CASE REPORT

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Disseminated Enterovirus Infection Complicated by Rhabdomyolysis in a Child with Acute Lymphoblastic Leukemia

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ABSTRACT

Enterovirus is not a common cause of myositis and rhabdomyolysis in children. We report a case of a two-year-old boy with acute lymphoblastic leukemia with disseminated enterovirus infection complicated by hepatitis, myositis, and rhabdomyolysis. The case was managed successfully with supportive care and high-dose intravenous immunoglobulins.

Mild myositis is not uncommon in children and is mainly associated with influenza viruses. Enterovirus is a rare cause of myositis and rhabdomyolysis. Immunity against enteroviruses is largely antibody-mediated, and severe infections of disseminated enterovirus are generally associated with diseases characterized by low antibody levels.[1] We report a case of a child with acute lymphoblastic leukemia (ALL) who had severe disseminated enterovirus infection complicated by hepatitis, myositis, and rhabdomyolysis during the maintenance phase of chemotherapy.

CASE REPORT

A 25-month-old boy undergoing maintenance chemotherapy for ALL presented to the emergency department with a history of fever, rash over both palms and soles, and refusal to walk, associated with pain and swelling of both calf muscles for two days. Before the current presentation, he had repeated episodes of febrile viral illnesses with multiple different viruses isolated from nasopharyngeal aspirates and stools. One week earlier, he received intravenous vincristine and five days of oral dexamethasone as per his leukemia treatment protocol. According to the patient's mother, he had dark urine and mild cough, but no dysuria, recent trauma, sore throat, or other complaints.

Initial examination found the patient febrile (39.3 °C) with tachycardia (heart rate = 158/min). Oxygen saturation and blood pressure were within normal limits. There were multiple papulovesicular lesions on both palms and soles along with bilateral swelling and tenderness in the lower extremities, with a full range of motion at the knee and ankle joints [Figure 1].

Neurovascular examination revealed normal findings in both lower limbs. Though the urine dipstick indicated +2 for blood, urinalysis showed no red blood cells. Creatine phosphokinase (CPK) level was very high at 12769 U/L (normal range = 39–308 U/L). Complete blood count parameters showed lymphopenia (0.3–0.8 × 10^3/mm^3) and a high platelet count (540 × 10^3/mm^3) on the day of admission, which normalized after two days and remained normal throughout the follow-up period. He initially had a high creatinine level (38 umol/L), which improved after hydration to 23. Other laboratory results including serum electrolytes, uric acid, blood gases, coagulation profile, and urine electrolytes were within their normal ranges. Alanine transaminase and aspartate transaminase levels peaked respectively on the seventh and sixth day of admission with 972 U/L and 2453 U/L.

Tests for acute hepatitis (hepatitis A and E virus serology), cytomegalovirus, Epstein-Barr virus, and adenovirus polymerase chain reaction (PCR)

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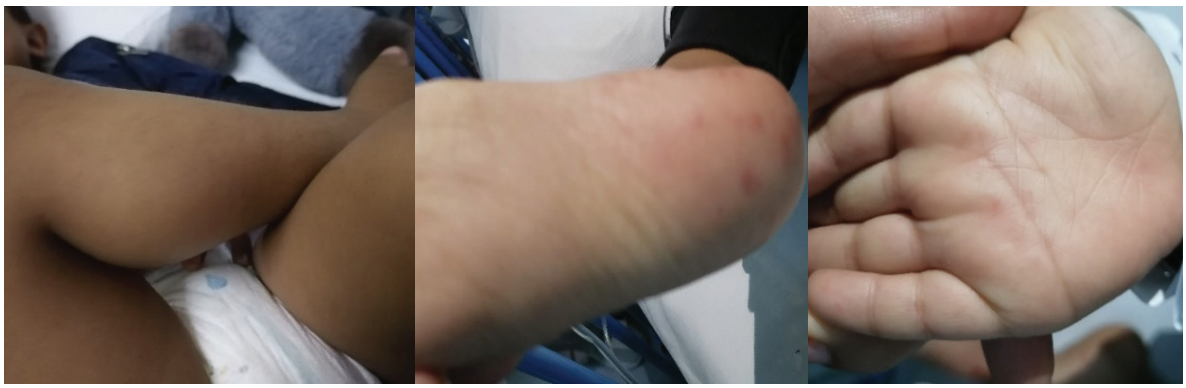

Figure 1: Clinical presentation of enterovirus infection showing the papulovesicular eruptions of enterovirus on the hand and foot, and tender swelling of the calf muscles.

yielded negative results. Enterovirus PCR was positive in blood and respiratory secretions. Creatine kinase MB level of 1059.3 U/mL (normal range = 0–25 U/mL) and troponin level of 85 U/mL (normal range < 14 U/mL) were high. The patient's respiratory secretions were negative for other respiratory viruses including those associated with influenza A or B, parainfluenza, respiratory syncytial virus, and SARS-CoV-2. His immunoglobulin (Ig) G levels were in the low normal range of 4.7 g/L (normal range = 2.3–14.1 g/L).

Chest X-ray and echocardiogram yielded normal results. However, the electrocardiogram showed sinus tachycardia and nonspecific ST and T-wave changes. Doppler ultrasound examination of both legs was not suggestive of deep vein thrombosis or soft tissue collections.

The patient was managed with aggressive hydration on 1.5 times maintenance fluids using dextrose 5% in 0.45% normal saline. Because of the presence of disseminated enterovirus in an immunocompromised child, he was administered intravenous immunoglobulin (IVIG) at 1 g/kg/day for two days.

Repeat CPK (46 194 U/L) peaked on day five of the hospital stay and then showed a declining trend thereafter [Table 1]. The patient was discharged on the eighth day and followed-up weekly. The painful swelling of the calf muscles and refusal to walk resolved gradually over the next few weeks.

DISCUSSION

The current case represents a severe enterovirus infection in a toddler with a weakened immune

Table 1: Serial laboratory results during hospital stay and upon follow-up.

Test	Normal range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8*	Day 17
BUN, mmol/L	2.5–6.0	3.2	4.1	2.9	5.0	2.5	2.2	2.5	4.0	4.3
Cr, mmol/L	17–34	38	33	23	23	25	24	27	23	32
HCO_3, mmol/L	22–26	20	23	22	26	23	24	24	23	19
Anion gap, mmol/L	8–12	14	9	7	8	11	8	11	8	13
Na, mmol/L	135–145	138	131	134	136	132	134	137	133	138
K, mmol/L	3.4–4.7	5.2	4.6	4.1	4.4	5.1	4.9	4.5	4.7	5.1
ALT, U/L	0–41	81	183	-	561	773	948	972	820	268
AST, U/L	0–40	77	314	-	1391	2342	2453	1554	906	206
CPK, U/L	39–308	-	12 769	-	37 445	46 194	31 198	12 085	9079	-
CK-MB, U/L	0–25	-	-	-	1048.1	1059.3	805.8	624.2	481.5	-
TROPT, ng/L	< 14	-	-	-	51	85	75	82	75	-
Platelet count	140–450	540	-	346	219	374	396	312	278	439
Lymphocyte	1–4.8	0.8	-	0.3	0.4	0.5	0.7	0.9	0.8	1.1

*BUN: blood urea nitrogen; Cr: creatinine; HCO_3: bicarbonate; Na: sodium; K: potassium; ALT: alanine transaminase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; CK-MB: creatine kinase MB; TROPT: troponin T. *Day of discharge.*

system. Similarly, vulnerable groups include neonates and patients with profound B-cell deficiencies including X-linked agammaglobulinemia, hematopoietic stem cell transplantation recipients, and patients receiving anti-CD20 monoclonal antibodies.[1,2] Currently, there are no available guidelines on routine testing of IgG levels in children with low risk ALL while on maintenance chemotherapy. Holmes et al,[3] found that monitoring IgG levels and IVIG supplementation in those with low levels did not decrease rates of febrile infections in pediatric oncology patients during maintenance chemotherapy. However, the Children's Oncology Group Supportive Care Guidelines recommended monitoring of IgG levels with IVIG administration for low age-adjusted IgG levels if clinically indicated.[4]

Viruses are the most common cause of infectious myositis and rhabdomyolysis in children. They affect the muscles directly by tissue invasion or indirectly via immune-mediated mechanisms. The most commonly reported causes of viral myositis are influenza A or B viruses. However, several others including enteroviruses have been occasionally reported to cause myositis with or without rhabdomyolysis.[5] The affected children usually have diffuse symptoms of myositis, in addition to those associated with the causative viral pathogen.

Serotyping of the enterovirus was not done in the current case due to the nonavailability of the testing facility at our center. The diagnosis was based on the classic clinical presentation and related tests. Muscle necrosis was evident from the very high CPK level and the presence of myoglobin in urine. Acute infection in the current case was confirmed by detecting the virus in blood and respiratory samples by PCR.

Despite the very high CPK level that peaked at 46 194 IU/mL on the fifth day of admission, our patient had only a temporary mild elevation of serum creatinine on admission which fell to normal within two days of hydration. A similar observation was made by Soliman et al,[6] in a child with coxsackie virus-related rhabdomyolysis. In contrast, for pediatric post-traumatic rhabdomyolysis, CPK values of ≥ 3000 IU/L posed a significant risk for acute kidney injury.[7]

On note, our patient had a high platelet count on presentation, unusual in a child receiving chemotherapy. Li Q et al,[8] suggested that platelet counts were positively associated with the severity of hand, foot, and mouth disease (HFMD) caused by enterovirus 71. Moreover, they found that platelet counts were negatively correlated with interferon-gamma levels, but positively correlated with the frequency of Th1 cells.[8] However, this was not demonstrated in our patient who had absolute lymphopenia during the illness.

Treatment of disseminated enterovirus cases is mainly supportive. In addition to supportive treatment with maintenance fluids, our patient was administered high-dose IVIG, leading to rapid improvement. This mode of management has been reported elsewhere to improve the clinical outcome and odds of survival in immunocompromised patients and newborns.[1,9] As per a meta-analysis by Jiao et al,[10] IVIG use helps resolve HFMD with a high dose of 1 g/kg/day having a better prognosis. IVIG combined with supportive care for children with severe HFMD, resulted in shorter rash progression time, shorter fever resolution time, and a faster clinical cure.[10] Benefits and adverse effects should be carefully weighed when deciding on IVIG treatment for severe enterovirus infection.

CONCLUSION

Disseminated enterovirus infection can be serious in immunocompromised children, including those with low-risk ALL in the maintenance phase. Clinical presentation may include viral myositis, rhabdomyolysis, hepatitis, pneumonitis, and myocarditis. Thorough clinical assessment of different organ involvement is required to assess clinical severity and determine management. Supportive measures with aggressive hydration in addition to IVIG may result in a good clinical outcome.

Disclosure

The authors declared no conflicts of interest. Written consent was obtained from the patient's father.

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