Case Report

Acute Promyelocytic Leukemia: Microgranular Variant - M3v

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Acute myeloid leukemia (AML) is characterized by a differentiation block leading to accumulation of immature cells[1].

Among AML, acute promyelocytic leukemia (APL) represents a distinct subtype which accounts for 7% of all the FAB variants in adults and 9% in childrens[2]).A high hemorrhagic risk and a complete response to the differentiative agent all-trans-retinoic acid (ATRA) are the main clinical features of acute promyelocytic leukemia. Two main subtypes of APL have been recognized, the common hypergranular leukopenic form –M3 and a microgranular hyperleukocytic variant- M3v[3].We report a case of microgranular variant . Review of literature is also presented.

Case Report :

A fifteen years male presented in medical emergency with complaint of fever for last three months.Fever was intermittent ,sometimes highgrade with no associated features.Patient had sorethroat and bruising at the injection sites(received froma G.P.)for last five days.On general physical examination pallor was positive.One left supraclavicular (1.5cm) and one right submandibular(1cm) lymphnodes were enlarged. Systemic examination was unremarkable .Labortory investigations revealed hemoglobin level of 5.5 gm/dl and a total leucocyte count of 14600/ul,82 % of which were blasts.Platelet count was 40,000/cu mm.Bone marrow aspiration was carried out and revealed hyperplastic smears and fragments. Erythropoiesis and graulopoiesis were hypoplastic while megkaryocytes were reduced.There was infilteration of bone marrow with blast cells which constituted more than 70% of the nucleated marrow cells.These cells had oval , convulated ,cleaved and reniform nuclei. Some (20%) of the blast cells showed fine granules while others were agranular.Sudan Black staining was strongly positive in all of the blast cells. Patient was diagnosed as a case of ACUTE PROMYELOCYTIC LEUKEMIA AML-M3-V(microgranular variant).

Discussion

The diagnosis of acute leukemia is established in most cases by bone marrow aspirate that demonstrates at least 30% blast cells[4]. FAB classification has been the basis for the diagnosis in AML since 1976[5]. The antigen expression and analysis for numerical or structural chromosomal abnormalities of leukemic cells are now feasible . Karyotypic analysis is of prognostic importance and should be performed on all diagnostic specimens of bone marrow aspirate. Immunophenotypic analysis may be useful to confirm the disease classification in selected cases[4].The estimated incidence of acute promyelocytic leukemia (APL) is approximately 6 cases per 10 million people per year with no apparent differences between sexes[6]. The age of APL cases is younger than that of other acute myeloid leukemias[6,7]. APL may be recognized by different cytological pictures: (i) Hypergranular APL, the most typical form, showing promyelocytes with cytoplasm packed with granules. Most of the primary granules may be incorporated into Auer rods, sometimes stacked in bundles. (ii) Microgranular APL(M3V), characterized by fine dust-like granulation in the cytoplasm; some promyelocytes may even appear agranular by light microscopy. Most of the cells show bilobed or folded nuclei, a picture which may simulate that of acute myelomonocytic leukemia (iii) APL characterized by cells with high N/C ratio, and strongly basophilic cytoplasm with either sparse or no granules[8]. The variant form of acute promyelocytic leukaemia (AML-M3V) 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[9]. In M3v, the absolute blast cell count is significantly higher ,relates inversly with the propability of remission and early hemorrhagic deaths are more frequent[2] .As in typical AML-M3 disseminated intravascular coagulopathy is present in the M3-variant[9].

Acute promyelocytic leukaemia arises following a reciprocal translocation $t^{15;17}$ that fuses PML (promyelocytic myleoid leukemia)gene on chromosome 15 with RARA (retinoic acid receptor alpha)gene on chromosome 17.This translocation is present both in typical AML M3[10,11,12,13,14,15,19] and M3v[12]. The PML-RARA fusion protein targets and disrupts nuclear multiprotein complexes called PODs, ND10 or NBs, a process which is associated with a block in myeloid differentiation leading to APL[10]. Inactivation of the p53 and retinoblastoma (Rb) tumor suppressor genes is also associated with the pathogenesis of leukemia through effects on the cell cycle, and manipulation of these genes can affect differentiation of AML cells[1]. Among the human malignancies that respond to differentiation therapy ,(14)acute promyelocytic leukemia is the first example where complete remission (CR) can be achieved in up to

90% of patients by using a differentiation inducer, all-trans retinoic acid (ATRA)[15]. Remission induction consists of a standard protocol with 3 days daunorubicin and 7 days of cytosine arabinoside followed by one course of consolidation treatment. Post consolidation treatment could be either standard maintenance, intensive consolidation courses, autologous or allogeneic transplantation, according to the guidelines of the treatment protocols[16]. Clinical trials have demonstrated that ATRA followed by or combined with conventional chemotherapy may be more beneficial than chemotherapy alone for inducing complete remission [17]. ATRA is an active metabolite of vitamin A that differentiates the malignant cell clone, corrects the coagulopathy[18] and induces complete remission in the vast majority of patients with Acute promyelocytic leukemia[19]. With differentiation therapy, when successful the leukemic cell mass is reduced to allow restoration of normal hematopoiesis[1]. Currently available clinical results show that the combination CR rate in newly diagnosed APL,increase from about 80% (with chemotherapy alone) to more than 90%, and M3V patients and those presenting with high leukocyte counts seem to benefit particularly from this combined therapy. ATRA followed by chemotherapy also reduces the incidence of relapse (particularly of early relapse) as compared to chemotherapy alone. However, treatment with ATRA is still complicated by the risk of hyperleukocytosis and potentially fatal ATRA syndrome in 5-25% of the patients[20, 21], characterized by fever, dyspnea,hypotension pleural and pericardial effusios[22]. Acute promyelocytic leukemia (APL) should be taken as a medical emergency which requires rapid diagnosis and tailored treatment[11] and M3v must be recognized promptly because of the very high early hemorrhagic risk[3] .The hemorrhagic complications have been attributed to a combination of intravascular thrombin generation, excessive fibrinolysis and/or proteolytic activities released from blast cells[23]. APL persues a rapidly fatal course if untreated. With appropriate antileukemic therapy, CR can be achieved in the majority of patients and the patients show a longer duration of CR when compared to other types of AML:APL having a better response to chemotherapy , as well as higher cure rates than other subtypes[7].

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