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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. 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 cytology 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+ 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-
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 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 hepatosplenical gamma delta T-cell leukemia/lymphoma

T cells in the thymus comprise two subtypes based on their surface expression of either $\alpha\beta$ or $\gamma\delta$ T-cell receptors (TCR) [1]. The TCR of $\alpha\beta$ T cells, which form the majority, is encoded by alpha and beta genes, whereas the TCR of $\gamma\delta$ T cell is encoded by the gamma and delta genes [2]. $\gamma\delta$ T cells constitute only about 5% of lymphocyte
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 6. Flow cytometry of bone marrow aspirate showing cytoplasmic CD3 and TCR γδ positivity.
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