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Hepatosplenic T-cell Lymphoma with Coexistent HIV and Malaria: A Rare Clinicopathologic Entity

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Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a rare type of Non-Hodgkin Lymphoma (NHL), grouped under the mature T-cell neoplasms, which is derived from peripheral γδ (or less commonly αβ) cytotoxic T cells [1]. The disease mostly occurs in young male adults (median age of 34), is characterized by B-symptoms and hepatosplenomegaly at presentation and lymphadenopathy is usually absent [2]. The predominant laboratory findings include pancytopenia and abnormal serum liver enzymes and, as the disease progresses, pancytopenia gets worse because of a combination of bone marrow failure, hypersplenism, and/or hemophagocytosis associated with the disease [3]. Histologically is characterized by primary extranodal involvement of medium-sized lymphoid cells, typically within the sinusoids of the liver, spleen and bone marrow [4]. The immunophenotype of the malignant cells is typically: CD2+, CD3+, CD4−, CD5−, CD7+, CD8−, CD56+/-, γδTCR+ [4] CD7+/−, and CD4−/CD8− or, more rarely, CD4−/CD8+ [7]. Cytogenetic studies support the diagnosis of HSTL but are not specific. Isochromosome arm 7q is a recurrent chromosomal abnormality detected in most patients with HSTL, either in isolation or in association with other abnormalities, most notably trisomy 8 [5]. The pathogenesis is poorly understood, with data mainly from case reports or small retrospective studies [6,7]. Nevertheless, up to 20% of HSTL cases arise in patients with chronic immune suppression, including in recipients of solid organ transplants, in patients receiving chemotherapy, or in those treated with immunosuppressive agents [8]. HSTL in patients with previous malaria infections has been described in few cases and its presence in HIV-infected patients has only been described once [9,10]. The disease exhibits an aggressive clinical course with a poor response to current chemotherapeutic regimens. Most patients die from disease progression within 2 years of diagnosis and the 5-year overall survival rate is 7%. Yet, recent reports suggest that intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation (SCT) may result in long-term remissions [11]. The authors herein describe an extremely exceptional association: a case of HSTL in a HIV-infected patient who suffered three previous malaria infections.

Case Report

A 53 year-old man with a medical history of diabetes mellitus presented with a 4-month history of fever, night sweats, fatigue, productive cough, recurrent respiratory infections and a 10 kg weight loss. He had been working in Angola in the last 11 years as an engineer and had returned to Portugal recently. While in Angola he reported three previous episodes of malaria. Physical examination was significant for mucosal and conjunctival pallor and a marked hepatosplenomegaly (palpable spleen 6 cm below the costal margin) no lymphadenopathy was noted. Laboratory studies revealed the following: white blood cell count of 3350/μL (absolute neutrophil count, 1088/μL), hemoglobin of 7.5 g/dL and platelet count of 92000/μL. Renal and liver function

tests were within normal limits. Serum lactate dehydrogenase (LDH) was 582 U/L (normal level, 135-225 U/L) and uric acid was 9 mg/dL (normal level, 2.6-6.8 mg/dL). Plasmodium antigen was negative. The serology for human immunodeficiency virus (HIV) was positive, with CD4 T cell count of 110 cells/μL (700-1100 cells/μL) and CD4/CD8 ratio 0.2 (normal ratio 1,1-4,0). Computed tomography (CT) of the chest, abdomen and pelvis revealed hepatomegaly and splenomegaly and there was no evidence of lymphadenopathy (Figure 1). His bone marrow biopsy was mildly hyper cellular with sinusoidal infiltration by cells that were positive for CD3 which highlights the sinusoidal infiltrating pattern (Figure 2a,b). It also has atypical lymphocites, neoplastic T lymphocytes positive for CD8 and negative for CD4 (Figure 2c,d). Flow cytometry performed on the bone marrow aspirate further characterized them as γδ T cells CD2+/CD3+/CD4−/CD5−/CD7+/CD8+/CD56+). Bone marrow cytogenetic study revealed a normal male karyotype. The patient was diagnosed with stage IVB HSTL and was treated with 4 cycles of ICE (ifosfamide 5g/m^{2} on day 2, carboplatin AUC 5 on day 2, etoposide 100 mg/m^{2} on days 1, 2 and 3) alongside with antiretroviral drugs (emtricitabine, tenofovir and
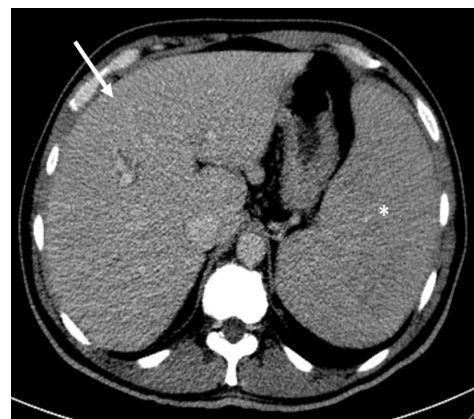

Figure 1: Abdominal computed tomography demonstrates massive hepatomegaly (→) and also splenomegaly (*) in a patient with hepatosplenic T-cell lymphoma.

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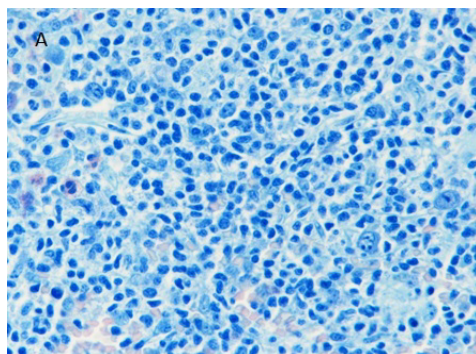
Figure 2a: Morphologic features and immunohistochemical findings in the bone marrow aspirative (in HSTL). A, representative Nodular infiltrate of small to medium size lymphocytes.
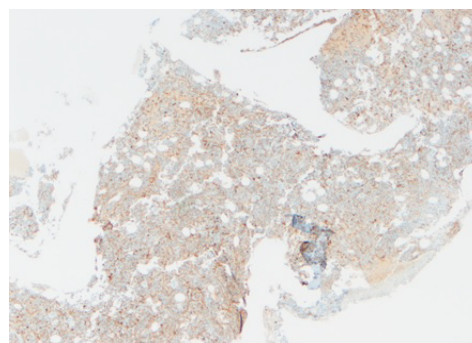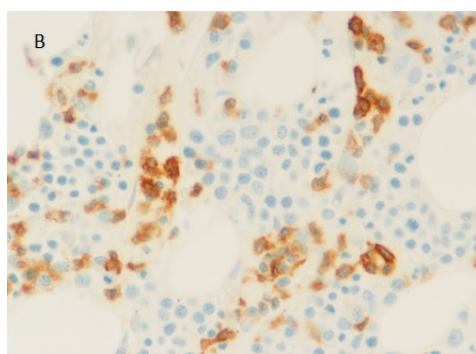

Figure 2b: The HSTL cells in the bone marrow are positive for CD3, which highlights the sinusoidal infiltrating pattern (CD3, original magnification x400).
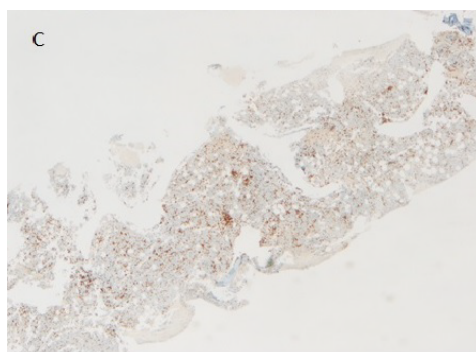

Figure 2c: Neoplastic T lymphocytes positive for CD8 (CD8, original magnification x20).

darunavir). Treatment was well tolerated with one hospitalization, for neutropenic fever of unknown etiology that resolved with supported care. Four months and following the treatment with ICE, physical examination was remarkable for non-palpable spleen. CT scan at this time revealed no organ enlargement. Repeat bone marrow biopsy demonstrated normocellular marrow with no evidence of abnormal lymphocytes, consistent with morphological remission. Nearly 2 months following the final cycle of ICE, the patient underwent auto-SCT following conditioning with BEAM (carmustine, etoposide, cytarabine nd melphalan) chemotherapy. The patient is currently 12 months from time of diagnosis and 6 months post auto-SCT and remains in clinical remission.

Figure 2d: Neoplastic T lymphocytes negative for CD4, presence of rare CD4+ positive lymphocytes (CD4, original magnification x40).

Discussion

HSTL is a rare aggressive type of peripheral T-cell neoplasm that was first described by Farcet, Gaulard et al., in 1990, and since then only a limited number of cases have been reported [12]. The patient described presented with common clinical and laboratory features found in this entity: B-symptoms, hepatosplenomegaly and cytopenias. Abnormal cytokine releases from the neoplastic T-cells are thought to be responsible for the systemic symptoms. The spleen and liver enlargement is caused by infiltration and proliferation of malignant T-cells within these organs Anemia and thrombocytopenia have largely been attributed to hypersplenism and to infiltration of the bone marrow by neoplastic cells and neutropenia, that is less commonly encountered, is associated to the interferon γ production by neoplastic γδ T cells that suppress hematopoiesis in the bone marrow. The diagnosis was performed by a combination of histology, flow cytometry and cytogenetic analysis. Tumor cells originate from peripheral γδ (and less common αβ) cytotoxic memory T-cells of the innate immune system. Cytogenetic abnormalities namely isochromosome arm 7q, either in isolation or associated with trisomy 8 is present in most cases. Serum bilirubin level ≥1.5 mg/dL, αβ TCR expression, and trisomy 8 each correlated significantly with shorter overall survival and event free survival [13]. The events leading to HSCT remain to be elucidated. Of interest, however, HSTL has been associated with immunodeficiency since approximately a quarter of the patients have a history of immune suppression, including those in post-transplant setting, or those treated with immunosuppressive agents such as azathioprine and infliximab for Crohn's disease. Additionally, a few cases have been reported in association with viral (Epstein-Barr virus, hepatitis B virus and HIV) and parasitic (malaria) infections [14,15]. With regard to the association between HSCT and viral infection, it has been postulated that chronic antigen stimulation in the setting of immune deficiency might have a role in the pathogenesis of HSTL [16]. Although viruses do not seem to transform the T cells directly by integration into their DNA, the chronic antigen stimulation from viral infection may drive the proliferation of polyclonal γδ T-cells, setting the stage for cytogenetic and molecular anomalies, such as iso chromosome arm 7q, and eventually transforms a T-cell clone. As far as malaria is concerned, a relationship between previous P. falciparum infection and lymphoma genesis has not been proven. Yet, lymphoma genic stages might be consequence of antigenic stimulation of γδ T-cells since these cells are significantly higher in healthy individuals living in regions where malaria is endemic as well as in patients with previous parasite exposure.

A standard treatment for HSTL has not been established and

the disease exhibits an aggressive clinical course and carries a dismal prognosis. The patient treatment consisted of chemotherapy with ICE regimen followed by autologous stem cell transplantation (SCT). Allo-SCT was not performed because of the lack of a suitable donor.

To date, a variety of therapies have been used including steroids, alkylating agents, purine analogs and splenectomy showing a generally disappointing and limited efficacy. In the last decade, a number of reports suggested a better outcome with high dose chemotherapy followed by allogeneic stem cell transplantation [17]. The EBMT Lymphoma Working Party recently reviewed the outcome of HSCT patients who underwent allogenic (18 patients) or autologous (7 patients) stem cell transplantation. With a median follow-up of 36 months, 50% of patients were alive after allo-SCT and the three-year OS and PFS was 54% and 48% respectively. In contrast, of the seven auto transplanted patients, five relapsed and subsequently died, one was lost to follow-up 2 years after stem cell transplantation and one was alive and progression-free 58 months after transplantation. Despite the small sample size and limited follow-up, this study provided evidence that allo-SCT can result in long term disease control and suggested that the better results achieved with allo-SCT when compared to auto-SCT were due to the potential benefits of the graft-versus-lymphoma effect. This case report highlights the need to be aware of the potential association of this rare form of NHL with HIV, so that a diagnosis can be readily established and the patient managed aggressively, with early consideration of SCT.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, et al. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-90.

2. Calvaruso M, Gulino A, Buffa S, Guarnotta C, Franco G, et al. (2014) Challenges and new prospects in hepatosplenic γδ T-cell lymphoma. Leuk Lymphoma 2457-65.

3. Shi Y, Wang E (2015) Hepatosplenic T-Cell Lymphoma: A Clinicopathologic Review With an Emphasis on Diagnostic Differentiation From Other T-Cell/Natural Killer-Cell Neoplasms. Arch Pathol Lab Med 139: 1173-80.

4. Weidmann E (2000) Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. Leukemia 14: 991-7.

5. Jonveaux P, Daniel MT, Martel V, Maarek O, Berger R (1996) Isochromosome 7q and trisomy 8 are consistent primary, non-random chromosomal abnormalities associated with hepatosplenic T gamma/delta lymphoma. Leukemia 10: 1453-5.

6. Ashmore P, Patel M, Vaughan J, Wiggill T, Willem P, et al. (2015) Hepatosplenic T-cell lymphoma: A case series. Hematol Oncol Stem Cell Ther 8: 78-84.

7. Patkar N1, Nair S, Alex AA, Parihar M, Manipadam MT, et al. (2012) Clinicopathological features of hepatosplenic T cell lymphoma: a single centre experience from India. Leuk Lymphoma 53: 609-15.

8. Belhadj K, Reyes F, Farcet JP, Tilly H, Bastard C, et al. (2003) Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 102: 4261-9.

9. Hassan R, Franco SA, Stefanoff CG, Romano SO, Diamond HR, et al. (2006) Hepatosplenic gammadelta T-cell lymphoma following seven malaria infections. Pathol Int 56: 668-73.

10. Morabito L et al. (2009) Hepatosplenic γδ T-cell lymphoma in a HIV-infected patient: report of an exceptional association with emphasis on cytomorphological features. 2009 poster 1720, 14th congress of the European Hematology Association

11. Tanase A, Schmitz N, Stein H, Boumendil A, Finel H, et al. (2015) Allogeneic and autologous stem cell transplantation for hepatosplenic T-cell lymphoma: a retrospective study of the EBMT Lymphoma Working Party. Leukemia 29: 686-8.

12. Farcet JP, Gaulard P, Marolleau JP, Couedic JP, Henni T, et al. (1990) Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta. Blood 75: 2213-9.

13. Yabe M, Medeiros LJ, Tang G, Wang SA, Ahmed S, et al. (2016) Prognostic Factors of Hepatosplenic T-cell Lymphoma: Clinicopathologic Study of 28 Cases. Am J Surg Pathol 40: 676-88.

14. Tsunematsu S, Natsuizaka M, Fujita H, Otsuka N, Terashita K, et al. (2014) Hepatosplenic gamma-delta T-cell lymphoma associated with Epstein-Barr virus. Intern Med 53: 2079-82.

15. Ozaki S, Ogasahara K, Kosaka M, Inoshita T, Wakatsuki S, et al. (1998) Hepatosplenic gamma delta T-cell lymphoma associated with hepatitis B virus infection. J Med Invest.44: 215-7.

16. Engels EA (2007) Infectious agents as causes of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 16: 401-4.

17. Rashidi A, Cashen AF (2015) Outcomes of allogeneic stem cell transplantation in hepatosplenic T cell lymphoma. Blood Cancer J 5: e318.