Autoimmune Lymphoproliferative Syndrome with Langerhans Cell Histiocytosis Diagnosis: A Case Report

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Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of lymphocyte apoptosis characterized by nonmalignant lymphadenopathy, splenomegaly, immune dysregulation, and autoimmune cytopenias. Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid precursor cells, primarily presenting as bone, soft tissue, lung, skin, and pituitary lesions. The association between the two diagnoses is uncharacterized. Here we describe a patient presenting with fever of unknown origin, cytopenias, and failure to thrive. She was diagnosed with ALPS, then subsequently LCH, within three months. This case highlights the diagnostic and management challenges associated with these two rare diagnoses.

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Abbreviation Key

Abbreviation	Full term/phrase
LCH	Langerhans cell histiocytosis
ALPS	Autoimmune lymphoproliferative syndrome
UTI	Urinary tract infectio
FTT	Failure to thrive

Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of lymphocyte apoptosis characterized by nonmalignant lymphadenopathy, splenomegaly, immune dysregulation, and autoimmune cytopenias. Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid precursor cells, primarily presenting as bone, soft tissue, lung, skin, and pituitary lesions. The association between the two diagnoses is uncharacterized. Here we describe a patient presenting with fever of unknown origin, cytopenias, and failure to thrive. She was diagnosed with ALPS, then subsequently LCH, within three months. This case highlights the diagnostic and management challenges associated with these two rare diagnoses.

Main Text

Introduction

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of lymphocyte apoptosis, characterized by nonmalignant lymphadenopathy, splenomegaly, immune dysregulation, and autoimmune cytopenias[1,2]. There are known genetic defects associated with ALPS, although they are not required for diagnosis[3]. ALPS can be challenging to diagnose, as clinical presentations can vary or be incomplete. This syndrome usually presents early in life, and treatment aims to improve the constellation of symptoms. Treatment modalities include corticosteroids, rituximab, sirolimus, and mycophenolate mofetil[4,5]. The dysregulated cell division in ALPS also places patients at increased risk for developing lymphoid malignancies[6].

Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid precursor cells that is frequently characterized by a mutation of the MAPK gene pathway[7]. LCH primarily presents as bone, soft tissue, lung, skin, and pituitary lesions. A BRAF V600E mutation has been reported in 57% of patients with LCH, and pathology confirms the diagnosis with granulomatous lesions that are CD207 positive[8,9]. LCH is often treated with conventional chemotherapy, such as vinblastine and prednisone[10].

This case report describes the unique presentation of a patient diagnosed with ALPS and LCH in short succession.

Results (Case Report)

A 10-month-old female was admitted to our hospital for several weeks of persistent fevers. Her past medical history was remarkable for four separate urinary tract infections (UTI), all of which grew *E. coli* and were successfully treated with antibiotics. Additionally, she had intermittent bloody stools before her presentation.

During her first hospitalization at our institution, she was diagnosed with an *E. coli* UTI , and voiding cystourethrogram revealed vesicoureteral reflux. She had normocytic anemia with a hemoglobin of 5.7 gm/dl and a reticulocyte count of 3.9%. Her peripheral blood smear revealed thrombocytopenia, reactive lymphocytes, and monocytosis. These results were attributed to anemia of chronic disease, as well as gastrointestinal bleeding of unknown etiology. She was also noted to have failure to thrive (FTT) and delayed developmental milestones. She was discharged home to complete a course of cephalexin for her UTI.

Five days after discharge, she was readmitted for persistent fevers despite compliance with the prescribed antibiotics. Her hemoglobin had decreased to 4.8 gm/dl, her reticulocyte count had increased to 9.2%, and she was transfused with packed red blood cells. A bone marrow aspiration and biopsy revealed rare hemophagocytosis with no other significant findings. Abdominal imaging revealed splenomegaly. Ferritin was normal (129 ng/mL). Soluble interleukin-2 receptor was elevated at 12900 pg/ml (reference range <1033

pg/ml). The remainder of her workup was unremarkable or non-contributory, including renal ultrasound, echocardiogram, celiac panel, preliminary immunological studies, and an extensive infectious disease workup. Due to persistent diarrhea in the setting of prolonged antibiotic usage, *C. difficile* treatment was initiated with oral vancomycin, but there was no improvement in her intermittently loose, bloody stools. Esophagogastroduodenoscopy and colonoscopy revealed erythema and friability throughout the colon, and multiple biopsies showed nonspecific, diffuse inflammation. Her fevers resolved, and her gastrointestinal symptoms eventually improved without additional intervention.

Genetic testing revealed a c.1567T>C mutation in*CASP10* , diagnostic of ALPS-caspase (CASP)10. TCRαβ+ CD4- CD8- cell count was normal. Subsequently, she was started on sirolimus therapy.

Approximately two months after starting sirolimus therapy, she was hospitalized for progressive left-sided facial swelling and dry, flaky scalp changes. Imaging confirmed an erosive lesion involving most of the sphenoid bone, bilateral inferior orbital walls, and bilateral squamous portions of temporal bones. Additional smaller lesions in the right mandible and right mastoid air cells were observed. Biopsy revealed LCH with a BRAF V600E mutation. Positron emission tomography revealed fluorodeoxyglucose-avid regions localized to the skull and facial bones. The patient began treatment with vinblastine and prednisolone with subsequent resolution of the facial swelling and cytopenias.

Discussion

To our knowledge, this is the first patient to be described with both ALPS and LCH. The diagnosis of multifocal LCH was made less than three months after starting sirolimus for ALPS. Initiation of prednisolone for the treatment of LCH led to the resolution of facial swelling, but also led to resolution of bloody stools and cytopenias, which were her primary symptoms related to ALPS. This is notable because corticosteroids are also first-line treatments for ALPS[4].

While both ALPS and LCH are characterized by inflammatory and cellular dysregulation, the cellular pathways leading to these diagnoses are quite different. The pathophysiology of LCH is characterized by alterations in myeloid precursor cells, while ALPS is characterized by molecular signaling disruptions in lymphoid cells. ALPS patients are known to have a higher risk of malignancy, including leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma[6,11]; however, ALPS has not been explicitly linked to LCH.

As this case illustrates, it is often challenging to diagnose ALPS, and frequently an extensive workup is obtained before diagnosis. Indeed, this patient had an incomplete diagnosis for ALPS (Table 1)[1]. While she was found to have a pathologic germline mutation of *CASP10,* autoimmune cytopenias, and hypergammaglobulinemia (all of which are common in ALPS), she did not have elevated numbers of peripheral TCRαβ+ CD4- CD8- cells. Although*CASP10* mutations typically have autosomal dominant inheritance, patients with mutations in *CASP10* can have variable presentations, and these patients may not exhibit classic diagnostic features for ALPS, thus requiring genetic confirmation to make the diagnosis[11,12].

Our patient initially presented with FTT, fever, and cytopenias, each reported in ALPS-CASP10 and LCH[4,11,13,14]. The patient also had persistent fevers, prompting hospitalization. ALPS and LCH, as with other malignancies, can and should be considered in the setting of persistent fevers and FTT. This also calls into question whether LCH was present at the time of ALPS diagnosis. The dry patches on the patient's scalp were present before her presentation and initially attributed to seborrheic dermatitis; however, they were likely a manifestation of LCH and are a common presentation of LCH[13].

This case exemplifies an unusual presentation resulting in the concurrent diagnosis of LCH and ALPS and emphasizes the importance of continued evaluation when a patient's clinical presentation does not entirely meet diagnostic criteria. Genetic testing and further workup were ultimately needed to lead to the correct diagnosis and treatment of ALPS. Once treatment began for LCH, the patient had significant improvement in symptoms related to both LCH and ALPS. While some cases have highlighted a link between ALPS and other diagnoses of histiocytosis, including Rosai-Dorfman Disease and histiocytic sarcoma,[15,16] concurrent diagnosis of ALPS and LCH has not been reported previously, and these diagnoses share no

known association. Further research is needed to explore any potential associations.

Conflict of Interest Statement: No authors have a conflict of interest.

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