

MEGAKARYOBLASTIC TRANSFORMATION OF CHRONIC GRANULOCYtic LEUKAEMIA: A CASE REPORT

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SUMMARY

A 38 year old patient with chronic granulocytic leukaemia, subsequently presented with blast transformation nineteen months later. Conventional light microscopy and cytochemistry were not helpful in elucidating the type of blast cell. Electron microscopy however identifies the blasts to be of megakaryocytic series.

INTRODUCTION

For one century, cytochemical reactions have been used widely with Giemsa stain for the identification of normal and leukaemic haematopoietic cells. However the study by light microscopy examination of films has its limitations. Now haematologists have turned to electron microscopy for the analysis of the fine structure of cells and for determining the nature of some poorly differentiated blasts.

We present here a case to illustrate the contribution of transmission electron microscopy in identifying the nature of the blast cells.

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CASE REPORT

The patient is a 38 year old Malay woman who was first seen in General Hospital, Kuala Lumpur in February 1980. She presented then with a few months history of progressive abdominal discomfort, low grade fever and lethargy. On examination she was pale and had hepatomegaly of 3 cm and splenomegaly of 20 cm. Her full blood picture showed haemoglobin of 6.8 g/dl, total white cell count of $313.5 \times 10^9/l$ with a differential of blasts 5%, myelocytes 84%, metamyelocytes 6%, neutrophils 2%, basophils 3%, platelets $606 \times 10^9/l$. Neutrophil alkaline phosphatase score was 2 per 100 neutrophils and chromosomal study showed positive Philadelphia chromosome. Bone marrow aspirate showed increased proliferation of myeloid and megakaryocyte cell lines. A diagnosis of chronic granulocytic leukaemia in chronic phase was made and she was managed on low dose continuous busulphan for 1½ years with satisfactory control of her haematological indices.

In October 1981 (19 months after diagnosis) she presented with generalised bone pain, left hypochondrial pain, marked weight loss and fever. Full blood picture showed Hb 9.2 g/dl, WBC $500 \times 10^9/l$. with blasts 30% and platelets $197 \times 10^9/l$. The blasts were very undifferentiated with large nucleocytoplasmic ratio, prominent 1 - 2 nucleoli and very basophilic cytoplasm without any granules. Bone marrow aspirate showed heavy

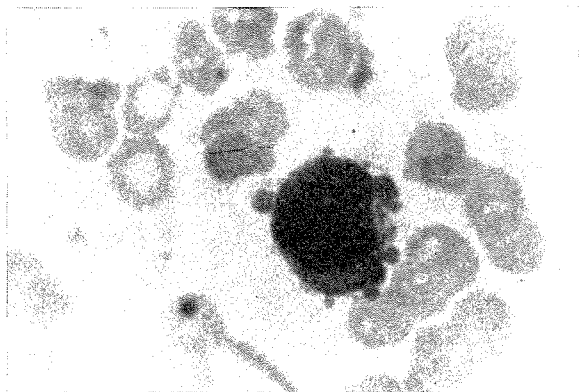


Fig. 1 Bone marrow aspirate showing a typical blast cell with cytoplasmic blebs, (x 400).

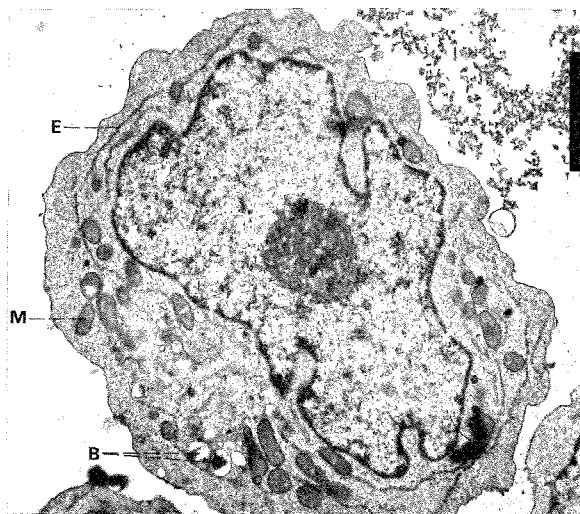


Fig. 2 Electron micrograph of a blast cell showing endoplasmic reticulum (E), mitochondrion (M) and Bull's eye granules (B). (x 8000)

infiltration of blast cells accounting for 60% of all nucleated cells. Many of these blasts showed cytoplasmic blebs suggestive of megakaryoblast (Fig. 1). Conventional cytochemistry was done on both peripheral blood and bone marrow aspirate. Further immunological study and electron microscopy were done on the peripheral blood.

MATERIALS AND METHODS

20 ml of blood was taken in heparin bottle to give a concentration of 20 Iu of heparin/ml of blood. Mononuclear blast cells were separated using lymphocyte separating medium (lymphoprep from Nyegaard and Co., As - Oslo). A smear was made and stained with May - Grunwald - Giemsa stain after separation to confirm adequate collection of blast cells. The blast cells were sent for cytochemical staining, immunological study and transmission electron microscopy study.¹



Fig. 3 Electron micrograph of Bull's eye granules (B) in a blast cell. (x 60,000)

RESULTS

Cytochemistry

Cytochemistry showed negative peroxidase, weakly positive PAS with a fine granular pattern. NASDA was positive, resistant to NaF and acid phosphatase was strong positive and was tartaric acid labile.

Immunological study

In view of the strong positivity with acid phosphatase, the blast cells were sent for sheep cell rosetting. The blast cells did not form rosette with sheep cells.

Electron microscopy

Transmission electron microscopy revealed uniform features of the blast cells. The blast cells had poor chromatin condensation and prominent nucleoli in the nucleus. Extensive network of smooth endoplasmic reticulum and many mitochondria were present in the cytoplasm (Fig. 2). Several characteristic 'Bulls' eye' granules were present (Fig. 3). Many platelets were seen in the vicinity of these blast cells (Fig. 4) and one of them showed presence of myelin body (Fig. 5).

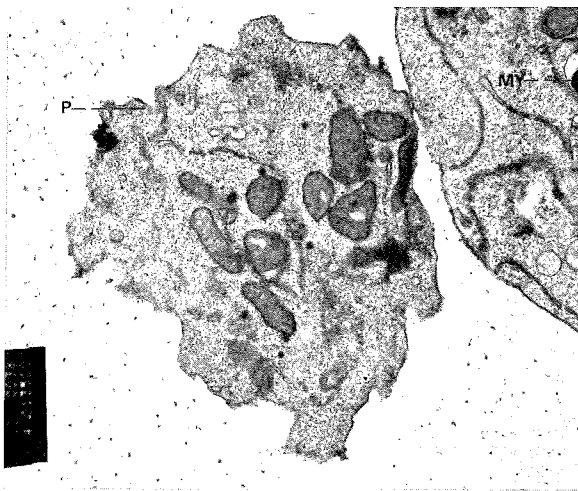


Fig. 4 Electron micrograph of a platelet (P) in the vicinity of a blast cell showing a myelin body (MY). (x 13,500)

DISCUSSION

The natural history of chronic granulocytic leukaemia can be divided into two phases. Most patients present in the stable chronic phase with adequate haemoglobin concentration and normal or often increased platelet counts. The aggressive therapy required for acute leukaemia is not necessary in these patients. The chronic phase is terminated by a transition of the disease to an accelerated or blastic phase. This can occur at any time in the course of the disease usually in a median time of 30 to 36 months. This blastic phase is characterised by extreme difficulty in inducing haematological remission by chemotherapy and death follows within a few weeks in most cases. Catovsky,¹ in a small series of 30 cases, showed that blast transformation occurred as follows : myeloblastic transformation 45%, lymphoblastic transformation 25%, monoblastic transformation 20% and megakaryoblastic transformation 10%. The morphological classification of the blast cells is often difficult as the blasts are very undifferentiated. Detailed cytochemical and immunological study help to identify the nature of the blast cells in many cases. However the introduction of the electron microscope has improved further the diagnostic accuracy of blast transformation as illustrated in this case.

Morphology at light microscopy level offers little help in classifying the blast cell type in this patient although the presence of cytoplasmic blebs in the bone marrow aspirate suggested the

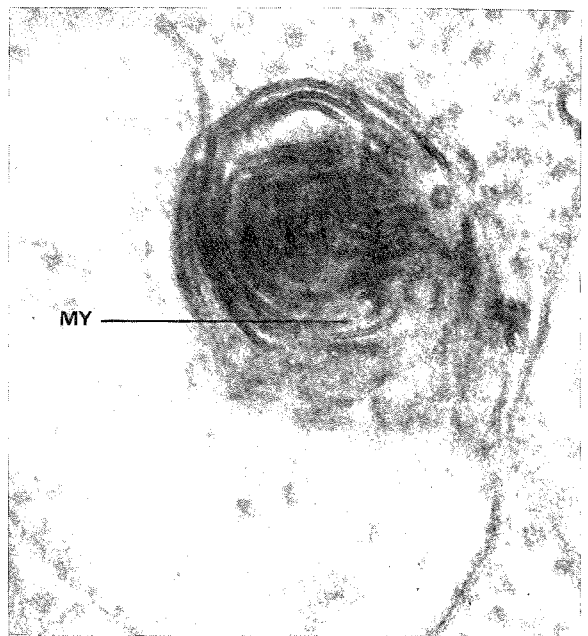


Fig. 5 Electron micrograph of a myelin body (MY) in a blast cell. (x 280,000)

megakaryoblastic origin of the blast. Cytochemical study had no added advantage here though the pattern of positivity with PAS and acid phosphatase reactions had been described with normal megakaryocyte.² Immunological study with sheep red cell rosetting showed that the blast cells were not likely to be T lymphoblasts. Terminal deoxynucleotidyltransferase (Tdt) assay (not available in Malaysia presently) would be helpful as it is raised typically in thymic derived lymphoblast.³

At the electron microscopy level, the morphology of the blast cells with the extensive smooth endoplasmic reticulum, characteristic 'Bulls' eye' granules,⁴ presence of myelin body⁵ and numerous platelets in the vicinity of the blasts were strong evidence that the blast cells were of megakaryoblastic type. Demarcation Membrane System (DMS) - characteristically seen in maturing megakaryocytic series was not present in these blast cells; presumably these blasts were of more primitive cell type - promegakaryoblasts.

The platelet peroxidase test, a cytochemical test at electron microscopy level, would be very helpful in identifying the blast cell type but it was unfortunately not done. In megakaryoblast, the platelet peroxidase is characteristically positive in

perinuclear space and endoplasmic reticulum, and negative in golgi cisternae and golgi vesicles. ⁶

Both G6PD and 6 phosphogluconate dehydrogenase isoenzymes studies and the presence of marker Ph' chromosome suggest that the abnormal clone in CGL arises from a common precursor of granulocytic, megakaryocytic and erythroid cells. ⁷ Further documentation of lymphoblastic transformation of CGL Ph' chromosomal positivity suggests that the abnormality lies in very primitive pluripotent stem cells.

Ultrastructure study of blast transformation in CGL is of great theoretical interest as the occurrence of megakaryoblastic transformation is further evidence suggesting that the disease involves a very primitive stem cell. It may also be of practical therapeutic value as we know that different blast cell responds differently to different cytotoxic drugs, for example the lymphoblastic transformation responds very well to corticosteroid. ⁸

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