

Beyond the Tumor: Invasive Fungal Infection Unveiled in HER2-Positive Breast Cancer Patient Mimicking Disease Relapse

Maryam Imran*, Muhammad Awais Majeed, Sameen-Bin-Naeem, Tahira Yasmeen, Neelam Siddiqui

Shaukat Khanum Hospital Lahore

Abstract

Introduction

Breast cancer is a major global health concern among all malignancies, with HER2-positive breast cancer representing a particularly aggressive subtype. It affects approximately 20% of patients and is associated with a high risk of relapse. The management of HER2-positive breast cancer has been significantly improved by targeted therapies, though challenges remain, especially in resource-limited settings. Invasive fungal infections are also common and can manifest as metastatic lesions in immunocompromised cancer patients undergoing intensive treatments making the diagnosis challenging for the oncologists.

Case Description

We report a case of a 39-year-old premenopausal female with relapsed HER2-positive breast cancer complicated by an invasive fungal infection. The patient initially presented with a 5 x 5 cm right breast lump, which was diagnosed as invasive ductal carcinoma, HER2-positive estrogen and progesterone receptor negative. Despite receiving chemotherapy with doxorubicin, cyclophosphamide, paclitaxel in the neoadjuvant setting and breast conservation surgery, the patient experienced disease recurrence. She was then treated with modified radical mastectomy followed by adjuvant chemotherapy TCH (trastuzumab, carboplatin, and docetaxel) six cycles. After three cycles, she developed high-grade fevers, renal impairment, and altered mental status. Imaging initially suggested ongoing infective vs metastatic process in bilateral renal and CNS parenchyma, so biopsy was performed from brain that revealed *Aspergillus flavus* infection. Treatment was adjusted to include antifungal therapy with voriconazole, and the patient's condition improved.

Practical Implications

This case underscores the critical need for biopsy of new or evolving lesions in cancer patients, particularly when imaging is not convincing enough for a relapse. Accurate diagnosis is essential to differentiate between disease progression and complications such as opportunistic infections. The occurrence of a fungal brain abscess in this patient highlights the importance of considering such invasive opportunistic infections in immunocompromised individuals, especially those undergoing intensive chemotherapy. Furthermore, the challenges faced due to the unavailability of targeted therapies in resource-limited settings emphasize the need for better access to advanced treatments and comprehensive management strategies. This case also calls for heightened vigilance and prompt diagnostic evaluation to address both cancer progression and potential opportunistic infections effectively.

Keywords

case report • HER2 positive breast cancer • invasive fungal infection • renal impairment • brain abscess

Introduction

Breast cancer is the leading malignancy globally, with a significant incidence reported in Pakistan, where it accounts for 22.2% of all cancer cases [1]. Worldwide, there were 2.3 million new cases and 685,000 deaths from breast cancer in 2020 [2]. HER2-positive breast cancer, affecting approximately 20% of patients diagnosed with breast cancer [3], is known for its aggressive nature and high recurrence risk, though targeted therapies have improved outcomes [4]. Invasive fungal

infections, including aspergillosis, are commonly associated with cancer patients undergoing intensive chemotherapy or transplants due to prolonged neutropenia, with mortality rates between 30% and 60% [5]. This case illustrates the importance of biopsy for new image findings in cancer patients and highlights the challenges of managing HER2-positive breast cancer, particularly in resource-limited settings where targeted therapies may be inaccessible.

*Corresponding author: Maryam Imran

E-mail: maryamimran@skm.org.pk

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Case Description

A 39-year-old premenopausal woman presented with a right breast lump for 2 months, which upon clinical examination was found to be 5 x 5 cm, involving the nipple areola complex and axillary lymph nodes were clinically palpable. Imaging and biopsy confirmed invasive ductal carcinoma, grade II, HER2-positive, with negative estrogen and progesterone receptors. FNA of right axillary lymph node was consistent with disease involvement. She underwent 4 cycles of doxorubicin and cyclophosphamide, followed by paclitaxel, however due to limited resources she could not receive HER2-targeted therapy. Post-chemotherapy, she had breast conservation surgery with axillary lymph node dissection. Histopathology report showed 2 mm residual carcinoma and 5/9 positive lymph nodes. Radiation therapy was administered six weeks after the surgery to the right breast and axilla 5005 cGy. A follow-up mammogram was done 7 months after radiation revealed disease recurrence, and biopsy confirmed high-grade invasive ductal carcinoma Estrogen receptor 20% progesterone receptor negative and HER-2 positive. She underwent modified radical mastectomy followed by adjuvant chemotherapy TCH (trastuzumab, carboplatin, and docetaxel). After three cycles she developed systemic complications, including renal impairment indicated by deranged creatinine and altered mental status. Imaging pointed out potential bilateral renal and CNS parenchymal involvement with infection and metastasis being the differentials. After initially stabilizing her with dialysis support and broad cover antibiotics her brain biopsy was done that showed invasive *Aspergillus flavus* infection instead of disease involvement. After this infectious team was taken on board and antifungal treatment with voriconazole was initiated, her condition gradually improved, including the mental status and renal functions and she resumed her breast cancer treatment with chemotherapy and HER2 targeted therapy.

Diagnosis

The diagnosis process involved multiple stages. Initially, the diagnosis of HER2-positive invasive ductal carcinoma was established through imaging and biopsy. Upon recurrence, the differential diagnosis included disease progression, secondary malignancies, and opportunistic infections. Comprehensive imaging and biopsy, including brain MRI and fungal cultures, ultimately identified *Aspergillus flavus* as the causative agent of brain abscess. This diagnosis was crucial for guiding appropriate antifungal therapy and managing the patient's condition.

Management

Management included a multidisciplinary approach. The patient initially received chemotherapy without targeted therapy for HER2-positive breast cancer due to limited resources. Afterwards surgery was done, and adjuvant radiation therapy was given. However, after 7 months of treatment she experienced recurrence and was subsequently treated with TCH. The onset of systemic symptoms prompted further evaluation, revealing renal involvement possibly due to disease process and a brain abscess. Antifungal therapy with voriconazole was initiated following neurosurgical biopsy confirming *Aspergillus flavus*. The patient's condition improved with appropriate treatment of infection, and she continued her treatment of breast cancer. Ongoing management included close follow-ups to monitor her response to treatment and any potential complications.

Discussion

The management of HER2-positive breast cancer has evolved significantly with the advent of targeted therapies. HER2-positive breast cancer, characterized by overexpression of the HER2 protein, historically carried a poor prognosis due to its aggressive nature and high risk of recurrence and metastasis [6]. However, the introduction of HER2-targeted therapies, such as trastuzumab, pertuzumab and more recent agents like neratinib and tucatinib, has markedly improved patient outcomes [6]. These therapies work by specifically targeting the HER2 receptor, thereby inhibiting cancer cell proliferation and improving survival rates.

Despite these advances, the availability of HER2-targeted therapies remains limited in many resource-constrained settings. In such environments, patients often have to rely on conventional chemotherapy, which may not be as effective and carries a significant risk of relapse [7]. The case presented illustrates the challenges faced in such settings, where the lack of access to targeted therapies can result in a reliance on less effective treatment options and a higher likelihood of complications and relapse.

The patient's progression to a severe systemic infection highlights the risks associated with intensive chemotherapy and the immunosuppressive effects it induces. Invasive fungal infections, such as those caused by *Aspergillus* species, are significant concerns in immunocompromised patients, particularly those undergoing prolonged neutropenia due to chemotherapy [10]. Aspergillosis, while less common than *Candida* infections, is associated with high morbidity and mortality rates, particularly in patients with malignancies [5]. The diagnosis of *Aspergillus flavus* in this case underscores

the need for a high index of suspicion and thorough diagnostic workup when patients present with unusual symptoms during or after chemotherapy although this risk of invasive fungal infections with solids malignancies is less common but should always be considered in immunocompromised patients.

The occurrence of renal involvement and a brain abscess in this patient further complicates the clinical picture. While renal metastases from breast cancer are rare, they can occur and often indicate aggressive disease behavior [9]. The patient's renal findings prompted a comprehensive evaluation, suggesting fungal infection rather than malignant involvement. This highlights the importance of considering a broad differential diagnosis in the face of unusual presentations in cancer patients.

Additionally, this case underscores the importance of biopsy for new or progressive lesions in cancer patients. Re-evaluating receptor status in recurrent or metastatic disease is crucial, as discordance in receptor expression between primary and secondary tumors can impact treatment decisions [8]. The patient's change in receptor status from hormone negative to hormone positive in the recurrent disease highlights the need for reassessment of receptor status to tailor treatment appropriately.

Advances in diagnostic modalities, including improved culture techniques and molecular diagnostics, have significantly enhanced our ability to detect and manage fungal infections [11]. Early diagnosis and treatment of these infections are crucial for improving outcomes and reducing mortality. In this case, the timely intervention with voriconazole and surgical biopsy was instrumental in the patient's recovery.

The management of HER2-positive breast cancer, particularly in resource-limited settings, requires a multifaceted approach. Strategies to improve access to targeted therapies and enhance infection control measures are essential. International collaborations and health policy reforms could play a critical role in bridging the gap in therapy access [12]. Additionally, ongoing research into novel therapies and refined treatment protocols is necessary to address the evolving challenges in managing HER2-positive breast cancer and its complications. In conclusion, this case highlights the complexities involved in managing HER2-positive breast cancer, particularly in resource-limited settings. It emphasizes the importance of comprehensive diagnostic evaluation, the need for prompt treatment of opportunistic infections, and the impact of targeted therapies on patient outcomes. The case also calls for increased efforts to address disparities in treatment access and to advance research in both cancer management and infection control.

Conclusion

This case illustrates the intricate challenges of managing HER2-positive breast cancer, especially in settings with limited access to targeted therapies. The necessity of biopsy for suspected relapses and comprehensive evaluation for unusual metastatic sites are crucial. The emergence of opportunistic infections underscores the need for vigilant monitoring and prompt intervention in immunocompromised patients. A multidisciplinary approach is essential to optimize outcomes and address the evolving challenges in breast cancer management.

Author contributions

Conceived and designed the analysis: NS

Collected the data: NA

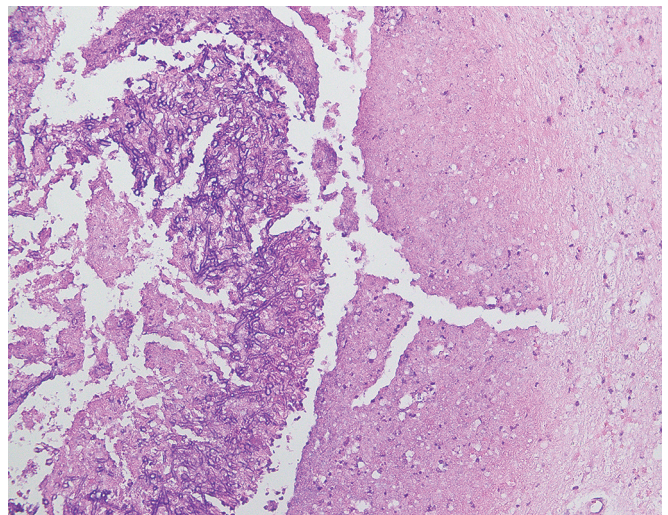
Contributed data or analysis tools: NA

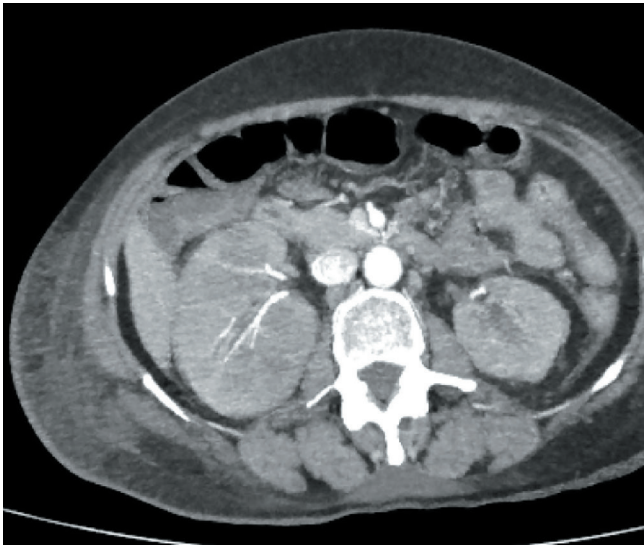
Performed the analysis: NA

Wrote the paper: MI, MAM, SBN, TY

Images

1. Bilateral kidneys are hypo-enhancing and appear edematous, right kidney being asymmetrically enlarged. Multiple hypodensities are noted within the renal parenchyma bilaterally, concerning for disease involvement
2. Histological evaluation reveals glial tissue showing extensive necrosis, mixed inflammation and colonies of branching septate fungal hyphae. PAS and GMS highlighting the branching septate fungal hyphae.





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