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A Follow-Up Case of Breast Carcinoma with the Unusual Visitor in Peripheral Blood: Unlock Feathered Edge Secret

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ABSTRACT

Background: Breast cancer is the most common cancer in women worldwide and in India. There are very few cases of breast cancer with peripheral blood dissemination having acute leukemia-like blast cells.

Case presentation: Here, we present a 44-year-old breast cancer follow-up patient presenting with leukemia-like blast cells in peripheral blood. The specific cytochemical staining and immunophenotyping assays on bone marrow biopsy revealed that atypical cells in her peripheral blood were from breast cancer metastasis. A comprehensive workup confirmed carcinocythemia in the present case and systemic chemotherapy and hormonal therapy were planned. However, she died 15 days after the carcinocythemia presentation. Carcinocythemia patients have a poor survival.

Conclusion: Because carcinocythemia cells can mimic leukemic blasts and share morphological features, the patient's medical history and a careful analysis of the feathery border of the smear are needed to make a definitive diagnosis.

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INTRODUCTION

Solid tumor cells spreading through the circulatory system in peripheral blood smears are rare and the individual cells are called carcinocythemia cells (CTCs), which mimic blast cells of acute leukaemia.¹ This condition typically manifests in the advanced stages of cancer.¹⁻³ While uncommon, the presence of carcinoma cells in peripheral blood smears might exhibit similar characteristics and can result in erroneously diagnosing acute leukemia in routine reporting.^{2,3} Carcinocythemia must be distinguished from hematological neoplasms by careful peripheral blood smear morphology, cytochemistry and immunophenotypic study of bone marrow biopsy.⁴ We here report a case with

circulating tumor cells in the peripheral blood of a follow-up case of infiltrating ductal carcinoma, not otherwise specified (IDC-NOS) having an acute leukemia-like blood picture.

CASE REPORT

A 44-year-old female patient presented at our hospital complaining of spontaneous bruising for a month and generalized weakness that had been present for 20 days. She had a past medical history of carcinoma breast for which a right modified radical mastectomy (MRM) was performed two years before showing positive expression for estrogen receptor (ER), progesterone receptor (PR) and Her-2neu (+3) immunohistochemistry (Figure 1A-D). She also received neoadjuvant chemotherapy followed by radiation therapy and six cycles of adjuvant hormonal therapy. Her routine complete blood count showed hemoglobin: 8.2 g/dL, total leukocyte count: 1.5×1000/μL, and platelet count: 30×1000/μL. A

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peripheral blood smear examination revealed a few clusters of atypical large mononuclear cells at the tail of the smear that were strongly suggestive of CTCs.

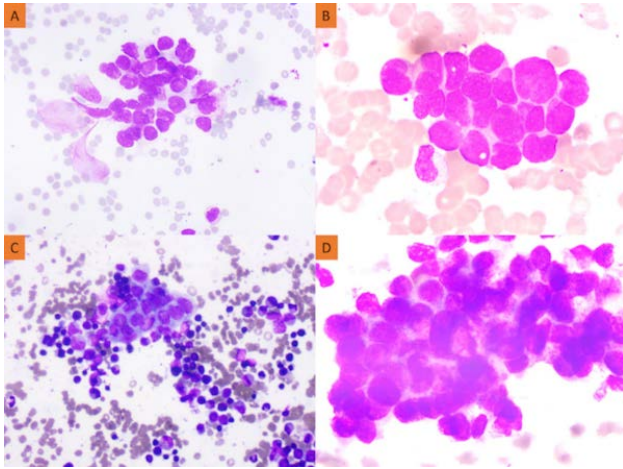


Figure 1. (A) Peripheral blood smear displaying clusters of atypical large mononuclear cells at the tail (Leishman stain, x100). (B) These atypical cells are having high nucleocytoplasmic ratio with a prominent nucleolus, coarse chromatin, and moderate amount of ill-defined pale basophilic cytoplasm (Leishman stain, x100). (C) Bone marrow aspirate smear showing cellular smears having small clusters and singly scattered tumor cells (Leishman stain, x400). (D) High-power view of a bone marrow aspirate smear displaying pleomorphic round to oval tumor cells disposed in dyscohesive clusters showing enlarged nuclei, moderate aniso-karyotic hyperchromatic nuclei, conspicuous nucleoli and moderate cytoplasm (Leishman stain, x100).

These cells were enlarged and had a high nucleocytoplasmic ratio with a prominent nucleolus, scattered chromatin, and a modest amount of pale basophilic cytoplasm (Figure 1A). Because of pancytopenia and the presence of suspicious atypical cells in a peripheral blood smear, a bone marrow aspiration was advised, which revealed numerous atypical cells disposed of in tubules and small clusters. The normal myeloid, erythroid, and megakaryocytic hematopoietic precursors were markedly reduced in number (Figure 1B, C). There were no Auer rods or cytoplasmic granules observed in the atypical cells. These cells were also negative for myeloperoxidase (MPO) cytochemistry. A provisional diagnosis of metastatic infiltrating ductal carcinoma of the breast was taken into consideration. Histopathology of paraffin-embedded bone marrow biopsy tissue showed diffuse infiltration by metastatic carcinoma disposed in ill-formed tubules and scattered singly in the stroma with marked desmoplastic changes (Figure 1D). ER, PR and Her-2neu immunohistochemistry stains were applied, which showed positive expression (Figure 2A-D). A definitive diagnosis of ductal carcinoma of the breast

infiltrating into the bone marrow was made based on morphology as well as immunohistochemistry. A computerized tomography (CT) scan of the chest, abdomen, and pelvis did not show any obvious signs of systemic disease. The patient initiated chemotherapy treatment, but unfortunately, she passed away within 15 days of being diagnosed with carcinocythemia.

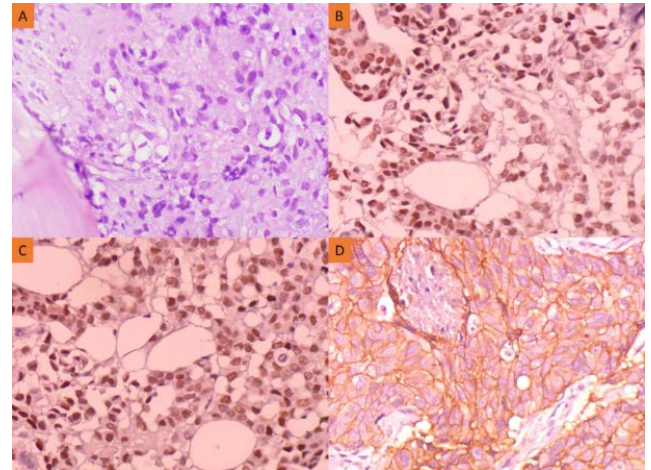


Figure 2. (A) Bone marrow biopsy shows intertrabecular spaces having diffuse infiltration by tumor cells disposed in the form of nests, and ill-formed tubules (H and E, x100). (B) Tumor cells show a positive nuclear expression of estrogenic receptor on immunohistochemistry (x400). (C) Tumor cells display a positive nuclear expression of progesterone receptor on immunohistochemistry (x400). (D) Tumor cells display a positive membranous expression of Her-2neu receptor on immunohistochemistry (x400).

DISCUSSION

Carcinocythemia is classified as a terminal condition resulting from the widespread invasion of the bone marrow. Ashworth first identified the existence of tumor cells in the peripheral circulation in 1869. However, it was not until 1976 that Cary *et al.* coined the name "carcinocythemia" to describe this condition in a patient with metastatic breast cancer.⁵ Subsequently, there have been only a limited number of cases documented in the literature, with breast cancer being the most prevalent source of circulating tumor cells (CTCs), followed by small-cell lung carcinoma. The literature shows that rhabdomyosarcoma, malignant germ cell tumors, urothelial carcinomas, Merkel cell carcinomas, melanomas, and carcinomas of uncertain primary origin are among the various cancers mentioned in case reports of CTCs.⁵⁻⁷

Gallivan *et al.* reported two cases of disseminated carcinoma in 1984, observing that although it was challenging to measure, circulating cancer cells typically make up less than 10% of all nucleated blood cells. Utilizing DNA polymerase chain reaction (PCR) to amplify genes is advantageous in cases



where there is a limited quantity of cancerous cells in circulation at higher centres.⁷

The detection of abnormal cells on the feathered edge of the peripheral blood smear of a patient with solid cancer after undergoing chemotherapy and radiotherapy may suggest the potential development of acute leukemia. After two years of chemotherapy and radiation therapy, the patient in our case, who had breast cancer, presented with pancytopenia. According to a few earlier studies, receiving radiation therapy raised the risk of acute leukemia by four times, while receiving radiation therapy together with chemotherapy increased the risk by seven times. The time interval between exposure and the event was 4.5 years.^{8,9}

It is widely recognized that cells of large size, such as blasts, platelet clumps, cryoprecipitate or endothelial cells, tend to migrate towards the periphery of the smear.^{1,10} In the present case study, the CTCs demonstrated clusters of atypical cells near the end of the smear tail. Therefore, it is essential to carefully examine the feathery edge of the smear when we analyze a peripheral blood smear, especially in a follow-up case of the malignant disease to detect carcinocythemia.

The enlarged size, chromatin patterns, and the presence of pale basophilic cytoplasm of the CTCs could lead one to mistake them for myeloblasts or monoblasts. Both circulating tumor cells (CTCs) and myeloblasts exhibit an increased ratio of nuclear-to-cytoplasmic content and tend to cluster at the feathery edge. In suspected scenarios, it is recommended to undertake a bone marrow examination along with the assimilation of cytochemical and immunohistochemical stains to identify these abnormal cells.^{1,11}

The presence or absence of circulating tumor cells serves as a valuable indicator for both progression-free survival and overall survival in metastatic breast cancer.¹² Carcinocythemia is a rare but important

event that occurs in advanced-stage malignancies, mostly of the breast and lung. It is diagnosed by evaluating a clinical context, morphology and immunohistochemistry. The majority of cases are linked to a poor prognosis and survival and occur in individuals with known, overt metastatic cancer. As demonstrated by a previous study that 80% of cases died within 6 months of the follow-up period.¹³ In breast cancer, the circulating tumor cells exhibit a sensitivity value of 50% and a specificity value of 93%.¹⁴ The literature shows that carcinocythemia is a fatal condition with a dismal prognosis.¹⁵

CONCLUSION

To get a conclusive diagnosis, it is essential to know the past medical history of the patient along with a close careful examination of the feathery edge of the smear because carcinocythemia cells may resemble leukemic blasts and share certain morphological characteristics.

ETHICAL CONSIDERATIONS

The patient provided written informed consent to publish the information and images contained in the case report.

CONFLICT OF INTERESTS

None to declare.

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DATA AVAILABILITY

All data relevant to the study are included in the article.

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