Acute Myeloid Leukaemia : AML M0 with 11q deletion

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Introduction

Acute myeloid leukaemia (AML) in the undifferentiated form can be a challenging. The prognosis of patients with AML- M0 is remarkably poor as compared to other WHO/FAB (French-American-British) subtypes. Conventional combination chemotherapy yields disappointing results. The reason for this may be the convergence of various unfavourable prognostic factors such as the high incidence of cytogenetic abnormalities, lack of differentiation features and the expression of immature markers such as CD34 and CD7 and the frequent expression of P-170 [1].

There are reports of a high frequency of mutations of *AML1* gene in AML M0. Patients with *AML1* mutations showed significantly higher leucocyte counts and higher marrow blast percentage, suggesting that this mutation is associated with greater cell proliferation, higher incidence of HLA-DR expression and higher frequency of IgH or T cell receptor (TCR) gene rearrangement [2]. Although many cases of acute myeloid leukaemias can be correctly identified morphologically with or without enzyme cytochemical analysis, immunophenotyping remains indispensable for proper identification of myeloid lineage in AML M0 [3].

We present a case of AML to highlight the problems encountered in diagnosis and management.

Case Report

A 24 year old male presented with a two week history of fever and weight loss of ten kgs over the past one month along with reduced appetite. There was no past history of any significant illness. General physical examination revealed a well built individual with Pallor, nontender bilateral axillary lymphadenopathy of the apical group and three cms soft, palpable spleen. Investigations revealed haemoglobin 9gm%, total leucocyte count 30000/cmm and platelets 70000/cmm.

Peripheral smear revealed 90% blast cells (Fig. 1). Blasts showed high NC ratio, finely distributed chromatin, two to three prominent nucleoli and no Auer rods. Cytochemistry revealed <3% myelo peroxidase (MPO) positivity. Chloroacetate esterase and non specific esterase (alpha naphthyl acetate esterase) were both negative. A bone marrow aspirate revealed similar morphology. Bone marrow dual colour flow cytometry revealed CD 34 (98%) positive, CD 33 (81%) positive, CD 3 (54%) positive(dim), CD7 (71%) positive, HLA-DR (97%) positive and CD13 (12%) positive.

Bone marrow conventional cytogenetic analysis done in RPMI media following standard unstimulated cell culture technique involving 25 metaphases, which revealed normal male karyotype in all the cells except five metaphases with deletion on the long arm of chromosome 11; 46,XY,del (11q) pattern. A final diagnosis of acute myeloid leukaemia AML M0 with unfavourable cytogenetics was reported.

He had no prospective bone marrow donors. He received induction chemotherapy with "3+7" regimen.. He developed febrile neutropenia on Day 8. He received intravenous broad

Fig. 1 : AML M0 (x100) Leishman Giemsa stain of peripheral blood smear

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spectrum antibiotics. By Day 10 due to a hypotensive episode and unabating fever, IV vancomycin was added with antifungals and piperacillin/sulbactam. Despite aggressive blood and component support the individual succumbed to his illness shortly thereafter as a result of massive intrapulmonary haemorrhage consequent to disseminated intravascular coagulation.

Discussion

The FAB/WHO criteria for diagnosis of AML- M0 includes <3% positivity for MPO/ Sudan Black by the blasts, positivity for myeloid markers and lack of B&T-lineage associated antigens by immunophenotyping. Rare cases showing expression of lymphoid antigens but positive for anti-MPO by immunophenotype are also considered sufficient evidence for a diagnosis of AML- M0 [4]. A suggested immunological approach for acute leukaemia diagnosis should also use monoclonal antibodies (MoAbs) for cytoplasmic MPO, CD3, and CD22/CD79a to avoid underestimation of AML- M0 and an incorrect diagnosis of acute lymphoid leukaemia (ALL) [5]. Thus the suggested criteria for AML- M0 would include for acute leukaemia undetectable or <3%MPO or Sudan Black positivity; lack of expression of lymphoid- specific antigens, cCD3 for T-lineage and cCD79a and cCD22 for B-lineage; positivity for any of myelomonocytic lineage antigens known not to be expressed on normal T or B lymphocytes or; positivity for MPO as detected by ultrastructural cytochemistry, immunohistochemistry or flow cytometry [6].

AML-M0 is characterized by a more frequent occurrence of complex karyotypes [7]. A possible “stem cell”/immature pattern that is more frequently associated with, but not restricted to AML- M0 and defined by the combination of CD34, terminal deoxytidyl transferase (TDT), complex karyotypes and abnormalities of chromosome 5 and/or 7 may account for the poor prognosis of AML-M0. AML-M0, because of its dismal outcome, can be considered a discrete entity; however from a biological point of view we still lack specific markers supporting this assumption.

Structural abnormality of the 11q23 band (11q23+) bearing the MLL gene translocation (MLL+) is a recurrent chromosome change in leukemia described in AML and in ALL, with a peak incidence in infant leukemia. A proposal by the World Health Organization specifies a separate category for AML with 11q23+/ MLL+. This notion has been supported recently by biologic studies; micro array analyses have shown that MLL+ acute leukemias (ALs) have a peculiar gene-profiling pattern that distinguishes them from all other ALs and that MLL+ leukemic blasts resemble very immature progenitor cells [4]. Extensive cytogenetic and

molecular studies have shown that 11q23/MLL is a highly promiscuous locus: more than 50 chromosomal loci have been described as 11q23 chromosome partners.

11q23+/MLL+ is described in 3-4% of AML cases [1] and is more frequent in younger subjects with de novo (5-7%) AML or with t-AML (10-15%) evolving after chemotherapy. The majority of 11q23+/MLL+ AML cases have monocytoid differentiation features and are classified in the M4 and M5 leukemia FAB subtypes. In our case, it was AML M0 subtype with 11 q deletion which is an extremely rare finding. 11q23 in AML with minimal differentiation is very rare and hence reported. In one study of 217 consecutive adult AML cases, 40 were AML M0 and only two of these cases showed 11q23 abnormality [1].

The clinical outcome of 11q23+/MLL+ AML is more heterogeneous. The Medical Research Council and the Southwest Oncology Group classify the risk for patients with AML with t (9,11) as intermediate and poor respectively. Our case of AML M0 with 11 q deletion died within eight days of starting therapy. This shows the poor prognosis in AML cases having 11q23 aberrations as enumerated in various studies [7,8]. To conclude, AML-M0 is a diagnostic and therapeutic challenge particularly when associated with 11q23 aberration.

Conflicts of Interest

None identified

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