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HEPATOSPLENIC T-CELL LYMPHOMA AS A CAUSE OF HYPERSPLENISM: A RARE CASE OF NON-HODGKIN LYMPHOMA REQUIRING SPLENECTOMY

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ABSTRACT

Hepatosplenic T-cell lymphoma (HSTCL) represents a rare and aggressive subset of peripheral T-cell lymphomas with complex diagnostic challenges. We present the case of a 26-year-old male who presented with progressive hepatosplenomegaly, persistent pancytopenia, and recurrent infections. Initial diagnostic workup, including multiple splenic biopsies and bone marrow evaluation, proved inconclusive. The patient underwent therapeutic splenectomy due to severe hypersplenism, yielding a 3,970g specimen. Despite postoperative complications requiring damage control surgery, the patient achieved sustained hematological improvement. Immunohistochemical analysis of the splenectomy specimen revealed an atypical T-cell population (CD2+/-, CD3+, CD7+) with CD56 coexpression, confirming HSTCL. This case emphasizes the importance of comprehensive differential diagnosis in cryptogenic hepatosplenomegaly and highlights splenectomy as both a diagnostic and therapeutic tool. Further research at specialized centers is warranted to better understand the long-term outcomes and potential benefits of splenectomy in HSTCL management.

Keywords: Hepatosplenomegaly. Hipersplenism. Pancytopenia. Splenectomy. T-Cell Lymphoma.

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Revista ARACÊ
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INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive neoplasm with extremely high mortality. First described in 1981 (Kadin et al., 1981), it is an uncommon entity among peripheral T-cell lymphomas, a subtype of non-Hodgkin lymphomas.

The term HSTCL was introduced in 1990 by Farcet et al. (Farcet et al., 1990), although it was provisionally recognized as “γδ hepatosplenic T-cell lymphoma” in the REAL classification in 1994, a designation later adopted by the World Health Organization (WHO) in 1997 (Harris et al., 1994; Harris et al., 1997). Following reports of even rarer cases expressing TCR αβ, the term HSTCL became widely adopted, as seen in the current WHO international classification of tumors (Gaulard et al., 2017).

T-cell receptors (TCRs) are heterodimers, predominantly composed of α and β subunits, but approximately 4% of circulating T lymphocytes express γ and δ chains. This Tγδ lymphocyte subpopulation is more commonly found in the red pulp of the spleen, where it accounts for roughly 30% of the local T-cell population (Boismenu et al., 1997; Born et al., 2006).

We report a rare case of HSTCL in a young patient with multiple infections and a challenging diagnosis following several negative histopathological evaluations.

CASE REPORT

A 26-year-old male presented with a clinical history of weight loss, retinal hemorrhage, fever, and hepatosplenomegaly associated with pancytopenia. During admission in a prior hospitalization, he underwent extensive evaluation, revealing splenomegaly with a splenic index (Figure 1) of 9260, which increased to 12260 after one month.

Figure 1. Calculation of the splenic index.

$$splenic\ index\ =\ length\ \times\ width\ \times\ thickness\ (cm)$$

At the time, based on clinical and epidemiological criteria, empirical treatment for visceral leishmaniasis was initiated using deoxycholate amphotericin B, later switched to liposomal amphotericin B, despite negative serologies and the absence of *Leishmania sp.* amastigotes in spleen biopsy and bone marrow aspirate.

Subsequently, during the same hospitalization, the patient was diagnosed with neurotuberculosis following a cerebrospinal fluid sample positive for GeneXpert MTB/RIF,

Revista ARACÊ
ISSN: 2358-2472

as well as ocular syphilis, for which he received treatment with crystalline penicillin for 14 days.

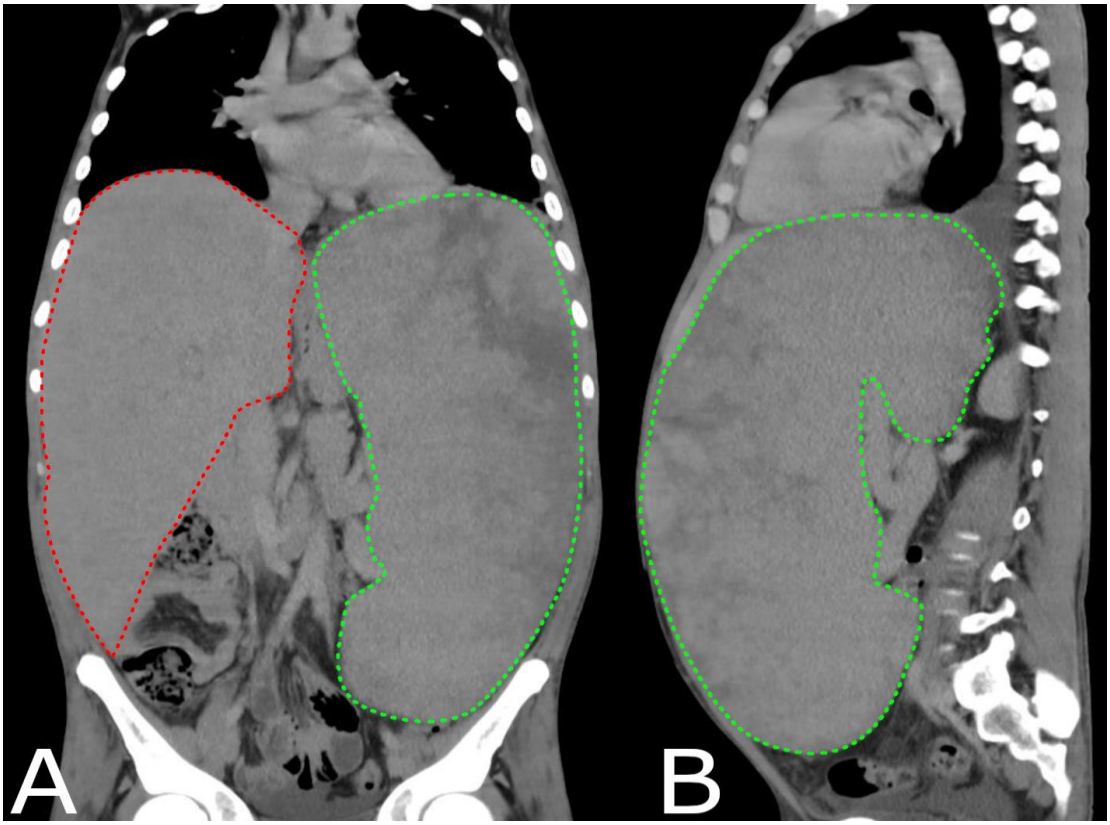
After discharge, the patient continued treatment and follow-up at a tertiary care center, attending a hospital-day program for neurotuberculosis. Due to hepatotoxicity from the first-line regimen, treatment was switched to levofloxacin, ethambutol, and amikacin.

Complementary laboratory tests showed no positivity for autoantibodies (anti-smooth muscle, anti-LKM1, anti-DNA, rheumatoid factor, anti-Ro, anti-La, anti-Sm, anti-RNP). Furthermore, both rapid tests and viral load assays for HIV were negative.

During follow-up, the patient exhibited worsening hematimetric parameters, requiring frequent blood transfusions and subsequent hospitalization for further evaluation.

Upon admission, a new computed tomography scan was performed (Figure 2), revealing a spleen that measured 22.9 × 12.7 cm in the axial plane and 33.5 cm in its largest longitudinal dimension, corresponding to a splenic index of 9740. Hepatomegaly and ascites were also noted. Peripheral blood immunophenotyping did not identify the underlying cause.

Figure 2. (A) Non-contrast computed tomography of the abdominal cavity showing marked hepatosplenomegaly in a coronal view. (B) Sagittal view highlighting splenomegaly. The liver is dotted in red and the spleen in green

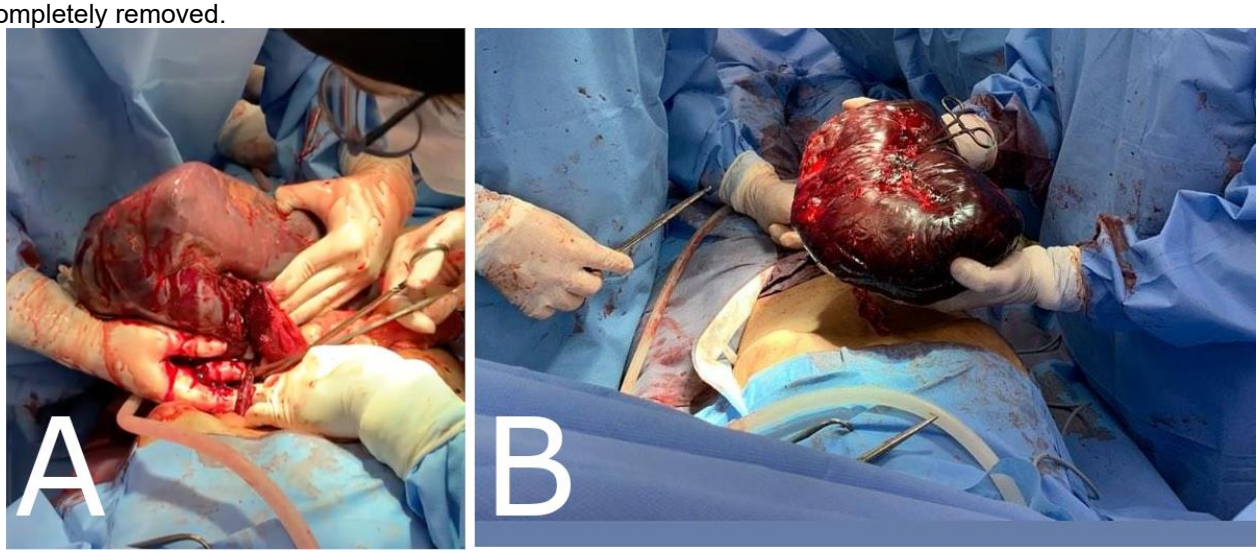


Revista ARACÊ
ISSN: 2358-2472

A splenectomy was planned under the working hypothesis of splenic lymphoma, despite two prior negative spleen biopsies and a negative peripheral blood immunophenotyping. The patient underwent *Haemophilus influenzae* type b vaccine (Hib), meningococcal conjugate vaccine (MenACWY), pneumococcal conjugate vaccine (PCV13), and hepatitis B vaccine. However, the surgery was postponed due to symptomatic COVID-19, for which treatment with Nirmatrelvir and Ritonavir (Paxlovid®) was administered.

A total splenectomy was subsequently performed, yielding a spleen measuring 29 × 23 × 14.5 cm and weighing 3,970 g (Figure 3). The surgery lasted approximately one hour and was performed without any complications. The spleen presented a nodular and friable surface, and upon dissection, violaceous and brownish areas were revealed, suggestive of old pericapsular infarctions and reparative fibrosis. The histopathological examination showed exuberant and atypical lymphoid infiltration.

Figure 3. (A) Intraoperative view showing the splenic resection during splenectomy. (B) The excised spleen, completely removed.



In the immediate postoperative period in the intensive care unit, the patient developed hemodynamic instability with a significant drop in hematologic parameters and 500 mL of sanguineous output through a drain. High doses of vasopressors were required, along with massive transfusion protocol and orotracheal intubation.

During surgical re-exploration, the abdominal cavity was filled with large blood clots. The splenic artery, splenic veins, and smaller branches showed no signs of active bleeding. The only identifiable bleeding source was oozing from the peritoneal surface previously in contact with the spleen, likely due to coagulopathy. Hemostasis of the peritoneal surface

Revista ARACÊ
ISSN: 2358-2472

was achieved using electrocautery, and tamponade was performed with 20 laparotomy pads, which were left in the cavity as a damage control measure.

After 72 hours, the patient returned to the operating room for pad removal and hemostatic revision. No active bleeding was observed. Another drain was left in place, and an absorbable gelatin sponge was applied to the peritoneal surface that had been in contact with the spleen. The patient was extubated the following day in the intensive care unit.

After four days of intensive care, the patient was transferred to the general ward, breathing spontaneously, off vasopressors, and with no further transfusion requirements. Following the completion of antibiotic therapy for febrile neutropenia, the patient was discharged on postoperative day 13, following a total of 38 days of hospitalization.

Immunohistochemical analysis of the splenectomy specimen revealed an exuberant and atypical lymphoid infiltration with white pulp atrophy. The infiltrate was composed of intermediate-sized cells with rounded nuclei, loose chromatin, and small nucleoli. The cells exhibited a T-cell immunophenotype (CD2+/−, CD3+, CD7+) with coexpression of CD56 and absence of cytotoxic granules such as Granzyme B (Table 1). There was no immunopositivity for CD4, CD5, CD8, CD30, CD34, or TdT, nor a phenotype suggestive of follicular helper T cells (FTH). These findings were consistent with hepatosplenic T-cell lymphoma (HSTCL) (Figure 4).

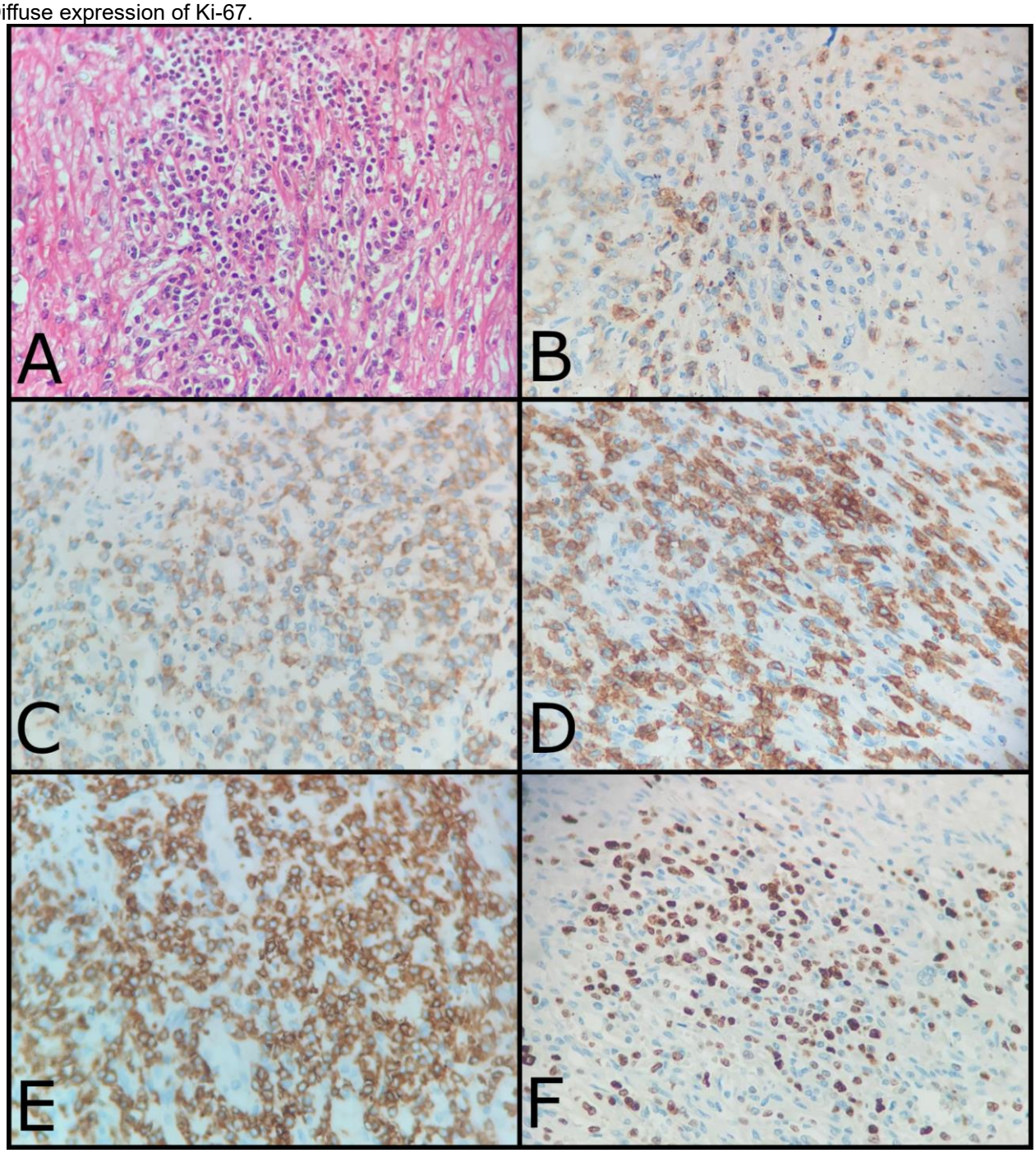
Table 1. Immunohistochemistry panel of splenectomy product. (+/-), weakly reagent. (+), reagent. (-), negative.

Antigen	Antibody	Result	Antigen	Antibody	Result
BCL6	Gl191E/A8	-	CD68	KP-1	-
CD10	SP67	-	CD7	SP94	+
CD2	MRQ-11	+/-	CD8	SP57	-
CD20	L26	-	DESMIN	DE-R-11	-
CD3	2GV6	+	EBV	CS1-4	-
CD30	Ber-H2	-	GRANZYME B	Polyclonal	-
CD31	JC70	-	HHF35	HHF-35	-
CD34	QBEnd10	-	Ki-67	30-9	+ (3-20%)
CD4	SP35	-	PD1	-	-
CD5	SP19	-	TdT	Polyclonal	-

Revista ARACÊ
ISSN: 2358-2472

CD56	MRQ-42	+			

Figure 4. (A) Exuberant and atypical lymphoid infiltration with a sinusoidal pattern in the splenic parenchyma, involving the red pulp and showing atrophy of the white pulp (HE, 100x). (B) Tumor cells displaying weak positivity for CD2 and mild positivity for (C) CD3. (D) Tumor cells diffusely positive for CD7 and (E) CD56. (F) Diffuse expression of Ki-67.



The patient was referred to the hematology-oncology service for further management and maintained stable hematimetric levels 9 months post-surgery, with no recurrence of any cytopenia (Table 2).

Revista ARACÊ
ISSN: 2358-2472

Table 2. Hematimetric values before and after splenectomy.

	D -2	D -1	D0 *	D1	D2	D4	D7	D24	D45	D80	D112	D223	Reference range
Hb (g/dL)	5.2	5.9	5.5	4.2	8.6	6.8	7.5	8.8	11.6	13.6	14.3	15.0	13.5-17
Hct (%)	14.8	17.0	15.9	11.5	23.8	19.6	22.5	27.3	34.8	38.1	41.7	43.7	41.0-53.0
Leukocytes (/mm3)	1310	1020	1280	14020	25640	11360	8410	6260	5890	7830	8880	8670	4,500-11,000
Band cells (/mm3)	78 (6)	81 (8)	128 (10)	560 (4)	2564 (10)	568 (5)	336 (4)	187 (3)	117 (2)	0	0	0	221-1,210 (5.0-11.0)
Neutrophils (/mm3)	1087 (83)	887 (87)	921 (72)	12057 (86)	20512 (80)	9088 (80)	6307 (75)	3943 (63)	3003 (51)	4776 (61)	5772 (65)	5375 (62)	1,620-7,260 (35.0-66.0)
Platelets (k/mm3)	32	37	32	76	202	223	428	961	523	489	438	376	150-400

Values in parentheses represent the percentage of band cells and neutrophils relative to leukocytes.
D0*, splenectomy. D -1, one day before splenectomy. D 1, first day after splenectomy.
D, day relative to splenectomy. Hb, hemoglobin. Hct, hematocrit.

DISCUSSION

Hepatosplenic T-cell lymphoma (HSTCL) is characterized by hepatosplenomegaly, which may be accompanied by abdominal discomfort, cytopenias (eventually pancytopenia), and B symptoms (fever, night sweats, and weight loss). Superficial lymphadenopathy is typically absent. Due to hepatic involvement, jaundice and elevated transaminases may occur. Other findings, such as hemolytic anemia, purpura, and other hematologic manifestations are common. This disease is more frequently observed in young male adults, as seen in the present case. Case series indicate that splenomegaly is present in nearly all patients, while hepatomegaly affects slightly more than half of them (Rahman et al., 2021).

The diagnosis is challenging. The presentation with hepatosplenomegaly and pancytopenia can be mistakenly diagnosed as visceral leishmaniasis, a condition particularly prevalent in the region of this report. Early stages may also be confused with viral and parasitic infections, such as malaria, which is also common in our region. Benign

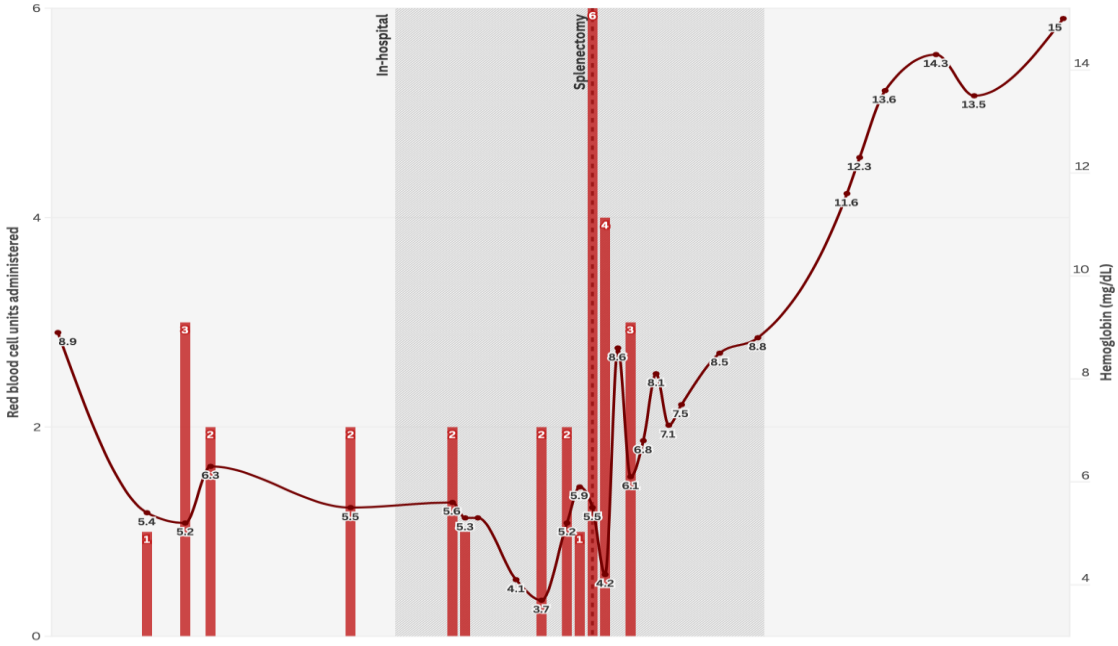
Revista ARACÊ
ISSN: 2358-2472

hematologic conditions, such as marrow suppression secondary to substances and idiopathic thrombocytopenic purpura, are also frequently misdiagnosed (Din et al., 2020).

Splenectomy was once the most common diagnostic procedure, but with current advancements, it has been largely replaced by bone marrow and liver biopsies (Rahman et al., 2021; Pro B et al., 2020). In our patient, the bone marrow biopsy did not assist in the diagnosis, as its involvement is variable (72-100%) (Vega et al., 2001; Yabe et al., 2016; Macon et al., 2001; Weidmann, 2000; Rahman et al., 2021).

The prognostic effect of splenectomy remains uncertain. Reports show immediate improvement in cytopenias after the procedure (Nagai et al., 2010), as well as variable improvements in the patient's condition (Weidmann, 2000). In our case, splenectomy was required due to progressive hypersplenism, with significant improvement following the procedure and sustained benefits (Figure 5).

Figure 5. Hemoglobin concentration curve (dark red line) and administered red blood cell concentrates (light red columns) over time. The dashed line indicates the date of splenectomy, and the shaded area represents the hospitalization period



Similar to any invasive surgical procedure, splenectomy presents inherent risks and potential complications. The blood dyscrasia typical of this condition may increase surgical risks, as seen in a patient who developed refractory bleeding after surgery and subsequently died (Sukrisman et al., 2023).

Revista ARACÊ
ISSN: 2358-2472

Pancytopenia, or sometimes just bicytopenia, is a subject of speculation. Bone marrow biopsy showing no evidence of involvement in these patients has led to hypotheses regarding marrow suppression by cytokines produced by Tγδ cells. One report highlighted the observation of emperipolesis in bone marrow biopsy, which could contribute to this phenomenon (Gabra et al., 2024). Bone marrow infiltration may also contribute to the degree of cytopenia. However, as seen in several reports, including the present one, with immediate improvement in cytopenias following splenectomy, the authors believe that hypersplenism is the primary factor associated with this condition (Lv et al., Hypersplenism: History and Current Status, 2016).

The prognosis for patients with hepatosplenic T-cell lymphoma remains highly unfavorable, as the median survival time is typically less than one year. Furthermore, the 5-year survival rate for these patients is alarmingly low, ranging between 10% and 15%, indicating the aggressive and often fatal nature of this rare form of non-Hodgkin lymphoma (Durani et al., 2017; Vose et al., 2008).

CONCLUSION

This study highlights the importance of a thorough differential diagnosis in cases of hepatosplenomegaly of unknown origin. Splenectomy, in such contexts, can serve as both a diagnostic and therapeutic approach, aiding in the identification of rare conditions like hepatic splenic T-cell lymphoma. Despite repeated attempts to diagnose lymphoma and multiple biopsies, the pathology only revealed an atypical lymphoid infiltrate until the immunohistochemistry panel was performed, which ultimately confirmed the diagnosis.

The prognostic impact of splenectomy in patients with this condition remains unclear. Further research, ideally in larger, specialized centers, is essential to better understand the long-term outcomes and potential benefits of splenectomy in treating and managing hepatic splenic T-cell lymphoma.

ETHICAL STATEMENT

This single-arm observational study was approved by the Ethical Committee on Human Research of the Hospital Universitário Maria Aparecida Pedrossian (CEP/HUMAP-UFMS) by protocol number CAAE: 85354724.3.0000.0320.

Revista ARACÊ
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Revista ARACÊ
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