Clinical Case Reports

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CASE REPORT

Progression of a hepatosplenic gamma delta T-cell leukemia/lymphoma on hyperCVAD/MTX and ara-C: literature review and our institutional treatment approach

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Key Clinical Message

A 24-year-old male presented with abdominal pain, fever, and palpable splenomegaly. His differential count revealed myelocytes, metamyelocytes, and nucleated red cells. A bone marrow biopsy confirmed a diagnosis of hepatosplenic gamma delta T-cell leukemia/lymphoma. We describe here our center's diagnostic and treatment approach for this rare leukemia.

Keywords

Chemotherapy, hematology, leukemia, lymphoma, medical oncology.

Case Presentation

A 24-year-old male presented with 2 weeks of abdominal pain, fever, weakness, and palpable splenomegaly. His complete blood count showed a white cell count of 20,000/cmm, hemoglobin of 6.8 g/dL, and platelet count of 42,000/cmm. His differential count revealed monocytosis, myelocytes, metamyelocytes, and nucleated red cells. His LDH was elevated at 1951 IU/L. Further testing showed prolonged PT and PTT, low haptoglobin, and a very high D-dimer suggesting disseminated intravascular coagulation (DIC). Testing for mononucleosis, hepatitis, and HIV were all negative. Cerebrospinal fluid (CSF) for cytopathology and flow cytometry were normal. A bone marrow biopsy was performed (Figs 1–6). A T-cell predominant infiltrate was noted with a sinusoidal pattern of infiltration. The T cells were predominantly atypical T cells, with a composite immunophenotype of CD3 and CD45 being brightly positive, TIA1+, TCR γδ+, CD4−, CD8+ (minority, dim), CD56+ (minority, dim), granzyme B− on flow cytometry. Testing for Epstein Barr Virus (EBV) and terminal deoxynucleotidyl transferase (TdT) were negative. This confirmed a diagnosis of hepatosplenic gamma delta T-cell leukemia/lymphoma. Computed tomography (CT) abdomen (Fig. 7) demonstrated splenomegaly. Induction chemotherapy was initi-

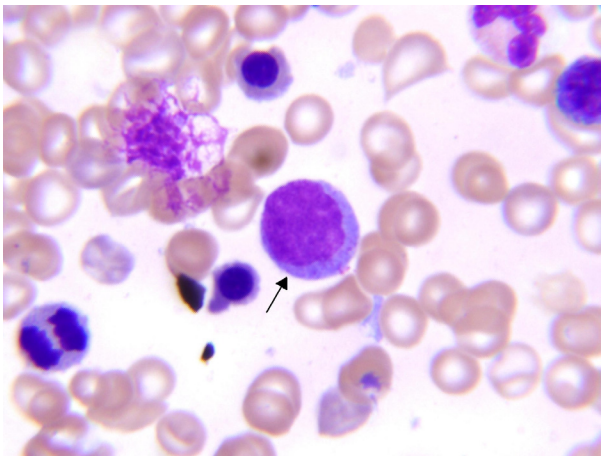

Figure 1. Leishman stain of bone marrow aspirate smear shows an intermediate sized cell with scant cytoplasm and blastoid nuclear morphology with nuclear irregularities. These comprised approximately 20% of aspirate smear cells.

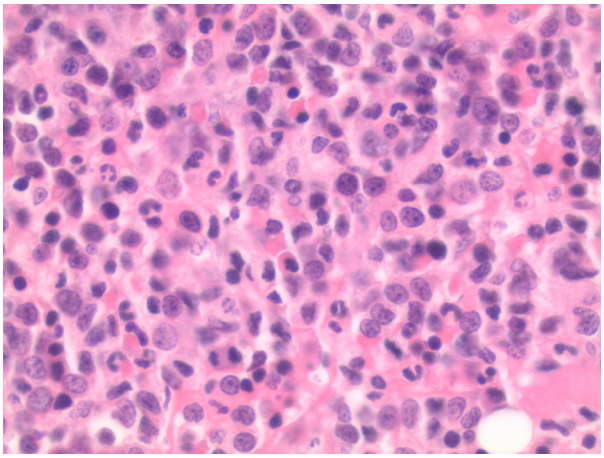

Figure 2. Hematoxylin and eosin stain of the clot section shows a hypercellular marrow with some preservation of trilineage hematopoiesis as well as a subtle, diffuse mononuclear infiltrate.

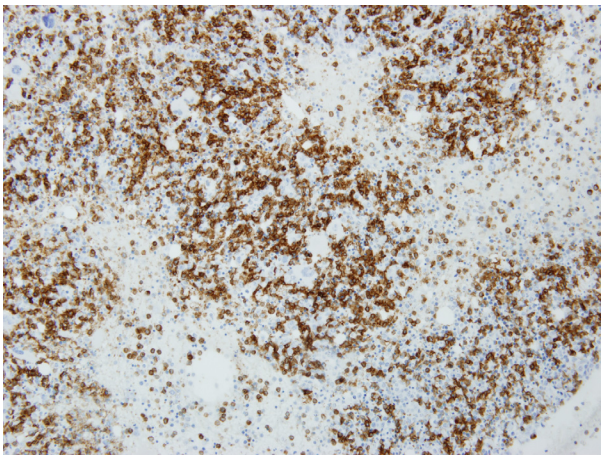

Figure 3. CD3 staining of bone marrow. Immunohistochemical stain showing markedly increased T-cell infiltrate with sinusoidal and interstitial pattern.

ated with hyperfractionated CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone)/(1A) alternating with high-dose methotrexate (MTX) and cytarabine (ara-C)/(1B). Intrathecal cytarabine (IT ara-c) prophylaxis was also started. A restaging bone marrow biopsy after cycles 1A/1B showed residual disease. Hence chemotherapy was changed to a second-line regimen comprising ifosfamide, carboplatin, and etoposide (ICE). He developed neurotoxicity from ifosfamide and sepsis from pneumonia. His cytopenias continued to get worse from disease progression requiring increasingly frequent transfusion support. A restaging CT scan of the abdomen after cycle 1 of ICE showed worsening splenomegaly. Given poor cytoreduction of his leukemia with

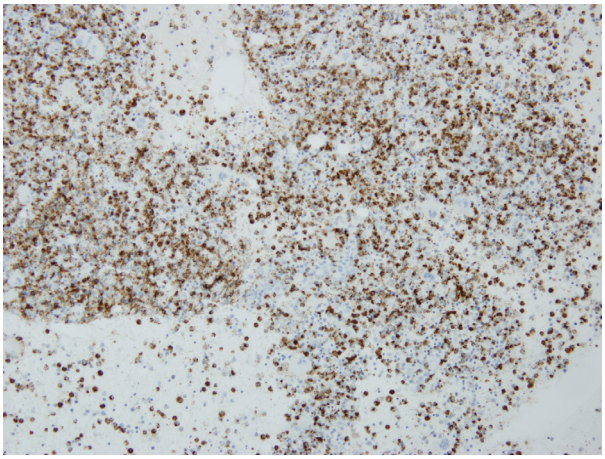

Figure 4. TIA-1 stain of bone marrow. Immunohistochemical stain showing cells positive for TIA-1.

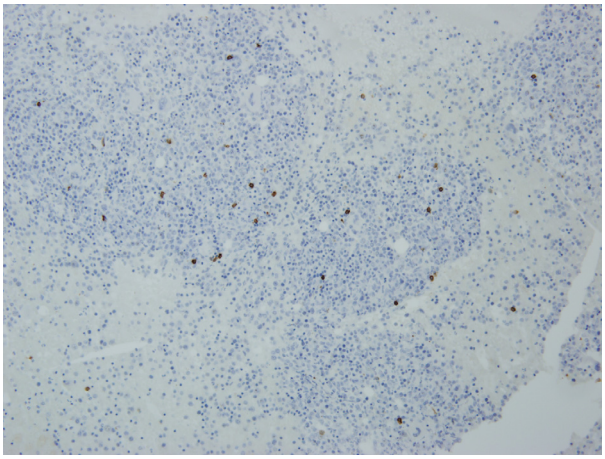

Figure 5. CD20 stain of bone marrow. Immunohistochemical stain showing only scant B cells.

chemotherapy, progressive multisystem organ dysfunction and worsening performance status he was considered transplant ineligible. He was eventually enrolled in hospice about 6 months from the time of diagnosis.

Discussion

Etiopathogenesis of hepatosplenic gamma delta T-cell leukemia/lymphomas

T cells in the thymus comprise two subtypes based on their surface expression of either αβ or γδ T-cell receptors (TCR) [1]. The TCR of αβ T cells, which form the majority, is encoded by alpha and beta genes, whereas the TCR of γδ T cell is encoded by the gamma and delta genes [2]. γδ T cells constitute only about 5% of lymphocyte

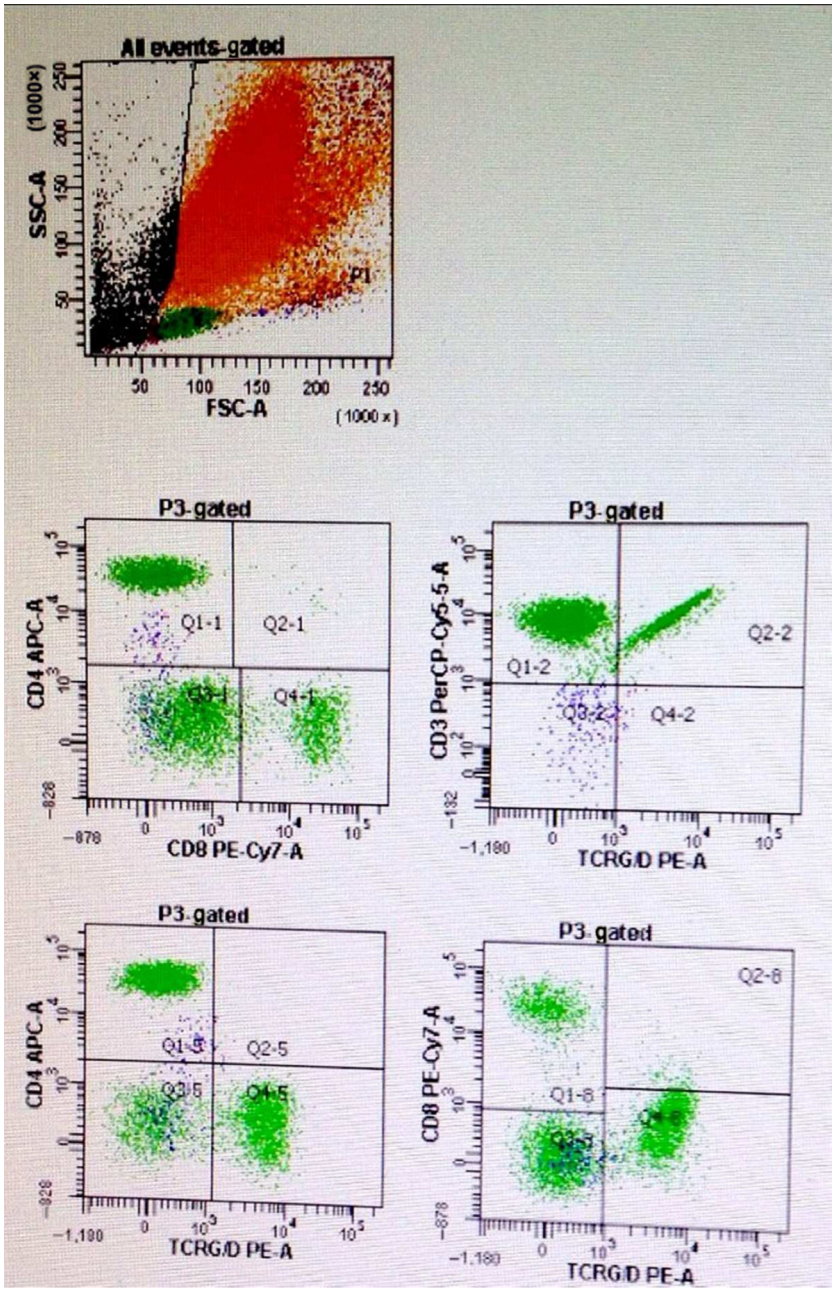

Figure 6. Flow cytometry of bone marrow aspirate showing cytoplasmic CD3 and TCR γδ positivity.

population [3]. αβ and γδ type T cells originate from a common multipotent double negative precursor in the thymus that homes itself there after originating from the bone marrow precursor lymphoid cells [4]. αβ T cells express CD4 or CD8 coreceptors [4]. αβ T-cell activations are restricted via MHC-directed antigen presentation. γδ T cells on the other hand do not express CD4/CD8 coreceptors, and do not require conventional antigen presentation through MHC expression for their activation [4].

Hepatosplenic gamma delta T-cell leukemia/lymphoma is a type of T-cell non-Hodgkin's lymphoma that arises from clonal expansion of γδ T cells which have suffered a derangement of their genetic machinery from unknown reasons. It has been hypothesized that chronic MHC unrestricted antigenic stimulation of γδ T cells seen in chronic infection/inflammation may be a causal factor [5]. This is based on the fact that these occur with a slightly higher incidence in immunosuppressed solid organ transplant recipients and HIV patients where

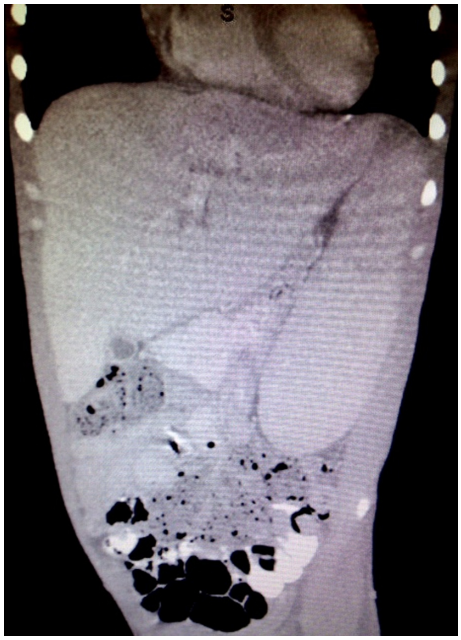

Figure 7. CT scan of the abdomen showing massive splenomegaly.

gamma delta T cells are overstimulated by varying antigenic challenges from repetitive infections [5, 6]. Associations with the use of infliximab, malaria, cytomegalovirus (CMV), and EBV have been reported [6–9].

Epidemiology

It is a rare peripheral T-cell lymphoma [10]. Median age at diagnosis is 34 years [11]. A slight male gender preponderance exists [11, 12].

Clinical features

All patients tend to have splenomegaly and bone marrow involvement [11, 12]. In a case series of 21 patients, the incidence of liver involvement was 67%, that of at least one B symptom was 80%, and that of lymphadenopathy was 13% [11].

This condition has a very aggressive clinical course. In a study by Falchook et al., median duration of complete remission (CR) was 8 months with CHOP like regimens. Median overall survival (OS) was 11 months. Patients who achieved a CR had a median OS of 13 months compared with 7.5 months in patients who did not achieve a CR [10].

Pathologic diagnostic correlates

This disease shows a distinct sinusoidal pattern of infiltration in the splenic red pulp with sparing of the white pulp. The liver also shows classic sinusoidal infiltration with sparing of hepatic portal triads. Bone marrow morphology is often nonspecific, but is notable for neoplastic cells in the sinusoids in early stages and an interstitial pattern of infiltration in the later stages [10]. Atypical appearing lymphocytes and hemophagocytosis may be noted. Immunophenotyping and TCR rearrangement are necessary for diagnosis [12]. Immunohistochemistry (IHC) is classically CD3+, TCRδ1+, TIA-1+, CD4−, and CD8−. TCR rearrangement shows a clonal rearrangement of the γδ gene of the T cell – a hallmark of this disease [10, 12]. Few cases have also shown rearrangement of the αβ gene [10]. Isochromosome 7q has shown a higher prevalence in this condition [10].

Our institutional treatment approach

After a diagnosis, which is usually made on a bone marrow biopsy and aspiration, we conduct a staging work up that comprises CT scan of the chest, abdomen, and pelvis looking specifically for lymphadenopathy and hepatosplenomegaly. We perform a MRI brain only if symptoms suggest neurologic involvement. A lumbar puncture (LP) is carried out in all patients for performing a cerebrospinal fluid (CSF) flow cytometry and cytopathology for involvement of the nervous system. One prophylactic dose of intrathecal ara-c is administered at the conclusion of this first LP.

All of our cases undergo a multidisciplinary review at a leukemia tumor board meeting prior to initiating treatment. Our standard first-line therapy is HyperCVAD alternated with MTX and high-dose cytarabine (ara-c) along with intrathecal prophylaxis, to achieve cytoreduction followed by consolidation with allogeneic bone marrow transplant (allo-SCT), if eligible. We assess response with a restaging marrow after completing the first cycle of HyperCVAD to help arrive at a decision about continuing the same chemotherapy regimen versus switching to an alternative regimen.

If HyperCVAD is not possible given a poor performance status of the patient, we use a clinical trial as our standard second-line approach, if one is available.

In the absence of a clinical trial, we approach our patients based on their clinical status.

- If clinical status is relatively well maintained, then a combination regimen such as ICE/DHAP/ESHAP is employed.
- If clinical status is not favorable, then a single agent approach, such as with romidepsin or pentostatin is considered, unless a poor performance status dictates eligibility for supportive care alone.

Although alemtuzumab may be employed as a single agent, it may not be tolerated by patients with a poor performance status.

During their chemotherapy treatments, we offer our patients supportive treatment with prophylactic antibiotics, antivirals, and antifungals, judicious transfusion support, and prophylaxis against tumor lysis syndrome.

We routinely involve specialized chemopharmacists and chemonurses to be a part of our support team for the preparation, dosing, and monitoring of chemotherapy. We also involve an appropriate palliative pain service and hospice support service when the clinical need arises.

Conflict of Interest

None declared.

References

1. Bruno, L., A. Scheffold, A. Radbruch, and M. J. Owen. 1999. Threshold of pre-T-cell-receptor surface expression is associated with ab T-cell lineage commitment. Curr. Biol. 3:559–568.
2. Yan-Ling, W., Y.-P. Ding, Y. Tanaka, L.-W. Shen, C.-H. Wei, N. Minato, et al. 2014. γδ T Cells and Their Potential for Immunotherapy. Int. J. Biol. Sci. 10:119–135.
3. Roden, A. C., W. G. Morice, and C. A. Hanson. Immunophenotypic attributes of benign peripheral blood γδ T cells and conditions associated with their increase. Arch. Pathol. Lab. Med. 2008. 132:1774–1780.
4. Kreslavsky, T., M. Gleimer, A. I Garbe, and H. von Boehmer. αβ versus γδ fate choice: counting the T-cell lineages at the branch point. Immunol. Rev. 2010. 238:169–181.
5. Poccia, F., M. Wallace, V. Colizzi, and M. Malkovsky. 1998. Possible protective and pathogenic roles of gamma delta T lymphocytes in HIV-infections (Review). Int. J. Mol. Med. 1:409–413.
6. Couzi, L., X. Lafarge, V. Pitard, M. Neau-Cransac, C. Dromer, M. A. Billes, et al. 2011. Gamma-delta T cell expansion is closely associated with cytomegalovirus infection in all solid organ transplant recipients. Transpl. Int. 24:e40–e42.
7. Tsunematsu, S., M. Natsuizaka, H. Fujita, N. Otsuka, K. Terashita, F. Sato, et al. 2014. Hepatosplenic gamma-delta T-cell lymphoma associated with Epstein-Barr virus. Intern. Med. 53:2079–2082.
8. Hassan, R., S. A. Franco, C. G. Stefanoff, S. O. Romano, H. R. Diamond, L. G. Franco, et al. 2006. Hepatosplenic gammadelta T-cell lymphoma following seven malaria infections. Pathol. Int. 56:668–673.
9. Kelsen, J., A. Dige, H. Schwindt, F. D'Amore, F. S. Pedersen, J. Agnholt, et al. 2011. Infliximab induces clonal expansion of γδ-T cells in Crohn's disease: a predictor of lymphoma risk? PLoS One 6:e17890.
10. Falchook, G. S., F. Vega, N. H. Dang, F. Samaniego, M. A. Rodriguez, R. E. Champlin, et al. 2009. Hepatosplenic gamma-delta T-cell lymphoma: clinicopathological features and treatment. Ann. Oncol. 20:1080–1085.
11. Belhadj, K., F. Reyes, J. P. Farcet, H. Tilly, C. Bastard, R. Angonin, et al. 2003. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 102:4261–4269.
12. Wang, F. X., X. J. Zhang, and Z. R. Dong. 2005. A case of hepatosplenic gammadelta T cell lymphoma. Zhongguo Shi Yan Xue Ye Xue Za Zhi 13:505–508.

