IDCases 18 (2019) e00597

Contents lists available at ScienceDirect

IDCases

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Infectious mononucleosis like illness with costochondritis and profound relative lymphocytosis due to Coxsackie A

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ARTICLE INFO

Article history:
Received 8 May 2019
Received in revised form 9 July 2019
Accepted 9 July 2019

Keywords:
EBV
CMV
Coxsackie A & B
IM-like illnesses
Atypical lymphocytes
Relative lymphocytosis
Maculopapular rash

1 Introduction

Infectious mononucleosis (IM) like illness is characterized by fever, fatigue, often bilateral posterior cervical lymphadenopathy, exudative or non-exudative pharyngitis, splenomegaly and a rash. IM like syndrome laboratory features include mildly elevated serum transaminases (<5xn), lymphocytosis (>51%) with or without atypical lymphocytes. The IM syndrome is classically caused by Epstein – Barr virus (EBV) (85%) and less commonly may be due to cytomegalovirus (CMV) (10%) or *Toxoplasma gondii.* [1–3] Other etiologies of (IM) like syndrome, <1.5%, include viral hepatitis, adenovirus, rubella, Herpes simplex, Human herpes virus -6 (HHV-6), parvovirus B19 and HIV [4–6]. Only rarely has (IM) like illness been ascribed to Coxsackie B virus (two cases due to B) and only one case has been reported due to Coxsackie A [7–10]. We present a 35 year old female with (IM) like syndrome with fever, fatigue, chest pain due to costochondritis (usually due to Coxsackie B), macular rash, and relative lymphocytosis (>51%) The clue to the diagnosis was her costochondritis which prompted ordering Coxsackie A and B titers. Her markedly elevated Coxsackie IgG A_{24} titers 1:1600 (n < 1:100) which were diagnostic.

2 Case

A 35 year old female was admitted for evaluation of fever, fatigue and rash. Three days prior to admission she developed profound malaise and fever of 103 °F with chills. She also complained of prominent headache and a noted central rash. She denied known sick contacts or recent travel. She had no allergies and was not taking any medications.

On admission her vital signs included a temperature of 103 °F, heart rate of 130/minute. Physical examination was unremarkable except for a truncal non-blanching and non-pruritic macular rash sparing her face, palms, soles and exquisite point tenderness over a right anterior chest costochondral cartilage. There was no conjunctival suffusion or cervical adenopathy. Laboratory tests included a white blood cell (WBC) count of 2.5 K/uL (n = 3.9–11 K/ul) with 60% lymphocytes (n = 21–51%), 5% atypical lymphocytes (n = 0–5%) and 10% neutrophils (n = 42–75%). Her platelet count was 184 K/uL (n = 160–392 K/uL). The erythrocyte sedimentation rate (ESR) was 58 mm/hr and C-reactive protein (CRP) was 3.7 mg/L (n < 3 mg/L). Serum aspartate aminotransferase (AST) was 73 IU/L (n = 13–39 IU/L) alanine aminotransferase (ALT) was 69 IU/L (n – 4–36 IU/L) and alkaline phosphatase was 82 IU/L (n = 25–100 IU/L). Her serum lactate dehydrogenase level was not elevated.

On hospital day #2 (HD #2) she spiked a fever to 102.9 °F. Her WBC count decreased to 2.1 K/uL and her relative lymphocytosis increased to 79% (n = 21–51%). Fevers decreased by HD #3 and her

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https://doi.org/10.1016/j.idcr.2019.e00597

Table 1
Differential Diagnosis of Relative Lymphocytosis.

Infectious causes	Non-infectious causes
Acute infection (convalescence)	Acute lymphocytic leukemia[a]
Whipple's disease	Chronic lymphocytic leukemia[a]
Tuberculosis	Carcinomas
Brucellosis	Multiple myeloma
Pertussis[a]	Rheumatoid arthritis
Tularemia	Hashimoto's thyroiditis
Secondary syphilis	Myxedema
EBV[a]	Adrenal insufficiency
CMV[a]	Thyrotoxicosis
Human herpes virus – 6 (HHV – 6)[a]	Vasculitis
Viral hepatitis	Dilantin (DPH)
Mumps	p-amino salicylic acid (PAS)
Rubella	Serum sickness
Varicella zoster virus (VZV)[a]	
Kala-azar	
Toxoplasmosis[a]	
Histoplasmosis	
Rocky Mountain spotted fever	
Chikungunya fever	
Typhoid/enteric fever	
MERS	
Coxsackie virus[a]	

Adapted from: Cunha CB, Cunha BA (Eds). Antibiotic Essentials (15th ed) Jay Pee Medical Publishers, New Delhi, 2017.
[a] May develop extreme lymphocytosis.

macropapular rash was less intense. Her serum transaminases peaked on HD #3, with an ALT of 109 IU/L (n = 4–36) and AST 88 IU/L (n = 13–39 IU/L). Monospot and HIV screen were negative. Her IgM and IgG titers for EBV, CMV, HHV-6, parvovirus B19, and *Toxoplasma gondii* were negative. Fevers resolved by HD #4. Coxsackie A_{24} titer of 1:1600 (n < 1:100). All Coxsackie B and A IgG titers were negative, *i.e.*, only Coxsackie A_{24} was highly elevated.

3 Discussion

The diagnosis of EBV or CMV infectious mononucleosis (IM) in immunocompetent hosts is relatively straightforward. Fevers and sore throat with debilitating fatigue are the usual symptoms of EBV or CMV IM. On physical examination, non-exudative pharyngitis with bilateral posterior cervical adenopathy are common findings. In addition, a truncal maculopapular rash and splenomegaly may be present. In terms of non-specific laboratory tests with EBV or CMV, after 2 weeks lymphocytosis with atypical lymphocytes is the rule. (Table 1) Mildly elevated serum transaminases and an elevated ESR are other common laboratory abnormalities with IM like illnesses due to EBV, CMV, HHV-6. A specific serologic diagnosis is made by demonstrating an elevated IgM EBV or IgM CMV titer [1–3]. Unlike other viral routinely testing, IgM titers are not done with Coxsackie viruses because of cross reactions and diagnosis is based on highly elevated IgG titers.

The Coxsackie A and B infection is clinical with supporting laboratory data. In this case, the patient presented with a IM-like illness rarely due to Coxsackie viruses. Accordingly, Coxsackie titers are not ordinarily ordered in the workup of Monospot negative IM. However, in this case, the clinical association of costochondritis and Coxsackie B prompted ordering Coxsackie A and B IgG titers. The usual diagnostic problem with interpreting Coxsackie A/B IgG titers is to differentiate past exposure from re-activation infection. Typically, post-exposure titers are low (usually 1:8 – 1:128 and involve multiple serotypes. While PCR culture and other Dx methods may be preferable, this single A_{24} titer is diagnostic due to the degree of elevation and that it alone was singularly increased.

IM like illnesses should be suspected when tests for EBV and CMV are negative or if other clinical features suggest an alternate diagnosis. In the case presented, several elements of an IM like illness were present [4–6]. However, costochondritis was the clue to the diagnosis that prompted serological testing for Coxsackie A and B. The cause of her IM like illness was Coxsackie A_{24} [7–10].

4 Conclusion

For clinicians, her case is most interesting from three aspects., Firstly, her profound relative lymphocytosis of 79% is reportedly rare and is usually occurs only with EBV or CMV IM. Secondly, her costochondritis, which is usually due to Coxsackie B, is rarely due to Coxsackie A. Lastly, an IM like illness due to Coxsackie A is extremely rare, and we believe this to be only the second such reported case. Furthermore, it is the only Coxsackie A case with such a profound relative lymphocytosis of 79% (n = 21–51%).

References

[1] Hurt C, Tammaro D. Diagnostic evaluation of monocucleosis-like illness. Am J Med 2007;120:911.
[2] Horowitz CA, Henle W, Henle G, Polesky H, et al. Heterophil-negative infectious mononucleosis and mononucleosis-like illnesses. Laboratory confirmation of 43 cases. Am J Med 1977;63:947–57.
[3] Horowitz CA, Henle W, Henle G, et al. Clinical and laboratory evaluation of Cytomegalovirus induced mononucleosis in previously healthy individuals. Medicine 1966;65:124–34.
[4] Steeper TA, Horowitz CA, Ablashi DV. Salahuddin SZ, et el. The spectrum of clinical and laboratory findings resulting from human herpes virus- 6 (HHV-6) in patients with mononucleosis-like illnesses not resulting from Epstein- Barr virus or cytomegalovirus. Am J Clin Pathol 1990;93:776–83.
[5] Horwitx CA, Henle W, Henle G. Diagnostic aspects of the cytomegalovirus mononucleosis syndrome in previously healthy persons. Postgrad Med 1979;66:153–9.
[6] Cunha BA, Chawla K. Fever of unknown origin (FUO): CMV infectious mononucleosis of lymphoma? Eur J Clin Microbiol Infect Dis 2018;37:1373–6.
[7] Calabro JJ. Costochondritis. N Elgl J Med. 1977;296:996–7.
[8] Altman R. Clinical aspects of Enterovirus infection. Postgrad 1964;35:451–9.
[9] Biesbroeck L, Sudbury R. Viral exanthems: an update. Dermatol Ther (Heidelb) 2013;433–8.
[10] Lerner AM, Klein JO, Levin HS, Finland M. Infections due to Coxsackie virus group A, type 9 in Boston 1959 with special reference to exanthemas and pneumonia. N Engl J Med 1960;263(1265).