Acute lymphoblastic T cell leukemia restricted to the central nervous system: Case report

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ABSRTACT: Acute Lymphoblastic Leukemia (ALL) accounts for 15 to 20% cases of all leukemia in adults and less than 10% of this patients will have Central Nervous System (CNS) infiltration at diagnosis. CNS leukemia is defined as morphologic evidence of leukemic blasts in cerebrospinal fluid and, or cranial nerves palsies with or without significant neurologic dysfunction. The majority of studies show that the patient already has leukemic blasts at peripheral blood and bone marrow when recognized the CNS infiltration, or it appears few months after acute leukemia diagnosis. The rarity of this report is that bilateral facial nerve palsy occurs in less than 2% of all the facial palsy cases and is a very uncommon form of ALL presentation. Between those few patients, all had blasts at peripheral blood, bone marrow or mediastinal mass at the same time of the diagnosis. This clinical case describes a unique situation that the patient had been diagnosed with acute T-cell leukemia because of bilateral facial nerve palsy and without any other evidence of the disease. During a follow up of five years, the patient did not develop bone medullar leukemic infiltration.

Key Words: *Acute lymphoblastic leukemia; Lymphoblastic leukaemia; Lymphoblastic lymphoma.*

Acute Lymphoblastic Leukemia (ALL) is an hematological malignant disease that can involve the Central Nervous System (CNS). CNS leukemia in ALL is uncommon at diagnosis as well at the time of first relapse [1]. Around 7% of CNS infiltration occurs at diagnosis being 51% by B-cell involvement and 41% T-cell subtype [1,2]. The CNS is an immunologically privileged site that is isolated from the blood system by blood–brain and blood–CSF barriers. The cells that enter the CNS and in filter the meninges are characterized by high expression of Vascular Endothelium Growth Factor A (VEGF), that regulate the transendothelium migration through CNS microvascular endothelial cells (Munch V). After transiting CP epithelial cells and/or meningeal postcapillary venules, leukemia cells are initially localized to the leptomeninges on the surface of the brain and within the CSF. Leukemia cells then migrate into the deeper meningeal tissues surrounding vessels in the cortex and white matter (Virchow–Robin or perivascular spaces). Only late in the disease is the pial-glial membrane destroyed and leukemia cells identified within the brain parenchyma [3]. Several risk factors have been associated as a high risk situation for CNS leukemia as: younger adults, mature B-cell subtype, Philadelphia chromosome positivity. When the CNS is involved by leukemia at diagnosis, is more probable to the patients also have lymph node enlargement, mediastinal mass, or other extra-medullary localization [4]. The diagnosis assessment of this condition relies on the use of neuroradiology, Conventional Cytology (CC) and Flow Cytometry (FCM). Neuroradiology and CC have a limited sensitivity with higher rates of false negativity results. FCM has a superior result, mainly when low levels of CNS infiltrating cells are present. Neuroradiographic methods, as Computer Tomography (CT) and Magnetic Resonance Imaging (MRI), are available to evaluate a patient with suspected CNS involvement. However, the detection power of those techniques decrease when it comes to evaluation of patients with suspected leukemic meningitis [4].

Positive findings are less than 25% and even the MRI, that is more sensitive, cannot be a stand-alone detective tool. A normal MRI does not provide certainty about the absence of occult CNS disease in the course of ALL because it has an estimated 65% of false negative. Cerebral Spinal Fluid (CNF) examination associated with immunophenotyping is the most useful laboratory test in the diagnosis of ALL CNS involvement. Abnormalities includes elevated protein (50 mg/dL), decreased glucose concentration (<60 mg/dL) and increased White Blood Count (WBC), more than 5 cells/mm^3. The presence of leukemic cells in the liquor is diagnostic of CNS involvement. Flow cytometry with immunophenotyping is a valuable tool for detecting phenotypically abnormal cells representing 0.01% of events [4]. Acute leukemias are a diverse group of malignancies with a range of clinical presentations, prognoses, and preferred treatment protocols. Immunophenotypic evaluation is essential to accurate diagnosis and classification of acute leukemia. Multiparameter flow cytometry provides a rapid and effective means to collect this information, as well as providing prognostic information and a modality for minimal residual disease evaluation [5]. In relation to the symptoms, patients may experience nausea and vomiting, leg and arm weakness, seizures, headaches, changes in mental alertness or confusion, facial weakness, double vision, hearing loss and/or swallowing difficulties, secondary to isolated or multiple cranial nerve palsy. It also can occur posterior reversible encephalopathy syndrome or cerebrovascular disease with neurocognitive impairments. The nerve most commonly affected in ALL is facial nerve (cranial nerve VII). The 7th nerve nucleus is located in the base of the pons. Upon its exit from the brainstem, the 7th nerve must cross the subarachnoid space before entering the internal auditory meatus. This is the most likely site of nerve involvement in the presence of meningeal infiltration and pathological cells in the CSF [6]. Bilateral involvement, however, is an extremely rare entity. Bilateral facial paralysis is a diagnostic challenge which may manifest itself as either a simultaneous or alternating form, occurring in 0.3%–2.0% of patients that present with facial paralysis [7]. The differential diagnosis of facial paralysis is broad and includes congenital, autoimmune, traumatic, neurologic, infectious, metabolic, neoplastic, toxic, iatrogenic and idiopathic etiologies. There are few cases in literature in which acute lymphoblastic leukemia opened the diagnosis with Bilateral Facial Palsy (BFP). Furthermore, the presented case, to the best of my knowledge, is the first case describing T-cell leukemia with expression only in the CNS since the diagnosis.

METHODS

Retrospective analysis of the patient clinical history and exams, after formal consent of the patient for publish his clinical history and photos. Being the last follow up of this patient in December 2018.

CASE REPORT

41-year, male, went to the emergency department of a private hospital in Recife-Brazil, in January of 2014, complaining of intense headache, mainly near to pre auricular right region, and peripheral facial palsy at the same side. He said that the symptoms progressed fast during last 15 days. One week after, the patient developed the same palsy at the left side, followed 5 days later, by superior eyelid ptosis ipsilateral, and in sequence, more one week after, occurred the right eyelid ptosis. The patient developed a very rare condition of bilateral simultaneous facial palsy that represents a challenge

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diagnostic in medicine. Simultaneous onset is defined by involvement of the other side within 30 days of the onset of first side. This situation, in general, represents a symptom of a complex systemic disease, occurring in 0.3 to 2% of facial palsy cases [8]. The patient couldn't open both eyelids or smile, giving him a "mask face", and, beside it, he had continuous headache. There were no others neurologic symptoms (Figures 1 and 2). He had no prior history of fever, weight lost, viral infection or vaccination. Also, there were no associated comorbidity.

At physical exam, no lymph nodes or organomegaly were palpable. The radiologic images exams of the brain, either the MRI and tomography, both were normal. The study of the cerebral spinal fluid showed a cellularity of 1.365 cells/mm^3, 100% of them lymphocytes, with high level of protein (307 mg/dL). Serology tests were negatives at liquor. The flow cytometry study revealed the result compatible with T-cell ALL with atypical expression of CD10 (Table 1) no molecular biology study was done at diagnosis. Hematologic exams were all normal, including hemogram, myelogram, and bone marrow biopsy. Tomography of thorax and abdomen had no enlarged lymph node, with normal liver and spleen.

The treatment was initiated with high dose dexamethasone (40 mg/daily) during firsts 4 days, and intrathecal (IT) therapy with methotrexate 12 mg, cytarabine 70 mg and dexamethasone 2 mg, twice a week until clean the liquor of neoplastic cells, which happened after the fourth treatment dose. At sequence, the IT chemotherapy was done once a week for more one month and then after every 28 days for IT treatment and liquor study. During the first week of IT chemotherapy the headache improved. At the end of the first month the patient was able to open his eyes, but still persisted with bilateral facial palsy (Figure 3). The patient had a full recovery of his facial and eyes movements within 6 months. The patient stayed asymptomatic for 11 months when he complained of paresthesia at his chin and right side of the jaw. New radiologic exams were normal, the liquor analysis showed only elevated protein ratio, with no neoplastic cell. The results of hemogram, LDH, and myelogram were also normal. Because of the possibility of peripherical nerve infiltration, and before laboratory relapse, the patient initiated systemic chemotherapy with Hyper-CVAD protocol, not followed by bone marrow transplantation. Within four years of follow up, the patient had full recovery and no relapse.

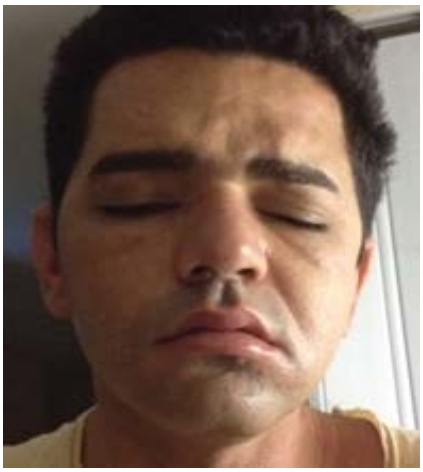

Figure 1) *Patient is asked to open his eyes, lift his eyebrows and smile, but, as shows the photo, he can't do it*

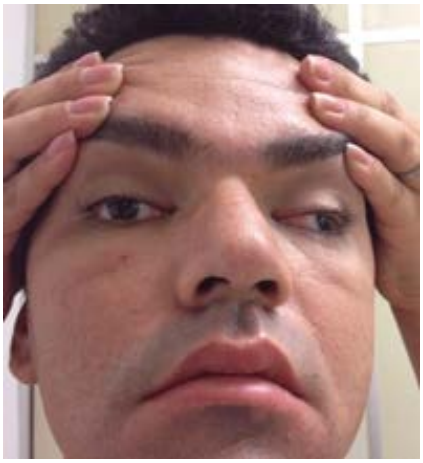

Figure 2) *Patient eyebrows and superior eyelids are being elevated by his wife's hands. It is also possible to observe the palsy of the medial muscle of the left eye that is lateral deviated*

TABLE 1
Immunophenotype of cerebral spinal fluid at diagnosis

Panel	Result	Percentual	Panel	Result	Percentual
Cd45-cd34	Negative	-	Cd22m	Negative	-
Cd45	Positive	99%	Cd2	Positive	98%
Cd34	Negative	-	Cd1a	Positive	79%
Cd3m	Positive	18%	Cd5	Positive	97%
Cd4-cd8	Positive	81%	Cd3cito	Positive	79%
Cd4	Positive	88%	Tdt	Positive	89%
Cd7	Positive	97%			
Cd33	Negative	-			
Cd19-cd10	Negative	-			
Cd19	Negative	-			
Cd10	Positive	79%			
Cd16-cd56	Negative	-			

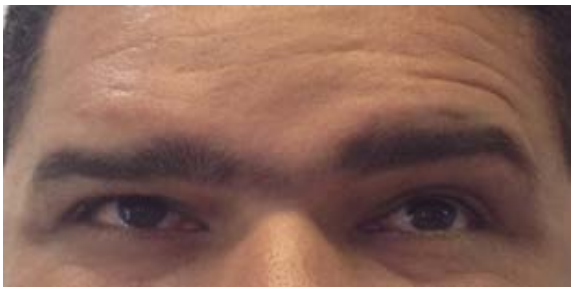

Figure 3) *Patient could open his eyes and lift one eyebrow after one month with IT chemotherapy twice a week*

DISCUSSION

Acute lymphoblastic leukemia most commonly occurs in the pediatric population. However, it is responsible for 20% of adult leukemia cases and carries a significantly poorer prognosis than in children, with overall five-year survival rates of 30%–40%. CNS involvement at the time of acute lymphoblastic leukemia diagnosis is noted in about 6% of patients. The rate of detection of CNS disease is maximized by including cytological evaluation with flow cytometry [9-11]. This clinical case has many points of interest. A low percentage of ALL patients have CNS infiltration at diagnosis and, between then, it is very rare to not develop a bone marrow disease during a short period of follow up. Other unusual situation is that leukemia infiltration of CNS is associated with a very bad prognosis and, fortunately the patient has been an exception, staying without relapse 5 years after the diagnosis. The patient had no risk factor for CNS ALL as mediastinal mass, high leukocytes count, or lymphadenopathy. The T-cell immunophenotype has less probability than B cell subtype to infiltrate the CNS. At this particular case, the status of Philadelphia chromosome is unknown because of financial difficulty to do the exam of BCR-ABL on this patient at that occasion [12].

Of patients who develop CNS leukemia, rarely is the cranial nerve palsy bilateral and even more rarely is the initial presenting symptom of ALL. There have been some reports of an association between facial palsy and acute leukemia in the literature [13-19]. But, in all them there were bone marrow involvement at the time of diagnosis or at short period of time after it. At this present case, the disease isolated at CNS made the diagnosis and definition of an appropriate treatment complex, because of the absence of similar case in the literature. There are some case reports with bilateral facial palsy at leukemia diagnosis, but all them have blasts at peripheral blood and

bone marrow, or mediastinal mass that shows the disease is not exclusive of the CNS [6,13-22].

Bilateral simultaneous facial palsy is a rare entity and has an incidence of only 1 per 5 million populations per year. It is rarely idiopathic (under 20%), whereas unilateral is mostly idiopathic (over 50%). It may be the presenting feature of a potentially life-threatening illness. The differential diagnoses of bilateral facial palsy include congenital, traumatic, infectious, neurological, metabolic, neoplastic, and toxic causes [14,17]. Facial palsy in lymphoid malignancies has been reported with accompanying meningeal involvement. The presence of neoplastic lymphocytes or myelocytes in arachnoid tissue cause meningeal leukemia. These malignant cells proliferate at shallow walls of veins and extending through the surface to the arachnoid emerging arteries, veins, arterioles, venules, and that cross the brain. Neuropathy occurs due to compression and damage of the nerve and their vessel by infiltration of leukemic cells, which might have been a mechanism in our case [17,23]. The cranial nerve most commonly affected is cranial nerve VII, although bilateral involvement is rare. The diagnosis was made by conventional cytology and flow cytometry immunophenotyping of CSF, because the neuroradiology exam was normal. As shown in Table 1, the immunophenotype shows positivity to CD45 that is a common antigen used to define the population of the cells, then CD2, CD3c, CD7 are pan T cell marker, being the CD3c the most lineage-specific marker of T cell differentiation. TDT and CD1a are marker of immature lymphoid process. The CD10 (CALLA) is a common acute lymphoblastic leukemia antigen, it also is a marker of mature B cell lymphoma [24]. At the beginning, as the patient had no bone marrow involvement, the therapy focused only at the CNS. After one year, when few neurologic complains appeared, was initiated systemic chemotherapy although the exams of the liquor as the neuroradiologic exams, and the bone marrow showed no signal of new infiltration. The patient did not do radiotherapy or bone marrow transplant, as the symptoms promptly disappeared after the institution of chemotherapy. The literature describes treatment approach with intrathecal plus systemic chemotherapy, followed or not by radiotherapy of CNS. Some studies describes also the role of allogenic bone marrow transplant for those patients with CNS infiltration at diagnosis or at relapse, indeed it is important to notice that all patients had systemic disease at least on the period of diagnosis [4,7,10,15,25-32].

CONCLUSION

The presentation of ALL with CNS involvement at diagnosis is not common. It is necessary to be aware that this situation can appears as an isolated or multiples nerve palsies, even without the presence of blast cells infiltration at peripheral blood or bone marrow. Bilateral facial palsy is very rare and, in general, it is associated with an underlying complex systemic disease, being neoplasia one of the possibilities. The patient had T-cell ALL that was localized only at CNS, what represent less than 5% of cases at diagnosis, and did not had the subsequent evolution for a systemic usual ALL. A complete and prolonged response was achieved after treatment with intrathecal and systemic chemotherapy.

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