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(CASE REPORT)

Pulmonary and cerebral leukostasis as an unusual case in a patient with chronic leukemia in chronic phase: Case report and literature review

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Abstract

Hyperleukocytosis is defined as an absolute white blood cells count greater than 100.000cel/ml, being more common in acute myeloid leukemia (AML) than in chronic myeloid leukemia (CML). CML is the predominance of mature granulocytes, its main manifestation is hyperleukocytosis, that can increase the risk of pulmonary and cerebral leukostasis; although this event is uncommon in patients with CML in chronic phase. We present the case of a 38-year old male who presents with hyperleukocytosis that progress to hypoxemic respiratory failure and multiple intracerebral hemorrhage, treated with cytoreduction and tyrosine kinase inhibitors; without leukapheresis, with appropriate clinical evolution. Leukostasis is a high mortality complication that should be considered in patients with hyperleukocytosis who presents with neurological or respiratory distress, and constitutes a medical emergency in which treatment can't be delayed.

Keywords: Leukemia; Hyperleukocytosis; Leukostasis; Cerebral leukostasis; Pulmonary leukostasis

1. Introduction

Chronic myeloid leukemia (CML) is an asymptomatic disease, more than 30% of the patients with CML remain asymptomatic for long periods of time. CML is classified into three phases: chronic phase (CP), accelerated phase (A), and blastic crisis phase (BC) [1] (table 1). Leukostasis is a rare but severe complication, even mortal in CML, that has been associated with decreased tissue perfusion, which is often indicative of adverse prognostic features in patients with CML [2]. It is a medical emergency that is characterized by extremely elevated leukocyte count over 100.000 cell/ml, that affects the microcirculation of some organs such as lungs or brain. The pathophysiology is not cleared yet, but there are some theories, one of these theories is the hyperviscosity of the blood due to increased blast cell count that has less deformable capacity than mature cells, generating plugs in the microcirculation, reducing blood flow and leading to tissue hypoxia. Another theory is the cell interaction with the endothelium that increase products of accelerated metabolism and cytokines, promoting cell adhesion to vascular endothelium and endothelial damage. [3-4].

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Table 1 Classification phases of Chronic myeloid leukemia (CML)

CML – CP	**CML – A**	**CML - BC**
0-10% of Blasts cells in peripheral blood, bone marrow or both	10-19% of Blasts cells in peripheral blood, bone marrow or both	>20% of Blasts cells in peripheral blood, bone marrow or both
Thrombocytopenia (<100x109/L) with response to treatment	Persistent thrombocytopenia (<100x109/L) non-treatment related or without treatment response	Extramedullary proliferation
Splenomegaly and increased of leukocytes with response to treatment	Progressive splenomegaly and increased of leukocytes without response to treatment	Large foci or blast cells accumulation in bone marrow biopsy

CML-CP: Chronic myeloid leukemia chronic phase, CML-A: chronic myeloid leukemia accelerated phase, CML-BC: chronic myeloid leukemia blastic crisis phase

2. Case report

A previously healthy 38-year-old male, who performs regular physical activity, presents with a 3 months history of non-specific symptoms such as asthenia, adynamia, weight loss and myalgia. Three days before admission to a high complexity hospital in Medellín (Colombia), he also reported fever and headache. During physical examination his blood pressure was 99/59 mmHg, heart rate 109 beats per minute, respiratory rate 26 breaths per minute, temperature of 38ºC and hepatosplenomegaly. Laboratory results found 425.910/uL leukocytes, hemoglobin 9.5 g/dl, platelets count of 140.000/uL. Because of high risk of complications and ventilatory failure, he was admitted to the intensive care unit (ICU). Due to a peripheral blood cytometry with 3.73% blasts, compatible with CML-CP and added to his clinical presentation, we decided to start cytoreduction with cytarabine and hydroxyurea; also allopurinol and a single dose of rasburicase were given for the high risk of tumor lysis syndrome, as prophylaxis.

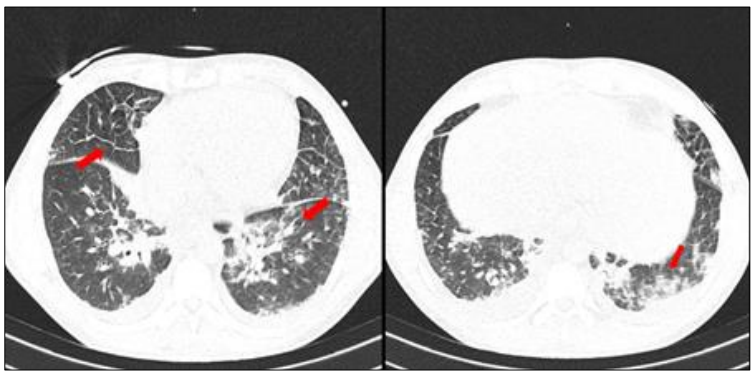

Figure 1 Chest CT image showed interlobular septal thickening, diffuse ground glass opacities, and bilateral pleural effusion

After 48 hours of medical treatment, clinical deterioration progressed to respiratory failure that forced to star non-invasive ventilatory support with high-flow nasal oxygen (HFNO). Chest CT showed progression of alveoli infiltrates and rounded subpleural lesions (figure 1); brain CT findings of multiple cortical-subcortical hemorrhagic lesions (figure 2 and 4). Coagulation test results were prothrombin time (PT), 16.6sec with 13.9sec control, international normalized ratio (INR) 1.42, activated partial thromboplastin time (PTT) 37.7sec with 30.2sec control and fibrinogen 550 mg/dl.

After HFNO support failure, orotracheal intubation with invasive mechanical ventilation was needed. Severe hypoxemia (PaO2/FiO2 ratio < 100 mmHg) despite mechanical ventilation required to start prone ventilation. Polymerase chain reaction (PCR) reported 85% BCR ABL gene, confirming CML-CP (figure 3). Sokal index and Hasford score reported intermediate to high risk, initiating management with nilotinib (second-generation tyrosine kinase inhibitor), showing appropriate cytoreduction from over 50% in leukocytes (table 2). Within days, PaO2/FiO2 ratio was over 300 mmHg, therefore pronation and neuromuscular blocking was suspended, leading to decreasing sedation/analgesia, achieving a non-agitated 0-RASS awakening and extubation on the 6th day.

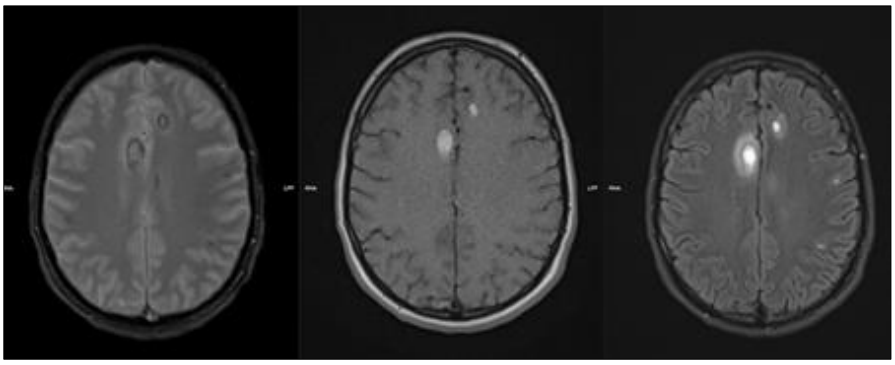

Figure 2 Intraaxial lesions of hyperdense behavior in T2 and flair sequences in the subcortical cortical region

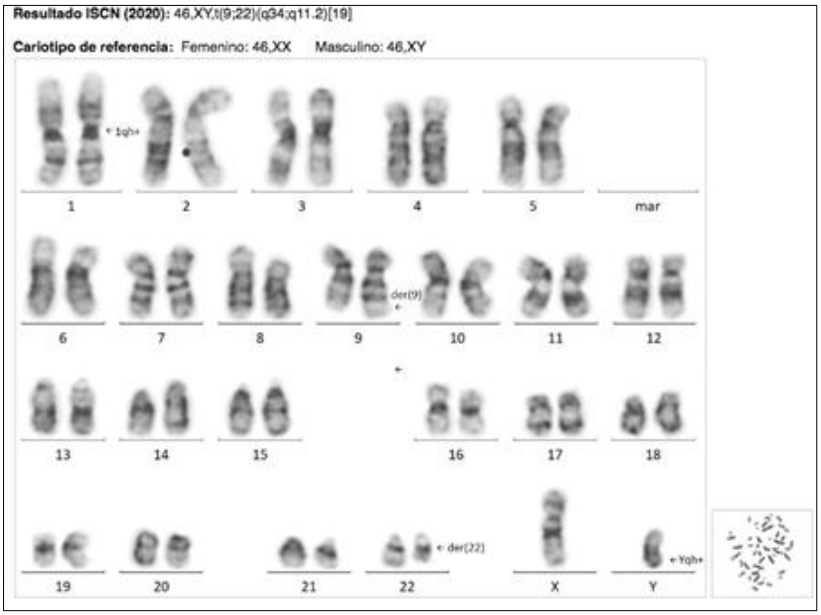

Figure 3 Karyotype. The male chromosome complements with a translocation between the long arm of chromosome 9 and the long arm of chromosome 22, increasing the length of heterochromatin of the long arm of chromosome 1 (1qh+) and the long arm of chromosome Y (yqh)

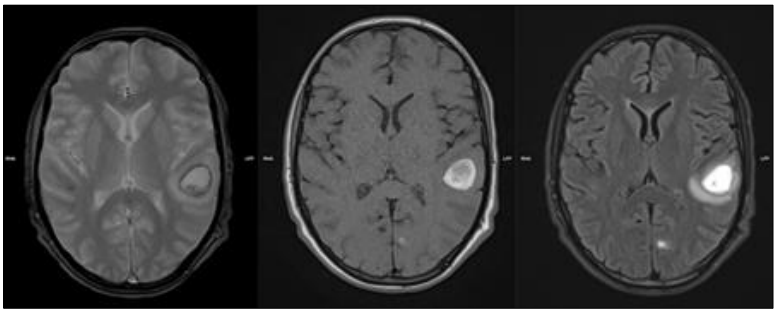

Figure 4 Bleeding at the level of the left parietal lobe

Control tomography showed a significant improvement in pulmonary lesions, although brain hemorrhages increase in size. Brain magnetic resonance imaging shows perilesional edema without midline shift. The patient had satisfactory clinical evolution, without neurological deterioration. Antibiotic therapy (piperacillin-tazobactam) was suspended due to the lack of isolation of microorganisms in cultures (blood and tracheal aspirate samples), negative respiratory film array, negative serial serum galactomannan, and no data of systemic inflammatory response. He was discharged a few

days later for outpatient follow up with oral nilotinib. Fortunately, it should be noted that this patient did not require transfusions, eventually this could worsen the hyperviscosity and lead to the clinical deterioration or slow down the recovery.

Table 2 Evolution of laboratory test throughout hospital stay

	1st ICU day	3rd ICU day	5th ICU day	8th ICU day	10th day hospitalization	12th day hospitalization
Leucocytes cels/mm3	431.740	204.930	53.530	14.770	11.120	8.710
Hemoglobin g/dl	8.5	8.1	7.7	7.3	8.6	8.7
Platelet #/uL	115.000	92.000	95.000	113.000	193.000	232.000
PaO2/FiO2 mmHg	229	123	316	317	323	386

3. Discussion

Table 3 Literature review summary of chronic myeloid leukemia (Chronic Phase) patients who developed an intracerebral hemorrhage

Author	Gender/age	Leukocyte * 10*9/l	Platelet 109/l	INR	Location of bleed	Management	Pulmonary leukostasis	Outcome
Tsai et al 2004(10)	F/12	182	229	NA	Right frontal and anterior thalamus	Hydroxyurea interferón alfa cytarabine leukapheresis	NA	Dead (9 days)
Muta et al 2010 (11)	F/46	419	288	1,22	Cerebellar	Cytarabine, imatinib	NA	Alive
Cho et al 2011(12)	M/33	186	NA	NA	Right parietal extradural	Craniotomy hydroxyurea imatinib dasatinib	NA	Alive
Kapur et al 2013 (13)	M/52	685	168	1,6	Multiple hemorrhage	Hydroxyurea nilotinib	NA	Alive
Olfa et al 2015(14)	M/26	260	291	NA	Right parietal	Manitol dexametasone	NA	Dead (12 h)
Kouzuki et al 2018 (15)	M/16	175	59	1,19	Right temporal	Hydroxyurea craniotomy	NA	Dead (9 days)
Wang et al 2020 (16)	M/45	572	218	1,19	Right frontal	Craniotomy hydroxyurea imatinib dasatinib ponatinib	NA	Alive
Takahashi et al 2021 (17)	F/14	754	172	1,42	Multiple hemorrhage	Allopurinol heparin imatinib nilotinib	NA	Dead (14 days)
Ashaf et al 2022 (18)	M/22	447	202	1,7	Right frontotemporal	Right hemicraniectomy and duraplasty imatinib	NA	Alive
Our case 2022	M/38	443	130	1,56	Multiple hemorrhage	Hydroxyurea allopurinol nilotinib	Reported	Alive

F: Female. M: Male. NA: Not Available. INR: International Normalized Ratio

Reviewing medical literature until 2022, we found 9 case reports worldwide of cerebral leukostasis in patients with CML in the chronic phase (Table 3); of these 9 cases, 3 cases were in the pediatric population and 6 in the adult population, reaching mortality of 43%. So far there are no reports of cases of combined cerebral and pulmonary leukostasis in patients with CML-CP. This is an extremely rare case of cerebral and pulmonary leukostasis in a patient with Chronic Myeloid Leukemia in chronic phase (confirmed with 3% blasts, PCR BCR ABL 85% and karyotype with positive Philadelphia chromosome).

Pulmonary leukostasis may be the major cause of death in patients with hyperleukocytosis, being more frequent in Acute Myeloid Leukemia (AML) or CML in a blast crisis. It is characterized by impaired oxygenation, tachypnea, dyspnea, and bronchoalveolar-interstitial infiltrates. Because they are no specific signs, it leads to consider differential diagnoses such as alveolar hemorrhage, pulmonary infiltration, infectious process and pulmonary thromboembolism. Cerebral leukostasis has multiple clinical presentations, from asymptomatic to coma and brain death, and in many cases cortico-subcortical hemorrhagic lesions can be observed in neuroimaging [5].

Leukostasis requires early treatment, since mortality can range from 20 to 40% after a few days (less than 7 days), due to respiratory distress and cerebral intraparenchymal hemorrhage. The combination of the pulmonary and encephalic presentation can reach mortality as high as 90% [3, 6]. The 3 bases of treatment are life support, hydration, and cytoreduction-specific cancer therapy with/without leukapheresis [7]. Leukapheresis is a strategy that has managed to reduce the number of leukocytes faster than conservative treatment, however, the impact it has to reduce complications has not been shown to be propitious [8,9].

In this case, cytoreduction therapy started early with subcutaneous cytarabine at a dose of 100 mg/day, combined with hydroxyurea with partial response. Given the high risk of tumor lysis syndrome, prophylaxis was initiated with hydration, rasburicase, and allopurinol. The patient presented clinical deterioration, only up to targeted treatment with nilotinib, given Hasford and Sokal score intermediate risk, greater cytoreduction was obtained, with improvement in oxygenation index, obtaining weaning from mechanical ventilation before 7 days. Despite demonstrated bleeding intracerebral imaging, flow-up was performed while the patient was sedated, to assess the need for advanced neuromonitoring, given the limitation that occurs to perform a neurological assessment.

4. Conclusion

In patients with chronic myeloid leukemia who present hyperleukocytosis associated with neurological and/or pulmonary symptoms, urgent brain and chest CT must be taken. Cytoreduction therapy in these cases, before diagnostic confirmation, is essential, in addition to tumor lysis syndrome prophylaxis. Patients with symptomatic leukocytosis have an excessively high mortality rate if no immediate treatment is given. In patients with brain leukostasis, conservative management with tomographic follow-up is recommended; unless due to clinical deterioration and the size of the bleeding, decompressive craniotomy and invasive neuromonitoring is required. Brain rebleeding is a very common event in these patients, therefore clinicians must be aware in case of any neurological deterioration.

Pulmonary leukostasis should be managed as hypoxemic respiratory failure, without delay in invasive airway therapy, in order to begin mechanical ventilation under protective ventilation parameters and assess the need for prone ventilation. Due to rapid recovery of oxygenation after hyperleukocytosis is controlled, early ventilatory weaning can be performed. The rapid initiation of BCR/ABL protein kinase inhibitor has decreased progression to blast crisis and therefore mortality. Management with leukapheresis is optional owing its non-superiority to conventional management in various studies; despite its effectiveness in reducing leukocyte counts, the clinical outcomes in serious studies have not been very clear. The relevance of this case is the favorable outcome, despite the high mortality rates of these two complications with two target organs, he achieved a hematological response in the first month, and he is in the outpatient recovery process with the intake of nilotinib.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to declare.

Statement of ethical approval

The ethical committee of Centro Oncológico Antioquia approves our case report and publication

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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