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CASE REPORT

A fatal case of primary cutaneous gamma–delta T-cell lymphoma complicated by HLH and cardiac amyloidosis

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Key Clinical Message

Gamma–delta T-cell lymphomas (GD-TCL) are rare and rapidly fatal neoplasms that are often associated with Hemophagocytic Lymphohistiocytosis (HLH), a syndrome of fevers, cytopenias, and multiorgan failure that often leads to a rapid death. We report the first case demonstrating an association between GD-TCL, HLH, and cardiac amyloidosis, presenting a novel mechanism for rapid deterioration in these patients.

Keywords

Amyloidosis, cutaneous T-cell lymphoma, gamma–delta, hemophagocytic lymphohistiocytosis, primary cutaneous gamma–delta T-cell lymphoma.

Background

Peripheral T-cell lymphomas (PTCLs) are uncommon neoplasms, representing only 10–15% of non-Hodgkin's lymphoma, with an incidence of approximately 1.79/100,000 persons per year [1]. Gamma–delta T-cell lymphomas ($\gamma\delta$ TCLs) arise from immature T cells with γδ T-cell receptors (TCR). γδ T-cells comprise only 2–5% of peripheral T-cells, but appear to have a role in both the innate and adaptive immune systems, with both cytotoxic and regulatory properties [2, 3, 4].

$\gamma\delta$ TCLs represent a minority of these lymphomas, though they have been shown to have an aggressive course and portend a very poor prognosis [5]. The most recent WHO-EORTC classification identifies two major subtypes of $\gamma\delta$ TCLs, primary cutaneous gamma–delta T-cell lymphoma (PCGD-TCL), and hepatosplenic T-cell lymphoma (HSTL) [6]. PCGD-TCL is estimated to represent approximately 1% of cutaneous T-cell lymphomas (CTCLs) and HSTL is estimated to represent <1% of all non-Hodgkin's lymphoma [7–10]. Rare cases of PTCL, Not Otherwise Specified (NOS) have also been found to express $\gamma\delta$ TCRs.

While HSTL almost always arises from $\gamma\delta$ T-cells, $\gamma\delta$ variants of CTCL are incredibly rare. These two malignancies also arise from different $\gamma\delta$ populations: HSTL from the V1 subtype, and PCGD-TCL from the V2 subtype. PCGD-TCL is derived from activated cytotoxic T-cells that demonstrate granzyme B and perforin positivity. While PCGD-TCL is a cutaneous disease, it is extremely aggressive and has a predilection to spread viscerally. B symptoms are common and many patients may present with Hemophagocytic Lymphohistiocytosis (HLH) [5, 9, 11].

HLH is a potentially deadly syndrome thought to result from general immune dysregulation. In this situation, generalized cytokine release is thought to stimulate benign histiocytes to phagocytose other hematopoietic stem cells in a dysregulated fashion. This results in clinical features of fever, hepatosplenomegaly, and cytopenia. HLH is associated with hematological malignancies, viruses such as Epstein Barr Virus, and familial syndromes [12].

Despite the use of high-dose chemotherapy and autologous and allogeneic bone marrow transplant, PCGD-TCLs have a poor prognosis with an estimated 10% 5-year survival rate [5]. In a recent review comparing TCL with and without HLH, TCL complicated by HLH had survival times of no more than a year [13]. However, $\gamma\delta$ TCLs are associated with such a poor prognosis that presence of HLH may not statistically affect mortality [5]. In several

cases, following initiation of treatment (usually CHOP-based therapies), multiorgan dysfunction resulted.

In this paper, we discuss a rare case of PCCD-TCL in association with HLH and cardiac sudden death. Interestingly, the patient was also found to have cardiac amyloidosis which has not been reported in the setting of HLH or $\gamma\delta$ TCLs.

Case Presentation

A 70-year-old retired teacher with past medical history notable for hypertension, diabetes mellitus type II, and obesity presented with a history of fevers, altered mental status, and new skin nodules. The week prior to his visit, the patient was admitted to an outside hospital with a fever to 103°F and a 4-month history of pruritus, accompanied by a 2-month history of progressive mental status change. Hospital workup revealed Urinary tract infection and Clostridium difficile negative diarrhea. A CAT scan showed multiple subcutaneous nodules. A core needle biopsy of an axillary lymph node demonstrated an atypical lymphoid infiltrate with CD2+/CD3+/CD56+/TCR T-cells expressing the cytotoxic markers perforin, granzyme B, and TIA-1. The differential diagnosis was consistent with T-cell lymphoma. Additional immunostains demonstrated that the T-cells were negative for Beta-F1, indicating that they were of $\gamma\delta$ origin (Fig. 1).

The patient was admitted for rapid decline in mental status. While at home, the patient continued to have B symptoms, including fevers, chills, weakness, fatigue, and pruritus. At the time of admission, the patient's blood pressure was 94/57 despite the absence of cardiac history and concomitant antihypertensive medications, and the physical examination was notable for multiple subcutaneous nodules and prominent lower extremity edema. There was no hepatosplenomegaly on examination. The patient had normal renal function (BUN 19, Ct 1.1), unchanged from his baseline. The patient was

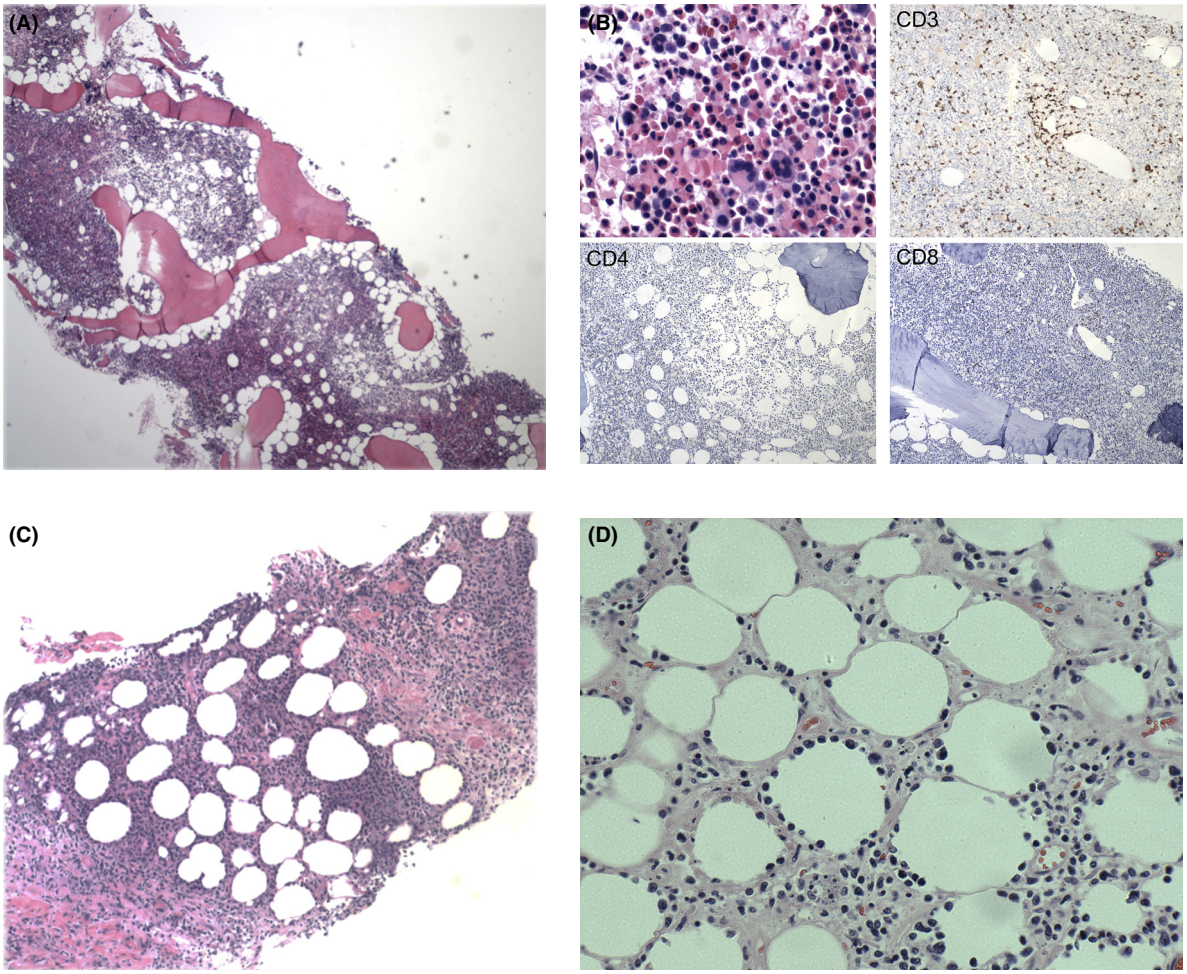

Figure 1. (A) Bone marrow low power, (B) Bone marrow high power- hypercellular bone marrow with evidence of hemophagocytosis, (C) Axillary lymph node low power, (D) Axillary lymph node high power—obliteration of all normal nodal architecture.

hyponatremic to a nadir of 121, and sodium normalized with intravenous fluids. A PET/CT scan was performed and demonstrated multiple hypermetabolic soft tissue masses, bilateral axillary lymphadenopathy, and splenic uptake. Laboratory studies at admission were notable for anemia (Hb 12.1 g/dL) and thrombocytopenia (Plt 97,000/μL) as well as a mild hepatic transaminitis (ALT 57 U/L, AST 70 U/L).

Because of high-spiking fevers, cytopenias, and the presence of T-cell lymphoma, he was considered to be at high risk for HLH. Further laboratory studies included ferritin, which was markedly elevated at 4610 ng/mL, and soluble IL2R, elevated at 16130 pg/mL. In addition, he was found to have low fibrinogen (112 mg/dL) and high triglycerides (248 mg/dL). A diagnosis of HLH was made based on the laboratory studies and clinical presentation and high-dose steroid therapy was initiated.

A bone marrow biopsy was obtained to evaluate for involvement by lymphoma and for involvement by HLH. The marrow biopsy demonstrated a hypercellular marrow for age (70% cellular) with 10–20% of the total marrow replaced by CD3-positive T-cells that were negative for CD4 and CD8, consistent with the population seen in the lymph node biopsy. T-cell gene rearrangements demonstrated clonality in the bone marrow. Hematophagocytosis was also noted in the bone marrow.

The night following admission, the patient continued to have fevers, worsened agitation, and dyspnea. A magnetic resonance imaging of the brain was unremarkable and an LP showed no atypical cells and flow cytometry was sent to assess for CNS's involvement of the patient's lymphoma. On the following day, he developed hypotension, bilateral tonic-clonic jerking, and became unresponsive. The patient was successfully resuscitated and was transferred to the Intensive Care Unit where he was intubated and pressors were initiated. He received broad-spectrum antibiotics for possible aspiration pneumonia. Bedside echocardiography was unremarkable showing normal wall motion, and EEG did not demonstrate epileptiform activity. The patient subsequently developed multiple petechiae and became anuric. Laboratory values were notable for lactic acid of 7.1 μg/dL, creatinine of 2.2 μg/dL, potassium of 5.8 μg/dL, and rising leukocytosis with a peak of 22,000/μL. Before further aggressive intervention could be initiated, the patient underwent a cardiac arrest. He was noted to have torsades de point that deteriorated into coarse ventricular fibrillation and progressed to asystole. Of note, he had no cardiac history and was on no arrythmogenic medications at the time of cardiac arrest.

At autopsy, extensive involvement by $\gamma\delta$ TCL was found in para-aortic lymph nodes, left axillary mass, bone marrow, liver, and lung. The heart showed extensive infiltration by malignant T cells (Fig. 2). Surprisingly, extensive infiltration of myocardium with pale, interstitial, subendocardial, and intramural eosinophilic deposits consistent with amyloid was also found. These deposits were Congo-red-positive, focally polarizable, positive on trichrome, and negative for amyloid A. There was no preferential expression of kappa or lambda light chains. Liquid chromatography tandem mass spectrometry studies revealed that the eosinophilic material was consistent with Transthyretin-related amyloidosis (ATTR).

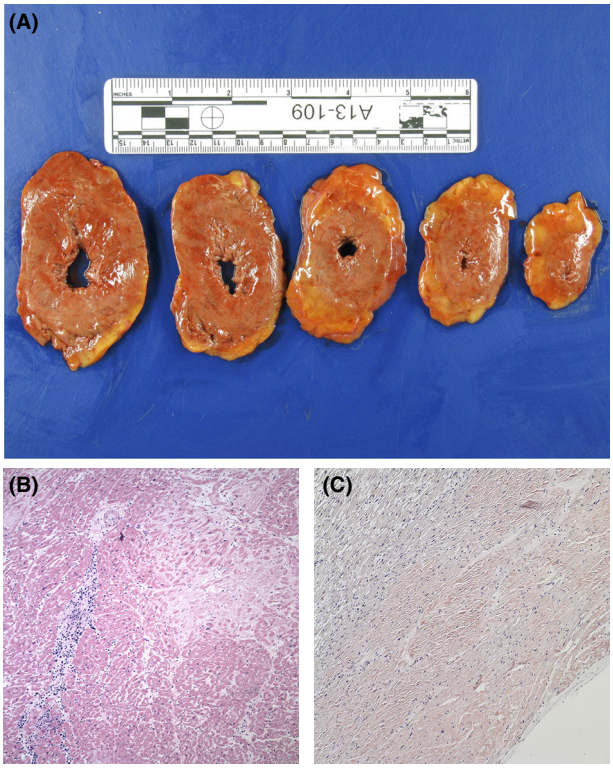

Figure 2. (A) Grossly enlarged heart (560 g), (B) Cardiac muscle—high power and with Congo red staining—demonstrating deposits of amyloid.

Discussion

HLH is a hyperinflammatory disorder characterized by cytokine storm and clinical manifestation of splenomegaly, fever, and cytopenias. Causes of HLH include malignancy, autoimmune disease, immunodeficiency, and infection. The pathogenesis of HLH is incompletely understood. The genes identified in familial primary HLH (autosomal recessive and X-linked) code for enzymes involved in the perforin-granzyme pathway, leading to ineffective apoptosis of NK and T-cells. This leads to a disruption in the homeostasis such that macrophages are activated and release proinflammatory cytokines such as

TNF-alpha, interleukin-1, and interleukin-6. This leads to an accumulation of activated macrophages and histiocytes undergoing hemophagoctosis [14]. It is thought that secondary events such as viral infection or malignancy may similarly disrupt these activation-induced apoptotic pathways and trigger a similar sequence of events.

Diagnostic criteria for HLH were developed in 1991 and updated in 2004 by Henter et al. (Table 1) [15]. In addition to the eight above criteria, HLH often presents with neurological manifestations, as demonstrated in this case [16]. However, these criteria are not universal and patients may have atypical presentations leading to a prolonged time to diagnosis. The use of biomarkers such a soluble IL-2 receptor and NK function assays have more recently been utilized with the goal of decreasing time to diagnosis and treatment. Other serum markers such a neopterin, a product secreted by activated macrophages, have been shown to be sensitive and specific for HLH [17]. The first protocol for HLH was the HLH-94 protocol, which included 8-week induction therapy with dexamethasone, etoposide, and intrathecal methotrexate to suppress the hyperinflammatory response.

PCGD-TCL is an uncommon and aggressive disease that is complicated by HLH and visceral involvement much more commonly than alpha–beta CTCLs [9]. In a 2012 multicenter series involving 53 patients with PCGD-TCL, HLH and CNS involvement were associated with disease progression. Patients had a median survival time of 31 months [11].

In 2008, Tong et al. compared TCL with and without HLH. As expected, patients with HLH had decreased survival rates, with a mean survival time of 40 days as compared to 2-year and 3-year survival rates of 40% and 30%, respectively, in the non-HLH group. Combination chemotherapy produced a survival time of no longer than 1 year in most cases. Six patients who received chemotherapy died from cardiac failure after their first cycle of CHOP [13]. It is unknown whether these patients may have demonstrated amyloid deposits as demonstrated in our case.

Table 1. Diagnostic criteria for hemophagocytic syndrome. Diagnosis is made if ≥5 out of 8 criteria are met.

Clinical criteria
Fever
Splenomegaly
Laboratory criteria
Cytopenias (≥2 cell lines affected)
Hypertriglyceridemia and/or hypofibrinogenemia
Low/lacking NK-cell activity
Hyperferritinemia
Elevated soluble sIL-2 receptor
Histopathologic criterion
Evidence of hemophagocytosis

Multiorgan failure has been documented in cases of HLH before the initiation of systemic chemotherapy, likely due to the effects of hypercytokinemia. In view of this observation, the first step to treating HLH is in controlling the exuberant immune response that occurs in this disease process. However, many patients are refractory to steroid therapy and are unable to undergo alternative therapy due to organ failure. Plasmaphoresis has been suggested as a possible therapy to decrease circulating levels of cytokines in the blood and decrease systemic damage and subsequent complications. Case reports have shown moderate success [18, 19]. Tong et al. used this approach on three patients in critical condition. Two of these patients survived 6 and 3 months; the third did not respond due to rapid CNS involvement [13]. However, no larger studies have been undertaken and no generalized protocols are in place with the exception of HLH-94.

In the case under review, amyloid infiltration of the heart and disruption in cardiac conduction was the cause of death. Amyloid has been infrequently discussed in relation to lymphoma. Cutaneous amyloid has been described in mycosis fungoides [20]. Single-case reports have described amyloid in the brain and kidney, leading to acute renal failure; death has been described in a patient with Hodgkin's lymphoma following lymphomatoid papulosis [21] and in amyloidosis involving the small intestine in Sezary syndrome [22]. However, cardiac amyloidosis in TCL has not been described. ATTR amyloid can occur in the setting of age-related changes. However, in this patient with no known history of cardiac disease, his acute decompensation was likely due to underlying subclinical cardiac infiltrative disease and his aggressive and infiltrative T-cell lymphoma. Moreover, there is little known about the association of HLH and amyloidosis, although a single Japanese study in 2000 found a significant correlation between serum amyloid A protein and ferritin in patients with HLH [23]. To our knowledge, this is the first documented case of systemic amyloid in association with HLH.

Conclusion

$\gamma\delta$ TCLs are rare diseases associated with rapid progression and HLH. HLH may lead to multiorgan failure prior to initiation of chemotherapy. Moreover, chemotherapy may precipitate a hyperinflammatory response in some patients. It is important to recognize the features of HLH and consider alternative therapies such as plasmaphoresis. There is little consensus on the best treatment for T-cell lymphoma associated with HLH, although etoposide containing regimens have been shown to be effective. The association of HLH with amyloidosis is poorly characterized but previous studies demonstrating early cardiac

deaths with CHOP, and our case demonstrates that this association should be considered, especially in patients who undergo early clinical deterioration. The onset of sudden death in our patient was likely multifactorial, related to both hypercytokinemia from HLH as well as cardiac dysfunction from amyloidosis and from infiltration of myocardium by gamma–delta T cells.

Conflict of Interest

None declared.

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