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# EBV Infection Resulting in Aplastic Anemia: A Case Report and Literature Review

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## Abstract

We describe a three year old girl who developed aplastic anemia concurrent with reactivation of EBV infection. Literature review yielded a list of 23 cases of documented EBV infection with aplastic anemia. Though acyclovir was used as one of the treatment modality in many cases including ours, its effectiveness is unclear. It would be beneficial to develop EBV associated aplastic anemia registry to prospectively evaluate Acyclovir's effectiveness. Also evaluation for evidence of EBV infection in all cases of idiopathic aplastic anemia would be useful.

**Keywords:** Aplastic anemia; Acyclovir

## Background and Introduction

Although in a majority of immunologically normal children, EBV infection is a benign illness resulting in no significant complications, some children have been reported to have life-threatening hematological complications. These include Coombs test positive hemolytic anemia, severe thrombocytopenia, agranulocytosis, and aplastic anemia [1]. We have recently cared for a 3 year old child who developed pancytopenia due to bone marrow failure associated with reactivation of EBV infection. Review of the literature showed only twenty-three reported cases with this association (Table 1 and references cited in the table). Severe but transient neutropenia and thrombocytopenia with EBV infection are common [1]. In addition several well documented cases of ITP transitioning into aplastic anemia have been found in the literature [2,3]. Thus one needs to be aware that in rare occasions, persistent bone marrow failure may follow what appeared to be transient cytopenia with EBV infection.

## Case Description

A three year-old African American female child presented with complaints of fever, irritability and lethargy for the past 6 days. She had decreased energy associated with fatigue, decreased appetite, respiratory symptoms, and cough. Mother noticed pallor. The child was given ibuprofen which provided temporary relief to fever. She also developed painful oral lesions on buccal mucosa, upper and lower lip and gums two days prior to admission. A painful raised lesion on left hip appeared on the day before admission. She also had diffuse small bruises on her skin. The patient was taken to an urgent care and found to have inflamed tonsils and anemia. She presented to our facility because of these complaints.

She had no significant past medical history. She was not taking any medications except Ibuprofen for fever and had no known allergies. The child's mother was treated for iron deficiency anemia and grandmother had sarcoidosis.

Physical examination revealed a febrile pale and acutely ill-looking girl with clear rhinorrhea. She had hemorrhagic painful blisters on lips and buccal mucosa, pharyngeal erythema with enlarged inflamed tonsils without exudates, and shotty non tender bilateral anterior cervical lymphadenopathy. She was tachycardic, the liver and spleen were not palpable. There was left hip ecchymosis with no restriction in range of motion.

Initial lab results showed WBC: 3.5 (neutrophils 7, lymphocytes 91, mono 1, eosino 1), Hb: 3.3 g/dL, Hct: 9.4 %, platelets: 6/μL, RBC: 0.96 million/μL, MCV: 97.8, Serum ferritin 198 (10-291 ng/ml), Serum iron 85 (50-170 μg/dL), TIBC 192 (261-478), iron saturation 44 % (21-42%). Serum folate and B12 were both elevated, >24 (5.4-24 ng/ml), and >2000 (211-911 pg/mL) respectively (Reticulocytes 0.01/μL). Peripheral smear showed macrocytosis, markedly decreased WBC with many mature lymphocytes, no blast, and no platelets. Chest X-ray was normal and showed no mediastinal mass. The bone marrow biopsy and aspiration showed 15% cellularity. The predominant cellular elements were mature lymphocytes. There were plasma cells, but mast cells were not increased. Fetal Hemoglobin was 7%. A PNH (paroxysmal nocturnal hemoglobinuria) test for Pi-Link Ag was normal. A DEB stressed blood chromosome breakage study was normal.

Pertinent viral studies showed: positive EBV VCA IgG and negative IgM. Blood EBV DNA quantitation showed 8,613copies/ml. EBNA IgG titer showed >750 (<18), EBV EA IgG titer also showed >150 (<9), both of which were extremely high, indicating reactivation of EBV infection. HHV 6 IgG antibodies titer was1:160, but IgM titer was <1:20. Parvo virus B19 DNA by PCR was negative. CMV IgG and IgM antibodies were negative. The patient received IV antibiotics; blood and platelet transfusions, became afebrile and was discharged in clinically stable condition. Subsequently patient did not improve, and had become transfusion dependent, though she remained free from any infections.

Three weeks after diagnosis, EBNA IgG titer was still >750. Bone marrow biopsy 1 month later showed identical findings to the first ones. We started her on prednisolone at 2 mg/kg/day and IV acyclovir daily for 7 days. Following Acyclovir treatment, EBV DNA quantitation showed <200 copies/ml of blood (undetectable), but she showed no hematological response. And thus one month later we started a regimen of ATG 40 mg/kg/day daily x 4 days, prednisolone 2 mg/kg/day, and cyclosporine 15 mg/kg/day one month after completion of

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| Ref No* | 1st author | Journal | Yr | vol-page | age | sex | evidence of EBV inf | treatment | status |
|---|---|---|---|---|---|---|---|---|---|
| [9] | Mir and Delamore | Scand J Haematol | 1973 | 11;314-8 | 20 | M | Paul-Bunnel test | prednisolone | recovered |
| [10] | Van Doornik et al. | Scand J Haematol | 1978 | 20:52-56 | 7 | M | Paul-Bunnel test, anti EBV VCA EBNA Ab | supportive | died |
| [5] | Shadduck et al. | Exp Hematol | 1979 | 7;264-71 | 17 | F | anti-EBV IgG & IgM, heterophile | prednisone, androgen, ATG | recovered |
| [11] | Lazarus and Baehner | Pediatr | 1981 | 67;907-910 | 12 | F | mono spot, "fluorescent antibody test" | prednisone | recovered |
| [12] | Ahronheim et al. | N Engl J Med | 1983 | 309;313-314 | 12 | F | VCA IgG & IgM, EBNA, genome by dot-blot | | died |
| [13] | Sullivan | N Engl J Med | 1984 | 311;314-322 | 3 | M | VCA IgG & IgM, neg Suthern blot | supportive | died |
| [14] | Sawka et al. | CMAJ | 1987 | 136;730-1 | 17 | F | monospot, VCA IgG rising | prednisone, Danazol, ATG | recovered |
| [15] | Schimke et al. | Am J Med Genetics | 1987 | 27:195-202 | NA | NA | VCA IgG, IgA | NA | died |
| [3] | Baranski et al. | Ann Int Med | 1988 | 109;695-704 | 29 | M | +mono spot, +EBV VCA IgM, Southern | ATG, acyclovir, cyclosporin | died |
| | Baranski et al. | | 1988 | | 25 | M | VCA IgG, IgA, EA, EBNA | acyclovir, ATG, androgen | died |
| | Baranski et al. | | 1988 | | 13 | M | Monospot, VCA IgG, EA, EBNA | Acyclovir, ATG | recovered |
| | Baranski et al. | | 1988 | | 15 | F | VCA IgG, EA | Acyclovir, ATG, cyclosporin, steroids | died |
| | Baranski et al. | | 1988 | | 22 | M | VCA IgG, EA, EBNA | prednisone, ATG | improved |
| | Baranski et al. | | 1988 | | 1.6 | M | VCA IgG, EA, EBNA | Acyclovir, Oxymethalone, ATG | no imrovement |
| [16] | Grishaber et al. | Am J Hematol | 1988 | 28:273-275 | 15 | F | +mono spot, +EBV VCA IgG & EBNA | prednisone | recovered |
| [2] | Weinblatt | Am J Pediatr Hematol Oncol | 1991 | 13;465-9 | 1 | M | VCA IgM | prednison, IVIG, ATG | partial recovery |
| [17] | Inoue et al. | Int Medicine | 1994 | 33;303-7 | 13 | F | VCA & EA IgG, EBV DNA by Southern blot | IVIG, G-CSF | died |
| [4] | Lau et al. | J Paediatr Child Health | 1994 | 30:74-76 | 9 | F | rising ab titers in EBV VCA IgG and EBNA, EBV genome + by PCR, acyclovir | ATG & Methylprednisolone | recovered |
| [18] | Anderlini et al. | Br J Haematol | 1999 | 106;159-61 | 17 | F | monospot, VCA IgM | steroids, IVIG, G-CSF, Epo, syngneic transplant x 2 after cytoxan & ATG | recovered |
| [19] | Kaptan et al. | Am J Hematol | 2001 | 67;252-255 | 22 | M | VCA IgG & IgM, EBV & HPVB19 DNA + by PCR | prednisone, acyclovir, IVIG, BMT | recovered |
| [20] | Nijhawan et al. | J Assoc Physic India | 2005 | 53:1079 | 11 | M | EBV IgM (VCA?) | supportive | died |
| | Nijhawan et al. | | 2005 | | 3 | M | VCA IGG, EBNA | dexamethasone, ATG | recovered |
| [21] | Ergene et al. | Transfus Apher Sci | 2007 | 37;125-9 | 48 | F | VCA IgG & IgM | G-CSF, supportive | recovered |
| | **Inoue S** | **Khan I** | **2013** | | **3** | **F** | **VCA IgG, EA, EBNA, EBV DNA copies** | **acyclovir, steroids, ATG, cyclosporin** | |

* indicates the number in the reference in the text

**Table 1:** EBV infection resulting in aplastic anemia.

acyclovir. Cyclosporin was continued following the cessation of ATG. Prednisolone was gradually tapered off.

Approximately 2 months after initial presentation, patient still showed EBNA IgG titers of 694 (<18), EBV EA IgG 52.2 (<9) and EBV DNA Quantitation 1216 copies (<200).

After receiving one cycle of ATG/CSA, she had partial response with recovery of WBCs but remained heavily transfusion dependent for RBCs and platelets. Two months after this therapy, EBV DNA was <200 copies, EBV EA IgG titer was 37.3 and EBNA IgG was >750. A second cycle of ATG and oral cyclosporine was given six months later.

Investigations for Fanconi anemia, Dyskeratosis congenita, congenital amegakaryocytic thrombocytopenia, and paroxysmal nocturnal hemoglobinuria (PNH) were negative. She is still transfusion dependent.

## Discussion

Aplastic anemia following primary EBV infection or in association with reactivation of EBV infection has been well documented in the literature, but must be rare, since we were able to find only 23 documented cases in the literature. The case described here is development of aplastic anemia apparently following reactivation of EBV infection, but there are

case reports of aplastic anemia after primary infection. Several patients developed clear cut ITP (with large platelets in blood and many marrow Megakaryocytes), only to develop bone marrow failure later resulting in aplastic anemia [2] (case 5 of Baranski et al.) [3]. Some patients did not have illnesses suggestive of infectious mononucleosis, yet when the patient developed aplastic anemia, there was serological or molecular evidence that patient had recent EBV infection [4], (patients 5 and 6 of Baranski et al.) [3]. These cases suggest that EBV induced aplastic anemia may be much more common than the literature indicates.

The current understanding regarding the rationale of immunosuppressive therapy for acquired aplastic anemia is based on experimental and clinical observations that suppressor cells in the patients inhibit autologous marrow hematopoietic cells growth. More than 30 years ago, Shadduck et al. presented in vitro evidence that patient's bone marrow cells inhibited normal myeloid colony growth in vitro. These inhibitor cells disappeared after the patient recovered with ATG treatment [5]. Kurtzman and Young described their observation that activated T cells by exposure to autologous EBV infected B cells inhibited hematopietic cell growth in colony culture [6]. A recent review on aplastic anemia by Young et al. [7] presented evidence that suppressor cells (effector cells) are $CD8^+$, $CD28^-$ cells. These cells disappear when patients achieve remission. EBV infection may stimulate oligoclonal expansion of these T cells in susceptible hosts.

Many patients were treated with Acyclovir (Table 1), but its role in the efficacy of treatment is unclear, since all the patients treated with acyclovir were also treated with other agents. The majority of the patients were treated with steroids and ATG, some with androgens. Thirteen of the 23 patients were documented to have recovered or improved. The remainder either died or their status is unknown. Most patients had severe aplastic anemia by Camitta's criteria [8]. Thus EBV associated aplastic anemia does not appear to be different from idiopathic aplastic anemia regarding the prognosis [9-15].

It is likely that some of the "idiopathic aplastic anemia" is triggered by an EBV infection, particularly because in small children EBV infection does not cause stereotypical symptoms [16-21]. It would be helpful to know if acyclovir is beneficial for the treatment in these cases, but at this moment it is unanswered. It would be useful to develop a registry of cases with aplastic anemia induced by EBV and examine the effect of acyclovir in these patients.

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