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Case report

Coxsackie B_5 infection in an adult with fever, truncal rash, diarrhea and splenomegaly with highly elevated ferritin levels

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ABSTRACT

Coxsackie viruses are enteroviruses most common in children. Coxsackie B viral infections often present with biphasic fever, headache, pharyngitis, nausea/vomiting, diarrhea and a maculopapular rash that spares the palms and soles. These clinical features may be present in other viral infections. We present a case of a hospitalized adult with rash and fever with highly elevated ferritin levels later found to be due to Coxsackie B_5. We believe this is the first case of Coxsackie B infection with otherwise unexplained highly elevated ferritin levels.

Introduction

Coxsackie B infections are most common in children, but may occur in adults. Clinical manifestations include fever, aseptic meningitis, costochondritis, pharyngitis, myocarditis, splenomegaly, diarrhea, and a maculopapular non-pruritic rash [1–5].

Peak incidence of Coxsackie B infections is during the summer months and often occur in outbreaks. Transmission is via the fecal/oral route usually secondary to contaminated fresh water (lake, river, swimming pool) exposure. Coxsackie B costochondritis is the only distinct syndrome (Devil's grip, Bornholm's disease) that can be diagnosed clinically [6–9]. The common disease manifestations of Coxsackie B infections, i.e., fever, aseptic meningitis, sore throat, diarrhea, and rash may be due to other enteroviruses [1,4,7].

The diagnosis of Coxsackie B infections is by viral culture and/or by demonstrating a four fold increase in IgM titers. The recovery of Coxsackie B viruses from rectal swabs/stool specimens is not, of itself, diagnostic of Coxsackie infection [4,7]. Viral throat swabs are usually culture positive earlier, i.e., first three days of illness than rectal swabs, but rectal swabs have a higher culture positivity than throat swabs. Later in Coxsackie B infection, rectal swabs are more likely to be culture positive. In patients with aseptic meningitis, Coxsackie B may be cultured from the CSF in ~30% of cases [2,7]. In viral culture, Coxsackie B show diagnostic cytopathogenic effects (CPEs) in cell culture within 5 days. Viral throat cultures, diagnostic CPEs are positive earlier than rectal/stool cultures [4,7,10].

The laboratory abnormalities associated with Coxsackie $B_{1\text{-}5}$ infections are non-specific. Neither leukopenia not atypical lymphocytes are present [8]. The ESR is not elevated, serum aminotransferases were normal [2,4,7].

We present an interesting case of Coxsackie B_5 in an adult with high fevers, a diffuse maculopapular rash, splenomegaly and watery diarrhea with mildly increased serum aminotransferases and highly elevated, otherwise unexplained, serum ferritin levels.

Case

A 54 y/o male presented with rash and fever. 5 days prior to admission he developed malaise with generalized weakness and fever of 103 °F. One day later, he developed nausea and vomiting and profuse watery diarrhea. He noted an erythematous macular rash on his thorax included his arms and thighs and abdomen. His rash began 3 days before admission. His only past medical history included benign prostatic hypertrophy and bilateral total knee arthroplasties. He denied travel or recent contact with sick persons. He has no known allergies, and was not taking any medications.

On admission, he was afebrile. Physical examination was unremarkable except for non-pruritic macular (blanching) rash involving the abdomen, back, and thighs, and sparing the palms and soles. He had a white blood cell count (WBC) of 8.3 K/uL and his platelet count was 62 K/uL (normal = 160–392 K/uL). Serum lactate level was 3.8 mmol/L (normal = 0.5–2.2 mmol/L). Serum sodium

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was 131 meq/L (normal = 138–145 meq/L) and potassium was 3.0 meq/L (normal = 3.7–5.2 meq/L).

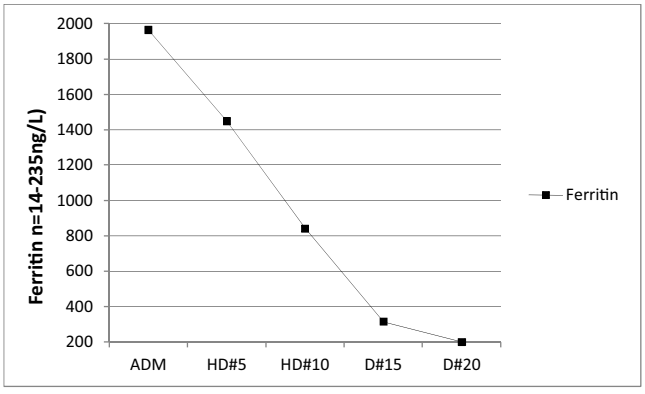
His ALT was 54 IU/L (normal = 4–36 IU/L), AST was 43 IU/L (normal = 13–39 IU/L), and alkaline phosphatase was normal. His procalcitonin (PCT) level was 7.95 mg/ml (normal > 0.5 mg/ml) but his ferritin level was highly elevated at 1965 ng/L. Chest X-ray was unremarkable. Abdominal CT scan showed mild splenomegaly.

Blood cultures, urine cultures, stool studies were negative and a workup for a viral etiology was ordered. He was treated empirically with doxycycline for 5 days. On HD #2, he spiked a fever of 103.8 °F and fevers of 102–103 °F continued. During his hospital stay, his leukocytosis peaked at 15.5 K/uL, on hospital day (HD) # 5 and his thrombocytopenia slowly resolved. EKG was unremarkable. The patient became afebrile on HD #7. After HD #5, the rash began to resolve, and his diarrhea resolved on HD # 8. Ferritin levels decreased but remained elevated (Fig. 1). Stool were negative for ova/parasites and enteric pathogens.

HIV RNA PCR was negative. Hepatitis B, hepatitis A and hepatitis C serologies were all nonreactive. Parvovirus IgM and IgG titers were unelevated. Adenovirus antibody levels were <1:8 (normal <1:8). Ehrlichia IgM and IgG titers were negative. Monospot test was negative, and EBV VCA IgM was negative and VCA IgG titer was 238 U/mL (normal <18.0 U/mL). HHV-6 IgM titers and CMV IgM were unelevated. Coxsackie A (A7, A9, A16, A24) IgM titers were negative. On HD #5, repeat Coxsackie A IgM titers remained negative. Coxsackie B IgM titers (B_{1-5}) were negative on admission, but on HD #5, Coxsackie B IgM titers (normal < 1:8) were elevated (B_1 = 1:32, B_2 = 1:64, B_3 = 1:32, B_4 = 1:32, B_6 = 1:64) and B_5 was highly elevated 1: 256. Coxsackie B_5 titers showed four-fold increase IgM titers diagnostic of acute infection, and viral stool culture was positive for Coxsackie B.

Discussion

Since Coxsackie B is more common in children, Coxsackie B viruses are often not considered in adults with fever, rash, splenomegaly, and diarrhea. In such cases, the diagnosis usually considered includes enteric fevers, and other infections. In this case, other causes of fever, fatigue, rash, and diarrhea were ruled out and the diagnosis of Coxsackie was confirmed by a four fold increase of B_5 IgM titers. Mildly elevated serum aminotransferases have not been previously reported with Coxsackie B infections. Mild aminotransferase elevations may be a non-specific clue to a variety of infectious diseases, e.g., Legionnaire's disease, Q fever, psittacosis, and their diagnostic significance is often overlooked. Among the enteroviruses, splenomegaly is uniquely associated with Coxsackie B_5 (Table 1). Clinical features of Coxsackie B infections not present in this case were biphasic fever, pharyngitis and abdominal pain.



HD = hospital day D = day of illness

Fig. 1. Serial serum ferritin levels in an adult with Coxsackie B5 infection.

Table 1
Clinical Syndromes Associated with Coxsackie B Enteroviruses.

Clinical Manifestations	Enteroviral Types
Diarrhea	Coxsackie A9, 6-9 ECHO 2,11-14, 18, 19, 22-24
Splenomegaly	Coxsackie B5 ECHO 9
Rash (maculopapular)	Polio I, III Coxsackie A2, 4, 5, 9, 16, Coxsackie B1, 3, 4, 5 ECHO 16, 9, 5, 4 1, 2, 3, 5, 7, 11, 12, 14, 18, 19

Adapted from: Drouhet V. Enteroviruses. In: Debre R, Celers J. (Eds). Clincial Virology. Saunders and Company, Philadephia, 1970.

The magnitude of his ferritin elevations were beyond that expected if ferritin was elevated as part of an acute phase response in this case there were no associated disorders to explain his highly elevated serum ferritin levels (Table 2). Fever, fatigue, and elevated serum aminotransferases may accompany a variety of viral infections with a predilatation for the liver e.g., EBV, CMV, HHV-6, but watery diarrhea is not usually a feature of these infections, and tests for these viruses were negative [8,10]. We conclude that Coxsackie B infection should be considered the differential diagnosis in febrile adults with a truncal maculopapular rash (sparing the palms/soles) and watery diarrhea, particularly if splenomegaly is present or if otherwise unexplained highly elevated ferritin levels are present. In this case, the diagnosis was confirmed by stool culture, and a four fold rise in IgM Coxsackie B_5 titer.

Table 2
Infectious and Non-Infectious Causes of Highly Elevated Serum Ferritin Levels.

Infectious causes	Noninfectious causes
Acute	Malignancies
Legionnaires disease	Preleukemia
West Nile encephalitis	Lymphoma
Pneumocystis (carinii) jiroveci	Multiple myeloma
Chronic	Hepatomas
HIV infection	Breast cancer
Ctyomegalovirus infection	Colon cancer
Active tuberculosis	Prostate cancer
	Lung cancer
	Liver/CNS metastases
	Myeloproliferative disorders
	Rheumatoid disorders
	Rheumatoid arthritis
	Adult Still's disease
	Systemic lupus erythematosus
	Temporal arteritis
	Renal disease
	Acute renal failure
	Chronic renal failure
	Liver disease
	Hemochromatosis
	Cirrhosis
	Anti-trypsin deficiency
	Chronic active hepatitis
	Cholestatic jaundice
	Miscellaneous
	Sickle cell anemia
	Multiple blood transfusions

Adapted from: Cunha CB. Infectious Disease Differential Diagnosis. In: Cunha CB, Cunha BA (Eds.) Antibiotic Essentials (15th Ed.) JayPee Medical Publishers, New Delhi, 2016; Kroll V, Cunha BA: Diagnostic Significance of Serum Ferritin Levels in Infectious and Non-Infectious Diseases. Infectious Disease Practice 27: 199–200, 2003.

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