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Case Report

COVID-19 related mucormycosis and hemophagocytic lymphohistiocytosis in a child with juvenile myelomonocytic leukemia

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ABSTRACT

Juvenile myelomonocytic leukemia (JMML) is a childhood hematological cancer that often results from mutations in the PTPN11 gene. This study aims to report an original proband with JMML, COVID-19, HLH, and mucormycosis phenotypes.

In JMML patients, secondary HLH associated with SARS-CoV-2 and mucor infection has not been reported in the literature. We identified a missense variant c.226G>C (p. Glu76Gln) (NM_001330437) in *PTPN11*.

The patient suffered from SARS-CoV-2-related secondary Hemophagocytic lymphohistiocytosis (HLH) and mucormycosis in the right eye and the synoidal ethmoidal sinuses, which eventually led to the patient's death due to cardiopulmonary arrest.

We report a child with JMML complicated with COVID-19-related secondary HLH and mucormycosis, which underlines the need for effective and urgent treatment to reduce further mortalities.

Keywords: JMML, secondary HLH, mucor, zygomycosis, COVID-19, *PTPN11* mutation

INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare pediatric hematopoietic malignancy frequently associated with *PTPN11* gene mutations, which dysregulate the RAS/MAP-K signaling pathway and drive clonal proliferation. Splenomegaly, hepatomegaly with lymphadenopathy, pallor and skin rash, thrombocytopenia, and anemia are common symptoms of JMML. Allogeneic hematopoietic

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stem cell transplantation remains the primary curative therapy.[1]

Mutations in the *RAS* signaling pathway genes may lead to JMML.[2] Mutations in *PTPN11* are also frequently found in 35% of JMML patients. The *PTPN11* gene is located on chromosome 12q24.13 and spans 91.568 bp.[3] The *PTPN11* gene encodes a phosphatase named Src Homology 2 domain–containing protein tyrosine Phosphatase-2 (SHP-2). SHP-2 functions in the signal transduction of several cytokine and growth factor receptors, such as GM-CSF and IL-3, and positively regulates the RAS/MAPK signaling pathway. Somatic *PTPN11* mutations render myeloid progenitor cells to become more sensitive to GMCSF, which leads to clonal expansion of monocytic and macrophagic cells in blood and bone marrow.[4]

Hemophagocytic lymphohistiocytosis (HLH), a severe inflammatory syndrome, can be primary (genetic) or secondary, often triggered by infections, malignancies, or autoimmune conditions.[5]

Given their compromised immune status, patients with underlying hematologic conditions like JMML are particularly susceptible to developing secondary HLH, especially when faced with infections such as SARS-CoV-2. Concurrent opportunistic infections, like mucormycosis, further complicate these cases.[6] This report details a unique case of a child with JMML and a somatic *PTPN11* mutation who developed severe COVID-19-related secondary HLH complicated by mucormycosis, ultimately leading to a fatal outcome. This case highlights the complex and often lethal interplay between these conditions, underscoring the critical need for prompt and aggressive management.

CASE REPORT

Necessary information was given to the patient and her family for the study, and a consent form was obtained. A 4-year-old Syrian immigrant girl was admitted to the hospital due to complaints of fever, cough, and runny nose. Depending on the thrombocytopenia and low hemoglobin level, she was referred to the pediatric hematology and oncology clinic. At physical examination, she had fever, abdominal distension, and the liver was 3-4 cm palpable. Complete blood count revealed Hemoglobin:7,8 gr/dl, Platelet:14000/mm^3 Leukocyte:6450/mm^3 Lymphocyte:3170/mm^3, Absolute Neutrophil Count: 650/mm^3. Other Laboratory test results showed elevated CRP (45 mg/L) and procalcitonin (3.9 µg/mL), reduced fibrinogen (95 mg/dL). Other parameters were as follows: INR: 1,29, d-dimer:1570, Antithrombin 3: 20 T/D, bilirubin:1,5/0,8, Albumin: 1,9, and Reticulocyte:1%. Coombs's test was negative. CD panel cells was within normal range: CD3: 2044 cells/cm^2, CD4: 912 cells/cm^2, CD8:1091 cells/cm^2, CD16/56:240.9 cells/cm^2, CD19:1335 cells/cm^2. CD4/CD8 ratio was decreased (CD4/CD8: 40/57). Antibody isotypes were within normal range. IgA:107 mg/dl, IgM:101 mg/dl, IgG:1452 mg/dl, IgM: 46.5 mg/dl (Table 1). She was treated with frozen plasma, erythrocyte suspension, and thrombocyte suspension, and was given Cefepime because of high fever. Because of persistent thrombocytopenia and anemia, Bone marrow aspiration was carried out twice. To assess the cytotoxicity of natural killer cells and rule out primary HLH, a cytotoxicity assay using a cell-tracking dye was performed.

Because of persistent fever, a SARS-CoV-2 PCR test was performed, and the result returned positive. The patient

Table 1. Criteria at Diagnosis of HLH

Criteria	At Diagnosis	Reference Value
1. Fever	Yes	
2. Splenomegaly	Yes	
3. Cytopenia (>2)		
Hemoglobin	8,3 g/dl	12-16 g/dl
Platelets	7x10^3 ul	130-400x10^3 ul
4. Hypertriglyceridemia and/or hypofibrinogenemia		
Tryglicerides	133 mg/dl	40-130 mg/dl
Fibrinogen	161 mg/dl	180-350 mg/dl
5 Hemophagocytosis	Yes	
6. Ferritin	140 ng/ml	4-67 ng/ml

was referred to the pediatric infectious disease clinic. The patient was suspected of having hemophagocytosis, and intravenous immunoglobulin (IVIG) was administered at a dose of 2 g/kg. Additionally, methylprednisolone was given at a dose of 30 mg/kg/day (for 3 days) and continued as 2 mg/kg.

COVID-19-related pneumonic infiltration was observed in her lungs. Skin petechial rash and hepatosplenomegaly appeared in the patient. Bacterial reproduction was not observed in the blood and urine. Despite the replacement therapy, thrombocytopenia and anemia continued. Therefore, bone marrow aspiration was examined once again. Hemophagocytosis was observed in the bone marrow aspirate (Figure 1a).

In vitro NK cytotoxicity test results were comparable between the patient and the healthy control (Figure 1b).

To identify the underlying genetic defect, clinical-exome sequencing was performed at the Erciyes University School of Medicine Department of Medical Genetics.

Molecular analyses revealed a missense variant c.226G>C (p. Glu76Gln) (NM_001330437) in *PTPN11.* The variant fraction was 17%. Given the patient's clinical presentation with JMML, the use of a bone marrow sample, the low variant fraction, and the known pathogenicity of the variant, this alteration was considered a somatic variant contributing to the patient's phenotype (Figure 1c). According to clinical exome sequencing results, the case was diagnosed as JMML.

In follow-up, pain in the right eye, redness, and edema around the eye developed. Necrotic areas were observed on intranasal evaluation, and the patient was operated on urgently for invasive fungal rhinosinusitis (Figure 1d) (Video). The patient was re-operated on three days later again due to the progression of necrosis to the facial skin and nasal septum (Figure 1e). The pathological examination of the patient's nasal tissues revealed fungal hypha growth (Figure 1f). Based on the clinical findings, treatment with liposomal amphotericin B was initiated empirically. Mucorales were isolated from the samples obtained. Despite two surgeries, the infection could not be

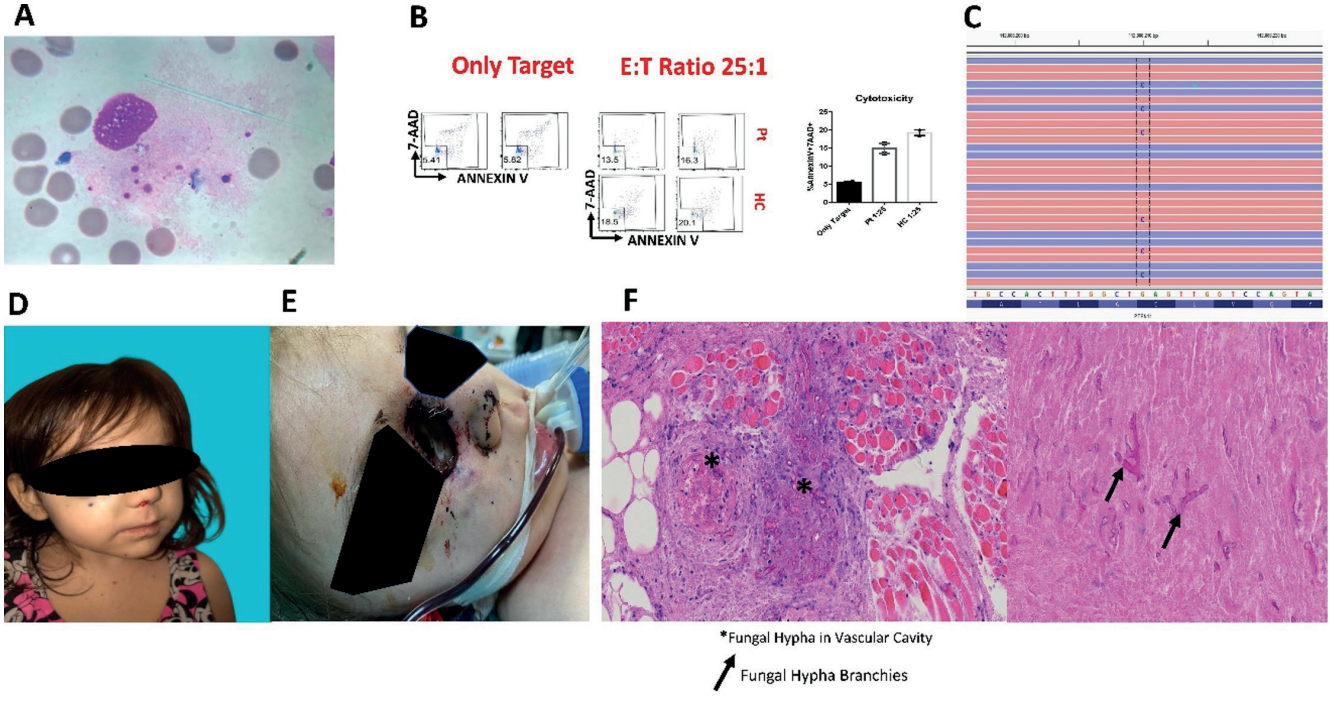

Figure 1. Patient presents with JMML phenotype, also with HLH and mucormycosis. **(a)** HLH was observed on bone marrow aspiration **(b)** Peripheral blood mononuclear cells isolated from the patients and healthy control showed comparable cytotoxicity to the target cells. (HC: Healthy Control, Pt: Patient) **(c)** Whole Exome Sequencing revealed a somatic missense mutation in the *PTPN11* gene **(d)** Patient's facial appearance before the ethmoidectomy, septectomy, and periorbital debridement operation **(e)** Patient's facial appearance after the operation **(f)** Fungal hypha in her nasal tissue; * symbol represents fungal hypha in vascular cavity and hypha branches indicated with ↗ symbol.

controlled and worsened, so posaconazole was added to the treatment. The general condition deteriorated during follow-up, and the patient died eight days after the onset of ocular findings and seven days after the first operation.

DISCUSSION

JMML is a rare but lethal disease, especially in early childhood, with an annual incidence of 1.2 per million children. The majority of JMML patients harbor mutations in *PTPN11, NF1, KRAS,* or *NRAS*. While somatic *PTPN11* mutations may cause JMML, the germline mutations may lead to Noonan syndrome. The symptoms and phenotype of Noonan syndrome are quite different than those of JMML.[6] Noonan syndrome is characterized by small stature, pulmonary valve stenosis, hypertelorism, mild intellectual disability, ptosis, and skeletal malformations. JMML usually presents in early childhood (2-4 years) with a male predominance. JMML occurs due to clonal proliferation of transformed hematopoietic progenitors and is marked with expansion of granulocytic and monocytic lineages.[1] In affected children with JMML, skin rash, pallor, cough, hepatomegaly, or splenomegaly are observed.[6] Our patient did not present with Noonan syndrome symptoms. Accordingly, clinical exome sequencing data revealed a somatic variant in the *PTPN11* gene, c.226G>C (p. Glu76Gln). The variant fraction was 17%. By the time the result was reported, the patient had died; therefore, no confirmatory study could be performed. Consistent with the *PTPN11* defect, she has thrombocytopenia, anemia, and hepatosplenomegaly.

HLH is a life-threatening disorder in children and adults. The primary or familial (F)HLH results from genetic defects. Mutations in *PRF1, UNC13, STX11, STXBP2* genes may cause F-HLH.[7] Molecular genetic analyses revealed no pathogenic variant in the genes associated with familial HLH. Secondary HLH may be observed due to malignancy, hematologic disease, or viral infections.[8] Prevalence of SARS-CoV-2 among pediatric cancer patients has been predicted as 1.3% which is higher than other pediatric populations.[9] Having a hematologic malignancy, such as leukemia, lymphoma, or having had hematopoietic stem cell transplantation, may increase the susceptibility of pediatric patients to COVID-19 infection.[9] Our patient showed secondary HLH related to SARS-CoV-2 infection. The observation that *in vitro* NK cell cytotoxicity was comparable between the patient and the healthy control supports this hypothesis. To treat HLH, IVIG and methylprednisolone were given. However, due to JMML, the treatment was ineffective.

Zygomycosis (Mucormycosis) infection has increased over the last decade and is particularly common among patients with hematologic malignancies or who have undergone HSCT.[10] Invasive fungi were known to be opportunistic pathogens causing sinusitis, rhinonasal infections.[11] The patient had swelling and a rash on the right eye, consistent with mucormycosis related to COVID-19. Her ethmoidal and sphenoidal sinuses were affected by mucor, and she also had necrotic lesions in her skin. Treatment approaches of mucormycosis depend on antifungal agents such as liposomal amphotericin B, Posaconazole, or other azole compounds.[12] She was treated with liposomal amphotericin B and posaconazole, but her clinical course did not improve. Our patient, to the best of our knowledge, is the first patient in the literature with mucor infection and COVID-19-related secondary HLH in a JMML case.

CONCLUSION

In conclusion, the coexistence of secondary HLH and mucor infection may be fatal for children with JMML. In our patient, SARS-CoV-2 infection contributed to a complicated clinical course with mucormycosis, HLH, and JMML. Secondary HLH due to SARS-CoV-2 infection, combined with the underlying somatic genetic defect in *PTPN11* and the concurrent presence of other causative infectious agents such as Mucormycosis became lethal.

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Ethical approval

This study has been approved by the Ethics Committee of Erciyes University (approval date 06.01.2021, number 2021/17). Written informed consent was obtained from parents of the patient.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: EU, KA; data collection: KA, FO, KK, AO, CA, AK, BSC, OC; analysis and interpretation of results: KA, HBA, EU, MD, HC; draft manuscript preparation: KA, HBA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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