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TRICHOLEUKEMIA AND THERAPEUTIC PERSPECTIVES IN A REFRACTORY CASE

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ABSTRACT

Tricholeukemia, also called hairy cell leukemia, is a chronic B-cell lymph proliferative neoplasm. It is a rare, more frequent disease in males. The clinical presentation is characterized by cytopenia, splenomegaly and non-specific symptoms such as asthenia and weight loss. The diagnosis is performed by immuno-phenotyping of bone marrow by flow cytometry, and the BRAFV600V mutation is present in most cases. Therapy is usually dramatic with purine analogues and other alternatives include newer drugs such as the BRAFV600E inhibitors. The objective of this study was to report a case of tricholeukemia with onset of follow-up at Tereza Ramos Hospital, Lages SC / Brazil, between 2018 and 2019. From the analysis of this case, it was concluded that the patient presented similar findings to the literature, with a clinical presentation and marrow phenotype characteristic, but little response to two treatment lines, constituting an atypical case and, therefore, subject to in-depth analysis.

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INTRODUCTION

Tricholeukemia, also called hairy cell leukemia (HCL), is a rare, chronic, B-cell lymphoproliferative disease that accounts for 2% of all adult lymphoid leukemias (Robak *et al*., 2015). The term tricholeukemiais based on the aspect of cytoplasmic projections of neoplastic cells observed by microscopy (Schrek and Donnelly, 1966). According to Tiacci *et al*., (2011), the disease is characterized by an indolent course, marked splenomegaly, progressive pancytopenia and rare circulating tumor cells, usually without lymphadenopathy. In the last 50 years there has been great development in therapeutics in relation to hairy cell leukemia (Tiacci *et al*., 2011). Prior to the introduction of purine analogues and alpha INF, survival was around 50 months (Sarvaria, Topp and Saven, 2016); with the use of this type of therapy, a 5-year survival rate of 95% and a 10-year survival rate of 80% (Allsup and Cawley, 2002). Despite this context, 10% of patients present primary resistance to purine analogs, while others may acquire it during treatment (Allsup and Cawley, 2002).

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Faced with this impasse, the advance in search of knowledge in genetics was considerable. Tiacci *et al*., in 2011, demonstrated that the BRAF V600E is the genetic lesion underlying hairy cell leukemia. Some studies have been done with the objective of testing new drugs with action at the level of this mutation. In 2015, a multicenter study by Tiacci *et al*. (2015) demonstrated the efficacy and safety of an oral BRAF inhibitor, vemurafenib, in patients with relapsed or refractory hairy cell leukemia with an overall response rate of 96% after an average of eight weeks. Medical management of the refractory disease is of paramount importance in order to prolong the survival of patients with the disease. In this context, the question is: how to identify the patient with hairy cell leukemia with refractoriness to first-line therapy? Its objective is to describe the occurrence of tricholeukemia in cases refractory to first-line therapy. It intends to reinforce the knowledge on the subject in order to improve the survival of these patients.

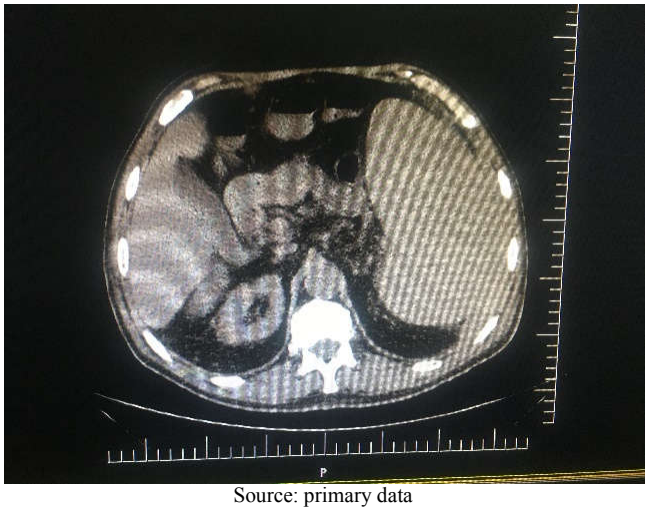
MATERIALS AND METHODOLOGY

This work consists of a case study. The data collection took place in 06/03/2018 until 06/01/2019, being held at the Tereza Ramos Hospital, located in Lages, Santa Catarina state, Brazil.

The study had a male participant. To include the participant in the study, he signed a Free and Informed Consent Term. Data was obtained through medical records analysis and outpatient follow-up. All the information in the present study was obtained respecting Brazilian ethical standards in compliance with Resolution 466/2012 of the National Health Council. The chosen research method allowed to increase the knowledge in the area, allowing to bring new therapeutic alternatives.

RESULTS

Case Report: Patient, male, 79 years old, Caucasian, vegetable farmer, native and from Lages-SC. At the hospital, in the hematology service, on March 6, 2018, he had left abdominal flank pain started seven days ago. Associated with the main symptom, presented asthenia and weight loss of 16kg in the last three months. Denied smoking, denied alcoholism.
On physical examination he had cutaneous-mucous pallor, without palpable peripheral lymphadenopathies. Cardiovascular and pulmonary device without changes. Abdominal examination with pain, at the superficial and deep palpation, in the left hypochondrium and palpable mass in the left flank. Laboratory tests were carried out at admission; hemogram associated with pancytopenia with erythrocytes = 3.00 million / mm^3; hemoglobin = 9 g / dl; hematocrit = 28.8%; red cell distribution width (RDW) = 29.7%; platelets = 60 mil / mm 3; leukocytes = 1400 / mm^3 and leukocyte differential with 52% lymphocytes, 40% segmented, 7% monocytes and 1% sticks; serological tests for Chagas disease, human immunodeficiency virus (IH), human T-lymphotropic virus (HTLV) I / II, syphilis and hepatitis; autoantibodies RNP / Sm, Ro / SS-A and La / SS-B, anti-DNA, rheumatoid factor and antistreptolysin O, all unreacted; (4.3 g / dl) and test for positive reactive protein C (20.5 mg / l). In total abdominal tomography (Figure 1), there is an important splenomegaly.



Source: primary data

Figure 1. Tomography of the whole abdomen, presenting splenomegaly

The myelogram revealed hypocellularity of the lymphoplasmocytic sector, with predominance. Cells of basophilic cytoplasm, grayish blue, with irregular borders, presenting hairy projections, suggestive of hairy cell leukemia. MO biopsy performed at the same time showed normo-cellular marrow compatible with age, with diffuse infiltration of lymphoid cells similar to tricholeukemia. The peripheral blood flow cytometric immuno-phenotyping test, performed on 06/03/2018, demonstrated the presence of 55% pathological cell populations with strong expression for CD20, CD22, CD11C and CD103. Expression for CD45, Lambda, CD200, CD79B, CD81, CD31, lambda, CD79B, 3, CD123 with no expression for Kappa, CD5, CD38 and CD23, CD10, CD43 confirming the suspicion of hairy cell leukemia. The patient underwent chemotherapy on 03/15/2018 with first-line therapy with the use of cladribine. It was infused intravenously for five days. On 08/28/2018 patient returns with clinic of asthenia and abdominal pain. He kept the USG of the abdomen with 20 cm splenomegaly on its largest axis. The result of peripheral blood immuno-phenotyping with detection of 1.8% of lymphoid B cells (CD19) with phenotype similar to 03/2018. The patient followed the treatment with a new protocol. Rituximab at a dose of 375mg / m2 was used for eight cycles. In the second cycle of treatment with rituximab evolved with persistent thrombocytopenia and refractory, also without response to rituximab. Currently undergoing treatment with pentostatin with difficult treatment response.

DISCUSSION

Hairy cell leukemia (HCL) tends to occur in older men more than in any other demographic group. The mean age at diagnosis is 52 years and there is a higher incidence in men compared to women of approximately 4:1 (Salamand Abdel-Wahab, 2015). Despite this, it is known that tricholeukemia can be diagnosed at more advanced ages as reported. Dores and co-workers, in a cross-sectional study published in the British Journal of Hematology, identified two age-based subpopulations of tricholeukemia upon diagnosis - early and late presentation. In fact, this study verified a pattern of bimodal incidence, with a peak at around 40 years and another around the 80 (Dores *et al*., 2008). Differing from the reported exposure to hairy cell Leukemina is also more common in whites than in any other breed. The proportion of whites to non-whites diagnosed with HCL was reported in almost 3: 1 (Salam and Abdel-Wahab, 2015; Robak*et al*., 2105). Contact with agriculture appears as a possible risk factor for the development of this neoplasm. Exposure to insecticides, herbicides and fungicides shows an association with the disease (Nordström, *et al*., 1998). Although this fact has not been analyzed directly, the patient in the case has direct contact with the local agriculture. The findings of pancytopenia in the patient (anemia, leukopenia and thrombocytopenia) corroborate with the literature. Most patients with HCL present symptoms related to splenomegaly or cytopenias (anemia, thrombocytopenia, neutropenia, monocytopenia), including weakness and fatigue, infections of variable severity and / or hemorrhagic findings, such as gingival bleeding, ecchymosis, epistaxis or menorrhagia (Sarvaria, Topp and Saven, 2016; Allsup and Cawley, 2002). Hairy cell leukemia may present itself to the clinician in a variety of ways. Approximately one fourth has abdominal fullness or discomfort due to splenomegaly (Golomb, Catovsky, and Golde, 1978) Spontaneous splenic rupture may occur and constitute a medical emergency (Golomb, Catovsky, and Golde, 1978). As exemplified in the case study, the diagnosis of HCL is usually made by bone marrow biopsy and aspiration in conjunction with immuno-phenotyping by flow cytometry. Abnormal cells exhibit antigen expression of cells, for example CD19, CD20, CD22 together with CD103, CD11c and CD25 (Swerdlow *et al*., 2016). Not all cases of tricholeukemia are treated as in the case study in question. Many patients with hairy cell leukemia are asymptomatic and may be observed for months or years after the diagnosis is

made before treatment is needed. There is indication of treatment in significant cytopenias; typical peripheral blood counts that warrant treatment include absolute neutrophil count <1000 / micro / L, hemoglobin concentration <11 g / dL or platelet count <100,000/micro/L, symptomatic splenomegaly or symptomatic adenopathy, and constitutional symptoms (Grever *et al*., 2017). The treatment of choice for HCL uses purine analogues. Within this group, the most common are cladribine and pentostatin showing similar response and survival rates (Allsup and Cawley, 2002; Sarvaria, Topp and Saven, 2016). Most patients obtain durable remissions with multiple cycles or with a single cycle of pentostatincladribine (Else *et al*., 2009). In a study of 233 patients followed up for a mean period of 16 years, cladribine and pentostatin resulted in similar overall response rates (100 versus 96%), complete response rates (Else *et al*., 2009).

The therapeutic regimen used by the patient was cladribine with eight cycles of consolidation with rituximab. This therapeutic scheme results in long periods of remission; however, rituximab is also associated with immunosuppression. Randomized trials are needed to confirm the superiority of long-term outcomes. In a Phase II study, 59 patients with a recent diagnosis of hairy cell leukemia who required treatment received an initial cycle of cladribine, lasting approximately one month later, followed by eight weekly treatments of rituximab. All patients achieved complete response and there were no serious toxicities. At an average follow-up of 60 months, the estimated five-year disease-free survival rate was 95% (Ravandi *et al*., 2011). Interferon alfa may be preferred for initial treatment with patients with severe pancytopenia and/or active infection to improve blood counts. It can also be used in patients who do not respond to treatment with purine analogues, but without many studies that prove their efficacy (Habermann *et al*., 1992). The initial treatment aims to achieve complete response defined as: Near normalization of the peripheral hemogram: hemoglobin> 11 g / dL; platelets> 100,000 / micro / L; absolute neutrophil count> 1500 / micro / L and regression of splenomegaly on physical examination. Absence of morphological evidence of HCL in peripheral blood smear and bone marrow examination (Grever *et al*., 2017). As could be seen in the report, it is a case of disease resistant to first-line treatments. For these patients we suggest an attempt of an alternative purine analogue (Else *et al*., 2009).

In 2011, Tiacci *et al*. Described the presence of the V600E mutation of the BRAF gene in exon 15 (Tiacci *et al*, 2011; Tiacci *et al*, 2015). This mutation, present in almost 100% of HCL cases, is related to a 15-valine substitution for glutamine in the BRAF proto-oncogene that leads to the activation of the RAF / MEK-ERK pathway, resulting in an increase in cell proliferation and survival, by inhibition of apoptosis (Robak*et al*.,2015; Tiacci*et al*., 2011). Studies have been done with the objective of testing new drugs with action at the level of this mutation. In one of these, tricholeucocytes were incubated in vitro with BRAF inhibitors (vemurafenib and dabrafenib) (Tiacci *et al*., 2011). Tiacci *et al*., described in his work with 28 patients with refractory or recurrent HCL that the mean duration of treatment was 16 weeks with a remission rate of 35%. In this case, after 23 months of follow-up, mean disease-free time was 19 months, in the group that received complete response and 6 months in the group that received partial response (Tiacci *et al*., 2015). Another beneficial alternative for the patient in the present case study would be the use of recombinant immunotoxins, which are proteins consisting of an antibody directed against an antigen present in neoplastic cells, and a toxin capable of destroying them, such as a Pseudomonas exotoxin (Kreitmanand Pastan, 2015). The studies focused on CD22 and CD25 as targets (Kreitmanand Pastan, 2015). Regarding CD22, in a phase 2 study using BL22 immunotoxin, 9 of the 36 patients with refractory or recurrent HCL presented CR (25%) after one course of therapy; Twenty patients were submitted to a second cycle, and in the total study 17 they achieved a complete response (CR) (47%) (SAVARIA, 2015). Subsequently, a version of this drug was developed, but with a higher affinity - moxetumomabpasudotox, reaching 46% CR in a phase I study where 28 patients with resistant or recurrent HCL were included (Kreitmanand Pastan, 2015)

Conclusions

In this case report, it is noted that clinical-epidemiological and laboratory presentation of hairy cell leukemia were similar to other reports in the literature. The report raises the discussion of therapy in a complex situation that is hairy cell leukemia refractory to the initial treatment. Although most cases are responsive to treatment with purine analogues, there is a considerable increase in refractory disease. Recent treatment regimens have demonstrated good response rates in these specific cases. It is pointed out that the knowledge of these therapies can increase the survival rate of these patients, and it is recommended to intensify the research on the subject.

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