CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION MIMICKING HENOCH-SCHÖNLEIN PURPURA

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Abstract

Introduction: Chronic active Epstein-Barr virus (CAEBV) infection is characterized by chronic or recurrent symptoms for at least 3 months, such as fever, hepatosplenomegaly and lymphadenopathy. The diagnosis is established due to the presence of anti-EBV antibodies or isolation of this infectious agent in affected tissues. Three cases of CAEBV infection mimicking Henoch-Schönlein purpura (HSP) were described.

Case 1: Female 3-year old patient with cervical adenomegaly, anemia and fever developed palpable purpura, haematuria and arthritis. CAEBV infection was established by serology test. She received methylprednisolone and acyclovir. She had generalized lymphadenopathy, hepatomegaly, splenomegaly, disseminated intravascular coagulation and deceased.

Case 2: Male 12-year old patient with persistent anemia, lymphadenopathy, hepatomegaly and splenomegaly had CAEBV infection diagnosis by serology test. He developed purpura and arthritis and received methylprednisolone.

Case 3: Male 13-year old patient had purpura, abdominal pain, haematuria, hepatomegaly, splenomegaly, lymphadenopathy, anemia and elevated liver enzymes. The cervical lymph node biopsy was positive to EBV infection. He received methylprednisolone and acyclovir, developing acute fulminant hepatitis and death.

Discussion: CAEBV infection mimicking HSP was rarely observed in our population

Keywords: Henoch-Schöenlein Purpura; Chronic Active Epstein-Barr Virus Infection; Children.

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Introduction

Chronic active Epstein-Barr virus (CAEBV) infection is characterized by chronic or recurrent infectious mononucleosis-like symptoms, such as fever, hepatosplenomegaly, persistent hepatitis and extensive lymphadenopathy. The diagnosis is established due to the presence of anti-EBV antibodies or isolation of this infectious agent in affected tissues[1,2]. Remarkably, to our knowledge vasculitis with purpura palpable associated with CAEBV infection was not previously described in the literature.

During a 26-year period (January 1983 to December 2009) there was 5367 patients followed up at the Pediatric Rheumatology Unit of Instituto da Criança, Faculdade de Medicina da Universidade de São Paulo. Three of them (0.05%) had vasculitis associated with CAEVB infection mimicking Henoch-Schönlein purpura (HSP) and were described. All of them fulfilled American College of Rheumatology (ACR) criteria for HSP diagnosis[3] and new criteria for HSP diagnosis named European League Against Rheumatism (EULAR), Paediatric Rheumatology International Trials Organisation (PRINTO) and Paediatric Rheumatology European Society (PRES) classification criteria[4]. The demographic data, clinical features and treatment of these patients are shown in Table I.

Case Reports

Case 1

A 3-year old girl was admitted in our University Hospital with cervical adenomegaly (Figure 1) and fever during one year. Serologic tests for EBV, cytomegalovirus (CMV), toxoplasmosis and human immunodeficiency virus (HIV) infections were negative. The abdominal ultrasound showed mild splenomegaly. Chest tomography evidenced extensive and bilateral axillary, mediastinal, paratracheal and hilar lymphadenopathy suggesting ganglionar tu-

Table I. Demographic data, clinical features and treatment of patients with vasculitis associated with chronic active Epstein-Barr virus (CAEBV) infection mimicking Henoch-Schönlein purpura

	Case Reports		
Variables	**1**	**2**	**3**
Demographic data			
Age at disease onset, years	3	12	13
Age at diagnosis, years	5	12.6	14
Gender	F	M	M
Clinical features			
Fever	+	–	–
Abdominal pain	–	–	+
Lymphadenopathy	+	+	+
Jaundice/ascites	– / –	– /–	+ / +
Hepatomegaly/splenomegaly	+ / +	+ / +	+ / +
Petechiae	+	–	–
Palpable purpura	+	+	+
Arthritis	+	+	–
Macroscopic hematuria	+	–	+
Laboratory exams			
Hemoglobin, g/dL	7.5	9.1	10.4
Platelets count, /mm3	387.000	110.000	87.000
Leukocytes, /mm3	3.600	3.400	18.200
Lymphocytes, /mm3	1.332	1.564	14.742
AST, IU/L	22	89	1.447
ALT, IU/L	26	96	466
GGT, IU/L	61	433	193
Total bilirubin, mg/dL	0,39	1.4	16.5
ANA	negative	negative	negative
Skin biopsy with leucocytoclastic Vasculitis	+	+	NR
Follow–up			
Deceased	+	–	+
Therapy	acyclovir IVMTP prednisone	IVMTP prednisone	acyclovir IVMTP prednisone

ALT – alanine aminotransferase, ANA – antinuclear antibodies, AST – aspartate aminotransferase F – female, GGT – gamma–glutamil transpeptidase, M – male, IVMTP– intravenous methylprednisolone, NR – not realized.

berculosis; however the cervical lymph node biopsy showed follicular hyperplasia without granulomatous inflammation, caseous necrosis and isolation of *Mycobacterium tuberculosis* in the culture. The patient failed to attend the appointments in our Hospital and when he returned a year later, he had palpable purpura not related to thrombocytopenia in upper limbs, abdomen (Figure 2) and lower limbs, and arthritis in the left ankle. At that moment, the laboratory exams showed hemoglobin 7.5 g/dL, white blood cell count 3.600/mm^3 (lymphocytes 1.332/mm^3), platelet count 387.000/mm^3, aspartate aminotransferase (AST) 22IU/L (normal 0-36), alanine aminotransferase (ALT) 26IU/L (0-29) and gamma-glutamyl transpeptidase (GGT) 61g/dL (14-26). Her erythrocyte sedimentation rate (ESR) was 56 mm/1st hour, C-reactive protein (CRP) was 101 mg/L (0-5), total bilirubin 0.39 mg/dL (0-1.0), urea 15mg/dL and creatinine 0.2mg/dL. The immunological status evaluation showed IgG 3350mg/dL (639-1.349), IgA 716mg/dL (84-354), IgM 917mg/dL (81-167), IgE 20.4UI/mL4 (0-90), C3 1.28g/dL (0.5-1.8) and C4 0.12g/dL (0.1-0.4). The response to vaccines

Figure 1. Cervical adenomegaly in a 3-year old girl with chronic active Epstein-Barr virus infection.

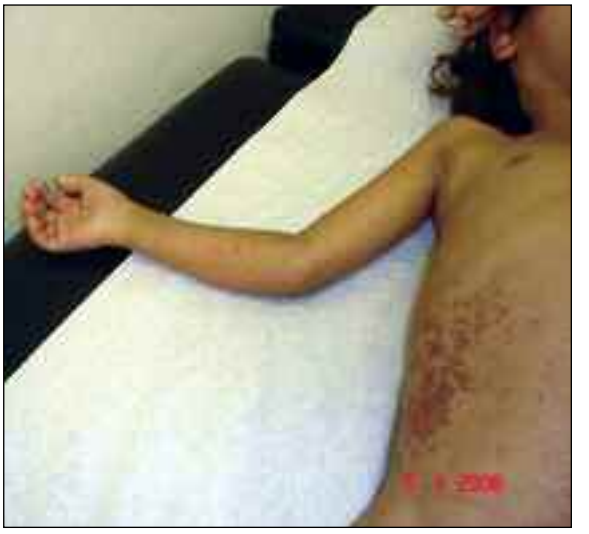

Figure 2. Vasculitis (palpable purpura) in upper limb and abdomen in a 3-year old girl with chronic active Epstein-Barr virus infection.

(measles and Hepatitis B) was normal and the subsets lymphocyte determinations by flow cytometry detected CD3 1949cels/mm^3 (605-2460), CD4+ 677cels/mm^3 (493-1666), CD8 1199 cels/mm^3 (224--1112), CD19 485 cels/mm^3 (72-520) and CD56/ /16+,CD3- 138 cels/mm^3 (73-654). Immunological tests showed negative for serum antibodies: antinuclear antibodies (ANA), anti double-stranded DNA (anti-ds DNA), anti-Sm, anti-cardiolipin (ACL) IgM and IgG and antineutrophil cytoplasmic autoantibodies (ANCA). Skin biopsy showed leucocytoclastic vasculitis without IgA deposit and she was treated with naproxen. After one month, she was hospitalized with generalized lymphadenopathy, hepatomegaly, splenomegaly, petechiae, palpable purpura on the legs and macroscopic hematuria. Abdominal tomography showed hepatomegaly, splenomegaly, and retroperitoneal, mesenteric and inguinal lymphadenopathy. Bone marrow aspirate was normal. At that moment, CAEBV infection was established by serology test IgM antibodies against viral capsid antigen (VCA) to EBV. She received intravenous methylprednisolone for 3 days and acyclovir for 21 days. After hospitalization she used prednisone and aciclovir for two months. Despite treatment, she was hospitalized in the intensive care unit due to pneumonia, hepatomegaly, splenomegaly, palpable purpura, disseminated intravascular coagulation and deceased.

Case 2

A 12-year old boy with recurrent pneumonia, acute otitis media, sinusitis chronic dacryocystitis was admitted in our Hospital with lymphadenopathy, hepatomegaly and splenomegaly for six months. The serologic tests for hepatitis virus A, B and C, EBV, CMV and HIV infections were negative. Cervical lymph node biopsy showed lymphoid follicular hyperplasia and liver biopsy evidenced reactive hepatitis with lympho-plasmacytic infiltration. At that moment, the laboratory exams showed hemoglobin 9.1 g/dL, white blood cell count 3.400/mm^3 (lymphocytes 1.564/mm^3), platelet count 110.000/mm^3, AST 89IU/L, ALT 96IU/L, GGT 433g/dL, ESR 40mm/1st, total bilirubin 1.4mg/dL, urea 35mg/dL and creatinine 0.7mg/dL. The immunological status evaluation showed IgG 1043mg/dL, IgA 191 mg/dL, IgM 244mg/dL, IgE 61UI/mL4, C3 1.0g/dL, C4 0.14g/dL. The response to vaccines (measles and Hepatitis B) was normal and the subsets lymphocyte determinations by flow cytometry detected CD3 587cels/mm^3, CD4+ 372cels/mm^3, CD8 196 cels/mm^3 and CD19 61 cels/mm^3. Immunological tests were negative for serum antibodies: ANA, anti-ds DNA, anti-Sm, ACL IgM and IgG and ANCA. Bone marrow aspirate was normal. After one month, he had cervical lymphadenopathy, hepatomegaly and splenomegaly. At that moment, CAEBV infection was established by serology test IgM antibodies VCA to EBV. Three months later, he had palpable purpura not related to thrombocytopenia on the legs and arthritis on the left elbow and ankles for two weeks with spontaneous remission. Skin biopsy showed leucocytoclastic vasculitis without IgA deposit. Six months

after there was recurrence of diffuse palpable purpura in the legs and arthritis in the ankles. He received intravenous methylprednisolone for 3 days and after prednisone for 3 years. There was no recurrence of the vasculitis and CAEBV infection with cervical lymphadenopathy and splenomegaly still ongoing.

Case 3

A 13-year old boy had palpable purpura not related to thrombocytopenia in lower limbs, abdominal pain and macroscopic haematuria with spontaneous resolution for one month and maintenance of hepatomegaly and splenomegaly for one year. At 14 years-old, he was admitted in our University Hospital with hepatomegaly, splenomegaly and cervical lymphadenopathy. The serologic tests to EBV, CMV, hepatitis A, B and C and HIV infections were negative. Bone marrow aspirate was normal. At that moment, the laboratory exams showed hemoglobin 10.4 g/dL, white blood cell count 18.200/mm^3 (lymphocytes 14.742/mm^3), platelet count 87.000/mm^3, AST 1447 IU/L and ALT 466 IU/L, GGT 193 g/dL, total bilirubin 16.5 mg/dL, urea 79 mg/dL and creatinine 1.0 mg/dL. The liver bio-psy showed acute necrosis and the cervical lymph node biopsy was positive to EBV infection. The diagnosis of CAEBV infection was established. He received intravenous methylprednisolone for 3 days, prednisone and acyclovir during 40 days. After 5 months, he presented jaundice, ascites, acute fulminant hepatitis with encephalopathy, disseminated intravascular coagulation and finally death.

Discussion

To our knowledge, this is the first study that evidenced vasculitis associated with CAEBV infection in a pediatric population mimicking HSP. This was a rare disease followed in our tertiary teaching paediatric hospital.

Of note, CAEBV infection is characterized by chronic or recurrent infectious mononucleosis-like signs and symptoms persisting for a long period of time and by the presence of anti-EBV antibodies[5] or detection of high EBV levels in tissues[1]. This infection could be associated with cellular immunological alterations[6] or without identifiable primary immunodeficiency[1], as observed in our patients.

The pathogenesis of CAEBV infection suggest that cells infected by this virus could stimulate oligoclonal lymphoproliferation of T and natural killer cells[1,2]. The hypercytokinaemia released by these cells may induce clinical manifestation of this disease[2,6]. Furthermore, genetic abnormalities (perforin gene and *SAP/SH2D1A* gene) associated with this disease have been recently described[2,7].

This infection occurs predominantly in males and the mean age at disease onset ranged from 5.3-11.3 years (range from 2 months to 53 years)[5,6]. The main clinical features of CAEBV infection in children and adults are persistent hepatomegaly (79-81%), splenomegaly (73-77%), anemia (44--47%) and lymphoadenopathy (40-70%)[5,6], as observed in our cases. CAEBV infection has high-mortality rate and life-threatening manifestations including liver failure (15%), intravascular coagulopathy (4-16%) and pneumonia (5-25%), as evidenced in two of our patients[5,6]. Other complications associated with persistent CAEBV infection are hemophagocytic syndrome, malignant lymphoma and leukemia[2].

Interestingly, all of our patients had cutaneous vasculitis and were misdiagnosed as HSP. According to a new paediatric EULAR/PRINTO/PRES criteria, a patient is classified with HSP in the presence of purpura or petechiae particularly in the lower limb (mandatory criterion) and 1 out of 4 of the following criteria: abdominal pain; leucocytoclastic vasculitis or proliferative glomerulonephritis (with predominant IgA deposit); arthritis or artralgia and renal involvement (hematuria or proteinuria). Remarkably, sensitivity and specificity of these new criteria were 100% and 87%, respectively[4].

Of note, anemia, hepatomegaly, splenomegaly and lymphadenopathy, that are common in our cases, were rarely described in HSP patients[8-10], and other secondary vasculitis should be excluded, such as chronic infections and malignancies. In addition, CAEBV infection with reticuloendothelial system involvement was not described in HSP patients.

Vasculitis associated with CAEBV infection was rarely reported, particularly optic disk vascultis in two cases[11] and progressive polyneuropathy with cutaneous erythema by leukocytoclastic-vasculitis in other[12]. On the other hand, acute EBV infection preceding HSP was reported in rare cases in pediatric population[13-15], including one of our patients with a variant of HSP in infants, named acute hemorrhagic edema[10].

Efficacious drug therapy for CAEBV infection is limited and the treatment is not well-known. Antiviral or immunomodulatory agents, such as acyclovir, have been used with partial response. In addition, immunosuppressive drugs, including corticosteroids, have been indicated in advanced disease[2], as utilized in our population. Furthermore, efficacious allogeneic bone marrow transplantation was recently reported in rare cases with severe disease; however a protocol should be established[2].

In conclusion, even rarely, CAEBV infection may mimicking HSP in pediatric population and the presence of important lymphoadenopathy associated to purpura should be a warning sign for this diagnosis.

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