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Case Study

Acute Promyelocytic Leukemia Revealed By Fatal Cerebral Hemorrhage With Disseminated Intravascular Coagulation (DIC) And Pancytopenia

Idrissi Kaitouni Samia¹, Ahroui Yassine², Abjaw Zakaria³, Lamhani Adil¹, Ribahi Houssam¹, Hachimi Abdelhamid³, Haouach Khalil², Eladib Ghassan¹

¹Obstetric Intensive Care Unit – Marrakech’s Mohamed VI University Hospital.

²Biological Hematology Service – Marrakech’s Mohamed VI University Hospital.

³Medical Intensive Care Unit– Marrakech’s Mohamed VI University Hospital.

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ABSTRACT

The diagnosis of acute promyelocytic leukemia (APL) or acute myeloid leukemia type 3 (AML3) according to the FAB classification, is by its early severity and its specific management, one of the rare real emergencies in hematology. Neurological involvement is a frequent complication of leukemia. However, it is very rare to discover the disease through this this complication. We report the case of a 33-year-old woman who presented with a fatal brain hemorrhage revealing acute promyelocytic leukemia (APL).

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Corresponding Author: *Dr Idrissi Kaitouni Samia, Obstetric Intensive Care Unit – Marrakech’s Mohamed VI University Hospital.*

INTRODUCTION

Acute promyelocytic leukemia (APL) is a rare disease. It is an aggressive form of acute myeloid leukemia (AML) of which it accounts for 10%. The diagnosis is based above all on the cytological recognition of abnormal cells in the blood in favor of the diagnosis [1].

As the APL does not have any symptoms of its own, it can be considered as another common disease. It usually occurs in middle-aged adults as paleness, shortness of breath, fatigue, frequent and persistent infections. An easy onset of abnormal bruising and bleeding is commonly seen. Neurological involvement is a fairly common complication of APL, but this is rarely revealing it [2,3]

We report through the case of a young 33 years old woman who had fatal brain hemorrhage which revealed acute promyelocytic leukemia (APL).

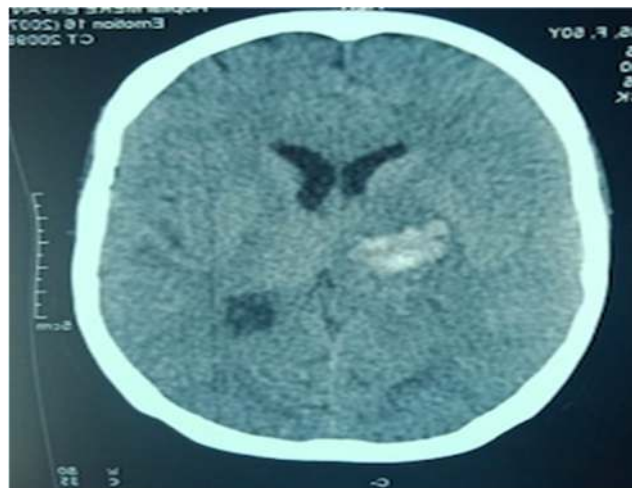
OBSERVATION:

A 33-year-old woman was admitted to the emergency department of Mohammed VI Hospital in Marrakesh following the sudden onset of consciousness disorders, left

hemiparesis, hematemesis and melena. This patient, with no notable medical history, had been complaining for two weeks of diffuse abdominal pain with minimal menometrorrhagia. Cerebral CT scan showed the presence of multiple cerebral hematomas; including a large one in the right capsulothalamic zone (Figure 1).

The biological assessment revealed pancytopenia with anemia of 2.9 g / dl, leucopenia of 2300 and thrombocytopenia of 14000 / mm³. The haemostasis assessment was suggestive of dissected intravascular coagulation (DIC) marked by a 50% decrease in TP. Fibrinogen was low at 0.84 g / l. Fibrin degradation products and D-Dimer dosages were not performed. Spinal smearing revealed heterogeneous infiltration of monocytes cells (32%), promyelocytic cells (with butterfly wing nucleus) and myeloblastic cells, MPO positive, indicating a variant AML3 according to the classification of FAB. The patient died overnight at the medical resuscitation department following her cerebral hemorrhage.

Figure 1: cerebral CT without injection showing the presence of a large capsulothalamic hematoma



DISCUSSION

Acute leukemias (AL) are a group of malignant haematological disorders characterized by clonal expulsion of precursors of blood cells blocked at early stages of their differentiation, the blasts. Despite significant progress in diagnosis and the understanding of their

pathogenesis and treatment, mortality from acute leukaemias remains high [4,5].

There are two main types: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Acute myeloblastic leukemia is a heterogeneous group of variable entity from a clinical, biological, molecular and prognostic

point of view [6]. Among the AMLs, there is an acute promyelocytic leukemia (APL) called variant M3 in the international FAB classification (The French–American–British). It is an aggressive form of acute myeloid leukemia (AML) and accounts for approximately 10% of cases [7,8]. It is characterized by an interruption of leukocyte differentiation at the promyelocytic stage, as a consequence of a chromosomal translocation t (15; 17) in myeloid cells. This translocation leads to a fusion of the RARA (retinoic acid receptor alpha) gene and has a direct impact on the treatment. APL are treated differently from AML[9]. The prognosis of APL following treatment is favorable, with a complete remission rate of more than 90% with overall survival at 2 years > 90%. It is the most curable type of leukemia [10].

APL is a disease that can occur at any age, but only 25% of cases are diagnosed before age 25. It is especially after 40 years that the frequency of the disease increases. The diagnosis of APL is based mainly on laboratory results showing pancytopenia and bone marrow examination revealing hypergranular promyelocytic cells. Immunophenotyping of promyelocytic cells is positive for CD33, CD13, CD64, CD117, CD123 and MPO, and negative for DR, CD34, CD15 and CD65. The diagnosis is confirmed by molecular examination (RT-PCR), anti-PML antibody treatment, and cytogenetic or FISH (fluorescence in situ hybridization) analysis of PML / RARA gene fusion[11,12]. Clinically, APL is generally showed as asthenia, fever, dyspnea, and weight loss. Easy appearances of bruising or haemorrhagic diathesis (epistaxis, hematuria, bleeding gums ...) in the context of bone marrow failure are frequently observed [13]. In addition, the cerebrovascular manifestations observed in leukaemias such as cerebral infarction, cerebral hemorrhage or cerebral venous thromboses are rarer. However, APL can exceptionally show as an abrupt hemorrhagic syndrome that can be fatal [14]. This is the case of our young patient who presented a fatal brain hemorrhage revealing an APL.

APL is associated with a state of hypercoagulability and a high risk of thromboembolic complications. Hemorrhagic events account for 40 to 65% of early deaths in APLs. However, several studies have analyzed the prognostic factors of cerebral haemorrhage. They showed that a high number of white blood cells at the time of diagnosis were an important factor in predicting hemorrhagic events [15,16]. Other clinical and laboratory parameters were assessed, such as ECOG performance status, age, morphological subtype, platelet count, ethnicity, body mass index, prothrombin level, activated partial thromboplastin time, lactate dehydrogenase, d-dimer, creatinine and fibrinogen levels. These parameters appear to be related to morbidity or mortality due to haemorrhage. Unfortunately, most of these assessments were based on a small sample of patients and the results were sometimes contradictory [17].

Cerebrovascular manifestations are mainly related to disseminated intravascular coagulation (DIC), which is that APL cells are themselves responsible for bleeding. DIC is related to an overall activation of coagulation leading to intravascular thrombus formation, platelet consumption and clotting factors especially Factor V, followed by secondary fibrinolysis [18].

DIC can be presented in two forms: Chronic DICs that evolve slowly (for weeks or months) and mainly cause venous thromboembolic events; acute DICs that evolve rapidly (in a few hours or days) and mainly induce hemorrhagic events. The frequency of DIC in patients with AML3 is higher compared to other AML, which explains the high rate of cerebrovascular manifestations in AML3 [19].

Therapeutically, the advent of a new approach with all-trans-retinoic acid (ATRA) has improved overall survival and significantly reduced bleeding-related mortality. By combination, treatment of the differentiating agent all-trans retinoic acid (ATRA) and cytotoxic chemotherapy, can be achieved in over 70% of patients. Recently, arsenic trioxide

(ATO) has emerged to be the most active single agent in the treatment of APL [20].

Conclusion:

The severity of acute promyelocytic leukemia lies in the appearance of a disseminated intravascular coagulation table (DIC) with a significant risk of rapid mortality by haemorrhage. Prevention and management of hemostatic abnormalities have so far failed and remain a challenge to achieve a higher cure rate for this disease. However, it is the AML that has the best prognosis whatever the age of the patient, if a rapid and appropriate care is initiated.

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