Case Report

**ALK-Negative Anaplastic Large Cell Lymphoma Presenting as Disseminated Intravascular Coagulation and Hemophagocytic Lymphohistiocytosis: A Potentially Fatal Presentation**

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**1. Introduction**

Disseminated intravascular coagulation (DIC) is common in critically ill patients and is usually secondary to sepsis. It can potentially confound a diagnosis of a fatal and uncommon disorder such as hemophagocytic lymphohistiocytosis (HLH). Both entities are clinicopathologic diagnoses with shared coagulation system abnormalities. Mortality from multiorgan failure can occur in up to seventy percent of patients [1]. We present a case of DIC initially managed supportively as being secondary to sepsis, with workup leaving HLH secondary to anaplastic large cell lymphoma (ALCL).

**2. Case**

A 69-year-old female with no known past medical history was brought to the hospital by ambulance for worsening shortness of breath and lethargy. At presentation, she was tachycardic, hypotensive, and hypoxic. Laboratory workup showed hemoglobin 13 g/dL, white blood cell count 2.61 × 10⁹/L, platelets 92 × 10⁹/L, alkaline phosphatase 212 IU/L, aspartate aminotransferase 166 IU/L, alanine aminotransferase 61 IU/L, and a normal coagulation profile.

Over the ensuing week, the patient’s pancytopenia worsened (Table 1). PTT was up to 99 seconds, PT 13.7 seconds, and fibrinogen 84 mg/dL. A computed tomography (CT) scan of the abdomen showed a right superficial inguinal centrally necrotic nodal mass measuring 5.3 × 2.3 cm and a right deep inguinal lymph node measuring 3.0 × 2.3 cm (Figure 1). Several incompletely characterized splenic masses were also seen. A core needle biopsy of the lymph node showed necrotic soft tissue with focal granulomatous reaction. Infectious disease workup was negative. Further studies showed a ferritin level of 32,522 ng/mL, a haptoglobin level of <20 mg/dL, a lactate dehydrogenase level of 982 IU/L, and low natural killer cell activity. A bone marrow biopsy showed many histiocytes and
significant hemophagocytic macrophages (Figure 2). A diag-
nosis of concomitant disseminated intravascular coagulation
and hemophagocytic lymphohistiocytosis was made. Dexam-
ethasone 10 mg/m² was started, and she received two doses of
etoposide 150 mg/m², resulting in a decrease in ferritin to
19,947 ng/mL and normalization of coagulation parameters.

An excisional inguinal lymph node biopsy showed an
atypical lymphoid infiltrate with extensive geographic ne-
ecrosis. Large pleomorphic and anaplastic cells with irregular
nuclei and finely dispersed chromatin were identified
(Figure 3). HT_he atypical large cells were positive for CD30,
CD2, CD4, CD43, MUM-1, and CD45 (variable). HT_here was
no significant expression of CD3, CD5, CD7, CD8, or EMA
and ALK-1, CD20, PAX-5, CD79a, CD10, BCL-6, CD138,
CD15, or BCL-2. The findings were consistent with
ALK-negative anaplastic large cell lymphoma.

The treatment of choice for HLH is treating the un-
derlying cause. The patient initially declined chemotherapy
given the rapidly declining functional status. However, after
three weeks of rehabilitation, her functional status improved
significantly, and thereafter, she received chemotherapy
treatment with the CHOP (cyclophosphamide, doxorubicin,
vincristine, and prednisone) regimen. A positron emission
tomography (PET) scan after four cycles showed resolution
of the right inguinal lymphadenopathy and the splenic
lesions.

3. Discussion

Primary systemic ALCL is a type of peripheral T-cell lym-
phoma which comprises about 2 percent of all non-Hodgkin’s
lymphomas. These are generally aggressive and four clinical
subtypes exist: anaplastic lymphoma kinase- (ALK-) positive
ALCL, ALK-negative ALCL, breast implant-associated ALCL,
and primary cutaneous ALCL [2]. Cases involving the ALK
gene translocation located on chromosome 2p23 fare sig-
nificantly better compared to ALK-negative cases. Several
translocations may be involved, the most common being
t(2;5), that causes the fusion of the nucleophosmin (NPM)
gene (5q35), coding for a nucleolar phosphoprotein, with the
portion of ALK on chromosome 2p23 that encodes the ALK
cytoplasmic domain. The NPM-ALK fusion product acts as
a constitutively active tyrosine kinase. In contrast, the
ALK-negative ALCL patients may have the t(6;7)(p25.3;q32.3)
translocation involving the DUSP22 gene and the
FRA7H fragile site in up to 30 percent of cases [3].

Given the aggressive nature of the disease, ALCL patients
present with rapidly progressive adenopathy and systemic
symptoms of fever, weight loss, and night sweats. Compared
to B-cell NHLs and HLs, T-cell NHLs are reported to be
complicated with HLH during their course of the disease, and
this confers a worse prognosis. ALCL is seen most often in
females and is associated with advanced stage at presentation,
frequent B symptoms, organomegalgy and lymphadenopathy,
cytopenias, liver dysfunction, coagulopathy, higher pro-
portion of bone marrow infiltration, and reduced overall
survival with or without definitive chemotherapy [4].

Hemophagocytic lymphohistiocytosis results from un-
controlled activation of cytotoxic T cells resulting in a cytokine
storm. It can be familial or secondary to an underlying dis-
order and has a mortality rate of up to 70% from multiorgan

| Laboratory parameter (units) | Normal range | Initial workup | Day 7 | Day 20 |
|-----------------------------|--------------|----------------|------|-------|
| Hemoglobin (g/dL)           | 14.0–18.0    | 13             | 8.5  | 8.7   |
| White blood cells (10⁹/L)   | 4.8–10.8     | 2.61           | 2.99 | 0.37  |
| Platelets (10⁹/L)           | 130–400      | 92             | 61   | 77    |
| PT (seconds)                | 9.95–12.87   | 12.5           | 13.7 | 12.5  |
| PTT (seconds)               | 27.0–39.2    | 28.7           | 99   | 28.7  |
| Lactate dehydrogenase (IU/L)| 60–200       | —              | 982  | 674   |
| Fibrinogen (mg/dL)          | 200–570      | —              | 84   | 650   |
| Haptoglobin (mg/dL)         | 34–200       | —              | <20  | <20   |
| Ferritin (ng/mL)            | 15–150       | —              | 32,522 | 19,947 |
| Total bilirubin (mg/dL)     | 0.2–1.2      | 0.0–0.2        | 0.46 | 0.49  | 0.35 |
| Direct bilirubin (mg/dL)    | 0.0–0.2      | 0.46           | 0.49 | 0.35  |
| Alkaline phosphatase (IU/L) | 30–115       | 212            | 274  | 210   |
| Aspartate aminotransferase (IU/L) | 0–41 | 166 | 122 | 25 |
| Alanine aminotransferase (IU/L) | 0–45 | 61 | 37 | 49 |

Table 1: Diagnostic workup.
failure. Clinical and laboratory features include fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, low or absent NK-cell activity, hyperferritinemia, and an elevated soluble CD25. Lymphoma is known to trigger HLH [5]. In the latter case, HLH- and lymphoma-directed therapy may be indicated given the critical nature of the disease process.

Lymphoma-associated HLH is rare with case reports in the literature. Shah et al. reported a case of ALK-positive ALCL in a fifteen-year-old male with a similar acute presentation and rapid decline as seen in our patient [6]. Xu and Burns report a case of ALK-negative ALCL in an HIV-positive male who fulfilled 6 out of 8 diagnostic criteria for HLH and succumbed to the disease within two weeks [7]. On the other hand, Sovinz et al. report a case of a 15-year-old male treated for HLH with the HLH-94 protocol following which a diagnosis of ALK-negative ALCL was made. He was then treated with ALCL 99 International Protocol, remaining in remission at four years of follow-up [8].

As described in our case and reported cases in the literature, the importance of early recognition and treatment for HLH cannot be emphasized enough. Even though treatment of the primary disorder in secondary HLH is the treatment of choice, lack of a definitive primary diagnosis must not delay HLH-directed treatment. The possibility of an underlying disease must be considered and appropriate biopsy specimens be obtained towards the goal.

4. Conclusion

Coexistent DIC is uncommon and can delay a diagnosis of HLH. Our patient was started on HLH-directed therapy based on clinical judgement, and later, she fulfilled five diagnostic criteria. Hence, prompt recognition and treatment of the underlying disorder is crucial to improve the outcomes.

Consent

Informed consent was provided by the patient reported in this manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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