

Case Report

Rapidly lethal secondary hemophagocytic lymphohistiocytosis predicted by fluorodeoxyglucose positron-emission tomography/computed tomography

ABSTRACT

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a rare disease with either an indolent or aggressive course. A 29-year-old male presented with fever, polyarthralgias, splenomegaly, retroperitoneal adenopathy, and laboratory findings consistent with Epstein–Barr-mediated sHLH. Consistent with a prior survival analysis by Kim *et al.*, splenic maximum standardized uptake value (SUV_{max}) >2.52 and bone marrow $SUV_{max} >3.13$ on ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) predicted an aggressive disease with poor treatment response. Despite optimal treatment, the patient rapidly progressed to death within 3 months of symptom onset. This case underscores the potential lethal nature of sHLH, and the evolving role of ^{18}F -FDG-PET/CT in predicting disease severity and treatment response.

Keywords: Fluorodeoxyglucose positron emission tomography/computed tomography, maximum standardized uptake value, rapidly lethal, secondary hemophagocytic lymphohistiocytosis, survival analysis

INTRODUCTION

Here, we present a 29-year-old male with rapidly lethal hemophagocytic lymphohistiocytosis (HLH) who died within 3 months of symptom onset despite prompt diagnosis and treatment. The patient initially had 1 month of cyclical fevers and severe lower hemibody polyarthralgias. Diagnostic workup demonstrated profound pancytopenia, thrombocytopenia, hepatosplenomegaly, hypofibrinogenemia, hyperferritinemia, and elevated phosphatase, thus meeting HLH diagnostic criteria.^[1] Bone marrow (BM) biopsy revealed hemophagocytosis. Epstein–Barr Virus (EBV) titers suggested recent or past infection, with high viral load clinically consistent with EBV-HLH. An ^{18}F -fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F -FDG PET/CT) maximum intensity projection [Figure 1] demonstrated diffuse splenic and osseous hypermetabolism.

Axial and sagittal fused images [Figure 2a-d] demonstrate maximum standardized uptake value (SUV_{max}) values from

multiple sites, notably, 7.1 in the spleen and 4.2 in L4 BM, as well as hypermetabolic peripancreatic and retroperitoneal adenopathy (white arrows). Subsequently, he was treated with HLH-94 protocol of dexamethasone and etoposide with rituxan for EBV viremia. Originally, he improved on this regimen; however, he relapsed with fevers, transaminitis, pancytopenia, disseminated intravascular coagulation, hyperferritinemia, and hypertriglyceridemia, prompting salvage therapy initiation. Two days later, the patient went into cardiac arrest and despite aggressive resuscitation efforts, succumbed to multiorgan failure.

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DISCUSSION

HLH is a rare, multiorgan disease, with similarities to lymphoma/leukemia, which can run an indolent or aggressive course. HLH pathophysiology is characterized by unchecked activation of cytotoxic T lymphocytes, natural killer cells, and macrophages resulting in hypercytokinemia and immune-mediated injury of multiple organ. This results in cyclical fevers, splenomegaly, and cytopenia with histological evidence of hemophagocytosis leading to elevated ferritin, lactate dehydrogenase, and soluble CD25.^[1,2] HLH can be broadly classified into two groups: primary HLH and secondary HLH (sHLH), with the former being due to genetic defects in cellular cytotoxicity, while the latter is associated with viral infections, especially EBV, malignancy, and autoimmune diseases.^[3] The etiologic distributions of sHLH vary significantly in different studies: a summary study found a 50%:57% infection to neoplasm;^[4] another found EBV in 70% cases;^[5] and finally, another found in 53.3% with treatment response and mortality ratios of 50:50.^[6]

While diagnostic criteria are firmly established based on clinical and pathology findings,^[1] identifying patients with aggressive sHLH remains a diagnostic dilemma. As ¹⁸F-FDG is absorbed in activated immune cells, including macrophages

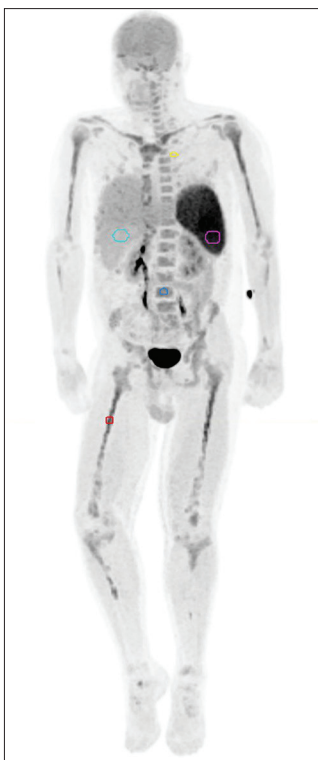


Figure 1: Demonstrates a ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography maximum intensity projection of a 29-year-old male with rapidly lethal hemophagocytic lymphohistiocytosis

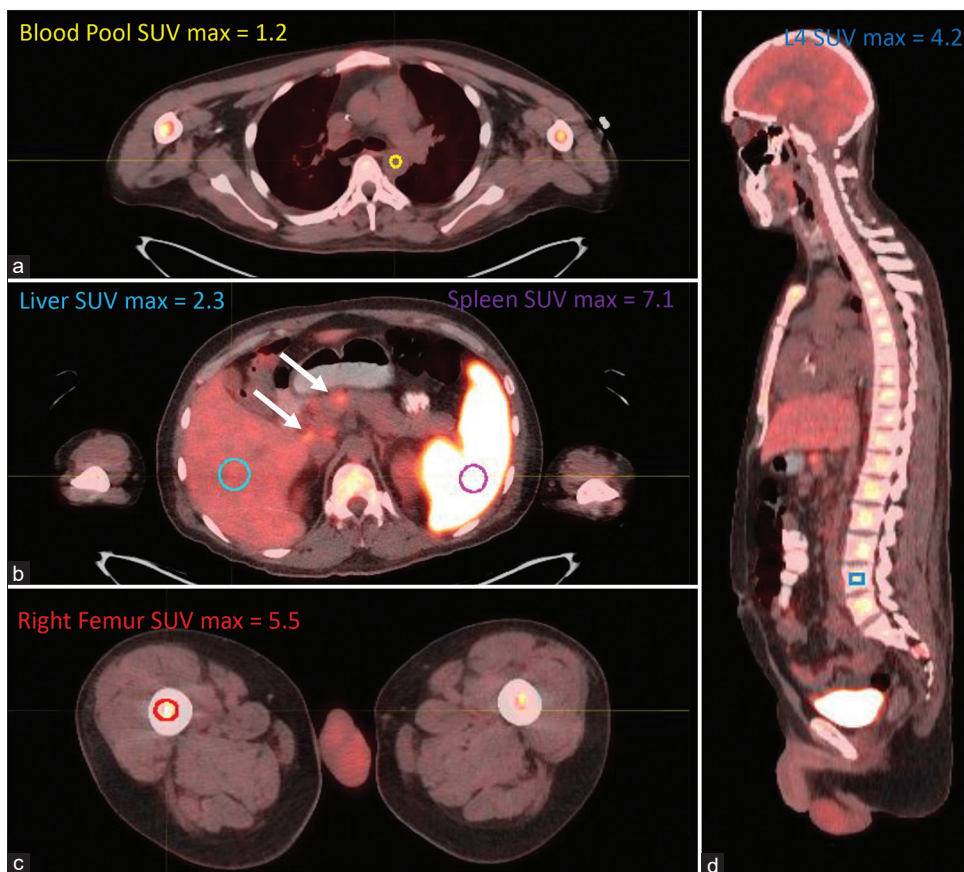


Figure 2: Demonstrates axial and sagittal fused positron emission tomography/computed tomography images (a-d) with maximum standardized uptake values from multiple sites

and T lymphocytes, multiple case studies of HLH have reported hypermetabolism on ^{18}F -FDG PET-CT.^[7,8] Kaplan–Meier survival analysis conducted by Kim *et al.* demonstrated that PET-CT parameters potentially predict poor outcomes in HLH,^[9] whereas clinical parameters failed to do so. Specifically, patients with an $\text{SUV}_{\text{max}} > 2.52$ in spleen, $\text{SUV}_{\text{max}} > 3.13$ in BM, and spleen to liver and BM to liver SUV ratios exceeding 1.19 and 1.27, respectively, were most likely to have an aggressive, potentially lethal disease course.^[9] Our patient demonstrated an $\text{SUV}_{\text{max}} = 7.1$ in the spleen and diffuse BM hypermetabolism with a representative L4 vertebrae $\text{SUV}_{\text{max}} = 4.2$. Liver SUV_{max} was 2.3 with spleen to liver and BM to liver SUV ratios of 3.09 and 1.83, respectively. As predicted by the analysis in Kim *et al.*, the patient had an aggressive disease with poor treatment response and rapidly succumbed to sHLH. Therefore, we corroborate the evolving distinctive role of PET-CT in stratification of HLH disease severity. ^{18}F -FDG PET-CT offers the best currently available means of identifying which patients have aggressive disease, thus requiring salvage therapy, and those patients in whom current treatment regimens are likely to be successful.

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Conflicts of interest

There are no conflicts of interest.

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