CASE REPORT

M3-Variant of Acute Promyelocytic Leukaemia A Case Report in a Malay Boy

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Summary

The variant form of acute promyelocytic leukaemia (AML-M3) possesses its own characteristic morphology, although usually a few of the cells may have cytoplasmic features of typical AML-M3. In contrast to typical AML-M3, this M3-variant form commonly presents with hyperleucocytosis. As in typical AML-M3, disseminated intravascular coagulopathy (DIVC) occurs in the M3-variant.

A boy with this morphological variant of AML-M3 is described. Uncharacteristically, his presenting white blood count was low, and DIVC was present before treatment was started. Six days into intensive chemotherapy his coagulopathy worsened and he subsequently died of intracranial haemorrhage. An alternative approach to the treatment of AML-M3, with the use of retinoids, is discussed.

Key Words: AML-M3, M3-variant, Disseminated intravascular coagulation (DIVC), All-trans retinoic acid

Introduction

The French - American - British Cooperative Group described the striking cytomorphologic features of the M3-variant (AML-M3V) of acute myeloblastic leukaemia about two decades ago. The nucleus of almost every cell in the peripheral blood is bilobed, multilobed or reniform. Most of these cells are devoid of heavy granulation which is the characteristic pattern of typical AML-M3. In fact they may contain only a few fine azurophilic granules, but in addition a few cells with all the cytoplasmic features of typical AML-M3 are usually present. In the bone marrow, the cells exhibit morphologic features which are closer to typical AML-M3. This M3-variant is rare; in 1981 Rajnoldi *et al* reported only 2% of their leukaemia patients suffered from this M3-variant[1].

The chromosomal translocation t (15;17) is associated with cases of both typical AML-M3 and the M3-variant. This balanced translocation is exclusively associated with these conditions and is often the only visible karyotypic aberration present. It has become the definitive marker of the disease.

Case Report

A five-year-old Malay boy was admitted to Hospital Universiti Sains Malaysia, Kelantan, on the 17th of August 1991 with a history of spontaneous bruising over the lower limbs and gum bleeding of one week duration. On the day of admission, he had continuous uncontrolled bleeding from the site of a molar tooth extraction done earlier on

the same day. There was no bleeding elsewhere or bone pain.

Examination revealed a relatively well boy who was afebrile but tachycardic (pulse rate 150/min). His right buccal mucosa was swollen and there was still active bleeding from the socket of the extracted tooth. The rest of the examination was normal; there was no pallor, lymphadenopathy or organomegaly.

Blood tests showed a haemoglobin of 7.8 g/dl, a total white blood cell count of $3x10^9$/L and a platelet count of $65x10^9$/L. There were no blasts seen in the peripheral blood film. His coagulation profile was as follows: prothrombin time (PT) 20 secs (INR 1.4), partial thromboplastin time (PTT) 49 sec (control 32.4 sec), bleeding time 24 min, fibrinogen degradation products (FDP) 160ng/ml.

The bleeding stopped after infusion of platelets and fresh frozen plasma. Bone marrow investigation was done, but no definitive diagnosis was arrived at and the patient was sent on home leave.

However the patient did not come back at the appointed time but returned only two weeks later with fever (38°C) and recurrence of bleeding gums. This time the right lobe of the liver was palpable 2 cm below the subcostal margin. Blasts (10%) were seen in the peripheral blood. Some of the blasts contained a few azurophilic granules, and occasional Auer rods were seen. A number of abnormal promyelocytes were present with bilobed nuclei, prominent golgi area but few cytoplasmic granules. The bone marrow aspiration repeated this time was densely hypercellular with reduced megakaryocytes. The majority of the cells were abnormal promyelocytes with bilobed, 'folded' or occasionally unilobed nuclei. The cytoplasm contained only a few azurophilic granules. An occasional Auer rod was seen, but no 'faggot cells'. No cytochemistry was performed on the bone marrow as too few slides were made for this to be carried out. Cytogenetic studies were not available at this hospital then and so were not performed.

The patient was subsequently started on induction chemotherapy consisting of intravenous (IV) cytosine arabinoside (Ara-C) at 100 mg/m^2 body surface area on day 1 and day 2, then 200 mg/m^2 on days 3 to 8; IV daunorubicin at 60 mg/m^2 on days 3 to 5 and IV VP16 at 150 mg/m^2 on days 6 to 8. On starting treatment, his PT, PTT and FDP were normal. However, two days after starting induction chemotherapy, the patient developed new petechiae on the face. Platelets were transfused to maintain the platelet count at more than $20x10^9$/L throughout the induction period and fresh frozen plasma was also given intermittently.

On day 6 of treatment, the patient was noted to be restless and behaving abnormally. He had three episodes of blood-stained vomiting and several generalised convulsions lasting for several seconds. Blood investigations showed disappearence of blasts, but evidence of disseminated intravascular coagulation. At that time a cerebral CT scan could not be done to confirm intracranial bleed. He became comatose with a decorticate posture and died on day 8 of induction chemotherapy.

Discussion

The morphology of promyelocytes in this patient's bone marrow with their bilobed nuclei, relative paucity of cytoplasmic granules and Auer rods is characteristic of AML-M3 variant. Typical AML-M3 cells would have had heavy granulation and, in many cases, bundles of Auer rods called 'faggot' cells. Unfortunately electron microscopic facilities were not available to demonstrate microgranules which are characteristically found in the cytoplasm of the M3-variant[2]. We were also unable to do cytogenetic studies on this patient, which would have been expected to show t (15;17) which has been associated with both typical AML-M3 as well as the M3-variant.

Our patient was unusual for the M3-variant in not presenting with hyperleucocytosis. In fact, he had a low peripheral white cell count which is the usual finding in typical M3-AML. In this, our patient resembles the cases described by Golomb *et al*[2].

Our patient had low grade DIVC on presentation, and this worsened during the early days of induction chemotherapy and led to a fatal outcome. DIVC, initiated by the release of procoagulant factors on

starting treatment, is a well known phenomenon in both typical AML-M3 and the M3-variant of AML. However hyperleucocytosis, usually found with M3-variant, seems to constitute an additional risk factor for DIVC in comparison to typical AML-M3[1]. Therapy with heparin has been recommended by some workers[1] but not by others. Moreover routine heparinisation is not included in the protocol (BFM 83) we used for this patient. Starting chemotherapy at lower doses may prevent early deaths due to bleeding, however, it is still not possible to define the best form and dosage of chemotherapy. It is agreed that the measures that are considered essential in the management of typical AML-M3, are equally essential in the management of the variant form. In particular the coagulation parameters should be monitored carefully in the first few days of chemotherapy.

A recent development in the management of AML-M3 is the use of retinoids which can modulate cell growth and cause terminal differentiation of the malignant promyelocytes by their action on a specific retinoic acid receptor[3]. Clinical trials by Warrell *et al*[3] have shown that all-trans retinoic acid (ATRA) is the best of the retinoids for the treatment of AML-M3. Using this agent, DIVC rapidly disappears and complete remission can usually be obtained.

Thus all-trans retinoic acid is now considered to be the best initial therapy for both typical and variant AML-M3. By the use of this differentiation therapy, the severe coagulopathy associated with aggressive chemotherapy as exemplified by our patient will usually be avoided. However after remission is achieved, consolidation with chemotherapy or bone marrow transplantation is still required[3].

References

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