemsa stain), Date 13/03/2024 - Abnormal Plasma cells displaying eccentric nuclei, coarse "clock-face" chromatin, prominent perinuclear hof, and presence of Russell bodies (Intracytoplasmic inclusions) reflecting immunoglobulin accumulation.

Recurrent hospitalizations were a significant part of her clinical course during the previous year. She was successfully treated with antibiotics after being admitted to the intensive care unit in November 2024 due to Bacterial pneumonia. She suffered a Left Hip Fracture from a fall in June 2025, which required a Left Total Hip Replacement (THR).

Again on August 11, 2025 patient arrived with complaints of high grade feverwith chills since 4 to 5 days, headache, dyspnea on exertion since 2 to 3 days, bodyache +, cough with expectoration and giddiness.

IV Meropenem with Tablet Clarithromycin, Tablet Oseltamivir and IV Flucanazole treatment was part of the initial management in the intensive care unit of a peripheral hospital for broadspectrum antimicrobial therapy along with IV Hydrocortisone and IV Deriphylline.

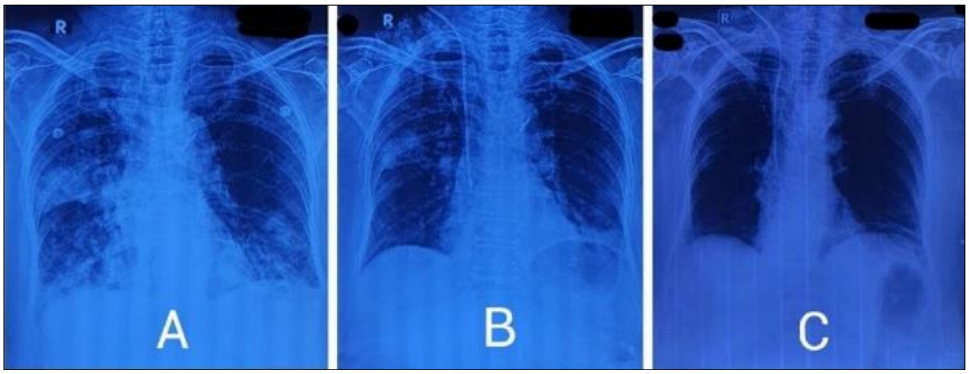
After four days, though, she did not show any improvement; her condition worsened, with oxygen saturation falling to 85%, and she experienced two episodes of atrial fibrillation. After that, she was moved to a Tertiary care facility, for more advanced treatment via cardiac ambulance with High-Flow Nasal Cannula (HFNC) support. She had tachycardia (pulse: 110/min) and respiratory distress (respiratory rate: 36/min) when she was admitted on August 15, 2025. Wheezing and bilateral crepitations were detected by auscultation. She was stabilized right away using a High-Flow Nasal Cannula (HFNC) and Non-Invasive Ventilation (NIV).

Date	Clinical Event Summary
February 2024	Onset of persistent lower back pain unresponsive to bisphosphonates.
March 2024	MRI reveals extensive patchy marrow lesions; Bone Marrow Biopsy confirms Multiple myeloma.
March - Oct 2024	Oncological management with 16 cycles of CYBORD regimen (Cyclophosphamide, Bortezomib, Dexamethasone).
November 2024	Initiation of maintenance oral chemotherapy with Lenalidomide. Admission to ICU for bacterial pneumonia (successfully treated).
June 2025	Left hip fracture due to a fall, requiring Left Total Hip Replacement (THR).
August 11, 2025	Admission to peripheral hospital with high-grade fever, dyspnea, and cough. CT Thorax shows segmental consolidations.
August 15, 2025	Clinical worsening (SpO2 85%, Atrial Fibrillation). Transfer to Tertiary Care Facility.
September 1, 2025	Discharged in hemodynamically stable condition.

Investigations

Parameter	Patient Value	Reference/Interpretation
Hemoglobin	11.6 g/dL	Mild Anemia
WBC Count	9,120 /µL	Normal range
C-Reactive Protein (CRP)	65.9 mg/L	Markedly Elevated (Ref: <5 mg/L)
Procalcitonin	Negative	Suggests non-bacterial or localized infection
NT-ProBNP	11,500 pg/mL	Severe Cardiac Stress / Heart Failure
Serum Galactomannan	Index 0.7	Positive (Ref: <0.5)
Beta-D-Glucan	Positive	Indicative of Invasive Fungal Disease
Sputum Culture	MRSA Detected	Methicillin-Resistant *S. aureus*
Blood/Urine Culture	Sterile	No bacteremia/fungemia detected

While procalcitonin and respiratory viral panels were negative, fungal biomarkers strongly indicated an invasive aetiology. Serum samples were used for fungal biomarker testing. Sputum microbiological analysis revealed Methicillin-Resistant *Staphylococcus aureus* (MRSA).



Serial Chest X-rays showing improvement along the course of treatment at tertiary hospital

a) Chest X-ray dated 15/08/2025: Patchy opacities are seen in right mid and bilateral lower zones. Overall appearance is suggestive of severe bilateral pneumonia, more pronounced on the right side.

b) Chest X-ray dated 23/08/2025: Follow-up radiograph demonstrates Interval increase in density of persistently seen patchy opacity in right mid zone, however there is interval decrease in patchy opacities in bilateral lower zone.

c) Chest X-ray dated 28/08/2025: There is significant interval reduction in right upper, mid and left lower zone opacities with near-complete resolution of previous consolidations.

A 2D-Echocardiography showed a reduced left ventricular ejection fraction (LVEF) of 40-45%, global hypokinesia, mild-to-moderate mitral regurgitation, and mild tricuspid regurgitation. Furthermore, segmental consolidation in the right middle and both lower lobes was detected by CT Thorax Plain chest imaging, along with ground-glass opacities and bronchocentric nodules indicative of an infectious disease.

Management and Therapeutic Rationale

The patient was managed with an aggressive, targeted antimicrobial and supportive regimen. Initially, the patient received Fluconazole and Anidulafungin empirically at the peripheral hospital. However, upon confirmation of positive serum Galactomannan (suggestive of Aspergillosis) and MRSA in the sputum, the antifungal therapy was transitioned to oral Voriconazole (200 mg). Voriconazole was selected for its superior efficacy against *Aspergillus* species compared to echinocandins.

Broad-spectrum antibacterial coverage was achieved with Inj. Zavicefta, Inj. Aztreonam, and Tab. Linezolid to address MRSA. Septran DS was added for *Pneumocystis* prophylaxis. Given the complex polypharmacy, strict vigilance was maintained for drug-drug interactions, specifically monitoring the QT interval and liver enzymes due to the combination of Voriconazole, Linezolid, and cardiac agents. Lenalidomide was temporarily withheld.

Concurrent cardiac management included the initial use of diuretics (Lasix) to address fluid overload and heart failure, which were discontinued following stabilization, while rate control was maintained using Ivabradine and Bisoprolol. The patient's clinical condition showed significant improvement; on Day 6, she was weaned from non-invasive ventilation (NIV) to nasal prongs and transferred out of the ICU. Following an additional eight days of ward monitoring and rehabilitation, she was discharged on September 1, 2025.

Complications

The patient's clinical course progressed to multisystem organ dysfunction driven by a polymicrobial etiology, involving confirmed MRSA pneumonia and probable invasive fungal disease. This infectious insult precipitated acute cardiopulmonary decompensation; specifically, left ventricular failure and pulmonary edema exacerbated the underlying Type 1 respiratory failure, which was further compounded by new-onset atrial fibrillation necessitating rate control. Consequently, therapeutic management was challenged by the risks of significant polypharmacy. The concurrent administration of antimicrobial agents (Voriconazole, Linezolid) and cardiovascular pharmacotherapy required vigilant monitoring for adverse drug-drug interactions, particularly those mediated by

CYP450 metabolism, while immunomodulatory therapy (Lenalidomide) was temporarily suspended.

Discussion

This case demonstrates the vulnerability of the "treated" myeloma patient. Opportunistic pathogens were made possible by cumulative immunosuppression, even though the myeloma was under control (post-CYBORD maintenance). An important warning sign was the primary center's initial inability to react to Meropenem. "Culture-negative" or non-responsive pneumonia in older patients with hematologic malignancies should prompt a search for resistant bacteria (MRSA) and fungal etiology (Aspergillosis or Pneumocystis).

Diagnostic Classification and Limitations

Based on the EORTC/MSG criteria, this case is best classified as probable invasive fungal disease. This classification relies on the presence of host factors (myeloma/immunocompromise), clinical features (pneumonia refractory to antibiotics), and mycological evidence (positive serum galactomannan and beta-D-glucan).

However, limitations must be acknowledged. No bronchoscopy or fungal cultures were obtained due to the patient's respiratory instability, precluding a "proven" diagnosis. Furthermore, false positives for serum galactomannan can occur due to the use of certain antibiotics (e.g., piperacillin-tazobactam) or in the ICU setting, although the concurrent beta-D-glucan positivity and clinical response to Voriconazole strengthen the fungal diagnosis.

Therapeutic Challenges

Antifungal therapy was justified by the positive fungal biomarkers, which likely prevented fulminant respiratory failure. The diagnosis was further complicated by cardiac involvement (AFib and heart failure) mimicking pneumonia symptoms. The elevated NT-ProBNP facilitated the identification of fluid overload, necessitating diuresis alongside antibiotics.

Treating infection in this population rarely involves a single variable; strong antimicrobials and cardiovascular medications must overlap, creating a risky polypharmacy situation. Research indicates that this combination increases the risk of serious drug-drug interactions, requiring professionals to balance infection control with cardiac stability. We selected Voriconazole due to its established track record in treating systemic fungal infections, providing a safety net against invasive fungal spread where the infectious drive is high.

Ethical Considerations

Informed consent for the publication of this case details and clinical images was obtained from the patient and her primary caregivers. Institutional ethics approval was waived for this retrospective case report.

Conclusions

This case highlights the fact that a standard antibiotic approach is frequently inadequate for elderly patients with Multiple myeloma who present with pneumonia. When first-line treatments don't work, it's critical to suspect fungal pathogens and resistant bacteria as soon as possible. The timely application of fungal biomarkers and the capacity to handle complex polypharmacy addressing sepsis, heart failure, and malignancy concurrently were critical to this successful outcome.

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