Journal of Biosciences and Medicines, 2022, 10, 129-135
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Erythema Nodosum Following EBV Infection in a Child

Elda Skenderi, Admir Sulovari, Gjeorgjina Kuli-Lito, Alberta Shkembi, Artemisa Shehu, Alma Babo

University Hospital Center "Mother Teresa", Tirana, Albania
Email: elda_skenderi@yahoo.com

How to cite this paper: Skenderi, E., Sulovari, A., Kuli-Lito, G., Shkembi, A., Shehu, A. and Babo, A. (2022) Erythema Nodosum Following EBV Infection in a Child. *Journal of Biosciences and Medicines*, **10**, 129-135.
https://doi.org/10.4236/jbm.2022.105012

Received: April 24, 2022
Accepted: May 23, 2022
Published: May 26, 2022

Abstract

Epstein-Barr virus (EBV) is one of the eight known human herpesviruses, which is widespread in nature and infects most of the world population. In infants and young children, primary infection is usually asymptomatic or produces an acute illness that is often not recognized as being due to EBV. It has a well-established oncogenic potential, and has been implicated in the pathogenesis of various autoimmune diseases. Here is reported the case of a 32-months old boy, who presented with a history of two days of low-grade fever, pain in both legs, swollen ankles and inability to walk. On physical examination, the child appeared moderately ill, without fever. On both shins were observed nodules 2 - 3 cm in diameter, red to bluish in color, firm and poorly demarcated. Clinically, a diagnosis of Erythema nodosus was performed. Laboratory examinations revealed increased inflammatory parameters. After a full workup, EBV was established as the causative agent. Erythema nodosum is the most common form of panniculitis in children; however, it is relatively uncommon in the pediatric population. It is a self-limited disease, and most of infectious origin in children. Although uncommon, EBV infection is a potential cause of pediatric erythema nodosum.

Keywords

Epstein-Barr Virus, Erythema Nodosum, Children, Panniculitis, Immunity

1. Introduction

Epstein-Barr virus (EBV), formally designated human herpesvirus 4, is one of the eight known human herpesviruses, which is widespread in nature and infects most of the world population. EBV was discovered in 1964 by electron microscopy of suspension cultures of African Burkitt lymphoma cells [1]. In 1968,

EBV was linked conclusively to infectious mononucleosis, which is its most common clinical manifestation [2]. Young children most likely acquire primary EBV infection from close contact that involves the exchange of oral secretions via shared items such as toys and bottles. In infants and young children, primary infection is usually asymptomatic or produces an acute illness that is often not recognized as being due to EBV, however, in adolescents and young adults, primary EBV infection frequently presents as infectious mononucleosis which is its main clinical syndrome. Like other herpesviruses, EBV virions have a double-stranded, linear DNA genome surrounded by a protein capsid, a protein tegument lies between the capsid and the envelope, which is embedded with glycoproteins that are important for cell tropism, host range, and receptor recognition [3]. Initial infection occurs in the oropharyngeal compartment. The host cells of EBV are mainly lymphocytes and epithelial cells [3]. An important consequence of EBV infection in B cells is that they are induced to activate their growth program and trigger differentiation into memory B cells, which are released into the peripheral circulation, decreased over time after primary infection but are never eliminated entirely [4]. A potent innate and adaptive immune response occurs during primary EBV infection, which controls infection, but does not eliminate it, and the virus persists for the lifetime of the infected individual. Healthy people continue to shed EBV for many months after their acute infection and are potentially capable of transmitting it [5] [6].

Infectious mononucleosis most often begins insidiously, with vague malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. Some patients experience an abrupt influenza-like onset, with fever, chills, body aches, and sore throat. The risk of developing infectious mononucleosis after primary EBV infection correlates with the age of the patient [7]. Children younger than 10 years of age are usually asymptomatic or moderately ill, with a partial infectious mononucleosis syndrome, although classic infectious mononucleosis can occur in this age group [8]. The vast majority of individuals who experience primary EBV infection, asymptomatic or with full-blown infectious mononucleosis, develop no serious consequences from lifelong infection. However, rare infection is not contained and results in the development of complications. Complications may be due to tissue-invasive viral disease or to immune-mediated damage. EBV has a well-established oncogenic potential, which under some circumstances can be life-threatening. Additionally, EBV infection has been implicated in the pathogenesis of various autoimmune diseases, such as multiple sclerosis [9].

2. Aim

This case was reported to highlight the role of Epstein-Barr virus as an etiologic cause of erythema nodosum in children.

3. Case Report

A 32-month-old boy admitted at the University Hospital Center "Mother Tere-

sa" of Tirana, Albania with a history of two days of low-grade fever, pain in both legs, swollen ankles and inability to walk. He had been a healthy child and full vaccinated. The child frequented day-care centers. All family members were healthy, and they did not keep domestic animals at home and consumed safe food. Remarkable in his medical story was a febrile illness almost three weeks ago associated with moderate grade fever for 3 - 4 days and cervical lymphadenopathy which was self-limited and recovered without use of antibiotics.

On physical examination the child appeared moderately ill, without fever. He was slightly irritated, neither stiff neck nor other neurological anomalies were observed. Neither pharyngeal injection nor cervical lymphadenopathy was observed. Respiratory and cardiac system appeared normal in examination. The abdomen was soft, not distended, bowl sounds were present, and liver and spleen were slightly palpable. Both ankles were mildly swollen, without redness or local heat, and the child could not walk. On both shins were observed nodules 2 - 3 cm in diameter, red to bluish in color, firm and poorly demarcated (**Figure 1**).

Laboratory examination revealed: WBC 17,100 cells/mm^3 (41% neutrophils, 52% lymphocytes), RBC 3,780,000 cells/mm^3, Hemoglobin level 10.7 g/dl, Hematocrit value 34%, Platelet count (PLT) 160,000 cells/mm^3, Erythrocyte sedimentation rate 32 mm/h (<15 mm/h), normal Aspartate aminotransferase 36 U/L (21 - 44 U/L), and Alanin aminotransferase 13 U/L (9 - 25 U/L), normal blood Urea Nitrogen (BUN) 35.2 mg/dL (10.9 - 36 mg/dL), normal Creatinine 0.53 mg/dL (0.38 - 0.54 mg/dL), serum Total Protein level 5.9 g/dL (5.6 - 7.5 g/dL), Albumin 3.9 g/dL (3.8 - 5.4 g/dL), low antistreptolysin titer (<50), elevated C reactive protein 3.8 mg/dL (<0.5 mg/dL), normal Fibrinogen activity 375 mg/dL (160 - 390 mg/dL), normal Ferritin value 76 ng/mL (13.7 - 79.8 ng/mL) (**Table 1**).

Microscopic examination of the peripheral blood smear showed no atypical cells. Radiologic examination of thorax revealed normal and ultrasonography of abdomen showed slightly increased liver and spleen.Ultrasonography of ankles and knees showed on changes in respective joints. Serology examinations for Salmonellosis, Mycoplasma pneumonia, Human immunodeficiency virus (HIV), Cytomegalovirus (CMV), Hepatitis A, COVID-19 were negative. Cultures of blood, throat, urine and feces resulted in no bacterial growth. MANTHOUX

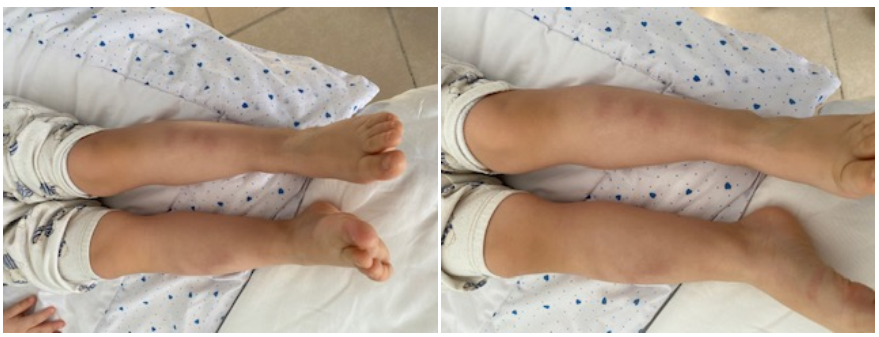

Figure 1. Erythematous nodules.

Table 1. Laboratory examinations values.

WBC	17,100 cells/mm^2 (4000 - 10,000 cells/mm^2)
RBC	3,780,000 cells/mm^2 (3,500,000 - 5,000,000 cells/mm^2)
Hemoglobin	10.7 g/dl (11 - 14 g/dl)
Hematocrit	34% (>35%)
PLT	160,000 cells/mm^2 (150,000 - 400,000 cells/mm^2)
ESR	32 mm/h (<15 mm/h)
ALT	13 U/L (9 - 25 U/L)
AST	36 U/L (21 - 44 U/L)
BUN	35.2 mg/dL (10.9 - 36 mg/dL)
Creatinine	0.53 mg/dL (0.38 - 0.54mg/dL)
Total protein	5.9 g/dL (5.6 - 7.5 g/dL)
Albumin	3.9 g/dL (3.8 - 5.4 g/dL)
ASLO	<50
CRP	3.8 mg/dL (<0.5 mg/dL)
Fibrinogen	375 mg/dL (160 - 390 mg/dL)
Ferritin	76 ng/mL (13.7 - 79.8 ng/mL)

Abbreviation: White blood cells (WBC), Red blood cells (RBC), Platelet (PLT), Erythrocyte sedimentation rate (ESR), Alanin aminotransferase (ALT), Aspartate aminotransferase (AST), Blood Urea Nitrogen (BUN), Antistreptolysin (ASLO), C reactive protein (CRP).

skin test for tuberculosis was negative. Serology panel resulted positive for both IgM and IgG antibodies. There was recommended the use of non-steroidal anti-inflammatory drugs (NSAIDs) and bed rest. The child was feeling well and playful in a few days. The erythematous nodules faded in three weeks without scaring. At the three month follow-up the child was healthy.

4. Discussion

Erythema nodosum (EN) is the most common form of panniculitis in children. However, it is relatively uncommon in pediatric population [10]. The incidence of EN is approximately one to five per 100,000 individuals. In adults, females are more affected than males with the ratio 5 - 6:1, whereas in children both genders are equally affected [11]. It is more common in young adults, with peak incidence in individuals between 20 and 30 years old, although erythema nodosum can occur at any age [12]. Eryrhema nodosum is characterized by the sudden onset of erythematous, firm, solid, deep nodules or plaques painful on palpation and mainly localized on extensor surfaces of the legs distributed bilaterally and almost symmetrical pattern. Erythema nodosum is associated with an inflammation of the septa in the subcutaneous fat tissue "a septal paniculitis", with a neutrophilic infiltrate around proliferating capillaries resulting in septal thickening in the early lesions sometimes associated with hemorrhage, however it is not as-

sociated with vasculitis. EN is considered a hypersensitivity response to various antigens from a wide range of precipitating factors such as infection, inflammation, neoplasm, and drugs [13] [14]. Evidence of circulating immune complexes in early lesions supports the suggestion that the antigen, antibody, and complement play a significant role in the pathogenesis, and circulating immune complexes may contribute to tissue injury. However, some authors have reported a lack of circulating immune complexes in uncomplicated EN, and a type IV delayed hypersensitivity reaction has been proposed [15]. Usually, nodules of erythema nodosum regress spontaneously within a few weeks, and bed rest is often sufficient treatment.

The child in the reporting case is at the age of 32 months. The mean age of erythema nodosum in childhood is reported as approximately 8 - 10 years [10]. Although erythema nodosum can occur at any age, it is unusual before the age of two years. The disease began abruptly with erythema, swelling, and tenderness over the ankles and inability to walk. It is estimated than in more than 50% of cases arthralgia and joint involvement begins during the eruptive phase or precedes the eruption by 2 - 4 weeks. The joint involvement resolved within 2 - 3 days, and soon after the eruptive phase of erythema nodosum began with red tender subcutaneous nodules over the extensor surface of both tibias, varying from 2 - 3 cm, poorly defined. During the second week lesions became red to bluish, tense, hard, and painful, fluctuant as in an abscess, but did not suppurate or ulcerate (**Figure 1**). As the diagnosis is based on clinical findings, it was obvious that the child was developing erythema nodosum. After making the diagnosis workup was directed towards finding the etiologic agent.

Erythema nodosum usually is idiopathic, but beta-hemolytic streptococcal infections are the most common identifiable cause accounting for approximately 45% of cases in children [10] [14]. So it was reasonable to perform throat culture and antistreptolysin titer as part of the initial workup to exclude group A beta-hemolytic streptococcal infection. The absence of gastrointestinal complaints and a negative result in stool examination excluded infection by Yersinia, Salmonella, and Campylobacter organisms. Normal chest radiography, the absence of adenopathy and a negative MANTHOUX test excluded a tubercular infection. The absence of atypical cells on peripheral blood smear did not point towards malignancies. In the recent medical story there was not reported the use of any antibiotics but a recent febrile illness almost three weeks ago associated with cervical lymphadenopathy was of great concern. It seemed as the child had suffered infectious mononucleosis recently. Serology panel of EBV confirmed recent infection with both IgM and IgG VCA-EBV elevated titers. Other rare causes of erythema nodosum as mycoplasma, cytomegalovirus and human immunodeficiency virus were excluded by serology.

Since EBV was discover in 1964 and its link with infectious mononucleosis was established a few years later, it was also linked to many lymphoproliferative disorders and autoimmune diseases in the following years. A potent innate and adaptive immune response occurs during primary EBV infection which controls

infection,but does not eliminate it. So the virus persists for the lifetime of the infected individual provided by a careful balance between the virus and the immune system. Sometimes this equilibrium is lost paving the way to autoimmune disorders. The skin is one of the organs affected by the immune dysregulation induced by EBV, with the most common entities being: EBV rash after antibiotic use, erythema multiforme and erythema nodosum.

EBV infection is ranked as a rare cause of erythema nodosum (less than 1%), however there are studies that have found EBV to be a more common cause of erythema nodosum specially in children. Garty in 2000 found EBV infections the second most common cause of erythema nodosum in children in Israel (17% of cases) after only streptococcal infection (25% of cases) [16]. The course of the disease is estimated to be benign and self-limited. The lesions in the presenting child resolved without sequel in three weeks.

5. Conclusion

Erithema nodosum is the most frequent type of panniculitis of autoimmune origin. It is a self limited disease, and most of infectious origin in children. Although uncommon, EBV infection is a potential cause of pediatric erythema nodosum.

Acknowledgements

We thank the medical staff of the General Pediatric Ward for the constant and precious support.

Consent

Consent of the parents is taken providing anonymity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Epstein, M.A., Achong, B.G. and Barr, Y.M. (1964) Virus Particles in Cultured Lymphoblasts from Burkitt's Lymphoma. *Lancet*, **1**, 702-703. https://doi.org/10.1016/S0140-6736(64)91524-7

[2] Henle, G., Henle, W. and Diehl, V. (1968) Relation of Burkitt's Tumor-Associated Herpes-Type Virus to Infectious Mononucleosis. *Proceedings of the National Academy of Sciences of the United States of America*, **59**, 94-101. https://doi.org/10.1073/pnas.59.1.94

[3] Kieff, E. and Rickinson, A.B. (2007) Epstein-Barr Virus and Its Replication, In Knipe, D.M., Howley, P.M., Griffin, D.E., Lamb, R.A., Martin, M.M., Roizman, B. and Straus, S. E., Eds., *Fields Virology*, 5th Edition, vol. II, Lippincott Williams & Wilkins, Philadelphia, PA, 2603-2654.

[4] Hadinoto, V., *et al.* (2008) On the Dynamics of Acute EBV Infection and the Pa-

thogenesis of Infectious Mononucleosis. *Blood*, **111**, 1420-1427. https://doi.org/10.1182/blood-2007-06-093278

[5] Jr. Balfour, H.H., *et al.* (2005) A Prospective Clinical Study of Epstein-Barr Virus and Host Interactions during Acute Infectious Mononucleosis. *The Journal of Infectious Diseases*, **192**, 1505-1512. https://doi.org/10.1086/491740

[6] Fafi-Kremer, S., *et al.* (2005) Long-Term Shedding of Infectious Epstein-Barr Virus after Infectious Mononucleosis. *The Journal of Infectious Diseases*, **191**, 985-989. https://doi.org/10.1086/428097

[7] Henke, C.E., Kurland, L.T. and Elveback, L.R. (1973) Infectious Mononucleosis in Rochester, Minnesota, 1950 through 1969. *American Journal of Epidemiology*, **98**, 483-490. https://doi.org/10.1093/oxfordjournals.aje.a121577

[8] Ginsburg, C.M., Henle, W., Henle, G. and Horwitz, C.A. (1977) Infectious Mononucleosis in Children. Evaluation of Epstein-Barr Virus-Specific Serological Data. *JAMA*, **237**, 781-785. https://doi.org/10.1001/jama.1977.03270350041018

[9] Munz, C., Lunemann, J.D., Getts, M.T. and Miller, S.D. (2009) Antiviral Immune Responses: Triggers of or Triggered by Autoimmunity? *Nature Reviews Immunology*, **9**, 246-258. https://doi.org/10.1038/nri2527

[10] Kakourou, T., Drosatou, P., Psychou, F., Aroni, K. and Nicolaidou, P. (2001) Erythema nodosum in Children: A Prospective Study. *Journal of the American Academy of Dermatology*, **44**, 17-21. https://doi.org/10.1067/mjd.2001.110877

[11] Blake, T., Manahan, M. and Rodins, K. (2014) Erythema Nodosum—A Review of an Uncommon Panniculitis. *Dermatology Online Journal*, **20**, 22376. https://doi.org/10.5070/D3204022376

[12] Leung, A.K.C., Leong, K.F. and Lam, J.M. (2018) Erythema Nodosum. *World Journal of Pediatrics*, **14**, 548-554. https://doi.org/10.1007/s12519-018-0191-1

[13] Litwin, L. and Machura, E. (2014) The Etiology and Clinical Manifestation of Erythema Nodosum in Hospitalized Children—Analysis of 12 cases. Preliminary Report. *Developmental Period Medicine*, **18**, 506-512.

[14] Schwartz, R.A. and Nervi, S.J. (2007) Erythema Nodosum: A Sign of Systemic Disease. *American Family Physician*, **75**, 695-700.

[15] Labbé, L., Perel, Y., Maleville, J. and Taïeb, A. (1996) Erythema Nodosum in Children: A Study of 27 Patients. *Pediatric Dermatology*, **13**, 447-450. https://doi.org/10.1111/j.1525-1470.1996.tb00722.x

[16] Garty, B.Z. and Poznanski, O. (2000) Erythema Nodosum in Israeli Children. *Israel Medical Association Journal*, **2**, 145-146.