

METASTATIC CARCINOMA TO BONE MARROW

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Summary

The haematological profile of 12 patients with metastatic carcinoma to bone marrow was reviewed. Most patients were anaemic with elevated erythrocyte sedimentation rate (ESR) at presentation. The criteria for identification of malignant cells in marrow aspirates and the problem of false positives were considered. The importance of trephine biopsy as part of the bone marrow examination was emphasized and the value of immunocytochemistry in the diagnosis of malignant deposits was briefly discussed.

Keywords: Metastatic carcinoma, bone marrow, trephine

INTRODUCTION

As early as 1935, Reich¹ showed that metastatic cells may appear in bone marrow aspirates. These findings were confirmed only a year later by other investigators.² The detection of metastatic carcinoma in bone marrow confers great value in the diagnosis and treatment of individual patients. This paper examines the haematological profile of 12 patients with metastatic carcinoma to the marrow seen over a period of 4 years in the University Hospital, Kuala Lumpur.

MATERIALS AND METHODS

Consecutive bone marrow aspirates and/or trephine biopsies of patients of the University Hospital, Kuala Lumpur were reviewed for the presence of metastatic carcinoma. The bone marrow aspirates were obtained from the posterior iliac crest or sternum. The smears prepared from concentrated marrow cells were routinely stained with May-Grunwald-Giemsa stain. The trephine biopsies were obtained with Jamshidi-Swaim biopsy needle from the posterior iliac crest. The specimens were fixed with Helly's solution for 3 hours and decalcified using 5% formic acid overnight. Sections of 5-6 μ m thickness were then cut after paraffin embedding.

We considered cells in marrow smears to be malignant only when they have features as outlined by Kingsley Pillers.³ The malignant cell is usually large, often with a large nucleus and a prominent nucleolus. The cells are characteristically adherent and occur in clumps or discrete sheets. They are usually found at

the margin of the smear where they can be picked up with low power scanning (Figs. 1 and 2).

RESULTS

Between 1982 and 1985, 2944 bone marrow aspirations were performed. 816 patients also had trephine biopsies performed concurrently. In 25 patients, bone marrow aspirations were performed to look for metastatic carcinoma; of these, 14 patients had concurrent trephine biopsies. Metastatic carcinoma were detected in 12 patients. In 9 patients, tumour cells were detected in both bone marrow aspirates and trephine biopsies while in another 2 patients (no concurrent trephine biopsies) these were present in marrow aspirates. In one other patient, tumour cells were present in the trephine biopsy only.

The age range of the 12 patients was 29 to 75 years. 8 of them were above 50 years old. 7 patients were male and 4 were female.

The primary site of tumour was known in 9 (75%) patients (Table 1). The peripheral blood findings (Table 2) indicated a frequent presence of anaemia. A leucoerythroblastic picture (i.e. presence of immature myeloid and erythroid precursors in the peripheral blood film) was seen in only 2 patients.

The ESR was measured in 9 patients at the time of presentation and it was markedly elevated in 4 of them (> 100 mm/hr) while in 4 others it was elevated > 40 mm/hr. Only in 1 patient was the ESR within normal range (0-20 mm in 1 hr).

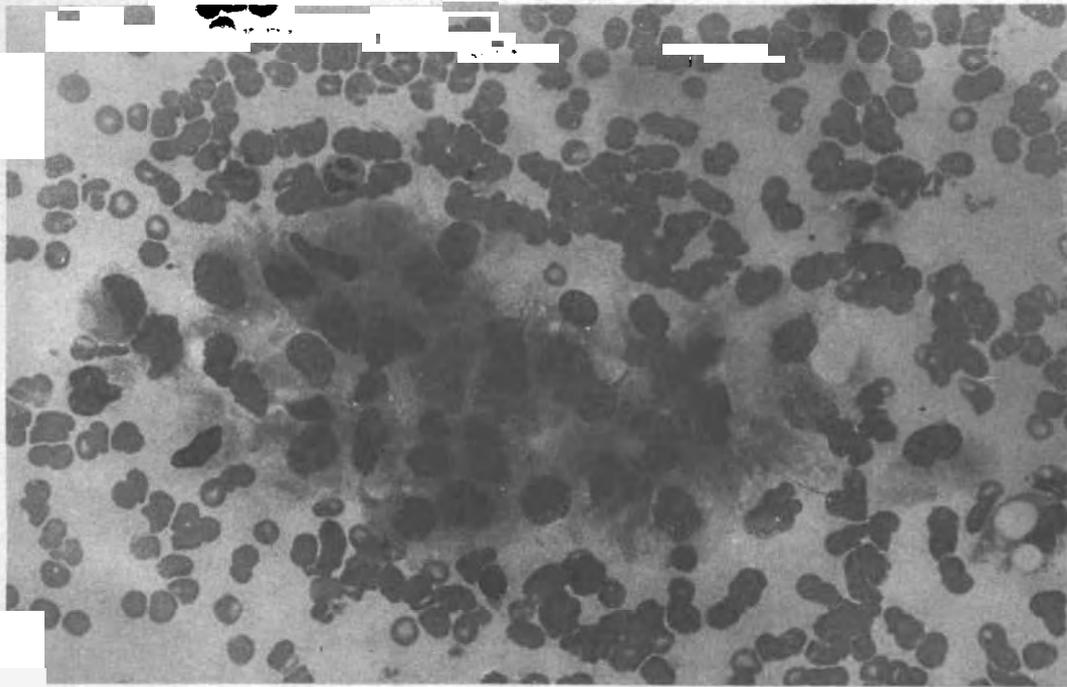


FIG. 1: Bone marrow aspirate showing cluster of malignant metastatic cells (primary site in stomach). H&E X 400.

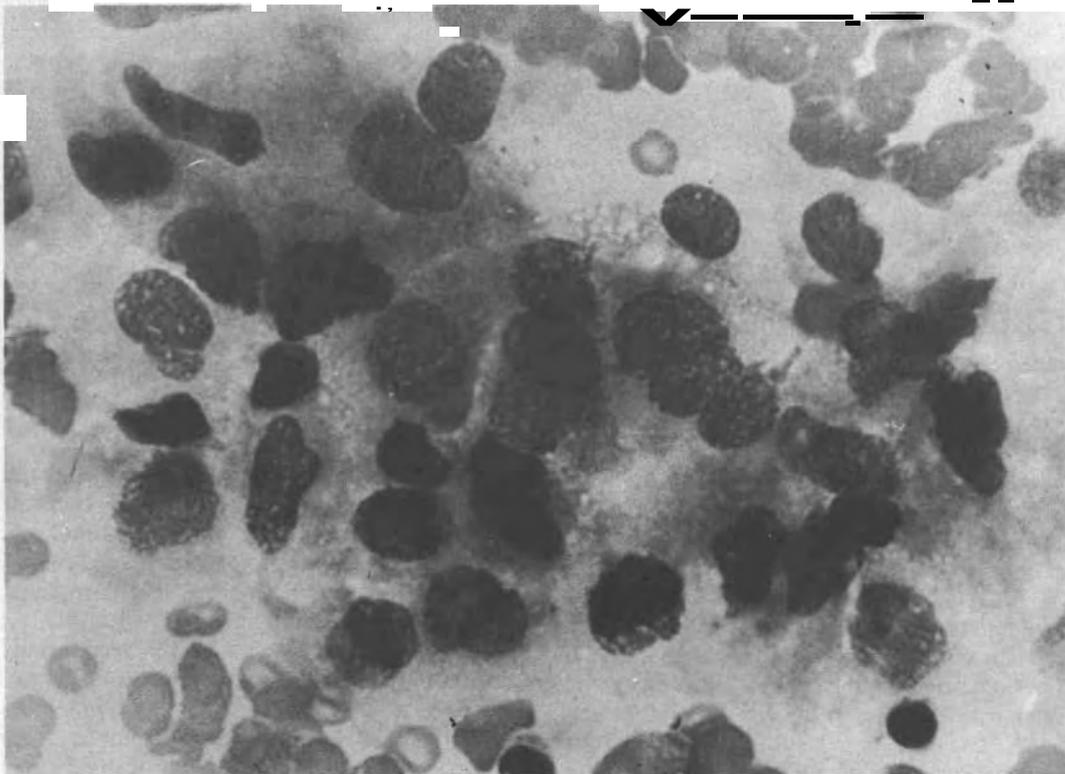


FIG. 2: Higher power view of Figure 1 showing malignant metastatic cells with large nuclei and stippled chromatin. They have lacy cytoplasmic borders and showed marked cohesiveness. H&E X 800.

TABLE 1
SITE OF PRIMARY TUMOUR IN
12 PATIENTS WITH EVIDENCE OF
MARROW DEPOSITS

Site of primary tumour	Number of patients
Prostate	3
Breast	2
Lungs	2
Thyroid	1
Stomach	1
Unknown	3

TABLE 2
HAEMATOLOGICAL PROFILE OF
12 PATIENTS WITH METASTATIC
CARCINOMA IN BONE MARROW

Peripheral blood findings	Number of Patients
Anaemia (<12 g%)	7
Thrombocytopenia (<150,000)	2
Leucopenia (<4,000)	1
Pancytopenia	1
Leucoerythroblastic picture	2

BONE MARROW FINDINGS

Aspirates: 11 out of the 12 patients had bone marrow aspirates which were positive for tumour cells. Although 7 out of the 12 aspirates were considered as 'inadequate' because of the absence of bone marrow fragments, tumour cells were nevertheless identified in all 7 cases. In all positive aspirates the metastatic tumour cells occurred in clumps. The morphological features and cytochemistry results (peroxidase and PAS stains) were not helpful in delineating the origin of the malignancies.

Trephine biopsies: Tumour cells were detected in the 10 patients subjected to trephine biopsies. It was also positive in 1 patient where the aspirate showed no tumour cells. The trephine biopsies were able to provide useful clues to the site of the primary tumour. In 6 patients, a definite glandular pattern was evident indicating adenocarcinoma (Figs. 3 and 4). Marked marrow fibrosis was appreciated

in 6 patients and marrow necrosis was seen in 1 patient. In 1 patient suspected of suffering from either a carcinoma or lymphoma, the use of immunoperoxidase staining using monoclonal antibodies revealed tumour cells immunoreactive for cytokeratin but negative for leucocyte common antigen (controls were used). These findings were strongly indicative of an undifferentiated carcinoma.

DISCUSSION

Francis and Hutter⁴ emphasized that any cancer can metastasize to the bone. Elvia *et al*⁵ reported that carcinoma of breast and prostate contributed to 30% and 28% respectively of all metastasis to bone. Other common primaries were from the genitourinary (10%) and gastrointestinal (10%) tracts. Our small series seems to concur with this pattern. In 13% of cases in Elvia's study the primary site remained undetermined while 3 (25%) of our patients belonged to the undetermined category. The relatively higher frequency of undetermined primaries was probably because our patients were subjected to less 'vigorous' investigations once it was found that the marrow was involved by a malignancy indicating disseminated spread of the tumour and thus limited therapeutic options.

Most of our patients had abnormal blood counts at presentation. Anaemia was a common finding. Various studies have suggested an incidence of anaemia in patients with carcinoma that ranged from 55% to 90%.⁶ Besides replacement of bone marrow by tumour cells, a combination of inadequate erythropoiesis and a moderately decreased red cell survival⁷ were recognised as the common mechanisms of anaemia in cancer. A leucoerythroblastic picture was seen in only 2 (17%) of our patients and in 19 (24%) out of 79 patients in Elvia's study. Hence a leucoerythroblastic picture is not a common finding in patients with metastatic carcinoma to bone marrow.

Although the diagnostic usefulness of ESR for detection of occult malignancy is limited, most patients with both malignant disease and a grossly elevated ESR had metastatic spread.⁸ However, it is important to note that a small percentage of patients with very high ESR did not have identifiable disease.⁹

The problem of false positives in the identification of malignant cells was elegantly examined by Emerson *et al*¹⁰ in a prospective double blind study. They detected false positives

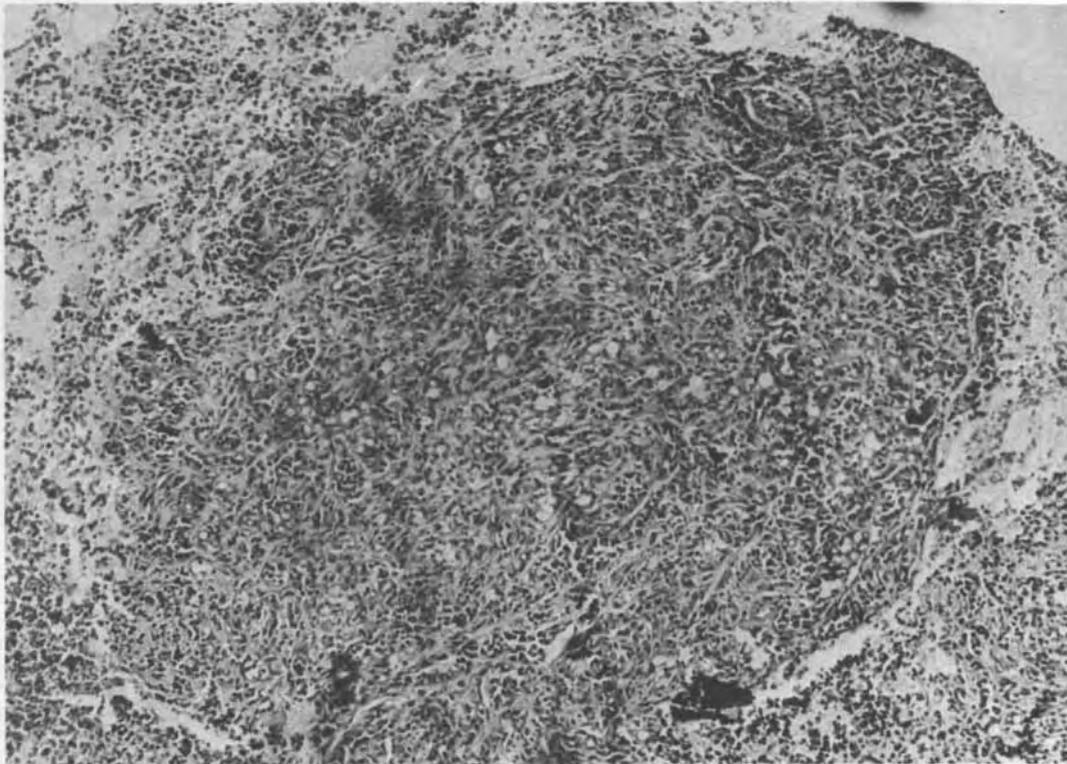


FIG. 3: Trephine biopsy from patient with prostate carcinoma with metastatic secondaries in the marrow. H&E X 200.

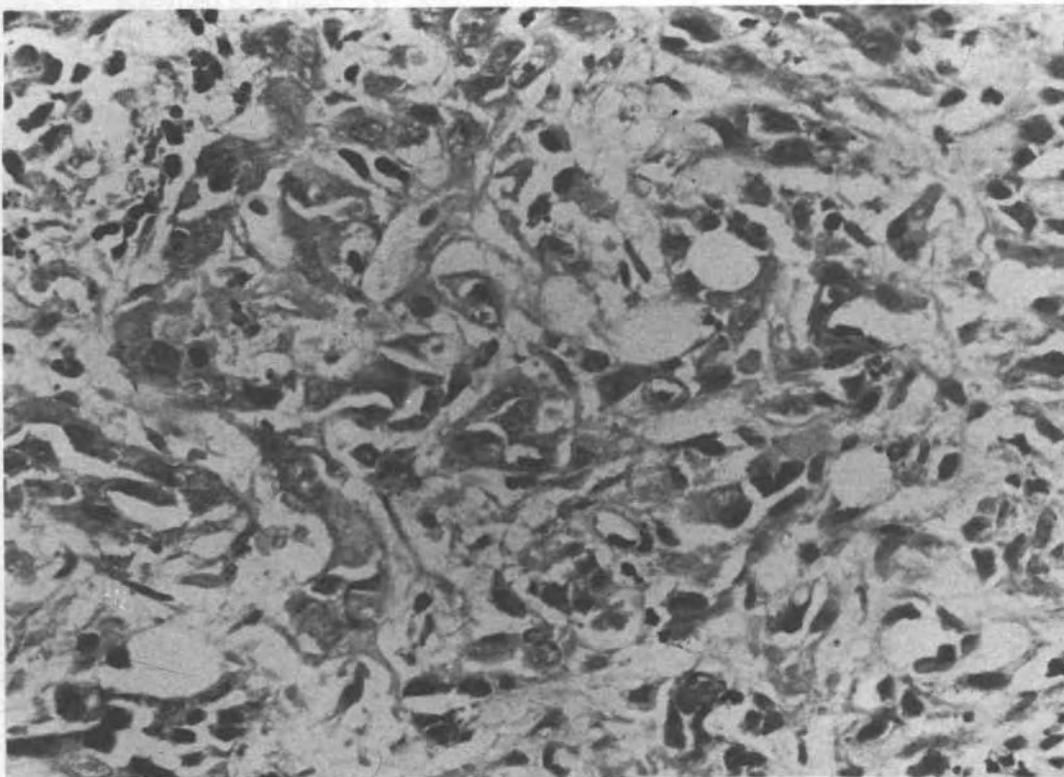


FIG. 4: Higher power view of Figure 3 showing malignant small glands with background of fibroblastic proliferation. H&E X 400.

in marrow aspirates in 22% of 100 patients with a variety of medical conditions. Osteoclasts, osteoblasts or nests of degenerating plasma cells and atypical megakaryocytes or histiocytes could mimic tumour cells. The problem of false positives in bone marrow aspirates can be reduced by concurrent trephine biopsy examination.¹ The histological features of the marrow also facilitate the identification of infiltrating neoplastic cells. Moreover, trephine biopsies have been reported to improve the diagnostic yield by 20 - 50% over that obtained by simple aspiration.¹²

I Myelofibrosis associated with metastases in the marrow space has been well documented.³ 6 patients in our study had marked marrow fibrosis in association with the presence of tumour cells. However, marrow fibrosis can be seen in other malignant diseases such as leukaemia, lymphoma and non-neoplastic conditions.⁴ In recent years, the ready application of immunological and histochemical markers to trephine biopsy specimens have greatly expanded the diagnostic information available. The detection of cytokeratin and leucocyte common antigen can be extremely useful in separating poorly differentiated carcinomas from haematopoietic malignant disease⁵ as illustrated in one of our patients. Similarly, metastatic prostatic carcinoma may be clearly identified by the presence of prostate specific antigen. However, it should be noted that conventional decalcified paraffin embedded sections are not as satisfactory as undecalcified sections because decalcification presumably destroys some of the immunological determinants. In addition, many additional markers applicable to plastic embedded sections are becoming available.¹⁶

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