Malaysian J Pathol 2006; 28 : 55 – 58

CASE REPORT

Extensive myelofibrosis responsive to treatment for acute erythroblastic leukaemia

Fadilah S-Abdul-Wahid[1,3] *PhD*, Raja-Zahratul-Azma Raja-Sabudin[2] *MPath* and Chooi-Fun Leong[2,3] *FRCPA*

Departments of [1]Medicine and [2]Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, and [3]Clinical Haematology and Stem Cell Transplantation Services, Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

Abstract

Intense myelofibrosis is rarely associated with *de novo* acute myeloid leukaemia (AML) except in acute megakaryoblastic leukaemia (AML-M7) where there is diffuse marrow fibrosis as a consequence of proliferation of neoplastic myeloid cells. AML associated with significant myelofibrosis developing both *de novo* or secondary to primary (idiopathic) myelofibrosis is characterised by a fulminant course and extremely poor prognosis, primarily due to treatment-resistant disease. The prognostic value of degree of marrow fibrosis in *de novo* AML has been poorly investigated. We describe a case of extensive myelofibrosis associated with acute erythroblastic leukaemia (AML-M6) that responded to induction therapy of the leukaemia.

Key words: myelofibrosis, acute erythroblastic leukaemia (AML-M6), acute megakaryoblastic leukaemia (AML-M7), primary (idiopathic) myelofibrosis, marrow fibrosis

INTRODUCTION

Acute myeloid leukaemia (AML) associated with intense marrow fibrosis may develop *de novo* or secondary to primary (idiopathic) myelofibrosis with myeloid metaplasia (MMM). Acute "malignant" myelofibrosis which is mostly associated with *de novo* AML-M7 is an uncommon fulminant disorder characterised by pancytopenia, minimal or absent splenomegaly, extensive fibrosis of the bone marrow (BM) and unresponsiveness to cytotoxic drugs[1]. Apart from M7, significant marrow fibrosis has been rarely described in the other subtypes of myeloid leukaemia but not in M6[2]. On the other hand, AML associated with established myelofibrosis occurred in up to 30% of patients with MMM[3], and the most frequent subtypes were M7 (25.4%), M0 (22.4%) and M2 (17.9%)[4]. In general, leukaemic transformation (LT) in patients with MMM leukaemia is fatal in 98% of cases after a median of 2.6 months. AML-like induction therapy resulted in no complete remission, a substantial (33%) treatment related mortality and a short median survival (3.9 months)[4]. The observation that AML associated with significant myelofibrosis is characterised by a rapidly fatal outcome raises the question of prognostic and therapeutic significance of marrow fibrosis in these disorders[4,5]. We describe a case of extensive myelofibrosis occurring in a patient with AML-M6 *de novo* and discuss the clinical relevance of marrow fibrosis in patients with acute leukaemia.

MATERIALS AND METHODS

A 42-year-old woman was referred for persistent thrombocytopenia of 3 months duration associated with fever and severe bone pain. There was no relevant past medical history. She had received prednisolone and several random platelet concentrates but her condition continued to deteriorate. On admission, she was febrile (temperature 38 ^{0}C) and pale. The peripheral lymph nodes, liver and spleen were not enlarged. The haemoglobin was 9.4 g/dl, leukocytes 4.5 x 10^9/l (neutrophils 3.6 x 10^9/l, lymphocytes 0.9 x 10^9/l), platelets 9 x10^9/l and serum lactate dehydrogenase (LDH) 4210 IU/l.

Address for correspondence and reprint requests: Associate Professor Dr. S Fadilah Binti S Abdul Wahid, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia. Fax: 603- 91737829, Tel no: 603-91702394. E-mail: sfadilah@mail.hukm.ukm.my

There was presence of 20% blast cells in the peripheral blood. BM aspiration on admission revealed dry tap on two separate occasions. BM biopsy showed marked, diffuse fibrosis (grade 4 reticular fibrosis) (Fig. 1A) and heavy infiltration (70-80%) with blasts (Fig. 1B). The trephine imprints showed numerous erythroblasts (Fig. 1C) that expressed CD13, CD34, HLA-DR and glycophorin A. There was minimal normal residual haematopoiesis and no

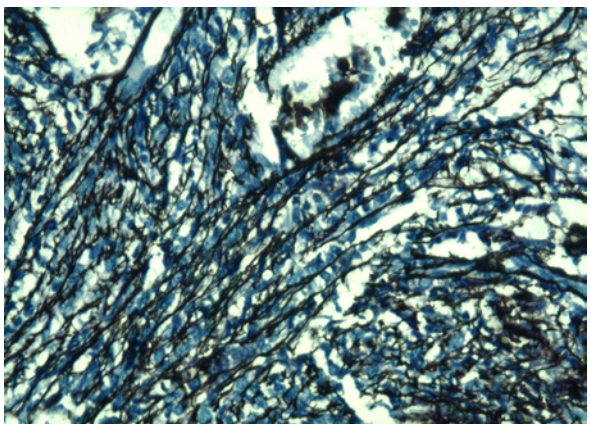

Fig. 1A.

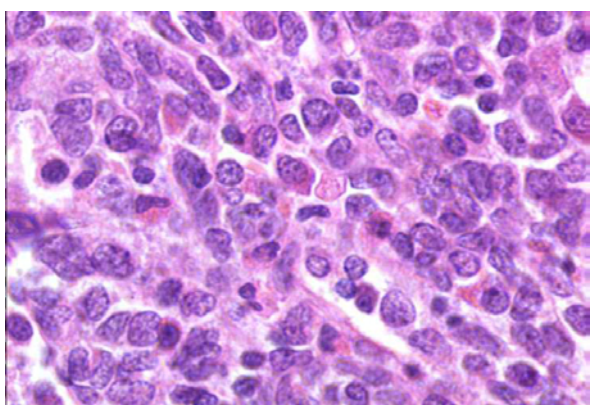

Fig. 1B.

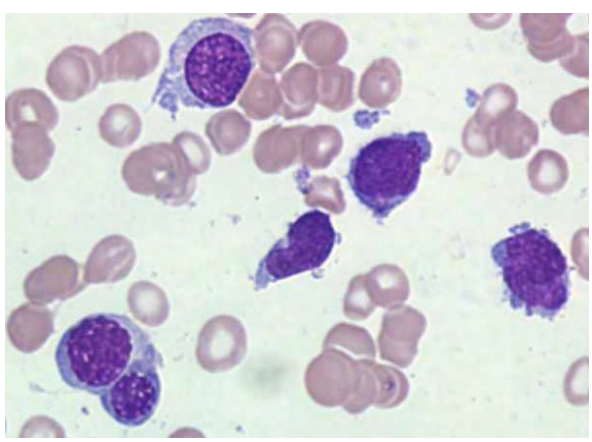

Fig. 1C.

FIG.1: Bone marrow trephine biopsy samples taken at diagnosis showing: [A] grade 4 reticulin deposition (Paraffin embedded, reticulin stain x 40), [B] hypercellularity and heavy infiltration with blasts (May Grunwald Giemsa x 40). [C] Bone marrow trephine imprint showing presence of numerous erythroblasts (May Grunwald Giemsa x 40).

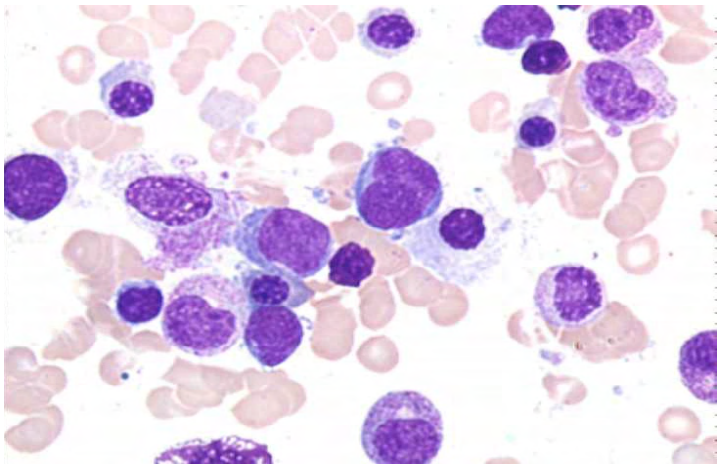

Fig. 2A.

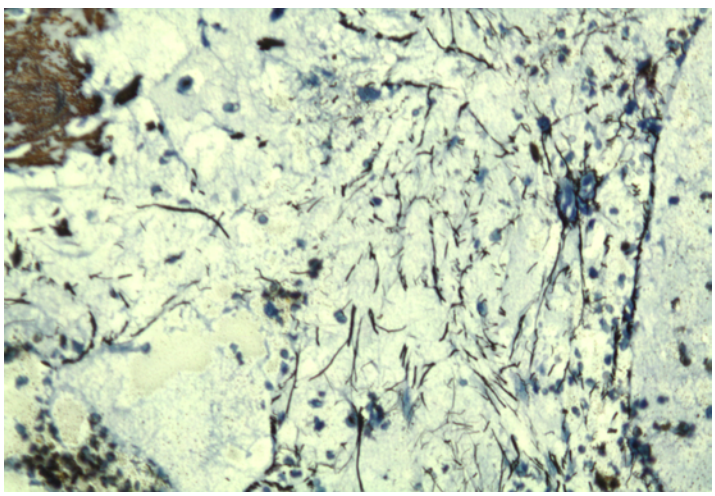

Fig. 2B.

FIG. 2: Bone marrow samples taken four weeks following induction chemotherapy. [A] Bone marrow smear showing normocellular marrow with presence of residual erythroblasts (May Grunwald Giemsa x 40). [B] Bone marrow trephine biopsy showing reduction in the reticulin fibres (Paraffin embedded, reticulin stain x 40).

significant myelodysplasia. Cytogenetic study was unsuccessful. A diagnosis of AML-M6 with marked myelofibrosis was made. She received standard induction chemotherapy consisting of cytosine arabinoside and daunorubicin resulting in resolution of the clinical symptoms, abnormal blood counts and serum LDH. Four weeks after induction chemotherapy, the BM smears were normocellular, with 10% blast cells (Fig. 2A) and the BM tissue showed focal, minimal fibrosis (grade 2 reticular fibrosis) (Fig. 2B). The patient was still alive 5 months after diagnosis (at the time of writing of this report).

DISCUSSION

Leukaemic transformation in patients with MMM should be suspected when there is a rapid increase in spleen size or sudden development of anaemia or thrombocytopenia. However the absence of splenomegaly in the present case excluded this diagnosis. Thus, it is likely that the marrow fibrosis occurred *de novo* in conjunction with the AML-M6.

Significant myelofibrosis is uncommonly seen in *de novo* AML except in M7. Tallmann *et al* reported marrow fibrosis, usually extensive, in all 20 patients with newly diagnosed M7 they saw between 1984 and 1997[1]. The mechanism for the

development of myelofibrosis in M7 is unclear. Terui *et al* (1990)[6] showed that megakaryoblasts secrete an active form of transforming growth factor-β that stimulates collagen synthesis by BM fibroblasts in a paracrine manner. Consequently, in M7, as the number of megakaryoblasts increase, marrow fibrosis accelerates, and symptomatic cytopenia begins to occur. Apart from megakaryoblasts, marrow fibrosis has been described in acute leukaemia evolving from myeloblasts, myelomonoblasts, lymphoblasts or undifferentiated blasts but not erythroblasts[2]. Myelofibrosis was not detected in 26 patients diagnosed between 1969 and 1991 with *de novo* M6[7].

The prognosis for patients with MMM who experience LT is extremely poor with regards to both survival and treatment response. In a recent study involving the largest cohort (2333) of MMM patients, almost all patients died around a median of fewer than 3 months and not a single patient achieved complete remission from standard induction chemotherapy[4]. Such an outcome might be considered even worse than expected from other instances of poor-risk AML. In acute lymphoblastic leukaemia (ALL), a progressive increase in marrow reticulin has been associated with impending relapse[8], thus patients presenting with marrow fibrosis will be systematically entered into high-risk group, and thus received intensified therapy. However, a subsequent report on 128 adults patients with newly diagnosed ALL showed that the persistence of normal residual haematopoiesis and intense leukaemic cells mitotic activity were both factors of favourable outcome, while BM fibrosis did not display any prognostic value[9]. Because of the rarity of M6 and M7 (4% and 1.2% of cases of *de novo* AML, respectively), the impact of marrow fibrosis on the response to standard treatment of AML and survival has not been systematically examined. Thus, it remains to be addressed if extensive myelofibrosis is responsible for the high rate of resistant disease and extremely poor median survival for all patients with M7 reported by Tallman *et al*[1].

In the present case, extensive myelofibrosis was observed at initial diagnosis of M6 and this abnormality improved following standard induction chemotherapy for AML. Thus, although the presence of concomitant intense fibrosis and AML as exemplified in M7 patients, has been typically regarded as heralding a poor prognosis, its occurrence may not necessarily bias the overall outcome, as appropriate therapy may result in the resolution of the intense fibrosis and thus assist the repopulation of the BM with normal regenerating haematopoietic cells as seen in our patient. Nonetheless, further studies are required to establish the prognostic usefulness of marrow fibrosis for predicting the outcome of patients with *de novo* AML, in particular M6 and M7.

ACKNOWLEDGEMENT

We are grateful to Professor Cheong Soon Keng for reviewing the bone marrow slides and Rozilaila Rahmat for typing the manuscript.

REFERENCES

1. Tallman MS, Neuberg D, Bennett JM *et al*. Acute megakaryocytic leukaemia: the Eastern Cooperative Oncology Group experience. Blood 2000; 96: 2405-11.
2. Amberger DM, Saleem A, Kemp BL, Truong LD. Acute myelofibrosis - a leukaemia pluripotent stem cell. A report three cases and review of the literature. Ann Clin Lab Sci 1990; 20: 409-14.
3. Cervantes F, Tassies D, Salgado C, Rovira M, Pereira A, Rozman C. Acute transformation in nonleukaemic chronic myeloproliferative disorders: acturial probability and main characteristics in a series of 218 patients. Acta Haematol 1991; 85: 124-7.
4. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A. Leukaemic transformation in myelofibrosis with myeloid metaplasia: a single institution experience with 91 cases. Blood 2004; 105: 973-7.
5. Thiele J, Kvasnicka HM, Zerhusen G *et al*. Acute panmyelosis with myelofibrosis: a clinicopathological study on 46 patients including histochemistry of bone marrow biopsies and follow-up. Ann Haematol; 2004; 83: 513-21.
6. Terui T, Niitsu Y, Mahara K *et al*. The production of transforming growth factor-β in acute megakaryoblastic leukaemia and its possible implication in myelofibrosis. Blood 1990; 75: 1540-8.
7. Olapade OI, Thangavelu M, Larson RA *et al*. Clinical, morphologic, and cytogenetic characteristics of 26 patients with acute erythroblastic leukaemia. Blood 1992; 80: 2873-82.
8. Frisch B, Bartl R, Burkhardt R. Bone marrow biopsy in clinical medicine: an overview. Haematologica 1982; 3: 245-53.
9. Thomas X, Le QH, Danaila C, Lheritier V, Ffrench M. Bone marrow biopsy in adult acute lymphoblastic leukaemia: morphological characteristics and contribution to the study of prognostic factors. Leuk Res 2002; 26: 909-18.