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RESEARCH ARTICLE

UNUSUAL REVELATION OF ACUTE PROMYELOCYTIC LEUKEMIA BY CEREBRAL SINUS VENOUS THROMBOSIS

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ABSTRACT

Cerebral venous thromboembolism is a rare cerebrovascular disorder reported in acute promyelocytic leukemia, witch is more known for bleeding complications as the leading cause of early mortality. We report a case of 28 years old Moroccan woman, diagnosed with cerebral venous thrombosis as an initial presentation of acute promyelocytic leukemia. As soon as the diagnostic was made, treatment by all trans retinoic acid combined to conventional chemotherapy concomitant to systemic anticoagulation were started. This combination of treatment was sufficient to obtain complete remission and led to a complete disappearance of the thrombosis as well as the neurological signs without squeal. This case highlights the importance of a rigorous and complete investigation that some thromboembolic events call for.

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INTRODUCTION

Promyelocytic acute leukemia (APL) accounts for 10 to 15% of acute myeloid leukemia (AML). The cytogenetic anomaly at the origin of this pathology is a reciprocal and specific translation between chromosomes 15 and 17, responsible for the fusion of the PML gene with the truncated alpha retinoic receptor (RAR-alpha) gene. This anomaly is required to confirm the diagnosis according to the LAM classification of the World Health Organization (Sanz, 2009). This chromosomal rearrangement results in the synthesis of an abnormal retinoic acid receptor that blocks the differentiation of promyelocytes. Clinically, it manifests as a diffuse and threatening hemorrhagic syndrome associated with exaggerated fibrinolysis induced by pathological promyelocytes expressing annexin II on their surface (Lo-Coco, 2013). In the absence of rapid and adequate therapeutic management, the natural evolution of this homeopathy is fatal mainly because of hemorrhagic complications, however with the advent of a differentiating agent, the all trans retinoic acid (ATRA) and of arsenic trioxide (ATO), it has become the most curable acute myeloid leukemia with an overall survival without relapse at 4 years of 77% and this due to the concomitant action of conventional chemotherapy and ATRA (Lehmann, 2011). However, even with an adequate and rapid treatment, the immediate vital prognosis can be engaged since so far 5 to 10%, until 31% of patients in the Swedish registry die to hemorrhagic complications and coagulation disorders secondary to abnormally high coagulant activity, hence the need for transfusion support and regular monitoring of coagulopathy (Breen *et al*., 2005). We report the case of an atypical and rare presentation of a LAP revealed by a cerebral venous thrombosis and will discuss its clinical and therapeutic aspects, while underlining the interest on the one hand to start a specific treatment by ATRA as soon as the LAP diagnosis is suspected, and secondly the establishment of anticoagulant therapy with the added risk of hemorrhages on an already existing coagulopathy site related to the disease.

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Case report: We report the case of a 28-year-old woman with one child and no particular pathological history, including no notion of personal or familial thromboembolic pathology, abortion or fetal loss in utero. The patient has never used oral contraceptives. The illness begun with the sudden onset of a syndrome of intracranial hypertension made of headache, incoercible jet vomiting and decreased visual acuity. The clinical examination found a conscious patient, pale, well oriented with a general condition, without signs of external bleeding. The ophthalmologic examination showed a clear decrease in visual acuity, the patient only counted the fingers in both eyes, and had bilateral semi-mydriasis.

Fundus examination revealed papillary edema of bilateral stasis and peri-vascular retinal hemorrhages. A CT scan with contrast injection was performed but did not find an intracranial expansive process or hemorrhage, however, the presence of the sign of the empty delta was noted. This anomaly was suggestive of cerebral thrombophlebitis, which was confirmed by magnetic resonance imaging (MRI), which found the presence of a thrombus involving the upper and the right lateral sinus and the MRI angio sequence showed that the flow was significantly reduced in the posterior part of the upper lateral sinus and in the lateral right sinus. The biological exam was performed, the blood count cell showed pancytopenia without peripheral blasts with white blood cell count at 2,9 G / L with 0.12 G / L neutrophils, anemia at 66 g / L and thrombocytopenia at 34 G / L. The bone marrow aspirate found an invasion consisting of 95% hyper granular blasts with the presence of Auer rods in fagots and concluded with acute promyelocytic leukemia (APL), corresponding to acute myeloid leukemia type 3 of the French-American Britishclassification (FAB). The conventional karyotype showed the presence of translocation between chromosomes 15 and 17 on the 20 mitoses examined. We did not use either immunophenotyping or molecular biology since the diagnosis of standard risk APL was obvious. The haemostasis assessment was performed daily and did not reveal any biological signs of disseminated intravascular coagulation (DIC). The levels of factors II, V, VII and X were normal. The rate of D-Dimer was high and the research of thrombophilia was negative, the research included C and S protein, antithrombin, and protein C resistance, the circulating anticoagulant testing was also negative.

Our therapeutic management consisted of an emergency hospitalization with initiation of continuous anticoagulant treatment with heparin at a curative dose of 500 IU / kg / day. At the same time, we had started All Trans Retinoic Acid (ATRA) at 45 mg / m² / d. Conventional chemotherapy corresponding to the APL 2000 protocol - revised in 2004 - was instituted on the 5th day of the ATRA. The course of chemotherapy was marked by a rapid decrease in signs of intracranial hypertension in a few days. On the other hand, visual clinical manifestations had evolved more slowly. Visual acuity remained stable while papillary edema was completely resorbed. After one month of anticoagulant treatment and chemotherapy, medullary remission was obtained and the MRI control demonstrated the disappearance of thrombosis and the normalization of the flow. Heparin therapy was discontinued and the patient completed her chemotherapy and maintenance treatment. Currently, with a follow-up of 55 months, the patient is in medullary and molecular remission maintained and recovered an almost normal vision with correction.

DISCUSSION

In general, APL is manifested by a diffuse and threatening hemorrhagic syndrome associated with exaggerated fibrinolysis induced by pathological promyelocytes expressing annexin II on their surface (Lo-Coco, 2013). Their prognosis is better than all other leukemia because of the concomitant action of conventional chemotherapy and a differentiating agent ATRA (Lo-Coco, 2013). In the absence of rapid and adequate therapeutic management, the natural evolution of this disease is fatal mainly because of the risk of hemorrhage. The pathogenesis of coagulopathy characteristic of APL is not yet clearly elucidated, initially attributed to the CIVD, recent publications have demonstrated complex interactions between coagulation activation and hyper-fibrinolysis considerably different from the CIVD (Trottier-Tellier, 2014). Regarding our case, the occurrence of venous thrombosis of the cerebral sinuses revealing a APL is both special and rare. To date and to our knowledge, 7 cases of APL associated with venous thrombosis of the cerebral sinuses have been reported in the literature, of which only 2 at diagnosis. In the other five cases, the thrombosis occurred either after treatment or at the end of it, several hypotheses about the role of ATRA and chemotherapy on the genesis of thrombosis were issued but not proven given the low number of reported cases (Rashidi, 2013). The incidence of venous thrombosis at diagnosis in AML varies between 2 and 3.3%, that of APL is the same in some series, higher in others and reaches 6.5% of all acute leukemia. whether ATRA treatment is started or not (7,8). In multivariate analysis, the potential risk factors for venous thrombosis (VT) during AML are 1.sex; women have 40% increased risk of developing VT without an apparent explanation, 2. the presence of at least two chronic comorbidities and 3.the establishment of a central venous catheter. On the other hand, the APL would not be a risk factor for the onset of VT (Ku, 2009).

However, the risk factors for VT associated with APL are the presence of the FLT3-ITD mutation, the expression of the CD2 differentiation cluster in immunophenotyping and hyperleucocytosis (Breccia *et al*., 2007). These APL-related VT are thought to be secondary to the excessive expression of tissue factor, the main activator of coagulation, present in the micro vesicles of leukemic blasts, as well as the exaggeration of the expression of the procoagulant cancer factor (PC), which is more specific to tumor cells and the production of thrombogenic cytokines by abnormal promyelocytes (Breccia *et al*., 2007). The specificity of our report is the particular localization of the thrombosis at the cerebral sinuses and revealing the APL, and on the other hand the APL which is not a usual etiology of the cerebral thrombosis, we underline by this observation the importance of a rigorous clinical examination and specialized investigations necessary for the diagnosis of abnormally located cerebral palsy in a young 28-year-old patient without risk factors for the occurrence of thromboembolic disease, as well as the speed of immediate management of which depends on the vital prognosis. In this context, the most important pathologies to look for are solid tumors, hematological malignancies, vasculitis, thrombophilia but also the antiphospholipid syndrome (Falanga, 2012).

Conclusion

To date, there is no clear and validated consensus by all regarding the prevention or treatment of these thrombosis. Thromboprophylaxis is believed to be effective in the prevention of venous thrombosis in acute leukemia patients, particularly during APL, but is not yet validated. The use of new anticoagulant agents should be studied to determine their place in the management of these leukemia.

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