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Clinicohematological Perspective and Dual Case Reports of Bone Marrow Metastasis with Review of Literature

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ABSTRACT

Metastatic tumours frequently include bone marrow as a primary site of metastasis. The presence of bone marrow metastases has been observed in several tumour types, with the most prevalent occurrences found in prostate, breast and lung carcinomas among adults and in small round cell tumours within the paediatric group. The presence of solid tumour metastases in the bone marrow is indicative of an advanced disease stage and is associated with a poor prognosis. In this study, we report two instances of malignancies that have demonstrated metastasis to the bone marrow. Specifically, we focus on gastric adenocarcinoma and mantle cell lymphoma, examining their respective patterns of bone marrow involvement and associated haematological findings. The bone marrow examination is a simple, effective, sensitive and cost-effective method for determining the stage and monitoring the prognosis of solid tumours.

Keywords- bone marrow, metastasis, prognosis, metastatic gastric adenocarcinoma, spillover of mantle cell lymphoma

INTRODUCTION

Adults with carcinomas of the breast, prostate, lung, stomach, colon, kidney, and thyroid frequently have tumours that extend to the marrow. Sarcomas showed a comparatively low frequency of marrow infiltration. Anaemia and thrombocytopenia-related signs and symptoms are frequently observed. The presence of a leucoerythroblastic blood picture is a well-established characteristic observed in cases of metastatic cancer involving the bone marrow, but not present in all cases. Their LDH level is higher than 500IU/L. The combined implementation of bone marrow aspiration and biopsy serves as a valuable approach for the identification and assessment of metastatic tumours [1].

Gastric cancer is as the fourth most prevalent malignant neoplasm and the third primary contributor to cancer-related deaths in males, as well as the fifth primary contributor to cancer-related deaths in females [2]. The most common sites of recurrence in gastric cancer include the abdominal cavity, peritoneum, lymph nodes, and liver [3,4]. The prognosis is bad in cases of isolated recurrence restricted to the bone and bone marrow [5].

Mantle cell lymphoma (MCL) is classified as a very aggressive form of B-cell non-Hodgkin's lymphoma (NHL) and is characterised by a specific chromosomal translocation, t(11;14)(q13;q32), which has been associated with the overexpression of cyclin D1 [6]. MCL is an infrequent and distinctive form of B-cell NHL,

characterised by its tendency to manifest in an advanced stage and often affecting many extranodal sites, including the bone marrow, spleen and peripheral blood [7].

Metastases in the bone marrow are mostly incurable [8]. Bone marrow aspiration is a readily accessible and economically efficient technique for rapidly detecting metastases. Patients diagnosed with solid tumours that have metastasized to the bone marrow typically exhibit symptoms such as anaemia, leucopenia, or pancytopenia [9].

CASE REPORTS

CASE 1

A 67-year-old male who was known case of stomach carcinoma was priorly diagnosed as adenocarcinoma of stomach came to the surgery out-patient department (OPD) of our institute with a complaint of generalized weakness and easy fatiguability for 2 months. Patient was of primary gastric cancer diagnosed in same institute 3 years back. He already had undergone surgery with chemotherapy and radiotherapy. He had started developing symptoms 2 months back. He also had complained of backache. On examination, he was pale with hepatosplenomegaly and lymphadenopathy. Clinically, it was suspected metastasis to bone which was further under investigation. All lab investigations were done [Table 1]. Peripheral smear revealed normocytic normochromic red blood cells (RBC) with nucleated RBC, Total leucocyte count was within normal limits and platelet showed thrombocytopenia. Patient had also undergone bone marrow aspiration which revealed clusters of neoplastic cells with a high N/C ratio, irregular chromatin with inconspicuous nucleoli and a moderate amount of cytoplasm. (Figures 1-3) It was diagnosed as metastatic adenocarcinoma of stomach in bone marrow. Then patient was lost to follow up.

Laboratory Tests	**Results**	**Normal Value**
Hemoglobin	9.3gm/dl	12.0-16.0gm/dl
Total leukocyte count	9300/mm^3	4000-11000/mm^3
Differential leukocyte count	Neutrophils - 72%	Neutrophils - 45-65%
	Lymphocytes - 26%	Lymphocytes - 25-45%
	Eosinophils - 02%	Eosinophils - 1-6%
	nRBC-6/100WBC	-
Platelets	1,20,000/mm^3	1,50,000 – 4,50,000/mm^3
Hematocrit	27.2%	35-50%
Mean corpuscular hemoglobin (MCH)	24pg/cell	26-32pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	30gm/dl	32.0-36.0gm/dl
Mean corpuscular volume (MCV)	82fl	80-100fl
Erythrocyte sedimentation rate (ESR)	120mm/hr	0-10mm/hr
Retic	1.0%	0.5-2%
Total iron binding capacity (TIBC)	227mcg/dl	250-450mcg/dl
Serum lactate dehydrogenase (LDH)	>1200U/L	140-280U/L
Peripheral blood smear	Dimorphic anemia	-
Bone marrow aspiration	Metastatic adenocarcinoma of stomach	-

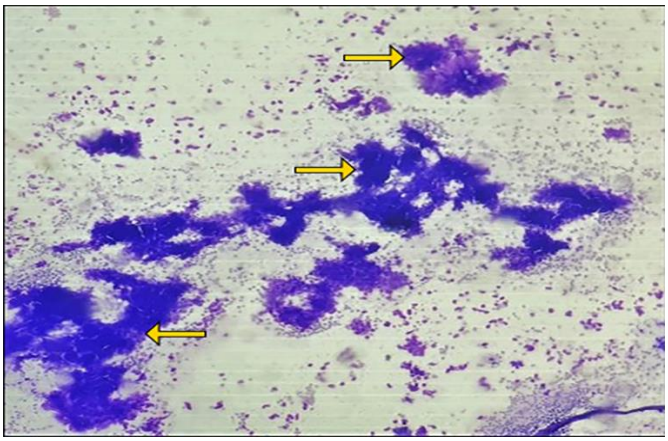

Figure 1: Bone marrow aspiration- neoplastic cells arranged in clusters, Giemsa, 100 X

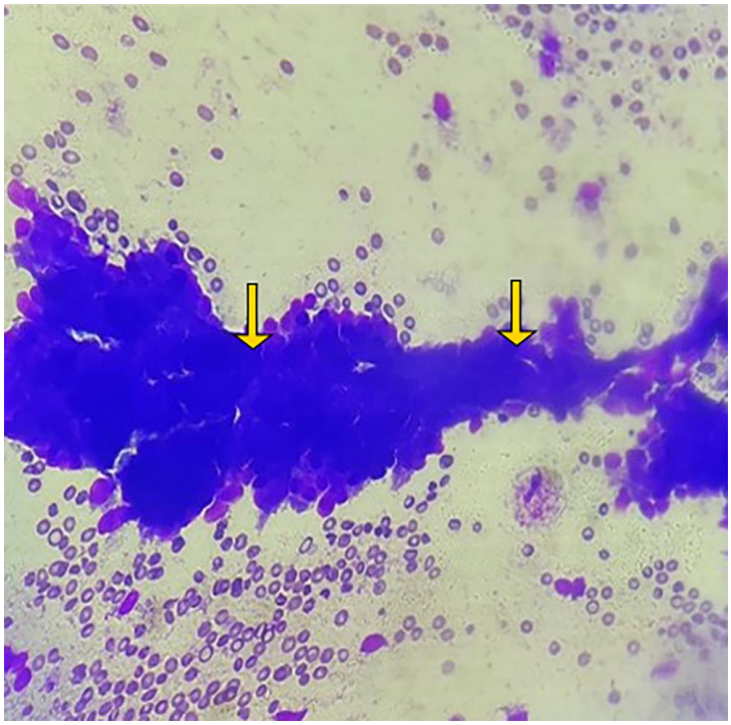

Figure 2: Bone marrow aspiration- neoplastic cells in papillae pattern with myeloid and lymphoid cells in the background, Giemsa, 400 X. 1000 X, respectively

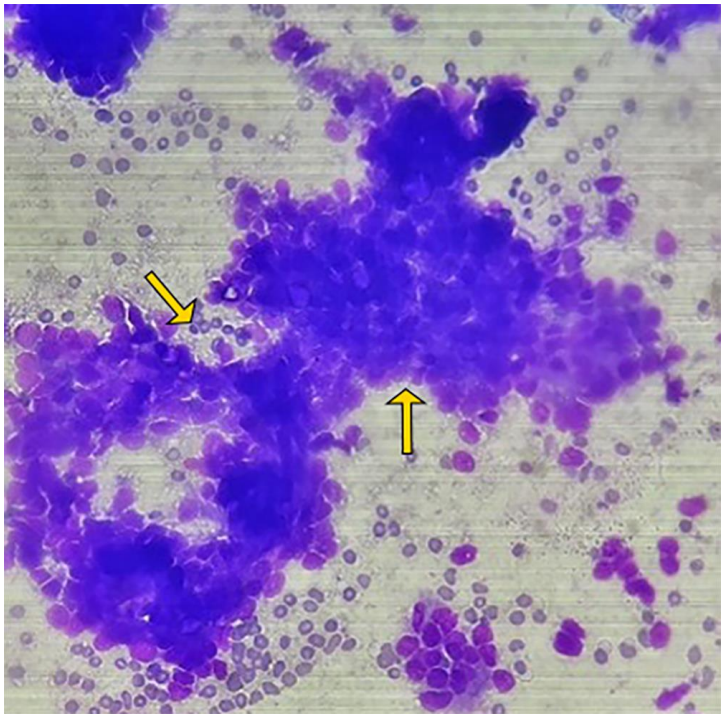

Figure 3: Bone marrow aspiration- neoplastic cells show high N/C ratio, irregular chromatin with inconspicuous nucleoli and a moderate amount of cytoplasm. Neoplastic cells also show overcrowding and overlapping.

CASE 2

An 80-year-old man, known case of non-Hodgkin's lymphoma, mantle cell lymphoma, patient presented with a two-month history of reduced appetite and pain in abdomen to surgery outpatient department (OPD) of our department. Sonography revealed extensive splenomegaly extending to the iliac region. Previous history of enlarged right axillary lymph node that was removed and on histopathology was diagnosed as NHL, Mantle cell carcinoma. IHC was performed and exhibited positivity for CD20, CD5,

cyclin D and Bcl2 and negative for CD 3, CD 10, CD 23 and BCL 6. Clinically, it was suspected anemia under investigation. All lab investigations were done [Table 2]. Peripheral smear revealed normocytic normochromic with leucocytosis. There was lymphocyte spillover in the blood smear. Patient had also undergone bone marrow aspiration which revealed hypercellularity with lymphocyte spillover into the smear [Figures 4-7]. It was diagnosed as infiltration of bone marrow by lymphoma cells (Spill Over of Mantle Cell Lymphoma).

Laboratory Tests	**Results**	**Normal Value**
Hemoglobin	8.9gm/dl	12.0-16.0gm/dl
Total leukocyte count	155000/mm^3	4000-11000/mm^3
Differential leukocyte count	Neutrophils - 3%	Neutrophils - 45-65%
	Lymphocytes - 97%	Lymphocytes - 25-45%
Platelets	98000/mm^3	1,50,000 - 4,50,000/mm^3
Hematocrit	24.4%	35-50%
Mean corpuscular hemoglobin (MCH)	23pg/cell	26-32pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	29gm/dl	32.0-36.0gm/dl
Mean corpuscular volume (MCV)	85fl	80-100fl
Erythrocyte sedimentation rate (ESR)	55mm/hr	0-10mm/hr
Retic count	2%	0.5-2%
Total iron binding capacity (TIBC)	220mcg/dl	250-450mcg/dl
Serum lactate dehydrogenase (LDH)	>1200U/L	140-280U/L
Peripheral blood smear	Dimorphic anemia	-
Bone marrow aspiration	Infiltration of bone marrow by lymphoma cells (Spill Over of Mantle Cell Lymphoma)	-

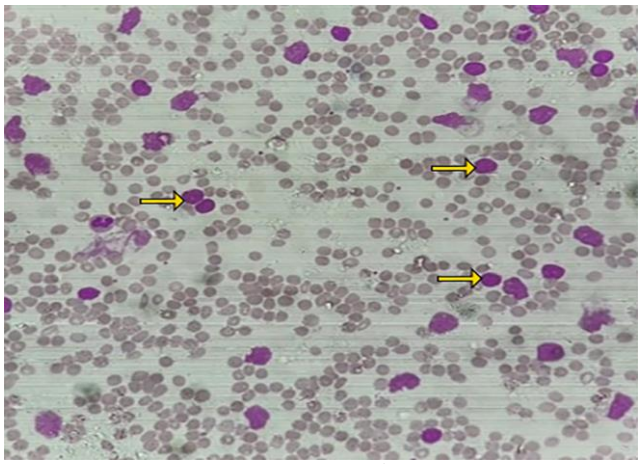

Figure 4: Peripheral Smear - leucocytosis with spill over of lymphocytes in the smear, Leishman (400X)

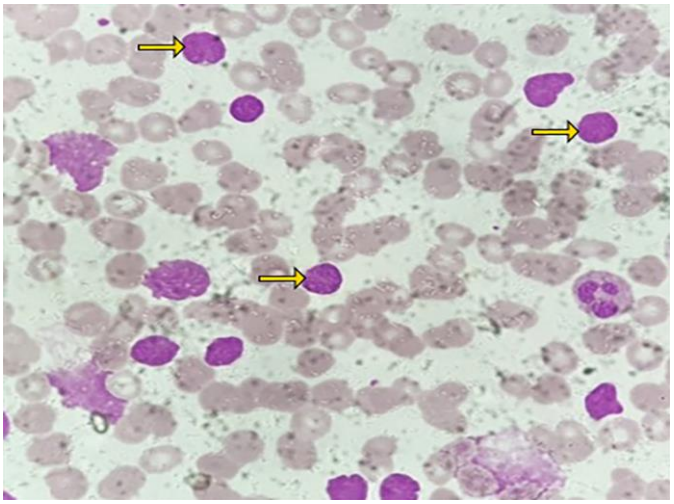

Figure 5: Peripheral Smear - small lymphoctes having round nucleus with densed chromatin and scant cytoplasm, Leishman (1000X)

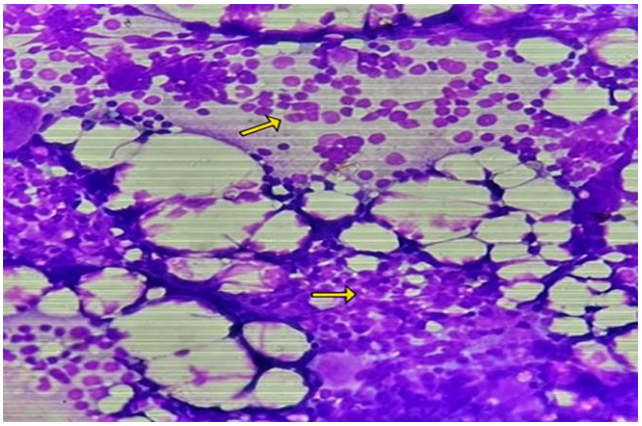

Figure 6: Bone marrow aspiration-hypercellularity with spillover of lymphocytes in the smear, Giemsa(100X)

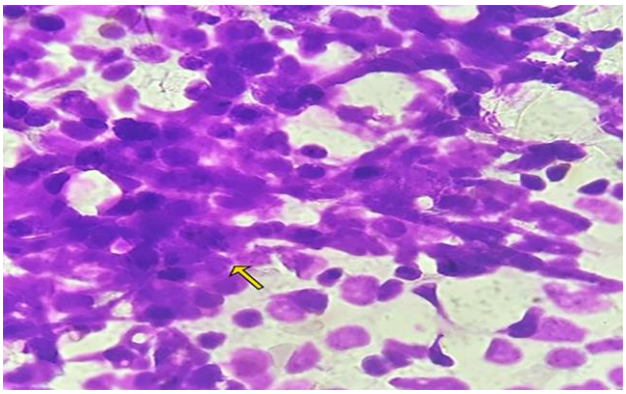

Figure 7: Bone marrow aspiration- lymphoma cells are round to oval nuclei with dense chromatin and scant cytoplasm, Giemsa (1000X)

DISCUSSION

Since bone marrow metastasis is thought to be a primary cause of death in patients with solid tumours, its detection becomes essential for clinical staging and prognosis, which in turn influences the choice of treatment [10]. It is not well understood what causes bone marrow metastasis. The multi-step cascade process of metastatic development involves local invasion and migration from the main tumour, as well as extravasation, colonisation, and proliferation in distant organs as well as intravasation into blood capillaries and survival in circulation [11]. Nevertheless, the process can be elucidated through the distinctive microenvironment of the marrow, which is abundant in cytokines, adhesion molecules, chemokines, and growth factors. According to existing literature, it has been asserted that a mere 0.01% of disseminated tumour cells (DTCs) that reach the bloodstream have the ability to endure and multiply in distant organs [12]. Bone metastasis is an important site for the spread of solid tumours, although with very low occurrence rates. The presence of bone marrow involvement serves as both an indicator of widespread metastasis of the tumour and a contributor to the development of cytopenias, hence increasing the possibility of mortality. Cytopenias have been found to diminish the efficacy of anti-neoplastic medicines employed in therapeutic interventions [9]. The presence of extensive marrow infiltration can lead to the development of anaemia and thrombocytopenia [9]. Patients who have bone marrow involvement may present with blood counts within the normal range, although certain disruptions in one or more series could lead to the development of cytopenias. While severe anaemia might pose a significant risk to one's life, it is worth noting that the problems associated with neutropenia and thrombocytopenia tend to result in higher rates of both morbidity and mortality. Patients with pancytopenia exhibit an increased susceptibility to complications compared to individuals without this condition [8].

Bone metastasis is a frequently observed in individuals diagnosed with breast cancer, lung cancer, renal cancer, prostate cancer, bladder cancer, and various other primary malignancies. However, it is rather uncommon in malignant tumours originating from the gastrointestinal system [13]. Gastric cancer typically exhibits metastasis to several organs such as the liver, peritoneum, lymph nodes, and lungs. However, bone metastases are few, accounting for approximately 13.4% of cases observed during autopsies, and are rarely identified as solitary lesions [14,15]. The typical route of metastasis for gastric cancer cells is primarily hematogenous, involving dissemination through the bone marrow. The gastric mucosa possesses a dense capillary network, while the bone marrow lacks lymphatic capillaries. [13]. The fact that bone metastasis is more common in the axial skeleton—the spine, pelvic bones, and sternum, for example—where adult hematopoietic bone marrow is more abundant—supports this theory. Hence, bone metastasis mostly affects the bone marrow rather than the bone itself. individuals with bone metastases from gastric malignancies have a comparatively poorer prognosis when compared to other types of solid tumours. The goal of treatment in a metastatic situation is to relieve the patient's symptoms in order to enhance their quality of life and extend their period of symptom-free survival [13].

MCL is a type of NHL that accounts for around 2.5% of lymphoid neoplasms in the United States and 7-9% of lymphoid neoplasms in Europe [16]. The most prevalent occurrence of MCL is observed in the adult population, with a median age of 60 years, and a male-to-female ratio above 2:1. The majority of patients have a median lifespan of 3-5 years and are not treated with current therapies. The prognosis for MCL is often unfavourable, even with intensive treatment, resulting in a median overall survival of approximately 3 to 5 years. Approximately 80% of patients exhibit extra-nodal involvement during their initial presentation, with identified sites including the bone marrow, spleen, Waldeyer's ring, and the gastrointestinal system [17].

The primary clinical manifestation observed in patients with bone marrow involvement is bone pain and the occurrence of pathological fractures [18]. According to the study conducted by Ozkalemkas et al, the patient's most prevalent presenting symptoms were constitutional symptoms and discomfort [19]. It is interesting to see how a newer approach can show marrow involvement in early-stage illness. The use of immunohistochemistry, clonal growth analysis, flow cytometry, and polymerase chain reaction (PCR) methodologies will provide a more comprehensive assessment of tumour infiltration frequency compared to conventional histological approaches [20]. Advanced diagnostic techniques such as magnetic resonance imaging (MRI) and bone scanning have demonstrated higher sensitivity in evaluating the degree of bone marrow metastasis. However, these procedures are limited to specialised centre as well as come with a substantial cost. In contrast, bone marrow examination is a simple, quik, and cost-efficient method that continues to be the optimal choice for detecting marrow metastasis in solid tumours and monitoring prognosis [8].

CONCLUSION

Patients in clinical practice should be suspected of having bone marrow metastases if they appear with unexplained haematological abnormalities such as thrombocytopenia and anaemia. The analysis of bone marrow smear and biopsy is a valuable method for the assessment of staging, prognosis monitoring, and treatment evaluation in cases of malignant solid tumours. In cases where the initial site is uncertain, trephine biopsy in conjunction with IHC remains the gold standard for determining the final diagnosis of marrow metastases. Solid tumours that affect the bone marrow are associated with an unfavourable prognosis.

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