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Lymphoma-associated hemophagocytic lymphohistiocytosis presenting as fever of unknown origin: a diagnostic challenge

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory syndrome driven by uncontrolled immune activation. In adults, it is most commonly secondary to infections, autoimmune diseases, or hematologic malignancies.

Case description: In January 2020, a 55-year-old man was admitted to the hospital due to weight loss, weakness, and recurrent fevers lasting for about one month. Laboratory findings showed pancytopenia, while C-reactive protein was slightly elevated. A computed tomography (CT) scan revealed enlarged mediastinal lymph nodes and hepatosplenomegaly. Bone marrow biopsy immunophenotyping did not suggest lymphoma. Anti-nuclear antibodies at a titer of 1 : 160 (speckled pattern) and the presence of anti-RNP/Sm antibodies were found, causing a temporary transfer to the Rheumatology Department, where the extensive diagnostic process was inconclusive. Due to clinical features of HLH (6/8 HLH-2004 criteria), fever, hepatosplenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, ferritin at 9,000 ng/ml, and sIL-2R (sCD25) at 25,000 U/ml, i.v. dexamethasone was administered. Endobronchial ultrasound transbronchial needle aspiration, and the subcarinal lymph node from mediastinoscopy did not show lymphoma infiltration. At that time, the histopathologic results of the initial bone marrow biopsy revealed infiltration by aggressive B-cell lymphoma, most likely diffuse large B-cell lymphoma.

The patient received 8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)-based chemotherapy, initially without rituximab and including etoposide in the first 6 cycles (CHOEP), with subsequent modifications due to toxicities. After the first cycle of chemotherapy, the clinical symptoms of HLH began to subside, and after treatment, a complete metabolic response of lymphoma was observed on positron emission tomography/computed tomography (PET-CT). Patient remained in observation. In 2025, the patient presented with fever and, after examination, met 5 HLH-2004 criteria again. Although lymphoma relapse was suspected, it was not found in repeated biopsies (bone marrow, lymph node excision, liver) until the results of the spleen biopsy were obtained. The patient received second-line chemotherapy according to the R-ICE (rituximab, ifosfamide, carboplatin, etoposide) regimen. After 4 cycles, disease progression was detected on PET-CT. The patient is currently awaiting treatment with chimeric antigen receptor T-cell (CAR-T) therapy.

Conclusions: Hemophagocytic lymphohistiocytosis in adult patients necessitates thorough evaluation for possible underlying malignancy, especially lymphoma. Repeated biopsies of different organs may be required. Glucocorticosteroid treatment, although life-saving, can obscure the diagnosis of occult lymphoma.