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Case Report

Hemophagocytic lymphohistiocytosis as the initial manifestation of bone marrow failure in a child with a TERC variant telomere biology disorder

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***Abstract*:** Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic hyperinflammatory syndrome, rarely associated with bone marrow failure (BMF). Telomere biology disorders (TBD) are caused by inherited defects in telomerase processes and can have heterogeneous presentations including idiopathic pulmonary fibrosis, cirrhosis, and BMF. We report a case of a 10-year-old male from Lima, Peru, who presented with HLH as the initial manifestation of a TBD. He experienced fever, gastrointestinal symptoms, and mucocutaneous involvement. Initial laboratory analyses revealed pancytopenia and elevated inflammatory markers. Despite symptomatic and antibiotic treatment, his clinical condition persisted leading to a suspicion of Kawasaki disease and, subsequently, HLH. Immunomodulatory treatment was initiated with a good clinical response. Bone marrow aspiration revealed severe hypocellular bone marrow and cytophagocytosis. Genetic studies identified a pathogenic variant in the *TERC* gene (n.110_113del), which was also found in the patient's mother and brother. HLH as the initial manifestation of BMF is rare. This case highlights the importance of considering TBD in children with BMF of unclear etiology and the value of genetic testing in such cases.

Plain language summary

A rare immune disorder reveals an unexpected genetic condition of the telomeres: a case report of a TERC gene mutation in a Peruvian child

We present a case of a 10-year-old boy who experienced persistent fever, abdominal pain, rash, and swelling. Despite initial treatments, his symptoms continued, and he developed bone marrow failure (BMF), showing low blood cell counts. Different diagnoses were proposed, including Kawasaki disease, but he was ultimately diagnosed with hemophagocytic lymphohistiocytosis (HLH), a rare, life-threatening condition where the immune system becomes excessively active, causing systemic inflammation. The boy responded well to immunomodulatory therapy. However, he continued to experience BMF and developed portal hypertension. A comprehensive diagnostic process, including genetic testing, confirmed the presence of a rare mutation in the TERC gene (nucleotide 110 to 113 deletion), crucial for the function of telomerase (which helps maintain the protective caps at the ends of chromosomes). The same mutation was also found in the boy's mother and brother, who had no symptoms. This is one of the few reported cases of TERC mutations in Latin America, and highlights the importance of considering genetic causes in patients with unexplained BMF and unusual presentations.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic hyperinflammatory syndrome.[1] Prompt diagnosis and treatment of this syndrome are critical because it has a high mortality rate.[2] Due to its unfavorable clinical course, HLH can be diagnosed retrospectively in patients with bone marrow failure (BMF), like aplastic anemia (AA),[3] or rarely as the initial presentation of this disease.[4]

Telomere biology disorders (TBD) are caused by inherited defects in telomerase processes.[5] Telomerase is an enzyme that slows down the telomere wear process and is made up of a catalytic component of telomerase reverse transcriptase (hTERT) and an RNA component (TERC).[6] Several pathogenic variants in the *TERC* gene that affect its function were reported.[7–10] TBD has heterogeneous presentations such as idiopathic pulmonary fibrosis, cirrhosis, and BMF.[6,11,12]

In this case, we report a 10-year-old male diagnosed with a pathogenic variant in the *TERC* gene (n.110_113del) presenting HLH as the initial manifestation of BMF. This case highlights the importance of considering TBD in children with BMF of unclear etiology and the importance of genetic testing for these conditions.

The reporting of this study conforms to the CARE statement.[13]

Case report

We report a 10-year-old male from Lima, Peru, who presented to the emergency department (ED) of the Hospital Nacional Edgardo Rebagliati Martins (Lima, Peru) in May 2020 with a 2-week history of fever, intermittent abdominal pain, watery diarrhea, and nausea. Nine days before admission, he developed lip edema, bilateral conjunctival injection, bilateral palpebral edema, and inflammation of the tongue. Six days before admission, petechiae appeared on his face and later spread to his lower extremities. Despite receiving outpatient symptomatic treatment with antipyretics, which provided partial relief, he continued to experience daily fever spikes. Additionally, he was treated with outpatient antibiotics, including amoxicillin and cephalexin.

The child had a medical history of controlled asthma (no regular medications, with the last acute asthma exacerbation 1 year ago) and reported an allergy to sulfa drugs. He had no history of surgeries. The family history included an older brother with incidentally diagnosed with asymptomatic thrombocytopenia and a female cousin with thrombocytopenia and portal hypertension, who underwent a splenectomy at 7 years of age (Figure 2).

During the physical examination in the ED, he was found to have a nonmucopurulent bilateral conjunctival injection, lip edema, tongue inflammation, and a maculopapular rash on the thorax, abdomen, and face (Figure 1). There was no cervical adenopathy. During the initial evaluation, diffuse abdominal pain was present and an abdominal mass in the right iliac fossa was found upon palpation. His vital signs were normal, with no signs of respiratory distress, neurologic deficits, or hemodynamic compromise.

Our patient underwent an abdominal ultrasound and computed tomography scan, which did not reveal signs of acute appendicitis. Instead, they showed a conglomerate of intestinal loops and inflammatory tissue at the hypogastrium and right iliac fossa levels. Diagnosis of appendiceal mass was made, which was resolved in follow-up imaging.

Initial laboratory analyses showed pancytopenia with severe neutropenia as shown in Table 1, molecular tests for SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus were negative. Direct immunofluorescence tests for respiratory syncytial virus, adenovirus, influenza A, influenza B, and parainfluenza 1–3 were also

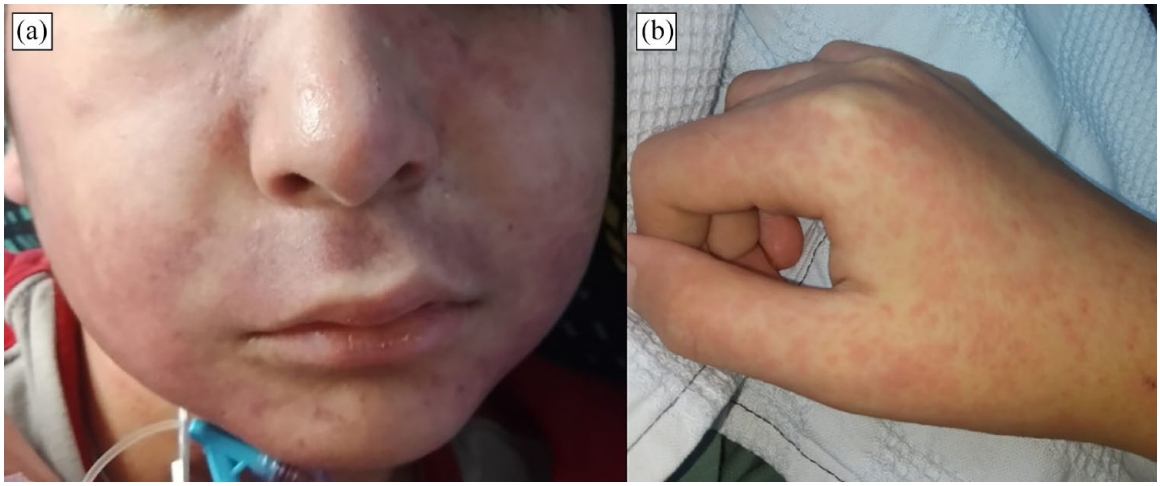

Figure 1. Cutaneous manifestations on the face (a) and on the extremities, hand (b).

negative. Suspecting an infectious etiology for the persistent fever, we initiated antibiotic therapy with meropenem, but the response was inadequate. The fever persisted, and palmar and plantar erythema were observed 2 weeks after admission. Blood and stool cultures were negative.

A diagnosis of Kawasaki disease (KD) was made based on the persistent fever and mucocutaneous manifestations. Treatment was initiated with human intravenous immunoglobulin (IVIG) at 2 g/kg and aspirin at 100 mg/kg daily, and antibiotic therapy was suspended. The patient responded well to the treatment, with the fever subsiding 2 days after starting IVIG. Additional laboratory analyses (Table 1) showed increased levels for the patient's age of ferritin, hepatic enzymes, lactate dehydrogenase, and D-dimer. Triglyceride levels and coagulation profile were normal. Echocardiography indicated adequate systolic function of the left ventricle with no alterations in the coronary arteries, and electrocardiography results were normal. An abdominal ultrasound found splenomegaly. Rheumatological markers (antinuclear antibody, antineutrophil cytoplasmic antibodies, complement C3 and C4, rheumatoid factor) and myocardial markers (troponin, NT-proBNP) were within normal ranges.

The fever returned 2 days later. HLH was considered due to persistent fever, pancytopenia, elevated ferritin levels, and splenomegaly. We initiated treatment with a second course of IVIG (one dose of 1 g/kg), dexamethasone (10 mg/m^2 of body surface area daily for 3 days), folic acid, and hydroxocobalamin. The fever subsided 2 days after starting this regimen.

Bone marrow aspiration and biopsy were performed, and results showed hypocellularity with myeloid and erythroid cells exhibiting maturative paucity. Activated macrophages and monocytes with cytophagocytosis of all the cellular lines were observed, with no blast cells or histiocytes present. Flow cytometry of the biopsy found no evidence of infiltration of blasts with a pathologic phenotype. Serology for Epstein–Barr virus (EBV) showed reactive VCA IgM, VCA IgG, and EBNA IgG. EBV viral load was undetectable. The total IgA, IgM, and IgE levels were within normal ranges. Peripheral blood flow cytometry found a decreased total lymphocyte population for his age, low T and B cell levels, and normal values of natural killer cells (Table 1).

The patient responded well to the treatment and was discharged 2 weeks after the second dose of IVIG. The fever did not recur, although pancytopenia persisted with milder severity. Etoposide was not administered. Clinically, the patient improved and the rash subsided. Outpatient treatment included 2 weeks of dexamethasone at 10 mg/m^2 daily followed by oral prednisone, along with supplementation of pyridoxine, folic acid, and vitamin B complex.

At 8 months of follow-up (March 2021) portal hypertension with persistent splenomegaly was identified by abdominal ultrasound. Upper

Table 1. Laboratory test results and reference ranges for the patient's age and sex.

Setting	Test name	Unit	Result	Reference range
First hospitalization	Platelets	$\times 10^9$/L	26	187–415
	Hemoglobin	g/dL	8.3	10–15.5
	White blood cells	cells/μL	1350	4800–10,800
	Neutrophils	cells/μL	70	1800–8000
	Lymphocytes	cells/μL	1100	1500–6500
	Lymphocytes (flow cytometry)	cells/μL	780	1500–6500
	T cells	cells/μL	601.73	1000–5300
	B cells	cells/μL	90.84	200–600
	Natural killer cells	cells/μL	84.99	70–1200
	C-reactive protein	mg/dL	9.8	<0.4
	Ferritin	ng/mL	6000	7–140
	Aspartate aminotransferase	U/L	208	21–41
	Alanine aminotransferase	U/L	125	5–30
	Lactate dehydrogenase	U/L	446	143–370
	D-dimer	mg/L	4.3	0.4–2.27
Second hospitalization	White blood cells	cells/μL	3520	4800–10,800
	Neutrophils	cells/μL	2180	1800–8000
	Platelets	$\times 10^9$/L	32	187–415
	Hemoglobin	g/dL	9.8	10–15.5
Third hospitalization	White blood cells	cells/μL	1330	4800–10,800
	Neutrophils	cells/μL	280	1800–8000
	Platelets	$\times 10^9$/L	30	187–415
	Hemoglobin	g/dL	8.6	10–15.5
Last outpatient tests	White blood cells	cells/μL	1700	4800–10,800
	Neutrophils	cells/μL	700	1800–8000
	Platelets	$\times 10^9$/L	21	187–415
	Hemoglobin	g/dL	9.9	10–15.5
	Aspartate aminotransferase	U/L	82	21–41
	Alanine aminotransferase	U/L	57	5–30

endoscopy found grade I–II esophageal varices and mild hypertensive gastropathy. Two years after the first hospitalization (February 2022), the patient was readmitted due to fever, diarrhea, and abdominal pain. Physical examination found scleral jaundice, pallor, and telangiectasia of the face. Complete blood count showed pancytopenia (Table 1). A liver biopsy was performed and the results indicated foci of atrophy and necrosis, and nodular regenerative hyperplasia consistent with portal hypertension. Fever and abdominal pain subsided during the 2-week hospitalization.

He had a third hospitalization 9 months later (November 2022) due to profound neutropenia (Table 1) and fever. Treatment included vancomycin, meropenem, and antifungals (caspofungin and fluconazole). COVID-19 infection was diagnosed based on positive antigenic and molecular tests for SARS-CoV-2. Bone marrow aspiration revealed severe hypocellular bone marrow. Filgrastim was initiated with an adequate response. Due to the persistence of fever, pancytopenia, splenomegaly, and elevated ferritin (>500 ng/mL), HLH was suspected. He received two doses of immunoglobulins (0.5 g/kg daily for 2 days) and methylprednisolone (1 g daily for 3 days), followed by ongoing corticosteroid therapy with prednisone. Samples from bone marrow aspiration and bone biopsy were obtained to perform genetic studies. The patient showed a gradual yet positive clinical response and was discharged 3 months after admission.

Sequence analysis and deletion/duplication testing for 574 genes associated with cytopenias (Invitae Inborn Errors of Immunity and Cytopenias Panel) showed a heterozygous variant n.110_113 in the *TERC* gene (NR_001566.1) which has been previously classified as pathogenic (Clinvar ID: 7325). With this result, and the patient's clinical manifestations, the diagnosis was TERC variant TBD. Additionally, the same mutation was detected in the patient's mother and brother, both of whom are asymptomatic; however, the brother has asymptomatic thrombocytopenia not requiring treatment. They are currently undergoing periodic check-ups. The mutation was absent in the father (Figure 2).

A bone marrow transplant was considered but ultimately declined following discussions with the family, due to concerns about potential complications. Androgen therapy was not offered due to limited evidence of its effectiveness and potential risk of complications. The patient is currently under supportive care for underlying conditions, with propranolol and regular outpatient follow-up, including blood tests, abdominal ultrasounds, annual elastography, and blood transfusions as needed. At the last follow-up on October 16, 2024, the patient remained clinically stable, although laboratory tests showed pancytopenia and elevated liver enzymes (Table 1).

Discussion

The phenotypes related to TBD in children include dyskeratosis congenita, BMF, pulmonary fibrosis, immunodeficiency, liver disease, and increased cancer risk.[14] Our patient began with symptoms resembling KD and later met the criteria for HLH requiring immunomodulatory treatment, further genetic testing revealed a mutation in the *TERC* gene.

HLH is characterized by immune dysregulation leading to multiorgan dysfunction.[15] Initially, HLH may resemble KD due to dermatological manifestations, but if there is multisystem dysfunction, HLH should be suspected.[16] Celkan described two cases of HLH in boys who presented persistent pancytopenia, acellular bone marrow, and AA, supporting the possibility that HLH may precede bone marrow compromise, resembling our patient's progression.[4]

TERC mutations are rare, detected in only 1%–2% of BMF cases.[10,17] Few studies have described the *TERC* gene mutation n.110_113 found in our patient.[8,9] Marrone et al. reported the case of a 6-year-old female with chronic iron deficiency anemia, dysphagia, and hypocellular bone marrow with no evidence of myelodysplasia, but associated with peripheral cytopenia.[8] Her family history included two brothers with congenital deafness and schizophrenia, one of whom had AA and died from carcinoma of the tongue, while another died following a bone marrow transplant for myelodysplasia. A third brother had normal hearing, normal blood counts, and no schizophrenia. Her mother was deceased, and her father died of acute myeloid leukemia.[8] Our patient presented with pancytopenia and bone marrow hypocellularity like the report by Marrone et al. In addition, there was a family history of thrombocytopenia in the older brother (asymptomatic) and in the cousin (who required splenectomy). Vulliamy et al. reported the same

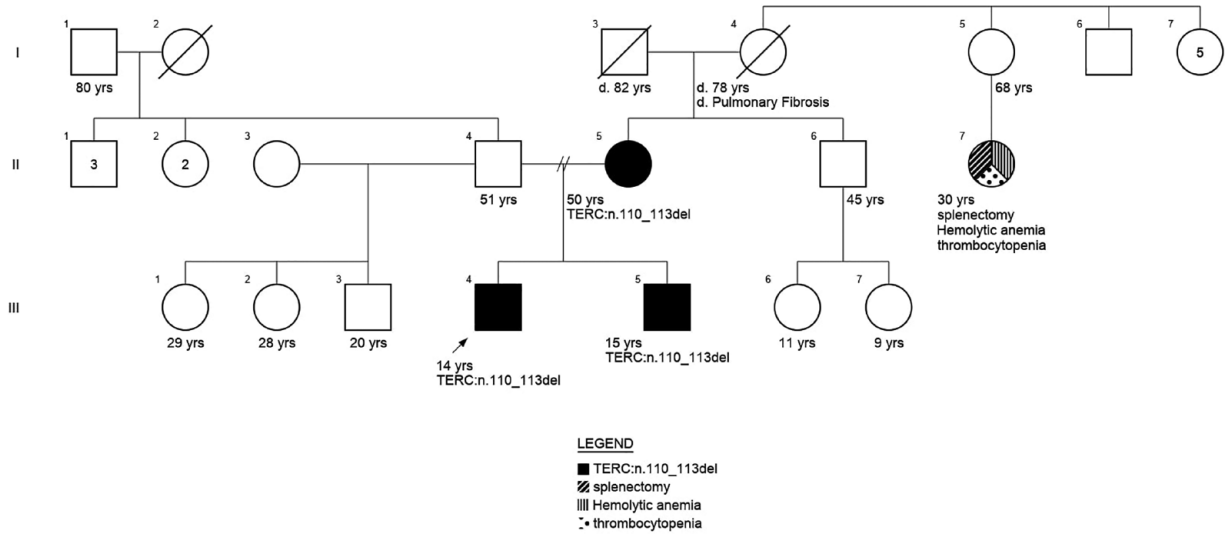

Figure 2. Pedigree of the family indicating affected members with the TERC: n.110_113del variant; the proband (arrow; III-4), his brother (III-5), and his mother (II-5).

mutation in a 26-year-old male with nonsevere AA, he had a sister who also had nonsevere AA.[9] Although both reports do not describe the initial presentation of HLH, they suggest that the family history of hematological diseases could lead to suspicion of this genetic mutation in the context of BMF. Our patient never developed lung injury and was not oxygen dependent; however, this *TERC* gene variant was identified in a 38-year-old woman with idiopathic pulmonary fibrosis.[11] In Latin America, there are limited reports of TBD associated with BMF. A case series in Brazil reported 29 patients with TBD who received a hematopoietic cell transplant, only 2 had a mutation in the *TERC* gene, but none of the variant n.110_113del.[18]

In our patient's family pedigree, his brother and his mother had the TERC n.110_113del variant (Figure 2). The brother has asymptomatic thrombocytopenia that does not require treatment, and the mother is asymptomatic. Although the thrombocytopenia could be due to multiple causes, since the brother also had the pathogenic variant in the *TERC* gene, we assume the cause to be a TBD. Similar to previous reports,[8,9] hematological alterations are present in the family tree.

TBD can lead to BMF through the depletion of hematopoietic stem cells and may cause immune dysfunction, potentially predisposing patients to develop HLH.[19,20] Further research is needed to clarify the mechanisms underlying this association.

Current treatment options for TBD include androgen derivatives, which may enhance telomerase activity, and hematopoietic cell transplantation, which is recommended for patients who fail to respond to androgen therapy or have hematologic malignancies.[14] In our patient's case, androgen derivatives were not offered due to the limited evidence supporting their efficacy and the risk of side effects, such as liver toxicity, which could pose a greater risk given his concurrent portal hypertension. Instead, a bone marrow transplant was proposed; however, after discussing potential complications, including the risk of exacerbating nonhematologic disease progression, the parents decided not to proceed with the procedure. Emerging treatments, such as gene therapy with telomerase, may offer new possibilities in the future, but they remain under investigation (ClinicalTrials.gov identifier: NCT04211714).

The initial approach to HLH is crucial, as initial manifestations are often nonspecific and may result from various triggers or patient-specific conditions, such as the telomere mutation in our case.[16] Recognizing alterations in blood series (cytopenias), elevated inflammatory markers, liver dysfunction, and coagulopathy in a patient with multisystemic deterioration raises suspicion

for HLH.[16] Additionally, hematologic findings such as recurrent cytopenias, unexplained thrombocytopenia, or hypocellular bone marrow, suggest the possibility of TBD, as in our case.[21]

Some authors suggested that it might be helpful to study the *TERC* gene in patients with AA, myelodysplasia, or acute leukemia,[8] and genetic testing may also be warranted in hemophagocytic syndromes, especially with family histories suggesting bone marrow compromise. Early diagnostic suspicion is crucial for improving survival,[1,2] and further research is needed to better characterize the clinical manifestations of this mutation.

Strengths of our study include the comprehensive evaluation by a multidisciplinary team of specialists from pediatrics, infectious disease, genetics, hematology, pediatric oncology, and pediatric rheumatology. All diagnoses were made by consensus among these specialists, and other possible causes were ruled out. Limitations include the delay in genetic diagnosis at the initial presentation due to logistical constraints, requiring testing to be conducted abroad. Likewise, the statement that BMF due to a TERC mutation may present as HLH should be approached with caution, making it necessary to individualize each case and conduct a thorough differential diagnosis, especially considering that hemophagocytosis acts as a hallmark in several conditions beyond HLH.

Conclusion

HLH as the initial manifestation of BMF is rare. Given the variable clinical presentation of TBD, which includes bone marrow compromise, it is important to rule out TBD in patients with undetermined BMF. This case underscores the importance of considering TBD in children with BMF of unclear etiology and highlights the value of genetic testing in such cases.

Declarations

Ethics approval and consent to participate

Ethical approval to report this case was obtained from the Hospital Nacional Edgardo Rebagliati Martins (Lima, Peru) Research Ethics Committee (approval no. 052-CE-GHNERM-GRPR-ESSALUD-2024) on April 5, 2024. Written informed consent to participate was obtained from the patient's mother.

Consent for publication

Written informed consent was obtained from the mother of the patient for his anonymized information to be published in this case report.

Author contributions

Daniel Medina-Neira: Conceptualization; Investigation; Writing – original draft.

Giancarlo Alvarado-Gamarra: Conceptualization; Writing – original draft.

Brenda Huamaní-Condori: Investigation; Writing – original draft.

Nelson Purizaca-Rosillo: Investigation; Writing – review & editing.

Noé Atamari-Anahui: Investigation; Writing – review & editing.

Erick Matos-Villena: Investigation; Writing – review & editing.

Raquel Garces-Ghilardi: Conceptualization; Writing – review & editing.

Matilde Estupiñan-Vigil: Conceptualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data and materials used in this case report are based on the medical records, imaging studies and pathological findings of our patient. Due to privacy and confidentiality considerations, access to the specific patient data and materials is restricted. Upon reasonable request, anonymized and de-identified data may be made available for research purposes, in compliance with institutional policies and ethical guidelines.

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