

Case Report

Lymphoproliferative Disease in a Non-Transplant Patient and Spironolactone's Activity Against Epstein Barr Virus

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Abstract

Description

Epstein Barr Virus (EBV) may cause lymphoproliferative disorder that can cause malignancies in patients who are immunosuppressed. These malignancies may be suppressed or reversed by antiviral therapy including spironolactone.

We present a case of a 66-year-old female who had been immunosuppressed through use of interferon and tumor necrosis factor (TNF)-active agents for multiple sclerosis (MS). She met the criteria for idiopathic CD4 T-lymphocytopenia or non-human immunodeficiency syndrome (HIV) acquired immunodeficiency syndrome (AIDS). She developed a reactivation of EBV due to the immunosuppression which caused a subset of Non-Hodgkin's Lymphoma. The patient was initially treated with valacyclovir but she developed brain lesions of lymphoma and was therefore switched to ganciclovir, after which the EBV viral load decreased. A year later her brain lesions relapsed. Therefore, she was placed on spironolactone in addition to ganciclovir, which successfully controlled the virus and prevented further relapse.

This case demonstrates spironolactone's ability to suppress EBV replication and assist with prophylaxes against EBV in high-risk patients undergoing solid organ transplant or immunosuppressed patients, hence limiting complications.

Keywords

Epstein-Barr Virus; Epstein-Barr Virus infections; EBV; post-transplant lymphoproliferative disorders; PTLD; spironolactone

Background

Epstein Barr Virus (EBV) infections are believed to play a major role in the development of lymphoproliferative disorders that occur after solid organ transplant. Post-transplant lymphoproliferative disorders (PTLD) include all clinical syndromes ranging from infectious mononucleosis to malignancies that contain chromosomal abnormalities.¹ Due to the advancement of treatments for autoimmune diseases, such as tumor necrosis factor (TNF) alpha inhibitors, PTLD can also be seen in patients being treated for autoimmune conditions. Immunosuppression makes patients susceptible to viral infections such as EBV even if they have not received a transplant. EBV cells would normally be destroyed by EBV cytotoxic

ic T cells, but in immune suppressed patients rates of proliferation of EBV will exceed the rate of clearance by the immune system, which will lead to accumulations of mutations.²

Spironolactone has been shown to inhibit EBV Sm protein which is essential for virus production, expression of viral capsid antigen synthesis and capsid formation.³ Spironolactone has also demonstrated the ability to inhibit EBV synthesis in ways not previously targeted with traditional antiviral medications.

Case Presentation

A 66-year-old white female with a past medical history of multiple sclerosis (MS), systemic lupus erythematosus (SLE) and breast infection

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was referred to an infectious disease specialist for mycobacterium avium complex (MAC) lymphadenitis.

The patient visited the infectious disease office for weakness and myopathy following a breast abscess drainage. Drainage cultures showed 3+ acid fast bacilli (AFB) compatible with AFB-MAC. Her lab results showed extremely low lymphocyte numbers and a positive EBV test result. HIV and human T cell leukemia virus tests were negative. In addition to MAC treatment, the patient was placed on valacyclovir. At follow-up, lab results suggested EBV reactivation and CD4 count of 51 confirming the diagnosis of non-HIV AIDS.

A few months later, she was admitted to the hospital for rectal bleeding and altered mental status. A computed tomography (CT) of the brain showed irregular enhancements of the brain with moderate vasogenic edema, smaller enhancing lesions of the left temporal lobe and left parietal lobe, and edema with mass effect. A CT of the abdomen and pelvis showed mild soft tissue nodularity in the greater omentum, suggesting peritoneal carcinomatosis with an unknown primary origin. Omental nodule biopsy results showed an atypical lymphoid population. Neoplastic cells were variably sized and included large cells, histiocytes and occasional plasma cells with geographic necrosis present. These biopsy findings were consistent with EBV positive lymphoproliferative disorder (B cell lymphoma from the EBV infection). A magnetic resonance imaging (MRI) of the brain showed multiple lesions that were concerning for tumor spread.

Due to the brain lesions, the patient was switched from valacyclovir to ganciclovir, resulting in her EBV polymerase chain reaction (PCR) viral load dropping from 45,000 to 6,000. A CT of the chest demonstrated improvement in the extensive bilateral parenchymal changes, bilateral pulmonary opacities and bilateral pleural effusions. A biopsy demonstrated no malignancy in lung tissue.

The patient was later admitted after 4–5 days of confusion which had been progressively worsening. A lumbar puncture was performed, which showed negative PCR for EBV, protein of 172 mg/dl, glucose of 41 mg/dl, negative

VDRL and negative culture. During admission, an MRI of the brain with and without contrast demonstrated focal deep and subcortical white matter hyper-intensity in the right frontal lobe, with several small nodular foci of enhancement, as well as nodular intraparenchymal focus of enhancement in the left occipital lobe. These MRI results were most consistent with a relapse of EBV. Therefore, the patient was placed on spironolactone in addition to ganciclovir for EBV treatment.

A repeat MRI months later demonstrated resolution of nodular enhancement in the right frontal lobe shown on a recent comparison study. The resolution of nodular enhancement confirmed that ganciclovir in combination with spironolactone was effective at suppressing EBV.

Discussion

Cases of PTLD represent a diverse spectrum of disease states that can vary in terms of clinical presentations. Disease can be nodal, extra-nodal, localized or disseminated.² The gastrointestinal tract is a common site for extra-nodal disease, and the central nervous system can also be affected in patients with PTLD. PTLD can resemble self-limited infection or can be indistinguishable from NHL. In the case presented here, a question exists as to whether the PTLD was caused by the post-transplant state or the medications used to treat of autoimmune disease.

The diagnosis and classification of PTLD are currently based on histologic criteria. In the immunocompetent host, EBV infections can be detected with antiviral capsid antigen IgM and IgG antibodies and anti-EBV antigen antibodies.¹ Pathologic examination of tissue is currently the gold standard for PTLD diagnosis. Ann Arbor Staging classification with Cotswold's modification is used to stage NHL and is recommended for staging of PTLD. Diagnostic challenges can include the availability of techniques to detect oncogene arrangements and mutations which may not be available in all centers.

Angioimmunoblastic T-cell lymphoma (AITL) is a subset of NHL. Patients typically present in the sixth or seventh decade of life. There is no

gender predilection for AITL. The clinical syndrome is characterized by generalized lymphadenopathy, hepatosplenomegaly, anemia and hypergammaglobulinemia. Many infectious diseases and agents have been reported to be associated with AITL including tuberculosis, cryptococcus, EBV, Human Herpes Virus-6, Human Herpes Virus-8, HIV and Hepatitis C virus. AITL typically presents with systemic illness such as B symptoms, generalized lymphadenopathy, hepatosplenomegaly and pruritus.

A characteristic feature of AITL is the presence of an increased number of EBV infected cells. Immunosuppression, whether from post-transplant medications or immunosuppressive drugs for autoimmune diseases, leads to reduced cytotoxic T cells and favors an increase in EBV infected cells. This causes mutations which can lead to the development of cancers such as diffuse B cell lymphomas, Burkitts lymphoma and AITL. Differential diagnosis for AITL includes the following: reactive hyperplasia, Hodgkin lymphoma, histiocyte large B cell lymphoma and peripheral T cell lymphoma.

Therapeutic Intervention

Preventative intervention for PTLD includes reducing immunosuppression therapy.¹ Pharmacologic interventions can be used when reducing immunosuppression fails. Pharmacologic interventions include B cell monoclonal antibody therapy in patients with presence of CD20 on PTLD tissue. B cell monoclonal antibody therapy has shown complete remission in 62.5% of patients in prospective multicenter trials.¹ Antiviral medications include acyclovir, ganciclovir and, more recently, spironolactone. Surgical interventions appear to be useful for treatment of isolated PTLD lesions with tumor debulking and management of local complications such as gastrointestinal hemorrhage or perforation.¹ Local radiotherapy may be useful for lesions that occur in the CNS. Interferon alpha has both antiviral and anti-proliferative activity and has the advantage of affecting the host immune response via T-helper cell type response. Rituximab therapy may be appropriate for treatment of PTLD and its low toxicity and high specificity for CD20 makes it an attractive option.

The optimal strategy for PTLD relies on prevention. Several studies suggest using antiviral

agents with activity against EBV and cytomegalovirus (CMV), since CMV is a co-factor in PTLD development. Antiviral drugs with activity against both EBV and CMV such as ganciclovir are preferred over acyclovir.² EBV can also have mutations in thymidine kinase, which would favor the use of ganciclovir. Studies that have examined the impact of antiviral prophylaxis in adults with EBV seronegative kidney transplants showed that EBV-related neoplasia incidence was significantly lower in patients who were treated with valganciclovir or ganciclovir versus patients who did not receive CMV prophylaxis.⁴

Spironolactone has been shown to inhibit the EBV Sm protein's function³, which plays an important role in enhancing the expression of late lytic cycle EBV genes. Spironolactone has also been shown to inhibit infectious EBV production and inhibit viral capsid antigen synthesis through Sm production inhibition. This is an important discovery, which demonstrates new mechanisms to inhibit EBV infections not previously targeted with traditional medications, such as ganciclovir and acyclovir. Spironolactone may be used for prophylaxes against EBV in high-risk patients undergoing solid organ transplant or patients on immunosuppressive medications for autoimmune conditions.

Publications regarding the outcome and clinical management of AITL are limited due to the rare nature of this disease. Patients will usually die from infectious complications due to immunodeficiency. Numerous treatment options have been reported such as CHOP therapy (cyclophosphamide, hydroxydaunomycin, oncovorin, prednisone), CVP (cyclophosphamide, vincristine, prednisolone) and VAP (vincristine, asparaginase, prednisone). Remission rate is approximately 50% but relapse rates remain high. Other regimens include cyclosporine A, which has direct cytotoxic effect on lymphocytes, and thalidomide, which has been used following relapse or refractory AITL, with promising results.⁵

Conclusion

Treating EBV can limit the complications of EBV infection in immunocompromised patients. Spironolactone has the ability to treat EBV in ways not achieved by other antiviral

medications. More studies are needed to assess the safety and efficacy of spironolactone's activity against EBV. Spironolactone may have the ability to prevent the reactivation of EBV and other herpes viruses in high-risk patients following transplants or immunosuppressive treatments.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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