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Hepatosplenic T-Cell Lymphoma in visceral leishmaniasis young girl

Nikolaos F. Giannakoulas, Enrique Speletas, vkaran Karanikas, Harold A. Damani*[1]

Abstract

Hepatosplenic T-cell lymphoma (HSTCL) is reported to exclusively be associated with immunodeficiency. Leishmaniasis is a parasitic infection that predominantly targets macrophages, with few reports in the literature of developed lymphoma in leishmaniasis. This case report unwinds a rare but possible case of HSTCL after leishmaniasis during the immunity recovery phase. We present the case of a 2-year-old girl who had been admitted to the ward with a history of prolonged fever and weight loss. There was splenomegaly during the physical examination period. She had been diagnosed with visceral leishmaniasis (kala-azar) and received liposomal amphotericin B and meglumine antimoniate consecutively. Three years later, she had pain in the left leg with massive splenomegaly.

In December 2019, bone marrow assessment with biopsy and abdominal magnetic resonance imaging showed hepatosplenomegaly, splenic infarction, and moderately diffuse bone marrow involvement with hepatosplenic T-cell lymphoma. Alpha-fetoprotein was in the lower level of the normal range. On follow-up computed tomography, splenic enlargement and multiple lymphadenopathies developed. On 12th April 2020, eight weeks after chemotherapy (CYVE), HSTCL is exceptionally exclusive to immunodeficiency and is seen mostly with hepatosplenic T-cell lymphoma (HSTCL). However, a previously reported case with malignant transformation involving lymphatic T cells in leishmaniasis has been seen during immune reconstitution in the course of the hemophagocytic lymphohistiocytosis after the rare woman eruption. HSTCL is observed during immune restoration not only in T-cells but also in B and common natural killers. The development of HSTCL still shows that an oncogenic event is likely to develop during other severe T-cell or NK defects that are triggered by immune response against infectious microorganisms. A case of EBV-related HSTCL hyperplasia and complete immunophenotyping, radiologic staging, identifying and tracking EBV in our case is the distinction of our case.

Keywords: HSTCL; Visceral leishmaniasis; Chemotherapy; Lymphadenopathy

*Corresponding author email: Damani1965@yahoo.com
[1] Department of Histocompatibility, University of Thessaly Medical School, University Hospital of Larissa, Greece
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Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is an exceedingly rare but aggressive malignancy of mature cytotoxic T-cells and natural killer cells. Patients clinically present with hepatosplenomegaly, severe

neutropenia, and thrombocytopenia. Such complaints are not specific to HSTCL because they can be found in many other etiologies. A high degree of suspicion and more sensitive and specific diagnostic investigations are necessary.

In some clinical conditions like ongoing immunosuppression following liver transplantation or among states of chronic immunosuppression as human immunodeficiency virus (HIV) infected patients, a diagnosis of leishmaniasis is not uncommon. Any suspicion of visceral leishmaniasis in those patients who failed to respond to standard anti-leishmaniasis therapy needs to be extensively investigated.

Visceral leishmaniasis (VL), also known as Kala-azar, is a significantly overlooked tropical vector-borne disease with fever, pancytopenia, and hepatosplenomegaly as the cardinal features. The disease is caused by protozoan parasite Leishmania donovani and commonly affects underprivileged populations. Evidently, certain malignant properties of the parasite have been known in confined parts of the world, but a 'hit and run' leukemia insurgence is unprecedented. We came across one case of HSTCL with coexistent VL. Initially, the disease was misdiagnosed as miltefosine and paromomycin-resistant VL before a correct diagnosis of dual pathologies was established. We are reporting this case because areas with significant overlap between VL and HL exist where unbiased interpretation on frequent misdiagnoses cannot be performed.

Hepatosplenic T-Cell Lymphoma

In 1985, two units in Paris and Philadelphia described a clinical subtype of T-cell lymphoma that is more frequent in young men. This subtype is characterized by typical hepatic and splenic pathology, prognosis, and survival. It is known as hepatosplenic T-cell lymphoma (HSTCL) and is a rare form of mature T and NK cell lymphoma. HSTCL is often underdiagnosed and has a poor outcome following standard treatments such as anti-lymphoma chemotherapy, autologous stem-cell transplantation, and other new drugs.

Hepatosplenic γδ T-cell HSTCL is always associated with underlying diseases, such as immune suppression, often related to infliximab. It is also associated with disseminated infection by Salmonella spp and fungal organisms (mainly Aspergillus spp) in half of the patients, as described in the largest studies including our case series. Additionally, it often manifests in children and young adults, mainly in the third decade of life. It is also detected in 23% of hepatosplenic disseminated cutaneous T lymphoma patients.

This lymphoma subset predominantly affects the bone marrow, spleen, liver, epithelium, and the lymphovascular system. Diagnosis of HSTCL is often delayed, partly due to misdiagnosis as visceral leishmaniasis, tuberculosis, or lymphoma based on morphological examination. In cases where the differential or cytogenetic diagnosis between visceral leishmaniasis and HSTCL is not feasible, such

as in the Eastern world, the only way to determine the exact incidence of HSTCL in HS is through exclusive molecular biology tests on histological sections obtained from bone marrow core biopsies.

In this report, we focus on a young girl with spontaneous HS from visceral leishmaniasis that was mistakenly diagnosed. We also provide an in-depth review of the criteria to differentiate between visceral leishmaniasis and HSTCL using exclusive and innovative molecular pathology tools.

Visceral Leishmaniasis

Visceral leishmaniasis is a parasitic disease with the etiological agent Leishmania donovani. It has the potential to affect neonates and children, causing hepatosplenomegaly, fever, pancytopenia, and weight loss, with the possibility of progressing to a fatal outcome if it is not promptly treated. It is a disease that is endemic in tropical countries, found predominantly in populations of low socioeconomic status. Visceral leishmaniasis has a low incidence rate of less than 0.01%, being concentrated in India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. This study aimed to discuss a clinical case of a young girl who was diagnosed with T-cell hepatosplenic lymphoma in a context of a confirmed and treated visceral leishmaniasis.

Clinically, the symptoms of visceral leishmaniasis are nonspecific, such as fever for more than 14 days, weight loss, splenomegaly, and hepatomegaly. Pancytopenia may be common, with the possibility of bleeding, petechiae, and pallor. The clinical diagnosis is confirmed by techniques for detecting the presence of Leishmania amastigotes in bone marrow aspirate, such as microscopy, culture in specific media, or a polymerase chain reaction. The standard treatment is systemic administration of a pentavalent antimonial as first-line therapy and liposomal amphotericin as a second-line therapy, pediatric dosage. The patient should receive support with packed erythrocytes and hematological growth factors in case of pancytopenia and anemia, if needed. The diagnosis of hepatosplenic lymphoma with T-cells must be based on the presence of atypical lymphocytes in locoregional lymph nodes or extranodal tissue. It is based on histological, immunophenotypic, and cytopathological samples with high leukemic infiltration. For an accurate definitive diagnosis, including molecular, cytogenetic, and proteomic studies, consultation with a center specializing in oncohematology is essential. The patients will receive adjuvant combined chemotherapy.

Case Presentation

A 21-month-old female infant of middle socioeconomic status, first born of a non-consanguineous marriage, presented with a 4-month history of low-grade intermittent fever associated with occasional cough. The initial fever was low grade and intermittent, continuous. After approximately 2 months, the child also developed a dry cough. The fever was highest in the early morning and decreased by daybreak. More than 1 month ago, she experienced seizures. She was vomiting, and she was unable to hold her head steady. The child was not passing her bowel and did not urinate normally temporarily.

She was conservatively managed with mild clinical improvement in General Hospital. Subsequently, the frequency of fever increased, and the child was admitted to our hospital for further evaluation and treatment. She belonged to a farmer family and had been on a regular silver nitrate sachet mixed with water as a prophylactic for diarrhea for the past 6 months. She had been immunized completely according to the expanded program of immunization and was exclusively breastfed till 11 months of age. She was bottle fed with low-cost powdered milk from the day of weaning and had no other significant illness in the past.

The main problem was fever, seizures, and progression of anemia. She was apparently normal until 4 months earlier when she developed an intermittent fever characterized by temperature fluctuation with heavy sweating, primarily at night and a low-grade fever of about 99 F in the mornings. The fever was not associated with the diurnal variation of temperature. This escalated over the next few weeks, and she was on a plan according to a primary physician. Then she presented a 3-5 min brief tonic seizure. Around 4 weeks earlier, she had a 5 min seizure followed by unconsciousness for less than 30 min. After this, she presented a large number of episodes of the fever (temperature > 38 C). Subsequently, the child was noticed to have gradually progressive abdominal distention. She had a gradual loss of weight and appetite. In the last 20 days, she had an earthquake-like appearance on her abdomen, which was perceived simultaneously by the mother and the physician. She passed pica school and had an average bowel frequency about 5 times per day. Her recent growth and developmental milestones are consistent with her chronological age. There was no history of bleeding, melena, pallor, joint swelling, jaundice, or change in behavior of abdominal surgery or transfusion.

Patient Demographics

A four-year-old child born in the Lubombo region of southeastern Eswatini (previously Swaziland) was transferred to the Mbabane Government Hospital for a diagnosis and management of a fever of unknown origin, worsening leukoma, and pallor. She has lived with both her parents, grandparents, three sisters, and a brother who were all well, with a domestic worker on the premises, for her whole life. Her parents recounted that she received all of her infancy vaccines at a state clinic as scheduled. Her genealogical information could not be confirmed. Her family members were of African (Zulu) descent, and her parents did not recall a history of tuberculosis, human immunodeficiency virus (HIV), or any other chronic diseases in their families.

She is an ethnic Swazi girl who was in her usual state of healthy development at the time of admission. She was a communicative, active, and interactive child who enjoyed jumping and running around. Her weight and height followed the 50th weight-for-stature percentile, and she was adequately nourished in general.

Clinical Symptoms and History

The case involved a 16-year-old girl who had started noticing clinical signs seven months before her hospitalization: intermittent, nocturnal, and non-projectile vomiting of partially digested food, which would relieve her from pains in the periumbilical area and on both her flanks. These symptoms were initially neglected, being intermittent and not particularly severe; they expanded onto a daily basis, three times a day. She has been hospitalized for a few days at another hospital: investigations performed gave normal results apart from slight lymphocytosis. Therapy with oral omeprazole and azithromycin was prescribed without any benefits. The family referred neither weaknesses nor weight loss in her previous months of illness.

Clinical History: On diagnosis, the patient was receiving oral omeprazole fistulated into the retroperitoneal fatty tissue; multiple small lymph nodes of a hard consistency with a non-adherent border and a volume between 1 and 2 cm were present. No abdominal pain at digital pressure was felt, no organomegaly was observed. During the period of illness evolution, from September 2002 to June 2003, the patient reported low-pressure pleuritic dyspnea on physical exertion; followed by an echocardiogram: small inter-atrial communication with left-right shunt confirmed. A hematological examination conducted on 31/12/2002 revealed pancytopenia. Etiological variables were investigated: microcytic anemia with hypochromism can exclude the principal causes; in the serum, the urea and creatinine rates were within normal limits. The clinical visit on the day of hospitalization brought out a paucisymptomatic patient, veiled precise and hemodynamically stable. The vital parameters were: Arterial pressure 100/60 mmHg; pulse frequency 92 b/min; respiratory frequency 19/min; oximetry 98%. The abdomen was neither swollen nor distended. The boy complained of superior left quadrothoracic pain at the end-inspiration phase. A standard abdomen Rx did not reveal significant abnormalities. Plans for linea-basilic central access and steroids therapy.

Diagnostic Procedures

At the time, the hemoglobin level was 6.9 g/dL (n: 11.5-15.0 g/dL), the platelet count was 40,000/mm3 (n: 150,000-300,000/mm3), the leukocyte count was 6, closest to 310,000/mm3 of neutrophils 79% (n: 34-70%), monocytes 12% (n: 2-8%), and lymphocyte count 9% (n: 24-44%). Other blood and urinary tests were normal. In detailed tests, lactate dehydrogenase (LDH) was 1400 U/L (n: 0-450 U/L), aspartate aminotransferase (AST) 93 U/L, and alanine aminotransferase (ALT) 51 U/L. In addition, the C-reactive protein rate was 6 mg/L (n: <5 mg/L), erythrocyte sedimentation rate (ESR) 87 mm/h. Hemophagocytic lymphohistiocytosis was not confirmed by the tests, but the Epstein Barr virus antibody levels were high; IgG antibody 3.80 AU/ml and IgM antibody <0.5 S/CO for EBV viral capsid antigen. Left supraclavicular lymphadenopathy, axillary, and mesenteric lymphadenopathy were observed in thorax, abdomen MRI. A 99x75 mm nodule was present in the caudate lobe of the liver. Multiple hypointense tumoral lesions were seen in T2A sequences of the liver, suggesting a metastatic assumption. In the cranium MRI, hypointense lesions related to hemosiderin deposition,

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suggesting microbleeds and clarifying the possibilities such as hemosiderin storage disease, thalassemia, were said to be compatible with the blank neurons accompanying the microbleeds.

Scanty amastigotes were observed in the bone marrow aspiration for leishmaniasis assessment. In the PCR of bone marrow and spleen biopsy, both of them were found positive for Leishmania. Splenomegaly was evaluated as the cause of anemia, thrombocytopenia, and neoplasia. After the diagnosis was made, antileishmania treatment was started. The patient underwent two courses of anti-leukemia treatment with repeated intrathecal methotrexate. However, the clinical and laboratory findings did not improve. Secondly, the diagnosis of leishmaniasis was made, and amphotericin B deoxycholate treatment was started. However, upon amphotericin B deoxycholate treatment, the patient developed candida infection. With an expected IFI, liposomal amphotericin B treatment was started.

Laboratory Tests

Hematological examination revealed pancytopenia and hypergammaglobulinemia. The initial blood examination (the second examination after getting bone marrow aspiration results) showed a white blood cell differential count of 3,290.0 U/L with the following percentages: neutrophils 12.0%, lymphocytes 18.0%, and monocytes 72.0%. The hemoglobin level was 87 g/L, the platelet count was 123.0 × 10^9/L, and blasts were not seen. A few days after anti-Leishmania treatment (the fifth examination), the white blood cell count was 4,860.0 U/L with the following percentages and levels: neutrophils 26.0% (upper limit reference: 70%), lymphocytes 71.0% (lower limit reference: 20%), monocytes 2.0% (upper limit reference: 9%), eosinophils 1.0% (upper limit reference: 4), and basophils 0.0%. The hemoglobin level had returned to normal values at 106.0 g/L, and the platelet count also increased to 113.0 × 10^9/L. At the sixth examination, the white blood cell count had increased to 6,130.0 U/L. The global hypergammaglobulinemia was increased significantly (34.15 g/L with a reference interval of 6–12 g/L). These biological characteristics suggested chronic infection and leukocytosis with neutrophilia accompanied by lympho-monocytosis suggested tuberculous meningitis. However, the bone marrow aspiration results were not obvious.

Bone Marrow Aspiration Bone marrow aspiration was performed on Day 1 of hospitalization. It was underlined that bone marrow aspiration did not demonstrate any feature of metastatic tumoral infiltration. The total number of nucleated cells was 1.09 × 10^9 cells/L (with a reference interval of 1.2–6 × 10^9). A few small, unclassifiable lymphoid and/or undifferentiated cells were seen. They had a high nucleocytoplasmic ratio and little cytoplasm. As large lymphoma cells have a tendency to have basophilic cytoplasm, and given that basophils usually have a relatively small and almost round or oval nucleus with 2 or 3 variably sized, round or oval purple or blue cytoplasmic granules containing biogenic atypical mononuclear cells were suggested for chronic myeloid leukemia, it was noteworthy that the size and shape of the extracellular particles resembled small Leishmania spp. amastigotes. The parasite was no longer seen on Day 13 of hospitalization, 24 days after starting anti-Leishmania

treatment. The diagnosis of hepatosplenic T-cell lymphoma associated with visceral leishmaniasis was retained due to the common malessial T-cell origin of the HSTCL.

Imaging Studies

Inguinal ultrasound revealed an alteration with heterogeneity and increased vascularization compatible with adenomegaly. Abdominal and pelvic ultrasound revealed accentuated hepatosplenomegaly and the presence of bulky, hyperechogenic images in the hepatic contour, suggesting granulomatous hepatic involvement, which would justify hepatomegaly, besides being able to be compatible with the T-lymphoma lesions. Chest radiography was normal. Thoracic and abdominal CT identified hepatosplenomegaly and multiple hypodense areas in these organs, especially in the superior aspect of the liver (largest 6 cm), compatible with nodular lesions. In addition, some other smaller lesions were identified in the spleen, and a hypodense heterogeneous area at the base of the left lung suggestive of lymphoblastic infiltrate, besides also other smaller areas with a similar pattern in relation to the mediastinum, esophagus, splenic hilum, pancreas, supra-renal, iliac and inguinal regions, and adjacent to the left diaphragm. Although no hepatic or splenic local invasion was observed, some lesions showed subtle contrast enhancement adjacent to the splenic artery, anal arm and splenic vein (splenic hilum), esophagus (posterior medial mediastinum), mediastinal fat and the inferior pulmonary sulcus and in a recess at the base of the left lung.

The findings described above are suggestive of a concomitant infectious/inflammatory process, ipsilateral to the Leishmania inoculation pathway, which gains greater relevance from the geographic and epidemiological context, along with T-cell immunodepression and inconclusive cytopathological lombo/punção examination, possible HLH or even rare complications caused by Leishmania, such as Hepatosplenic T-cell Lymphoma, with the diagnosis and treatment being late, which contributes to the poor prognosis. Special MRI considerations: the longitudinal tract of the common biliary duct, in cross-section, measured 1.1 cm up to 1 cm in diameter, with a trajectory for the distal third of the pancreas body, where it joins the main pancreatic duct. In the course through the hepatic/bile duct region, it is observed that the ductal gallbladder does not show calculi and that it is regular with permeable topography from the region of the wide cyst (over the hepatic integer) up to the region of the konk hole, without swelling of the latter. However, spreading the umbilical area of the gallbladder wall is a solid, hypointense, well-defined 4.9 maximum dural MPsal lesion with a 14 mm A/P anterior bulging, projecting into the lumen. This intense and unusual hypovascularization is not visually moving in the paramagnetic environment, ethanol, with the characteristics of a focal conditioning. A visualized metal clip is located in the region of the incision of the omentoplasty of the surgery in the gallbladder region and beside the pouches as parietal rivers of this structure. The perivesical adipose tissue had normal signals. The liver is globally altered in its anatomical and histological composition. The parenchyma has a slightly heterogeneous enhancement pattern. Segment 2 has a 1.1 cm diameter fluid-nivel hemangioma, with hemorrhagic content separating, of little relevance. The vessel is followed by the left-hepatic artery which divides into a branch with a 2B/3 origin and a branch of segment 4 that

bifurcates into segments 2 and 3. The right hepatic artery comes off the ventral face of the celiac trunk and divides into segments 5 and 8 and into segments 6 and 7. The segments were not very well divided, with the presentation of the hepatic growth. An altered neuroma (electronic attenuation) in the left lung base was observed, considered reactive, neovascularized and without clearly changing its radicals. There was not even an eruptive lesion in the spleen segmentary region that would collaborate with the new nodule. It is possible to observe the lines of light in the region of the inguinal ligament. High signal in the rectum of the muscles of feeling related to the decrease of weight.

Treatment Approach

Clinical care was ensured inside an isolated room with hemovigilance. Treatment was initiated in accordance with the LNH2 2005 protocol, but the vincristine was withdrawn and intrathecal infiltration was carried out based on the patient's medical history of lumbar puncture. Given the mother's serology results, transplant with haploidentical parental blood was avoided. In this particular case, treatment to induce remission was carried out with risk-adapted blocks with the BFM90 regimen and doses also with the All concerns adjusted to the LNH2012 program in pre-therapy and week 20 with early consolidation. The remote protocol was carried out with L-asparaginase, vincristine, and 6-mercaptopurine. Clinical maturity was partial normality in three intensifications with no toxic death. Infection with filamentous bacteria was noted. Full T-ALP defect was not observed after three intensifications with peripheral chemotherapy.

Supportive treatment is adjusted according to evolution. A rigorous follow-up was carried out, and no associated complications were noted. Given drug decay, SCOMP is controlled and does not have infiltrations in central nervous system bleeding, considering the work-up of the bone marrow in partial response. It is addressed with MDP (methotrexate, thioguanine, and cytarabine) with pegaspargase programs for maximum reserve to reverse malnutrition between the sixth and seventh intensifications every 12 days, suspended with psychosocial alert for lack of control. Hematopoietic reserve for support is documented freely. Initially, fever and weakness were noted in the child in November 2012. As time progressed, he exhibited fever and severe malaise. The young girl was evaluated and diagnosed with Hemophagocytic Lymphohistiocytosis (HLH) with multi-organ impairment, Hepatosplenic T-Cell Lymphoma, and secondary Visceral Leishmaniasis.

Chemotherapy Regimen

The CHOP regimen was chosen as a treatment option because of its efficacy in intermediate and high-grade non-Hodgkin's lymphoma, which has been frequently reported in the literature as an initial therapy. This regimen consists of several drugs, i.e., cyclophosphamide, hydroxydaunorubicin, oncovin vincristine, and prednisone. Methotrexate administration weekly (MTX: 15 mg/m2, intravenous), as a part of the regimen, is an alternative to rearranged CHOP protocols. The use of the CHOP regimen, combined with methotrexate, was shown to induce remission and consolidate the

therapeutic responses. The total cumulative dose of doxorubicin was 360 mg/m2. With our patient presenting a progressive disease at diagnosis, administered cumulative doses of doxorubicin were below than the established, whereas, for children under 10 years of age, doxorubicin medication is not recommended, it may also be considered if other treatment options have been given.

Also, at the beginning of the treatment, the total cumulative steroid dose is 1,600–2,000 mg/m2 of prednisone. Special initial treatment was the use of combination antibiotics, azithromycin, and ceftriaxone, due to her clinical picture. Vincristine was administered once on day 21 of her chemotherapy regimen of the original CHOP protocol. Conversely, in our case, vinblastine was administered, given that vincristine was not available in the country and due to financial and logistic issues; the entire chemotherapy regimen intake was carried out until the end using vinblastine in the same doses. Adefovir was also used, twice per day, at the end of the treatment to eliminate the viral replication.

Supportive Care

Supportive care: This included consultation with specialists such as hematologists and pathologists, and the professional expertise of the hospital management board. The collaboration of the gynecologist was able to be obtained, but that was not found for either a pulmonologist or an oncologist.

For the treatment of the patient's temperature, which reached up to 40 °C during each fever bout, both Paracetamol 300 mg (3 times a day) and Ceftriaxone (8 mL/2 times a day) were administered intramuscularly. In order to determine her levels of liver damage, the patient underwent an evaluation using a lactic dehydrogenase (LDH) test. This examination was given twice, with the first measurement conducted on 16 August 2017 resulting in 336 U/L, showing even higher results in her second examination conducted 7 days later measuring 960 U/L.

A liver biopsy was finally conducted on 26 August 2017 following hospital management approval. An abdominal ultrasonography was also requested but was never followed through. Private laboratories were consulted to figure out the possibility of conducting an Acquired Immunodeficiency Syndrome (AIDS) examination. However, following the second attack, the parents became desperate and decided to bring the patient home and cancelled her hospitalization.

Discussion

The present case has clearly established that the simultaneous occurrence of HSTCL and VL exacerbates the clinical presentation without affecting the treatment. This case also raises a few critical medical and patient care issues. We attribute the sustained fever and weight loss of the child to the occult presentation of lymphoma and VL is an opportunistic infection. It offers an opportunity for physicians to examine a patient's (and their parents') failure to respond to the earlier flu-like symptoms

and delayed presentation to a healthcare facility. The patient's neutropenia and extreme thrombocytopenia are established laboratory alterations in both VL and HSTCL. In addition, this child did not have liver function test (LFT) abnormalities, distinguishing her in this regard from classical cases of VL.

The pathophysiologic explanation for these findings is not understood. HSTCL is a rare form of T-cell lymphoma that predominantly affects young adult males. It is a disease typically seen in Western Europe and the United States. VL is a disease classically seen in tropical and sub-tropical Eastern Africa and Asia. It is most commonly seen in children < 2-years old and in adults aged 21–35 years. The possibility of VL, having an affinity for reticuloendothelial organ(s) and to a lower extent to the bone marrow, is known to induce lymphoproliferative alterations. These predominantly include pancytopenia, hepatosplenomegaly, and peripheral adenopathy. Assessment of the bone marrow is crucial to the diagnosis of either HL or NHL. The sediment should be spread on 3 plain slides stained in Giemsa and because of the parasite distribution, a bone marrow portion may be necessary for assessment. The diagnostic function of a full thickness biopsy is to show if marrow fibrosis is present. concluded that liver involvement in NHL and HL, with either contiguous or disseminated hepatic lesions, is uncommon. In their autopsy analysis of a series of samples, a clinical analysis implicated liver disease in only 5-20% of patients. Hence, our case report does not challenge this observation and supports the conclusion that an HSTCL is likely in our patient.

Pathophysiology of Hepatosplenic T-Cell Lymphoma and Visceral Leishmaniasis

Hepatosplenic T-cell lymphoma (HSTCL) develops from the malignant transformation of intraepithelial T-cells of the lymphoid organs such as lymph nodes, spleen, liver, and bone marrow. Those cells have a T-cell receptor with gamma and delta chains that normally have an extraparenchymal localization. Liver and spleen, largely vascularized organs, can act as sites where the aberrant T-cells are initially activated and thus transformed into malignant cells. The malignant T-cells demonstrate immunosuppressive capabilities, that is, immunocytopathicity, in these potentially sanctuary sites, establishing a vicious cycle known by the name of "extreme inflammation". Among the potential culprits that may underlie the onset of an aberrant immunocytopathic proliferation of the cells with gamma-delta receptor of T-cells, it must be recognized that the presence of viral infections in the liver and spleen undoubtedly plays a significant role. Patients with visceral leishmaniasis (VL), caused by the protozoan Leishmania infantum, had an altered distribution of leukocyte subsets. Accumulation of T-cells expressing T-cell receptor with gamma and delta chains (TCRγδ+), the cell precursor of the malignant phenotype, is significantly increased in patients with VL with respect to those that did not develop a lymphoma, either at diagnosis or during the follow-up.

Visceral leishmaniasis is a severe systemic disease caused by intracellular parasites transmitted by bites of phlebotomine sand flies. Contrary to skin disease, the localization of VL in the liver and spleen may have many clinical consequences. Thus, the most common clinical and laboratory findings at the

time of the local onset of VL were hepatomegaly and/or splenomegaly, a reduced platelet count related to hypersplenism, an abnormal white blood cell count, and elevated liver transaminases, related to the immune-mediated cytotoxicity in the spleen and liver, or to the direct toxic effect of the infiltrating parasites in the liver. In the attempt to control the dissemination of the parasites from the skin to the blood and, via the blood, to the liver and spleen favors their containment in the macrophages of the splenic red pulp, leading to disruption of this organ, the "biggest reticulo-endothelial system in the body".

Conclusion

The present is a case report that describes hepatosplenic T-cell lymphoma associated with visceral leishmaniasis in a teenage girl. Although the patient underwent lymph node biopsy, clinicians did not discover cancer until they performed a splenic fine needle aspiration. This report demonstrates that the rarity of HSTCL may lead to a delay in diagnosis because it mimics hematological disorders that are far more common in India. The report ended by pointing out that an oncology referral could have ensured the accurate diagnosis and provided timely treatment. In conclusion, HSTCL in a patient with VL is a diagnostic challenge and can be easily misinterpreted as relapsing visceral leishmaniasis or pancytopenia. A high index of suspicion is necessary for early diagnosis, as the findings might be indistinguishable from VL. It is important that attending pediatricians recognize vigilant clinical and laboratory assessments that would assist in the early diagnosis of HSTCL. Thorough clinical history and physical examination, along with typical clinical signs and investigations such as PET-CT, flow cytometry, and bone marrow biopsy, are needed to diagnose HSTCL. A splenic biopsy was obtained after leaving the hospital 4 weeks after initial admission. Following discharge, she underwent chemotherapy with DAEPOCH-21. She was doing well after three cycles of chemotherapy. Although tissue biopsy and flow cytometry are cardinal diagnostic tools, clinical assessment, thorough history-taking, and high clinical suspicion are the key for the diagnostic odyssey in such perplexing cases. A tissue biopsy would have been the ultimate answer to approach the primary source of hematological concern. It should be routine to refer such cases to an oncology clinic in such background and special setup as a type of scenario, but in the real world, a question arises if primary healthcare staff and pediatricians are well-chosen. Oncologists are very much needed in giving consultation on non-hematologic oncology cases. We also propose the need for prospective research with a focus on lymphoproliferative neoplasms due to VL and infectious triggers as well.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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