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

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Abstract

Mild myositis is not uncommon in children and is mainly associated with influenza viruses. Enterovirus is not a common cause of myositis and rhabdomyolysis. Here we report a 2-year-old boy with acute lymphoblastic leukemia with disseminated enterovirus infection complicated by hepatitis, myositis, and rhabdomyolysis. He was managed with supportive care and high dose intravenous immunoglobulins, and he improved slowly over few weeks.

Keywords: disseminated *enterovirus*, rhabdomyolysis, children, acute leukemia.

Introduction

Mild myositis is not uncommon in children and is mainly associated with influenza viruses. Enterovirus is not a common cause of myositis and rhabdomyolysis. Immunity against enteroviruses is largely antibody-mediated and severe disseminated enterovirus infections are generally associated with diseases characterized by low antibody levels.[1] Here, we report 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 acute lymphoblastic leukemia (ALL) presented to the emergency department with 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. One week earlier, he received IV vincristine and 5 days of oral dexamethasone as per his ALL treatment protocol. His mother stated that he had dark urine and mild cough, however, he had no dysuria, recent trauma, sore throat, or other complaints. On initial examination, he was febrile (at 39.3 ℃), with tachycardia (heart rate 158/min), maintaining oxygen saturation and blood pressure within normal limits. He had multiple papulovesicular lesions on both palms and soles. He also had bilateral swelling and tenderness in his lower extremities (figure1) with full range of motion at his knee and ankle joints. Neurovascular examination revealed normal findings in both lower limbs. Urine dipstick was +2 for blood, however, urinalysis showed no red blood cells. Creatine phosphokinase (CPK) level was very high reported at 12769 U/L (normal range 39 - 308). Alanine transaminase (ALT) and aspartate transaminase (AST) levels peaked at 972 U/L and 2453 U/L, respectively on 6th day of admission. Complete blood count parameters showed lymphopenia (0.3- 0.8 x10^3/mm^3) and high platelet count of 540x10^3/mm^3 on the day of admission, that normalized after 2 days, and remained normal throughout the follow up. He initially had a high creatinine level of 38 umol/L, which improved after hydration to 23. Other laboratory investigations including serum electrolytes, uric acid, blood gases, coagulation profile, and urine electrolytes were within normal range. Acute hepatitis screening (HAV and HEV serology), Cytomegalovirus (CMV) and Epstein Barr virus (EBV) serology, and adenovirus polymerase chain reaction (PCR) were negative. Enterovirus PCR was positive

from blood and respiratory secretions. CK-MB (1059.3u/ml, normal range 0-25) and troponin levels (85u/ml, normal <14) were high, and Electrocardiogram showed sinus tachycardia, and nonspecific ST and T wave changes, however, echocardiogram was reported normal. His respiratory secretions were negative for other respiratory viruses including influenza A/B, parainfluenza, RSV and SARS-CoV 2, and his chest X-ray was normal. Ultrasound/Doppler examination of both legs was not suggestive of deep vein thrombosis or soft tissue collections. Before his current presentation, our patient suffered repeated episodes of febrile viral illnesses with multiple different viruses isolated from nasopharyngeal aspirate and stools. His IgG levels were on the low normal range 4.7 g/L (normal: 2.3 – 14.1). He was managed with aggressive hydration at 1.5 times maintenance fluids using dextrose 5% in 0.45% normal saline. In view of disseminated enterovirus in an immunocompromised child, decision was made to treat with intravenous immunoglobulin (IVIG) at 1gm/kg/day for 2 days.

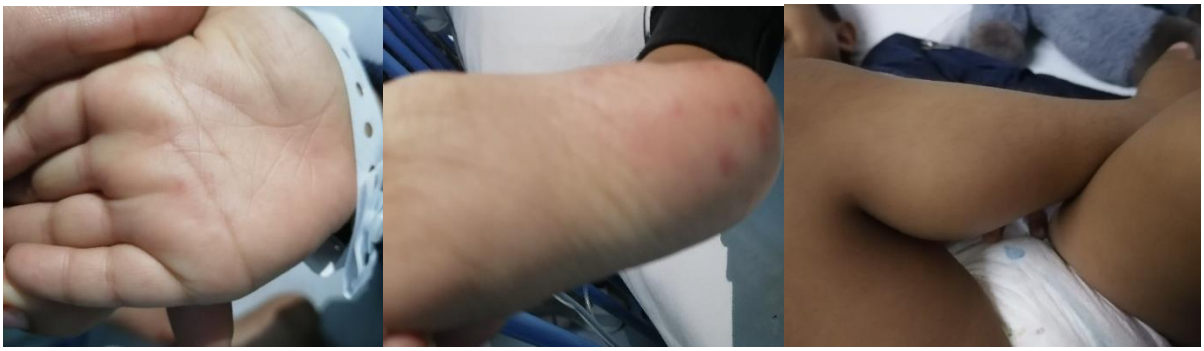

Figure 1: Clinical presentation of enterovirus infection: papulovesicular eruptions of enterovirus on hand and foot and tender swelling of the calf muscles.

Repeat CPK peaked at day 5 of the hospital stay (46194 U/L), then showed a declining trend on the 6th day and thereafter. (Table 1) The painful swelling of the calf muscles and refusal to walk resolved gradually over the next few weeks.

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

	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D17**
BUN(mmol/L)	3.2	4.1	2.9	5	2.5	2.2	2.5	4	4.3
Cr (mmol/L)	38	33	23	23	25	24	27	23	32
HCO3	20	23	22	26	23	24	24	23	19
Anion gap	14	9	7	8	11	8	11	8	13
Na(mmol/L)	138	131	134	136	132	134	137	133	138
K(mmol/L)	5.2	4.6	4.1	4.4	5.1	4.9	4.5	4.7	5.1
ALT (U/L)	81	183	-	561	773	948	972	820	268
AST (U/L)	77	314	-	1391	2342	2453	1554	906	206
CPK (U/L)	-	12769	-	37445	46194	31198	12085	9079	-
CK-MB (U/L)	-	-	-	1048.1	1059.3	805.8	624.2	481.5	-
TROPT (ng/L)	-	-	-	51	85	75	82	75	-
Platelet count	540	-	346	219	374	396	312	278	439
Lymphocyte	0.8	-	0.3	0.4	0.5	0.7	0.9	0.8	1.1

BUN: Blood Urea Nitrogen (mmol/L); Cr: creatinine (mmol/L); Na: Sodium ((mmol/L); K: potassium ((mmol/L) Cr: creatinine (mmol/L); CPK: Creatinine Phosphokinase (U/L). (Normal range 39 – 308); CK-MB: Cardiac isoenzyme of CK (U/L). (Normal range 0.0 – 25); ALT: Serum Alanine Transaminase (U/L) (Normal range 0 - 41) AST: Serum Aspartate Aminotransferase (U/L) (Normal range 0 - 40); TROPT: Troponin T (ng/L) (Normal range <14)

Discussion

Hereby, we report on disseminated enterovirus infection in an immunocompromised child, presenting with hand, foot, and mouth disease (HFMD), myositis and rhabdomyolysis, hepatitis, and myocarditis who was successfully managed with supportive measures and IVIG.

The current case represents a severe enterovirus infection that can be related to his weakened immune system. Immunity against enteroviruses is largely antibody-mediated, and severe disseminated enterovirus infections are generally associated with diseases characterized by low antibody levels[1]. This group include neonates,[2] and patients with profound B-cell deficiencies including X-linked agammaglobulinemia, hematopoietic stem cell transplantation recipients, and patients receiving anti CD-20 monoclonal antibodies[3]. 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 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.[4] However, the Supportive Care Guidelines from the Children's Oncology Group recommended monitoring of IgG levels with IVIG administration for low age-adjusted IgG levels if clinically indicated.[5] In our center, we noticed that low IgG levels were encountered in some patients who had repeated viral illnesses, and they improved on monthly supplements with IVIG. Our patient has low normal IgG levels when he got the infection.

There are multiple different etiologies which can be associated with childhood myositis, including infections and non-infectious causes. Noninfectious causes include autoimmune, genetic and endocrine diseases, medications adverse effects and electrolyte disturbances. Infectious causes include viruses, bacteria, parasites and fungi. Viruses are the most common cause of infectious myositis and rhabdomyolysis in children. Viruses may 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 other viruses, including enteroviruses, HIV, human T-cell leukemia-lymphoma virus (HTLV) type 1, and hepatitis viruses (B and C) were occasionally reported to cause myositis with or without rhabdomyolysis.[6] Recently, acute viral myositis and rhabdomyolysis was reported as a sole manifestation of Covid-19 as well.[7] Affected children usually have diffuse symptoms of myositis, in addition to symptoms and signs of the causative viral pathogen.

Serotyping of the enterovirus was not done as the testing is not available in our center. However, coxsackieviruses (group A and B) and ECHO viruses were the most commonly reported enteroviruses associated with myositis in children. In our patient, diagnosis was based on the classic clinical presentation, including localized muscle pain, tenderness on palpation or with movement, swelling, and weakness. Muscle necrosis was evident from the very high CPK level, and the presence of myoglobin in urine. Muscle biopsies are not warranted for diagnostic purposes, however, in animal models, the virus has been shown to produce degenerative necrosis of the muscle fibers. 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 to 46194 IU/ml on the 5th day of admission, our patient had only temporary mild elevation of serum creatinine that was noticed on admission and improved to normal within 2 days of hydration. A similar observation was reported by Sulaiman et al, in a child with coxackie virus related rhabdomyolysis.[8] In contrast, for pediatric post-traumatic rhabdomyolysis, CPK values of ≥3,000 IU/L posed a significant risk for acute kidney injury.[9]

On note, our patient had high platelet count on presentation, a finding that is not common in a child receiving chemotherapy. Li- Q et al suggested that platelet counts were positively associated with the severity of HFMT caused by enterovirus EV71. Moreover, they found that platelet counts were negatively correlated with interferon-γ levels, but positively correlated with the frequency of Th1 cells.[10] This finding was not demonstrated in our patient who had absolute lymphopenia during the illness. Other immune-hematological players have been suggested to influence the severity of HFMD. TGF-β1 suppresses the functions of Th1, Th2, NK cells, and CD4+ effector cells, and promotes generation and activity of Treg cells in cancer patients including CML.[11]

There is paucity of data on rhabdomyolysis complicating HFMD in children with acute leukemia. Meanwhile, severe disseminated enteroviral infection had been reported in patients with CLL/lymphoma treated with anti-CD20

monoclonal antibodies.[12] Rhabdomyolysis following severe coxsackie virus infection have been also reported in patients with chronic renal failure.[13] Additionally, in previously healthy young adults, severe and sometimes fatal rhabdomyolysis associated with HFMD had been reported during epidemics of the disease.[14-15]

Treatment of disseminated enterovirus is mainly supportive, however, there are some reports on a good prognosis in neonatal disseminated enteroviral infection with the anti-picornaviral drug pleconaril.[16] Treatment with IVIG was reported to have a good clinical outcome and improved survival in immunocompromised patients and neoborns.[2,17] Jiao et al presented a meta-analysis in which they found that IVIG use improves HFMD, with a high dose of 1g/kg/day having a better prognosis. IVIG when combined with supportive care for children with severe HFMD resulted in shorter rash progression time, shorter fever resolution time, and a faster clinical cure.[18] Benefits and adverse effects should be carefully considered 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 on 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.

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