IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Fatal cerebral hemorrhage revealing acute lymphoblastic leukemia with leukostasis

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SUMMARY

Neurological involvement is frequent in leukemia but is rarely the inaugural event. We report the case of a 15-year-old boy whose acute lymphoblastic leukemia was revealed by fatal cerebral hemorrhage associated with sepsis secondary to lung infection. Intracerebral hemorrhage remains a cause of death in hematologic malignancies. The patient presented with thrombocytopenia (24,000/mm3), leucostasis and hypofibrinogemia (1.10 g/L). Despite maximal medical and surgical treatment (platelets and fresh-frozen plasma transfusions, red blood cells transfusion, and craniotomy discharge), the patient died. The risk of death is high, and surgical treatment has not proven superior to medical therapy in terms of mortality rates and 6-month survival. Further studies are needed to define consensus guidelines for coagulation disorders induced by ALL and also to define the specific management in cases of ICH in childhood hematological malignancies.

Keywords: acute lymphoblastic leukemia, Intracerebral hemorrhage, treatment, prevention.

INTRODUCTION

Acute leukemia (AL) can frequently be complicated by neurological damage, but it is rare that this is the initial mode of presentation. We report here the case of a 15-year-old adolescent who presented a fatal intracerebral hemorrhage (HIC) revealing an acute lymphoblastic leukemia (AML) type B. ALL represents 80% of leukemias. It is not only the most common childhood leukemia but also the most common childhood cancer. It represents 31% of childhood cancers between 2 and 10 years old. The frequency of this disease varies by country. In France the incidence is 3.4 cases per 100,000 inhabitants for children under 15 years of age. There are approximately 400 new cases per year in France. The lowest incidence of the disease is observed in sub-Saharan Africa (1.18 per 100,000 inhabitants) and the highest is observed in Hispanic populations (5 per 100,000 inhabitants). The peak frequency is between 2 and 5 years and the sex ratio is 1 (boys and girls are affected in the same way) [1].

CASE REPORT

A 15-year-old teenager suffered a brutal coma on 02/25/2020. This patient, with no notable medical history, had been complaining for a few weeks of asthenia. On clinical examination, the patient is febrile, he had respiratory distress, with desaturation under oxygen 4L / min, he had a Glasgow score of 4/15, right flaccid hemiplegia, left areactive mydriasis, corneal reflexes weak. Vertical oculo-cephalic reflexes were absent, and horizontal ones preserved. The rest of the clinical examination was in favor of tracheobronchial congestion, epistaxis and spontaneous gingivorrhagia. The patient intubated and ventilated and a velopalatine hematoma was discovered within laryngoscopy, the cerebral scanner without injection showed a subarachnoid hemorrhage with a fronto-parietal left parenchymal hematoma measuring 52 mm × 72 mm in the axial plane with Cerebral ventricle hemorrhage of the left occipital horn , a mass effect on homolateral LV and on the midline which is deflected to the right with the start of subfalcine herniation (Fig. 1).

Probably infectious pneumonia was revealed on the chest scanner in the form alveolar condensation syndrome predominant at the right base. The patient was taken to intensive care where brain relaxation measures were undertaken. The biological assessment revealed a major leukocytosis at 420.103 / µL, a hemoglobin at 7.4 g / dL and a thrombocytopenia at 24.103 / µL. The hemostasis assessment raised suspicion of disseminated intravascular coagulation (DIC) marked by a reduction in PT to 50% and a moderate factor V deficit lowered to 40%. The fibrinogen was lowered to 1.10 g / L. The PDF and D-Dimers dosages were not performed.

LDH was increased to 1800 IU / L, CRP was 200 mg / l, and procalcitonin returned to 3 ng / ml. Aerobic and anaerobic blood cultures were performed, thus an additional infectious assessment. The blood smear found 91% blasts. The patient was put-on broad-spectrum antibiotics with an antifungal, a transfusion of blood and platelets was carried out, before his admission to the block for decompressive craniotomy. The cerebral angiography carried out there 24h, with arterial and venous sequences, showed neither vascular malformation, nor sign of cerebral thrombophlebitis, and concludes with angioscannographic criteria of encephalic death. The patient died in the intensive care unit on the night of 02/27/2020, following his cerebral hemorrhage due to cerebral engagement. Subsequently, the negativity of blast myeloperoxidase and the performance of immunophenotyping with flow cytometry confirmed acute lymphoblastic leukemia type B (LLA.B).

DISCUSSION

We report the case of a 15-year-old adolescent admitted with cerebral parenchymal hemorrhages revealing LLA.B, complicated by major hyperleukocytosis with severe thrombocytopenia and DIC. LA is a malignant hemopathy with infiltration and proliferation in the bone marrow, blood and tissues of immature hematopoietic cells called blasts. It is a serious illness which results in death within a few weeks without treatment [2]. Two types of LA are distinguished according to the origin of the blasts: Acute Myeloid Leukemia (AML), and ALL, where there are currently two types of classification for ALL: The FAB classification and the WHO classification. The FAB classification is less used defines three types: LAL 1, LAL 2, and LAL 3. The WHO classification is the most used [3], differentiates two types of LAL: LAL B and LAL T according to cytological characteristics and cytochemicals found on blasts. In the adolescent and young adult population, the incidence of ALL crosses that of AML. In this age group, ALL is less common than in children - where it accounts for almost a third of cancers - but also than in older adults due to the progressive increase with age of incidence of Philadelphia chromosome ALL. Thus, ALL accounts for only 13% of adolescent cancers (15–19 years) and 8% of those of young adults (20–24 years). Leukemia results in a rapid deterioration in the general condition with fever and night sweats. In fact, the proliferation of blasts is accompanied by a decrease in normal hematopoietic lines which results in the appearance of spinal cord insufficiency [4], which constitutes the mode of initial revelation with anemia, thrombocytopenia and neutropenia. All tissues and organs can be affected, including the lymph nodes, spleen and liver [2]. The biological diagnoses commonly used are NFS, myelogram, osteomedullary biopsy as well as lumbar puncture (LP). The biologists will study the slides of the myelograms in order to observe the cytological aspect of the blasts. Cytochemical reactions as well as cytogenetic techniques will also be used to determine and type the ALL with which the patient is affected. According to the characteristics present on the blasts, cytologists determine the lymphoid or myeloid character of the blasts [5]. The lymphoid blasts are small or medium in size and their cytoplasm is sparse. Conversely, the myeloid blasts often contain granules or rods called the body of Auer [6]. Cytochemistry makes it possible to highlight the enzymatic activities of the blasts. The negativity of Myeloperoxidase confirms the lymphoid lineage of LA [6]. Immunophenotyping is carried out using flow cytometry which is an essential complement in order to confirm the cell line involved in ALL [7]. The cerebrovascular manifestations observed in leukemias are cerebral hemorrhage, cerebral infarction, or cerebral venous thrombosis. They are linked to three main mechanisms, secondary to hematological pathology: disseminated intravenous coagulopathy (DIC), leukostasis and infectious vasculopathy by septic embolism.

The hemorrhagic syndrome is consecutive to a central thrombocytopenia, a DIC and vascular wall disorders. Rarely, the disease can reveal itself by a brutal hemorrhagic syndrome which can be fatal, and this less frequent in the ALL than in AML. In our case the DIC was rather attached to the ALL and to the sepsis. DIC is linked to a global activation of coagulation leading to the formation of intravascular thrombi causing ischemic strokes, the consumption of platelets and coagulation factors, in particular factor V, followed by fibrinolysis secondary to origin hemorrhagic complications [8]. The clinical expression of DIC ranges from the absence of clinical manifestation (DIC at least) to localized or diffuse hemorrhagic syndrome and / or thrombosis (venous or arterial) and it comes in two forms; the acute form with abrupt hemorrhagic onset associated with high mortality reaching 70%, and the subacute or chronic form often not very symptomatic on the biological tests [8]. DIC is a common complication in ALL, LAM4, and LAM5 [9]. It is almost constantly observed during LAM3 [8]. The correction of severe hypofibrinogenemia (<0.8 g / L) should not be discussed in view of the availability of human fibrinogen, its effectiveness and the absence of toxicity. In addition, the platelet transfusion thresholds could be revised upwards (<35,000 / mm3) when there are associated coagulation disorders. Vascular wall disorders, especially present in acute leukemias contribute to massive hemorrhage and they are due to an increase in vascular permeability by infiltration of the vessel wall by blasts, an increase in viscosity linked to leukostasis, and the existence of foci of extramedullary hematopoiesis within the vascular wall [10].

Leukostasis corresponds to the manifestations of hyperleukocytic syndrome, and is defined anatomopathologically, it is characterized by the formation of leukocyte and thrombi aggregates in the microcirculation, in particular cerebral

and pulmonary. It is rarer in ALL and rather present in hyperleukocytic ALL [11]. While it is the prerogative of chronic myeloid leukemias and acute myeloblastic leukemias, it is the most frequent complication of AML, linked to a major hyperleukocytosis which is defined by a leukocyte level higher than 100.109 / L, leads to a blood hyperviscosity [11]. It is responsible for thromboses and haemorrhages due to capillary fragility. The main manifestations of leukostasis are neurological, ranging from simple headache to confusion and coma with cerebral anoxia or cerebral hemorrhage, on the other hand the pulmonary manifestations which are most often in the foreground with a high probability of occurrence of respiratory distress, life-threatening and justifying intensive surveillance in intensive care [12]. Transfusion changes the blood rheology and should be avoided initially [12]. A cytoreduction strategy must be undertaken quickly. Several teams perform cytapheresis without demonstrating efficacy on survival and despite certain toxicity. The prescription of hydroxyurea (HYDREA®) generally makes it possible to rapidly decrease leukocytosis without significantly increasing tumor lysis syndrome [13].

Infectious septic embolus vasculopathy occurs on immunocompromised terrain and is prone to infections. Those infections are present during the inaugural period, they are mainly bacterial and mainly affect the lungs (1/3 of cases), the skin, the pharynx and the perineum. The clinical diagnosis of an infection is difficult due to the lack of specificity, often present at diagnosis. Antibiotic therapy covering community germs and broad spectra based on clinical call points must be started urgently in case of feverish syndrome in these patients. Expert recommendations for febrile neutropenia can be used [14]. In the autopsy series of patients with LA, almost 50% had HIC [15]. Report an autopsy series of 14 patients with cerebrovascular manifestations in the context of an LA. [15]. Six patients presented with intracranial hypertension (IH), and among them, two presented multiple cerebral hemorrhages, without coagulopathy but with a major hyperleukocytosis with with the anatomo-pathological analysis of the cerebral parenchyma of the hemorrhagic lesions, surrounded by leukocytes. The other four cases were part of a coagulopathy, mainly a DIC without hyperleukocytosis. The cerebral haemorrhages appeared either in the form of a single hematoma or in the form of multiple and punctiform haemorrhages, associated in all cases with other extra-cerebral haemorrhagic lesions (purpura, epistaxis...). Five cases of hemorrhagic infarction by fungal embolism have also been reported in patients with agranulocytosis. The main infectious agents responsible were Candida, Aspergillus and mucormycosis.

There are therefore three radiological profiles of cerebral hemorrhages linked to the different pathophysiological mechanisms; multiple hemorrhages by leukostasis, single and massive hemorrhage by DIC or severe thrombocytopenia, hemorrhagic infarction by fungal embolism. Several studies have analyzed the prognostic factors of cerebral hemorrhages in leukemias [16]. Subarachnoid and intraparenchymal hemorrhages have a worse prognosis than subdural hematomas [17]. In our observation, the biological assessment made it possible to make the diagnosis of ALL with major leukostasis, thrombocytopenia and DIC. The neurological events associated a massive intra-parenchymal hemorrhage responsible for death. The patient presented externalized hemorrhage on arrival (spontaneous gingivorrhagia, epistaxis) which is usually seen in cases of DIC, on the one hand, and on the other hand, to major hyperleukocytosis, causing a leukostasis phenomenon responsible for multiple hemorrhages by rupture of the small vessels.

CONCLUSION

Thanks to the progress made in the understanding and therapeutic management of ALL in children, adolescents and young adults, overall survival today has reached almost 90%. Polychemotherapy adapted to risk factors allows such results, but deaths represent 5% of cases (including 1% during induction) secondary to infectious or hemorrhagic complications [18]. The occurrence of IH is an important cause of morbidity and mortality in these patients. It exceptionally constitutes a method of LAL revealing. If their medical and surgical management does not differ in any way from that of IH occurring in other contexts, their prevention consists in the rapid treatment of hemostasis disorders related to DIC, leukostasis and early and rapid treatment of infectious complications. Other studies would be necessary to define a preventive or curative protocol in the event of a coagulation disorder as well as a precise course of action to be followed in cases of IH in the pediatric or adult young population suffering from malignant hemopathies.

FIGURES

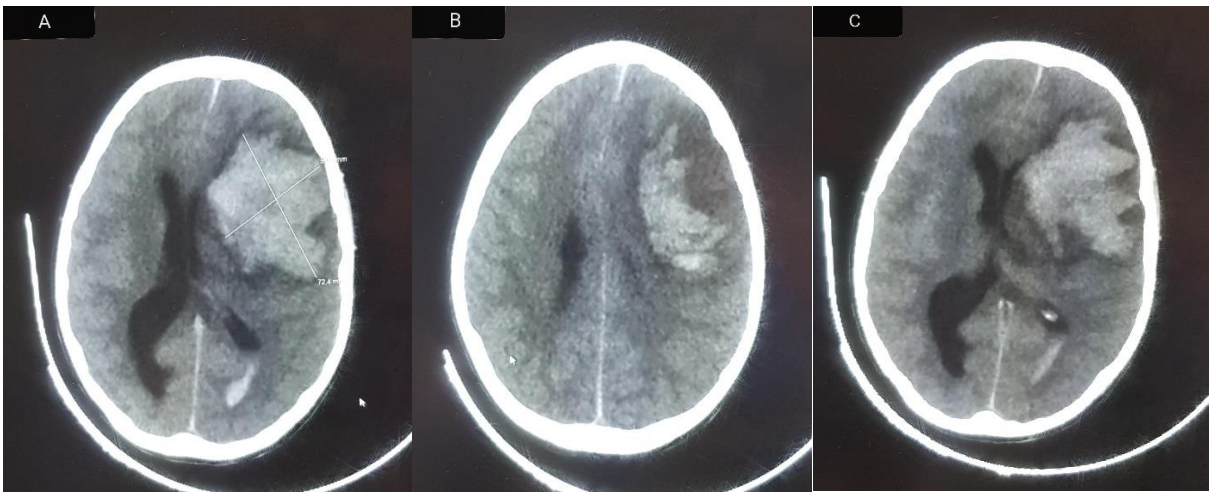

Figure 1. Cerebral scan without injection. A. Intra-parenchymal hemorrhages, and intra-ventricular hemorrhage in the occipital horn. B. Intra-parenchymal hemorrhages and perilesional edema. C. Intra-parenchymal hemorrhages, and mass effect and subfalcine herniation.

COMPETIMG INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

all the authors contributed to the realization of this article, the read and approved the final manuscript.

ACKNOWLEDGEMENTS

None

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