UNINGÁ Journal, v. 58, eUJ3549, 2021
doi.org/10.46311/2318-0579.58.eUJ3549
ISSN 2318-0579
Biological I, II, III and Health Sciences

HEPATOESPLENOMEGALIA BY HEPATOSPLENIC GAMMA DELTA T-CELL LYMPHOMA – CASE REPORT

HEPATOESPLENOMEGALIA POR LINFOMA HEPATOESPLÊNICO DE CÉLULAS T GAMA DELTA – RELATO DE CASO

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ABSTRACT

This report describes a case of hepatosplenic gamma delta T-cell lymphoma (LHCTGD) is a rare and rapidly progressing neoplasm, derived mainly from cytotoxic T cells. The peak incidence is in young adults, aged twenty to twenty-five years, being more prevalent in males. Clinically, patients may present abdominal pain, weakness, hepatosplenomegaly and marked thrombocytopenia, as well as systemic symptoms and absence of lymphadenopathy. In biochemical assessment is possible to observe: an increase in transaminases and alkaline phosphatase, anemia, pancytopenia and increased levels of lactate dehydrogenase. Regarding treatment, further studies are still needed, currently we have surgical intervention (splenectomy), chemotherapy regimens and hematopoietic stem-cell transplantation. This report presents the case of a 24-year-old male patient diagnosed with gamma delta T-cell hepatospelenic lymphoma and also a literature review carried out on the topic.
Keywords: Splenectomy. Splenomegaly. T Cells lymphoma.

RESUMO

Este relato descreve um caso de linfoma hepatoesplênico de células T gama delta (LHCTGD), uma neoplasia rara e de rápida progressão, derivada principalmente de células T citotóxicas. O pico de incidência é em adultos jovens, na faixa etária de vinte a vinte e cinco anos, sendo mais prevalente no sexo masculino. Clinicamente os pacientes podem apresentar dor abdominal, fraqueza, hepatoesplenomegalia e trombocitopenia acentuada, além de sintomas sistêmicos e ausência de linfadenopatia. Na avaliação bioquímica é possível observar: aumento das transaminases e da fosfatase alcalina, anemia, pancitopenia e o aumento do nível de lactato desidrogenase. No que se refere ao tratamento, ainda são necessários mais estudos, atualmente, dispomos desde procedimentos cirúrgicos (esplenectomia) até esquemas quimioterápicos e transplante de células tronco hematopoiéticas. Este relato traz o caso de um paciente de 24 anos, do sexo masculino diagnosticado com linfoma hepatoesplênico de células T gama delta e também uma revisão de literatura realizada sobre o tema.
Palavras-chave: Esplenectomia. Esplenomegalia. Linfoma de células T.

 Received: June, 07th, 2020; Accepted: December, 10th, 2020.

INTRODUCTION

Gamma-delta T-cell hepatosplenic lymphoma (HSTCL) is considered a rare and aggressive pathology that originates from gamma-delta lymphocytes. The first report described in the literature was in 1990 and since then, approximately 100 new cases have been recorded. It has a peak incidence in young males, in the age group of twenty to twenty-five years (FALCHOOK *et al*., 2009). This lymphoma is defined by the malignant proliferation of T-cells in the liver sinusoids, sinusoids, red pulp of the spleen and bone marrow.

The phenotype of T-cells frequently exposed is $CD2^{+}$, $CD3^{+}$, $CD4^{-}$, $CD5^{-}$, $CD7^{+-}$, $CD8^{-}$, with expression of gamma-delta or alpha-beta T-cell receptor (FOPPOLI; FERRERI, 2015). Based on regional differences in the receptor, the population of gamma-delta T-cells can be divided into the Vdelta1 and Vdelta2 subpopulations. Since Vdelta1 T-cells are found mainly in the intestine, Vdelta2 T-cells are distributed in the skin, tonsils and lymph nodes. Regarding the associated cytogenetic abnormalities, the isochromosome 7q with or without 8 trisomy is included (GOWDA; FOSS, 2019).

Some factors, such as chronic immunosuppression and prolonged antigen exposure, favor the uncoordinated growth of gamma-delta T lymphocytes resulting in the development of lymphomas that express gamma-delta T-cell receptor (RCT) (FOPPOLI; FERRERI, 2015). Clinically, patients may have symptoms B, which are: fever of unknown origin, night sweats and weight loss greater than 10%. In addition, severe hepatosplenomegaly and absence of lymphadenopathies increase the diagnostic suspicion.

The treatment includes the surgical intervention with splenectomy, in order to control thrombocytopenia and also assist in the diagnosis (FALCHOOK *et al*., 2009). Chemotherapy sessions may also be included and, in specific cases, bone marrow transplantation (TEY *et al*., 2008). This report addresses the case of a young adult male patient diagnosed with gamma-delta T-cell lymphoma and a literature review on the subject.

CASE REPORT

In order to carry out this study, we had the patient's consent to publish clinical data and disease progression.

A 24-year-old male patient was admitted to the hospital in April 2019, with a severe pain complaint in the left hypochondrial region, associated with anorexia, weight loss of 31 kg - in approximately two months - and abdominal distension. On physical examination, he had a globose abdomen, painless palpation and a large palpable mass in the left hypochondrium and flank, with no signs of peritoneal irritation. On admission to the hospital, imaging and laboratory tests were requested, which are shown in Table 1.

The imaging study with computed tomography (CT) of the complete abdomen (Figure 1) revealed hepatosplenomegaly, with the spleen measuring 34.1 cm (craniocaudal) X 24.0 cm (anteroposterior) X 16.6 cm (laterolateral), exerting a mass effect and deflecting adjacent structures, with intermingle hypodense areas that may be compatible with splenic infarction. In addition to the absence of both enlarged retroperitoneal and pelvic lymph node, as well as free liquid in the peritoneal cavity.

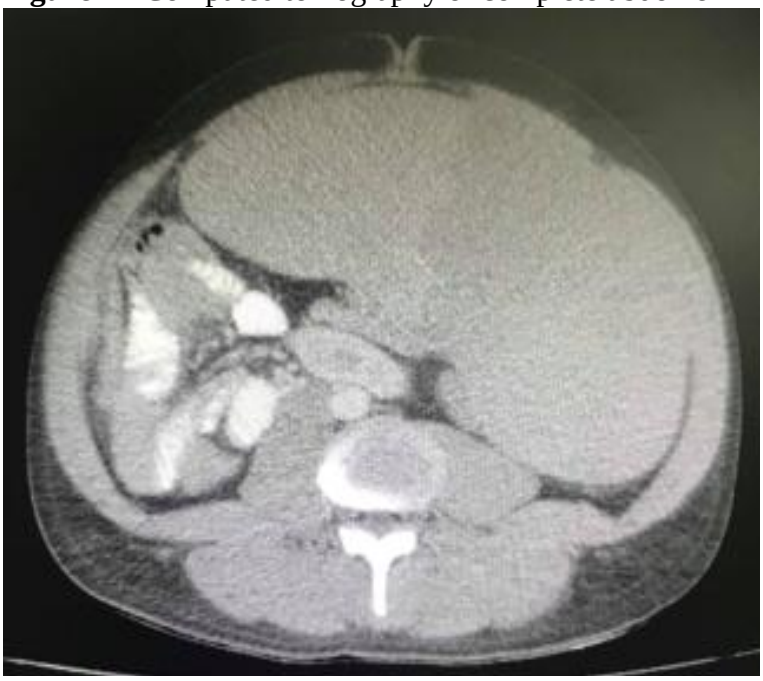
The patient underwent percutaneous splenic biopsy with a thick needle during hospitalization. A complete control abdominal CT scan was performed (Figure 2) demonstrating the presence of periesplenic hematoma, however, the patient had stable vital signs. It was chosen to carry out a conservative conduct. During hospitalization, the patient remained clinically well and with no drop in hemoglobin. Thus, he was discharged from the hospital with an outpatient visit to assess the biopsy result, which showed atypical lymphoid/myeloid proliferation with extensive necrosis, in splenic parenchyma.

Table 1 - Laboratory tests requested

Tests	Result
Hemoglobin	11.3 g/dL
Hematocrit	34.7%
Leukocyte	6000/mm^2
Rods	4%
Amylase	92 U/L
Total Bilirubin	0.69 mg/dL
Direct Bilirubin	0.33 mg/dL
Indirect Bilirubin	0.36 mg/dL
Albumin	3.94 U/L
Alkaline phosphatase	164 U/L
GGT (Gamma-glutamyl transferase)	88 U/L
Potassium	4.0 meq/L
T-protein	7.73 g/dL
Globulin	3.79 g/dL
Sodium	138 mEq/L
AST	181 U/L
ALT	61 U/L
PT	81.7%
Urea	24 mg/dL
INR	1.09
KPTT	30s
Creatinine	1.08 mg/dL

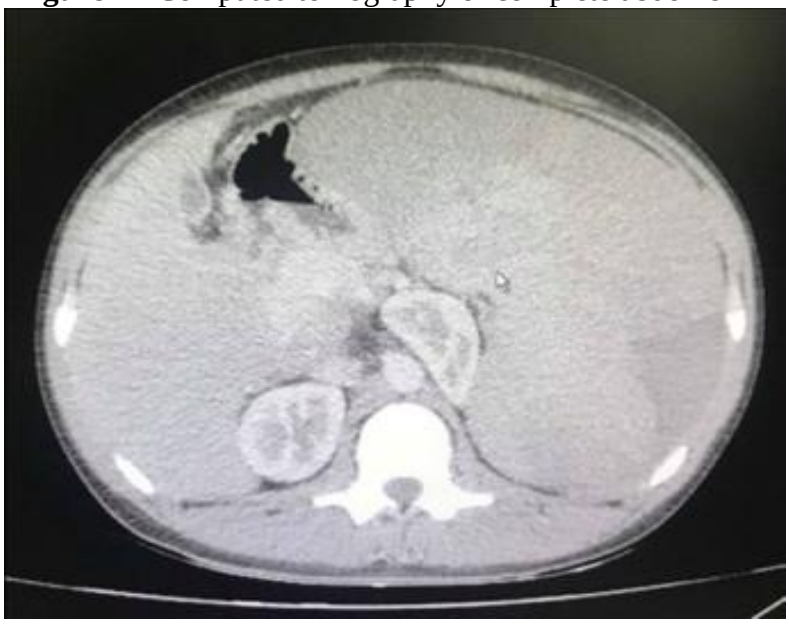
Source: the authors.

Figure 1 - Computed tomography of complete abdomen



Notes: Contrast-enhanced abdominal CT showing hepatosplenomegaly. Exercising mass effect, with intermingle hypodense areas. Absence of enlarged retroperitoneal or pelvic lymph nodes.
Source: the authors

Figure 2 - Computed tomography of complete abdomen

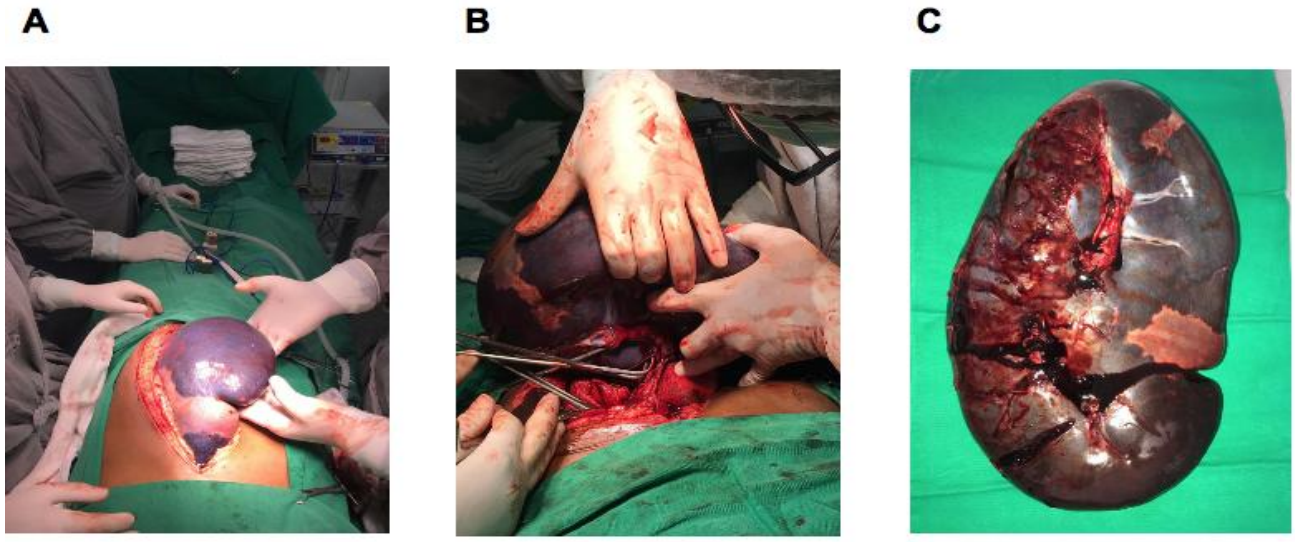


Notes: Total contrast-enhanced CT scan performed after guided biopsy demonstrating the presence of hematoma in the perisplenic region.
Source: the authors

A few days after hospital discharge, the patient returned due to clinical worsening, presenting abdominal pain, anemia (hemoglobin 9.4 g/dL), and thrombocytopenia. During medical evaluation, there was an imminent risk of splenic rupture related to the enlarged spleen. In view of the hypothesis of hypersplenism and expanding subcapsular hematoma, it was decided to recommend early surgical treatment.

During surgery, a median incision for splenectomy was performed, with a large spleen occupying the entire left flank of the patient up to the pelvic region, with the presence of a large subcapsular hematoma. The surgical procedure had no complications, with adequate ligation of all vessels, as shown in Figure 3.

Figure 3 - Illustrations of the moment of splenectomy



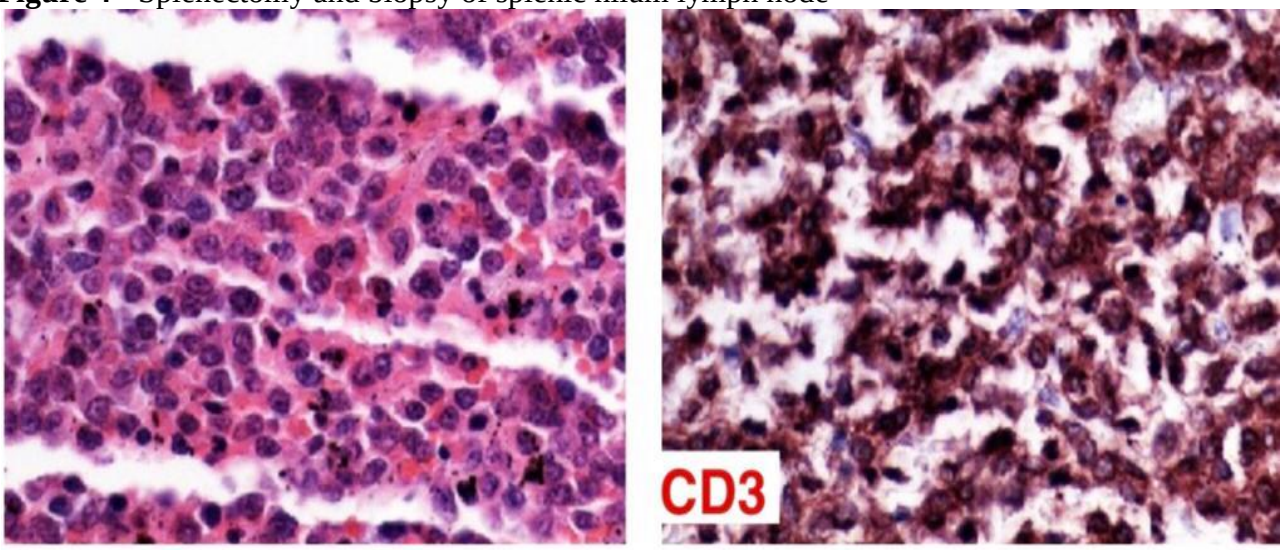
Notes: A**:** Median xiphopubic incision showing an enlarged spleen. B**:** Ligation of splenic hilum vessels. C**:** Surgical specimen photo.
Source: the authors.

Postoperative patient was referred to the Intensive Care Unit (ICU), where he remained for two days on spontaneous ventilation, hemodynamically stable, without the need for vasoactive drugs. Laboratory control tests showed a severe drop in hemoglobin to 6.5g/dL, platelets 120,000/mm3, C-Reactive Protein = 78 mg/L, potassium = 5.9 mEq/L, sodium = 140mEq/L, urea = 43mg/dL and creatinine = 1.78. Transfusion of three red blood cell concentrates was performed.

Approximately 36 hours after splenectomy, the patient presented hemodynamic instability, tachycardia and massive bleeding through the abdominal drain (1200mL). Initially, support and blood transfusion measures were performed, followed by urgent laparotomy. During surgery, a large volume of blood was identified in the abdominal cavity, but without evidence of active bleeding. This was then followed by thorough washing of the cavity with saline and closing the incision. In the postoperative period of the re-approach, the patient evolved with decreased abdominal drainage output (140mL of sero-hematic fluid), remaining stable and with conditions for hospital discharge for outpatient follow-up. In outpatient follow-up, he progressed without complications.

The result of the immunohistochemical study (Figure 4) revealed that it was Lymphoma T (CD3 +) with immunophenotype CD3 + / CD4 + / CD8- (Table 1). Peripheral blood collection was sent for immunophenotyping that showed a panel of 23% of mature T lymphocytes with normal phenotype, positive γδ TCR, CD4, CD5 and CD8 negative, suggestive of primary Gamma-Delta T-cell lymphoma. In addition to 22% of mature monocytes and 0.03% of myeloid precursor cells, again confirming the diagnosis of gamma-delta T-cell lymphoma.

Figure 4 - Splenectomy and biopsy of splenic hilum lymph node



Caption: Splenic parenchyma showing red pulp expansion at the expense of infiltration by small to medium atypical T lymphocytes. Presence of extensive areas of necrosis. Some paraffin blocks demonstrate lymph nodes partially altered by atypical T-cell lymphocytes of similar morphology. The immunohistochemical study, performed in the spleen, demonstrated that the atypical T-cell lymphocytes show immunoexpression for CD3 (right image), with coexpression for CD4, TIA-1, TCR-delta and negativity for CD8.
Source: Laboratório Bacchi.

With the diagnosis of malignancy confirmed by the histopathological study, the patient was referred to the reference service in oncology for follow-up procedures. In the oncological evaluation, due to the risk of tumor lysis and progression of the disease to the liver, it was decided to perform cytoreductive chemotherapy first, followed by the CODOX M IVAC protocol, in addition to HLA typing for allogeneic transplantation in the 1st remission. The spinal biopsy showed hypercellular bone marrow at the expense of myeloid hyperplasia with neutrophils and large cells suggestive of immature myeloid cells.

The patient continues with the CODOX M IVAC protocol in excellent general condition until the present date, August 2019.

Chart 1 - Immunohistochemical study. Individual results for the studied markers are summarized in the table below. The specific results regard the cells of interest in the context of each case.

Antibodies	**Clone**	**Result**
Ki-67 - Cell proliferation antigen	MIB1	**Positive**
CD3 - T lymphocyte receptor (epsilon chain)	SP7	**Positive**
CD20 - B lymphocyte antigen	L26	Negative
CD30 - Ki-1 antigen	Ber-H2	Negative
CD138 - Plasma cell antigen	MI15	Negative
Immunoglobulin Kappa Light Chain	A8B5	Negative
Immunoglobulin Lambda Light chain	EP172	Negative
Cyclin-D1 – cell-cycle regulatory protein (bcl-1)	SP4	Negative
Myeloperoxidase (cells of granulocytic lineage)	MPO-7	Negative
CD4 – T-helper cell antigen	4B12	**Positive**
CD8 - cytotoxic T cell antigen	C8/144B	Negative
TCR – T-cell receptor beta	8 A3	Negative
TCR- Delta, receptor antigênico de célula T delta, H-41 clone	H-41	**Positive**
CD56- NK cell antigen and T lymphocyte subpopulation	123C3	Negative
Granzyme B	GrB-7	Negative
TIA-1 antigen, associated with NK cells	2G9	**Positive**
Deoxynucleotidyl transferase (TdT)	EP266	Negative

Source: Laboratório Bacchi.

DISCUSSION

The gamma-delta hepatosplenic T-cell lymphoma develops from CD4- / CD8- thymic precursors. Tumor cells are concentrated in the spleen, bone marrow sinusoids and sinusoids of the liver (KRISHNAN; LUNNING, 2019).

These lymphocytes behave like cytotoxic cells, somehow simulating natural killer (NK) cells in their role as precursors in the nonspecific innate immune response. They are also able to make rearrangements in the T-cell receptor (TCR), a phenomenon that contributes to the clonal evolution of hepatosplenic T-cell lymphoma (HSTCL) mutations of events that express the genesis of the disease. Regarding immunohistochemistry, CD2 +, CD3 +, CD4−, CD5−, CD7 + -, CD8− and gamma-delta or alpha-beta are observed, and they express the T-cell phenotype. Most cases of HSTCL are gamma-delta variant (50-85%). Trisomy 8 and isochromosome 7q are the common cytogenetic abnormalities identified in the disease (FALCHOOK *et al*., 2009; GOWDA; FOSS, 2019; KRISHNAN; LUNNING, 2019).

Due to this extranodal distribution of malignant cells, the HSTCL received a distinct classification by the World Health Organization (WHO) in 2008. The incidence of this neoplasm is less than 1% in relation to all subtypes of peripheral T-cell lymphomas. It affects young adults between twenty and twenty-five years old, with a predilection for males (10: 1). It has a poor prognosis, with a global 5-year survival rate of just 7% (FALCHOOK *et al*., 2009; KRISHNAN; LUNNING, 2019; OKUNI *et al*., 2019).

Risk conditions for the development of HSTCL are: chronic immunosuppression and prolonged antigen exposure. In post-organ transplant patients, gamma-delta TCRs represent the majority of T-cell lymphoproliferative disorders (FALCHOOK *et al*., 2009; KRISHNAN; LUNNING, 2019).

The clinical picture of gamma-delta T-cell lymphoma is marked by the absence of lymphadenopathy, followed by constitutional symptoms and, mainly, increased hepatic and splenic volume (OKUNI *et al*., 2019). Biochemical evaluation shows anemia, pancytopenia and elevated transaminases, lactate dehydrogenase and alkaline phosphatase. Thrombocytopenia is constantly observed and may indicate disease progression (FALCHOOK *et al*., 2009; FOPPOLI; FERRERI, 2015; KRISHNAN; LUNNING, 2019).

Nowadays, histological study of bone marrow with immunophenotypic evaluation, analysis of peripheral blood with immunohistochemistry and also liver biopsy are modalities allied to the diagnosis. Histologically, neoplastic cells have a round nucleus with dispersed nuclear chromatin, large, pale and agranular basophilic cytoplasm. The immunophenotype generally defines 'double negative' T-cells (CD4- and CD8-), related to CD2 +, CD3 +, CD5-, CD7 +, TCR delta + (OKUNI *et al*., 2019).

It is proposed that isochromosome 7q may be the initial cytogenetic event, while other genetic abnormalities such as loss of the Y chromosome or trisomy 8 develop during the course of the disease. In macroscopy the spleen is markedly enlarged (weighing up to 6500g) and shows a brown cut surface (FALCHOOK *et al*., 2009; GOWDA; FOSS, 2019).

The most used treatment is the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) with favorable results in 30-45%. Patients who obtain complete remission of the disease at first, have an average interval of four months until they present a recurrence, marked by accelerated growth and less response to conventional treatment (FOPPOLI; FERRERI, 2015; KRISHNAN; LUNNING, 2019).

Voss *et al*. (2008) carried out a study with 14 patients with HSTCL, in which all had stage IV disease and an average age of thirty-six years. Better results were observed with non-CHOP induction therapy, which are methods based on ifosfamide, including together with this compound, etoposide and carboplatin or etoposide and cytarabine in high doses. Eight of these patients underwent non-CHOP therapy and five of them achieved remission, proceeding to autologous or allogeneic hematopoietic stem cell (HSCT) transplantation. HSCT can be offered to selected patients in order to prolong the remission period. However, when there are post-transplant recurrences, they are usually associated with a worse prognosis. Splenectomy is relevant for the control of thrombocytopenia, reducing the risk of spontaneous rupture of the spleen (FALCHOOK *et al*., 2009; KRISHNAN; LUNNING, 2019).

CONCLUSION

Gamma-delta T-cell hepatosplenic lymphoma is a rare disease with a poor prognosis. Diagnostic delay is often related to the absence of specific symptoms of the disease. Therefore, in the presence of a young male patient with thrombocytopenia and hepatosplenomegaly, the diagnostic hypothesis of HSTCL should be raised. Regarding the therapeutic arsenal currently available, further studies are needed, aiming to improve the expectation and quality of life of these patients.

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