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Case Report

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Reactivation of Epstein-Barr virus in aplastic anemia: A clinical challenge

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ABSTRACT

Acquired aplastic anemia is an unusual disease associated with pancytopenia characterized by hypocellular bone marrow. Aplastic anemia is an auto-immune disorder wherein patients would show a antithymocyte globulin (ATG)- induced hematological response after T-cell reduction. The combination of cyclosporine A and ATG as immunosuppressive therapy is considered as the standard treatment approach for patients with aplastic anemia. Epstein-Barr virus (EBV) infection in a patient with aplastic anemia is an unusual clinical presentation. A 49-year-old Asian female was presented to our hospital with dizziness and fatigue. The patient's platelet count was extremely low. A hypocellular marrow with lymphocytosis was observed with the help of a bone marrow aspirate and biopsy. The patient was given cyclosporine and eltrombopag as a bridge to primary therapy, i.e. antithymocyte globulin (ATG)/allogenic transplant considering she had pancytopenia. The patient developed platelet refractoriness. EBV polymerase chain reaction (PCR) was performed, considering the patient's atypical presentation. As per the results, it was significantly positive with 2250 copies/ul. A diagnosis of aplastic anemia with EBV infection was made. This is an unusual case of EBV in a patient with aplastic anemia. EBV infection can thwart the management of patients with AA.

1. Introduction

Acquired aplastic anemia (AA) is an uncommon disease associated with pancytopenia characterized by the hypocellular bone marrow. If left untreated, AA could be fatal for some patients. In most cases, patients with AA would show a typical response by antithymocyte globulins (ATG) induced T-cell reduction (Young et al., 2006). AA is considered as an immune-facilitated disorder.

The standard therapy for the treatment of young patients, specifically those with a suitable donor includes hematopoietic stem cell transplantation (HSCT). However, immunosuppressive therapy (IST) such as cyclosporine A (CsA) or ATG are considered as key treatment approaches in older patients or among those where HSCT is non-beneficial (Takahashi et al., 2015).

Epstein-Barr virus (EBV) is a type of γ-herpes virus

comprising of a linear DNA molecule of approximately 172 kb in length. EBV affects nearly 90% of the adult population worldwide. Infectious mononucleosis is often experienced by those exposed to the virus, specifically if the infection does not become clinically silent. EBV infection is lifelong. However, reactivation of EBV or a long latency can cause several lymphoproliferative lesions as well as hematologic malignancies (Stanfield, 2017). The scale of EBV-associated B-cell lymphoproliferative disorders (LPDs) is extensive, ranging from lymphomas to reactive lymphoproliferative lymphadenitis (Ok et al., 2015).

EBV associated diseases have been associated in people with immune deficiency. Patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) have a high risk of EBV reactivation including the development of EBV-related LPD (Van et al., 2011). Some of the key factors that influence the development of EBV-LPD in such patients include the use of T-cell depleted transplantation and ATG. EBV-LPD is an uncommon complication with rare cases becoming fatal. There is strong evidence citing that reactivation of EBV occurs in the majority of patients with severe AA who were treated with ATG (Scheinberg et al., 2007). Herein, we report an unusual case of EBV in a patient with aplastic anemia after treatment immunosuppressive therapy.

2. Case

A 49-year-old Indian female presented to our hospital with fatigue and dizziness. The patient also complained of dyspnea. However, the patient did not complain of of night sweats, fevers, weight loss, or chills. The physical examination was normal except pallor. The patient had no history of smoking tobacco use or any other substance abuse. A complete blood count was suggestive of pancytopenia with a hemoglobin of 4 grams per deciliter. The patient had a low total leucocyte count, 3800 per microliter (Neutrophil 12%, lymphocyte 80%, Monocyte 8%). The patient's platelet count was extremely low, i.e. 11.000 per microliter.

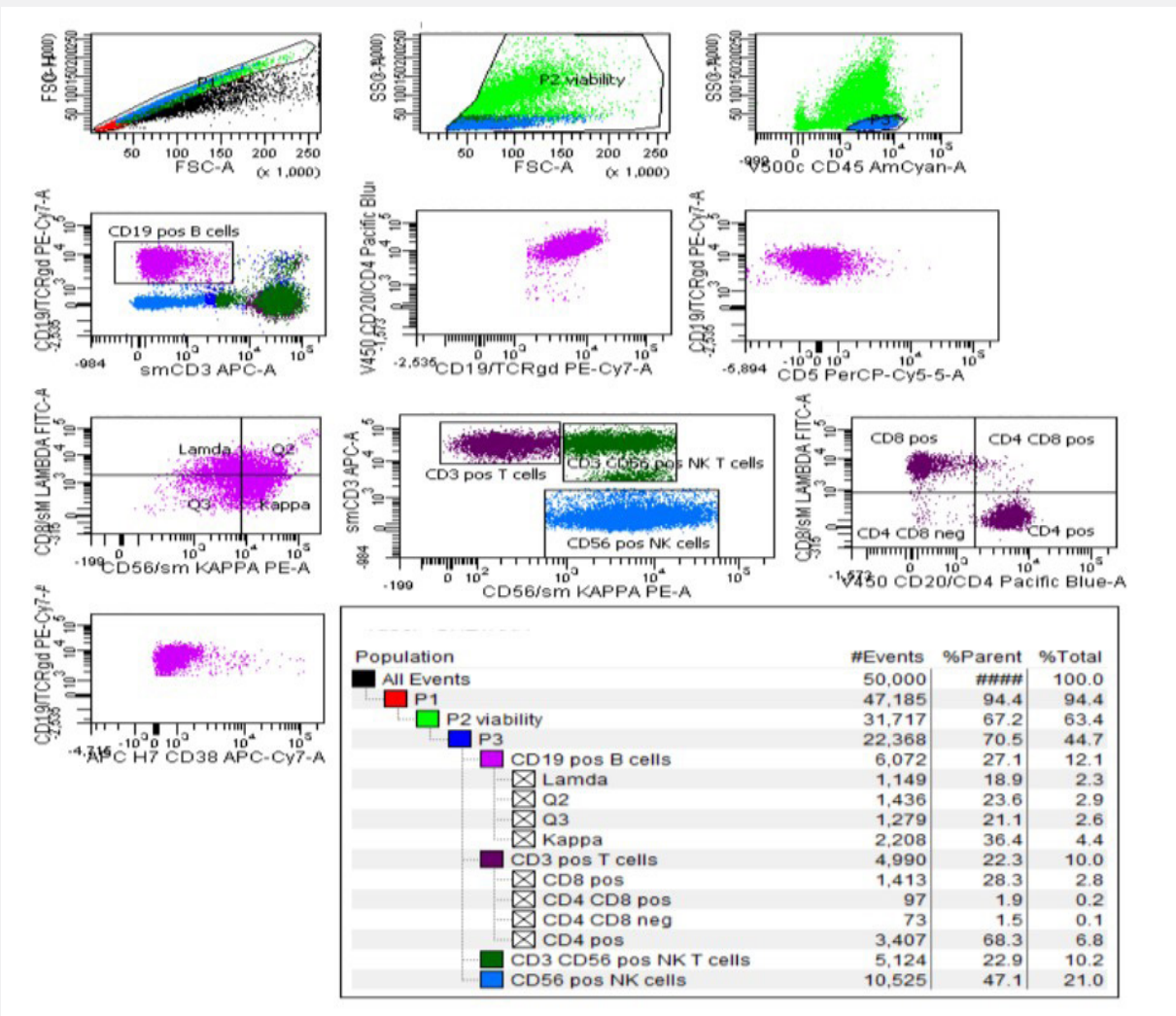

Fig. 1. Flow cytometry: 26% of the population comprised of NK cells (CD56+ve/sCD3).

A bone marrow aspirate and biopsy was performed that revealed a hypocellular marrow with relative lymphocytosis. Flow cytometry was performed to rule out malignancy. As per the results, 26% of the population comprised of monoclonal NK cells (CD56+ve/sCD3) (Fig. 1).

A bone marrow biopsy was performed that was hypocellular with normal immunohistochemistry. As the patient had severe pancytopenia, she was given cyclosporine and eltrombopag as a bridge to primary therapy, i.e. antithymocyte globulin (ATG)/allogenic transplant. Our differential diagnosis included aplastic anemia, viral infection-related pancytopenia, and lymphoproliferative disorders.

As the patient had lymphocytosis, a Positron Emission Tomography/Computed Tomography (PET-CT) was performed to look for any evidence of the lymphoproliferative disorder. PET-CT revealed activity in spleen without enlargement (Fig. 2). There was tiny cervical, inguinal, retroperitoneal and mesenteric lymphadenopathy. An increase in bone marrow activity was also observed. The patient's liver function tests (LFT) were deranged with indirect hyperbilirubinemia. The deranged LFT was attributed to eltrombopag. The patient eventually developed platelet refractoriness. The patient had poor platelet increments post single donor platelet (SDP) infusion. Unfortunately, we could not use the Human leucocyte antigen (HLA) matched platelets. As salvage, we used Intravenous immunoglobulin (IVIG) 400 mg/kg/day. After four days, her platelets improved significantly.

As per our multidisciplinary decision, we decided to commence therapy for aplastic therapy. As per the patient's atypical presentation we suspected and for EBV infection. Other vital viral tests such as cytomegalovirus infection (CMV) and parvovirus 19 were also considered. However, due to the patient's financial limitations, we relied on EBV tests only. EBV polymerase chain reaction (PCR) was performed and results were significantly positive with 2250 copies/ul.

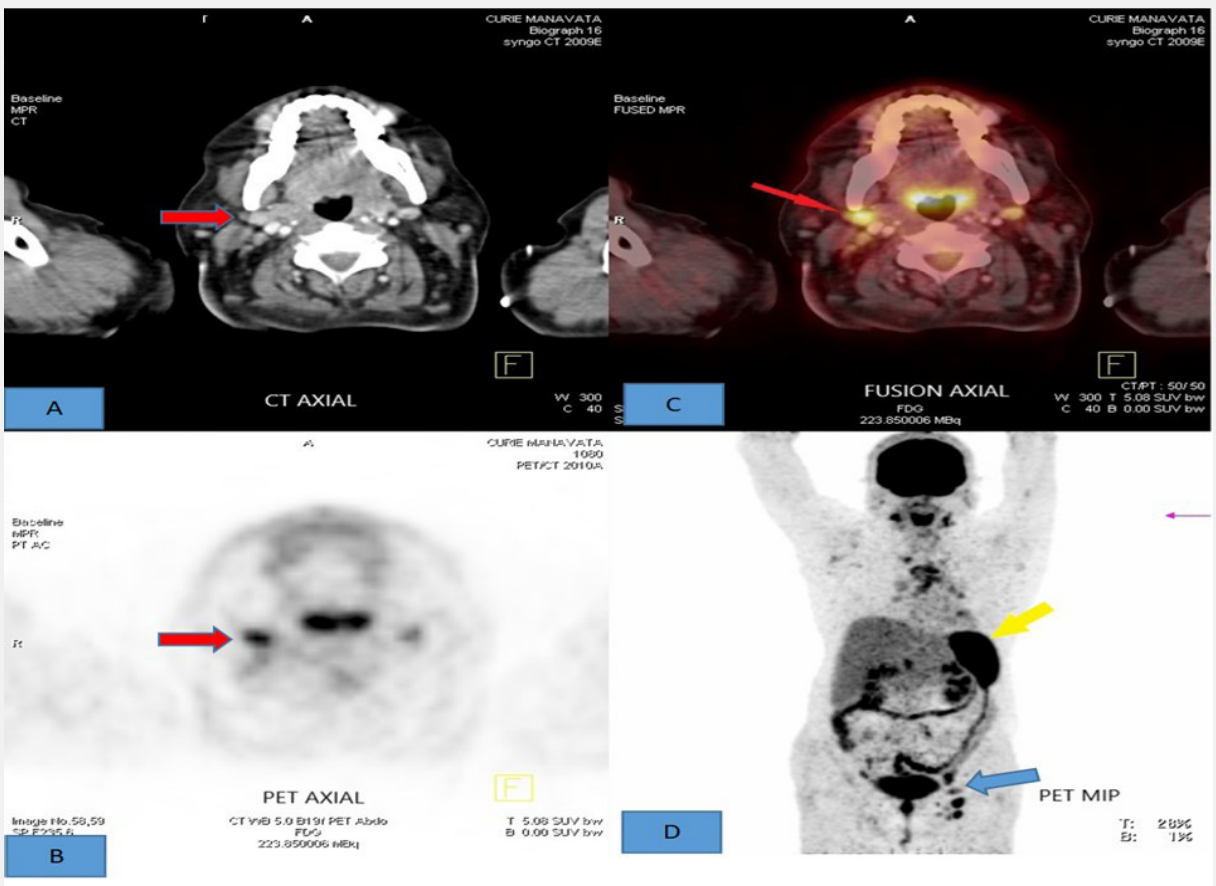

Fig. 2. Positron emission tomography.
A: CT Axial showing tiny cervical lymphadenopathy (red arrow).
B: PET Axial showing tiny cervical lymphadenopathy (red arrow).
C: Fusion Axial showing tiny cervical lymphadenopathy (red arrow).
D: PET WB-MIP revealed activity in spleen without enlargement (Yellow arrow).
It also shows Inguinal lymphadenopathy (Red arrow in D).

A diagnosis of aplastic anemia with EBV infection was made. The patient was on supportive care treatment along with a course of intravenous immunoglobulin (IVIG) and not received any antiviral treatment. After 4 weeks, EBV-PCR was repeated and titers were reduced to 50 copies/ul. Based on the reports, the patient was given successful definitive therapy in the form of ATG plus CsA. The patient has shown partial remission after 3 months' post-ATG and CsA treatment.

3. Discussion

Aplastic anemia is a bone marrow hematopoietic debacle due to several factors such as bone marrow fibrosis and bone marrow infiltration. Some of the most common clinical indicators of AA include infections, severe anemia, bleeding, and high risk of mortality. The pathogenesis of AA can be attributed to several underlying genetic factors. In the past few years, the activation of AA has been associated with environmental factors (viruses, drugs, antigens, or chemicals). Many scholars have cited the activation of lymphocytes and allied immune responses, specifically viral infections (Ihumura et al., 2010; Schenke, 2010; Khurana, 2014; Patel et al., 2017).

The EBV is a known human herpesvirus, discovered in 1964 by Epstein et al. in their study of malignant lymphoma in African children. EBV infections are common and span across many countries (Mashima et al., 2017). In the past few years, AA caused due to EBV infection has become a common observation. In a recent retrospective study, scholars have indicated that EBV plays a key role in the overall pathogenesis of AA (Zhang et al., 2018).

In patients with no pre-existing immunodeficiency, EBV infection is seldom complication by pancytopenia. The overall course of the disease is transient (Lazarus and Baehner, 1981; Purtilo et al., 1982; Anderlini et al., 1999). There have been a few cases of primary EBV infection in patients with AA (Shadduck et al., 1979; Ahronheim et al., 1983; Cabot et al., 1984; Grishaber et al., 1988). In all these patients, immunosuppressive treatment was the standard of care as in our case.

In our case, the patient had a hypoplastic bone marrow. She also presented with pancytopenia. Chromosomal analysis of the patient appeared to be normal. As per the bone marrow aspiration study, monoclonal lymphocytes were observed on flow cytometry. The patient had no hepatosplenomegaly, lymphadenopathy, or fever. However, reactivation of EBV occurred primarily before starting treatment. Severe immunosuppression was caused primarily due to CsA. It led to aggravated EBV-lymphoproliferation manifested in the form of severe thrombocytopenia not responding to the platelet transfusion. Flow cytometry had revealed NK cells. The EBV-driven NK-lymphocytosis may not necessarily be monoclonal. Post-IGV treatment, the EBV viral load had decreased significantly (50 copies/ul). In patients with aplastic anemia who undergo HSCT, EBV infection is likely to occur due to lymphoid or plasmacytic proliferations attributed to immunosuppression. They also include EBV-induced infectious mononucleosis-type polyclonal proliferation (Swerdlow et al., 2008).

The dilemma in diagnosis was created due to EBV reactivation which was giving the impression of lymphoproliferative disorder in this case. But, after treatment with IVIG, the platelet refractory had improved and EBV titer reduced significantly. Since the patient had limited finances, a follow-up PET-CT could not be obtained. The pathogenesis of EBV remains unclear. However, since EBV as an autoimmune disorder associated with the hyper-functioning of T lymphocytes, the correlation between the pathogenesis of AA and EBV infection requires further investigation. EBV infection can hinder the management of patients with AA. It can give a false impression of lymphoma. The clinician should be always kept in mind the possibility of viral infections before going with the management of such cases. Herein, we report an unusual case of fatal EBV infection in a patient with AA after being treated with Eltrombopag and CsA.

Disclaimer

None to declare.

Funding Sources

None.

Conflict of Interest

None.

Ethical Approval

All procedures performed on the patient were in accordance to the ethical standards of the institution research committee.

Informed Consent

Written informed consent was obtained from the patient for publication of this case in the text.

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