DOI: 10.7860/JCDR/2022/52653.15832

Carcinocythemia-associated Microangiopathic Haemolysis

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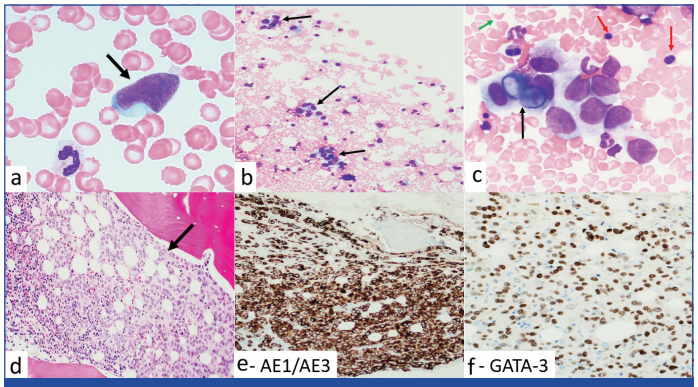
ABSTRACT

Carcinocythemia defined as the presence of circulating carcinoma cells in the peripheral blood identifiable on routine light microscopy is an extremely rare complication of widely disseminated and usually end-stage solid organ malignancies. Given the rarity of this entity, it can cause diagnostic challenges for pathologists interpreting the peripheral blood smear. Microangiopathic Haemolytic Anaemia (MAHA) has been reported in the literature in patients with carcinocythemia. The author reports a case of 57-year-old female with widely metastatic lobular breast carcinoma who presented with bleeding gums and worsening fatigue. Peripheral blood smear showed findings consistent with MAHA as well as numerous circulating adenocarcinoma cells. A bone marrow biopsy showed near-complete replacement of the marrow by metastatic carcinoma. This case brings to light the association of carcinocythemia with haemolysis. Given the high incidence of MAHA in carcinocythemia and the differential treatment, a careful screening of peripheral smears maybe warranted in patients with a known history of metastatic carcinoma and laboratory suspicion of haemolysis.

Keywords: Anaemia, Carcinoma cells, Peripheral blood smear

A 57-year-old female presented with a five days history of worsening fatigue, bleeding gums, and shortness of breath. Her past medical history was significant for metastatic lobular carcinoma of the breast treated with surgery and chemotherapy. A complete blood count (CBC) showed anaemia and marked thrombocytopenia (haemoglobin: 8.8 g/dL, platelets: 12,000 /uL). Additional laboratory investigation showed elevated serum lactate dehydrogenase (1223 U/L), unconjugated hyperbilirubinemia (2.7 mg/dL), low serum haptoglobin (<10 mg/dL), and negative Direct Antiglobulin Test (DAT). A peripheral blood smear was obtained due to clinical concern for haemolysis and showed a normocytic red blood cell population with increased polychromasia, occasional schistocytes, and frequent nucleated forms. In addition, rare isolated large bizarre cells with irregular nuclear contours and multiple prominent nucleoli were noted in the monolayer part of the smear [Table/Fig-1a]. Upon examination of the feathered edge, numerous additional clusters of abnormal cells were discovered [Table/Fig-1b] including some with intracytoplasmic mucin globules [Table/Fig-1c], consistent with peripheral blood involvement by adenocarcinoma (carcinocythemia). A bone marrow biopsy was performed and showed near-complete replacement of the marrow by diffuse sheets of metastatic carcinoma [Table/Fig-1d]. By immunohistochemistry, these neoplastic cells were negative for CD34, CD117, CD3, CD20, CD68, S100, and SOX10 (SRY-Box Transcription Factor 10) while positive for AE1/AE3 [Table/Fig-1e], GATA3 (GATA Binding Protein 3) [Table/Fig-1f], and mammaglobin, consistent with metastatic carcinoma of breast origin. The patient developed multiorgan failure and died six days after the bone marrow biopsy.

Carcinocythemia is defined as the presence of circulating carcinoma cells in the peripheral blood identifiable on routine light microscopy. It is an extremely rare complication of widely disseminated and usually end-stage solid organ malignancies. It is important not to confuse this condition with Circulating Tumour Cells (CTC); a term used to describe very minute amounts of non haematological malignant cells in the blood detectable only by highly sensitive molecular or functional assays [1]. The most common non haematologic malignancies reported to be associated with carcinocythemia are



[Table/Fig-1]: a) Peripheral blood smear showing an isolated carcinoma cell in the monolayer part of the specimen (black arrow) (Wright-Giemsa stain, 100X); b) Feathered edge of the peripheral smear showing clusters of carcinoma cells (black arrows) (Wright-Giemsa stain, 10X); c) A cluster of carcinoma cells with intracytoplasmic mucin globules (black arrow). In the background occasional schistocytes (green arrow) and nucleated red blood cells (red arrows) can be seen (Wright-Giemsa stain, 100X); d) Bone marrow core biopsy showing extensive infiltration by metastatic carcinoma (H&E stain, 10X); e) Carcinoma cells are positive for cytokeratin AE1/AE3 immunohistochemical stain (10X); f) Carcinoma cells show nuclear staining with GATA3 immunohistochemical stain (10X).

breast carcinoma, and small cell carcinoma of the lung, however, cases of rhabdomyosarcoma, malignant germ cell tumour, urothelial carcinoma, merkel cell carcinoma, melanoma, lung adenocarcinoma, and prostatic adenocarcinoma have been described [2]. Given the rarity of this entity, it can cause diagnostic challenges for pathologists interpreting the peripheral blood smear. Generally, the monolayer part of a peripheral smear is considered the optimal area for morphologic assessment as the cells are spaced apart and well preserved, however, these carcinoma cells when present tend to cluster at the feathered edge of the slide. The present case reinforces the importance of evaluating the feathered edge in all peripheral smears as large cells such as blasts or aggregates such as platelet clumps tend to cluster here.

Microangiopathic Haemolytic Anaemia (MAHA) has been reported in the literature in patients with carcinocythemia [3-5]. In a recent case series by Ronen S et al., two out of seven (28.5%) patients with carcinocythemia had laboratory and morphologic evidence of microangiopathic haemolysis [2]. The pathophysiology behind

this association is not completely understood. The proposed mechanisms include damage to the vascular endothelium by the malignant cells leading to increased release of von Willebrand Factor (vWF) multimers and direct traumatic contact between erythrocytes and circulating carcinoma cells within small blood vessels. Clinically, MAHA associated with carcinocythemia can be indistinguishable from Thrombotic Thrombocytopenic Purpura (TTP) but is reportedly associated with normal or only moderately reduced levels of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) and a lack of response to therapeutic plasma exchange [6]. In many cases, if the patient survives, the haemolytic state resolves with anticancer therapy [7]. Given the high incidence of MAHA in carcinocythemia and the differential treatment, a careful screening of peripheral smears maybe warranted in patients with a known history of metastatic carcinoma and laboratory suspicion of haemolysis.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 02, 2021
- Manual Googling: Nov 23, 2021
- iThenticate Software: Nov 30, 2021 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Sep 30, 2021**
Date of Peer Review: **Nov 22, 2021**
Date of Acceptance: **Dec 02, 2021**
Date of Publishing: **Jan 01, 2022**