**Progressive Multifocal Leukoencephalopathy (PML) in a Patient with Classic Hodgkin’s Lymphoma Post-Bone Marrow Transplant: A Case Report**

*Running head: PML in Hodgkin’s Lymphoma post-BMT*

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**Informed Consent**

A written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

**Abstract**

A 29-year-old male patient who underwent an autologous bone marrow transplant. He was initially diagnosed with Hodgkin's lymphoma and treated with 12 cycles of chemotherapy. Three months later, he presented with intermittent fever and underwent an MRI scan and a biopsy. Eventually, he was diagnosed with progressive multifocal leukoencephalopathy.

**Key words**: Multifocal Leukoencephalopathy; Hodgkin’s Lymphoma; Bone Marrow Transplant

**Key Clinical Message**

For effective treatment and a plan of action, such cases necessitate multidisciplinary board meetings with input from experts in surgery, pathology, cancer, and infectious diseases.

**Background**

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disorder of the nervous system that was first observed in a patient with chronic lymphocytic leukemia in 1958. [1,2] Primary infection is mostly asymptomatic and occurs most commonly in childhood. [2] The virus is transported to the kidney and lymphoid organs during primary infection and remains latent there. It is a very rare disease that mostly only affects people with weak immune systems, like those who have had organ transplants or are getting immunomodulatory therapy.([2] Its association with transplant recipients is significant since a study showed that even though bone marrow recipients have better chances of survival than solid organ recipients, there is no definite treatment with demonstrable therapeutic benefits. [3, 4] Most commonly, patients present with neurological deficits like diplopia, motor deficits like hemiparesis, and even altered mental status. Presentation may vary according to the stage and progress of the disease. After initial blood studies such as complete blood differential and imaging such as brain MRI, it is diagnosed by cerebrospinal fluid (CSF) analysis via lumbar puncture and polymerase chain reaction (PCR) for JCV. [1-4].

The rationale for reporting this case lies in the fact that, other than being an extreme entity, to the best of our knowledge, it is among the first few cases being reported in young males from Southeast Asia. This case report meets the SCARE criteria [5], and it shows that more research needs to be done on progressive multifocal encephalopathies.

**Case Presentation**

The patient is a 29-year-old male, Asian, who presented with complaints of fever, weight loss, decreased appetite, and weakness. Initial workup revealed multiple liver and spleen lesions on abdominal ultrasound. Further investigations that included a liver biopsy proved to be inconclusive. The patient was referred to our hospital for a bone marrow biopsy, which showed features of classic Hodgkin's lymphoma. He received his complete 6 cycles of chemotherapy: Adriamycin, Bleomycin sulfate, Vinblastine sulfate, and dacarbazine (ABVD). This was followed by a repeat PET/CT scan. The PET/CT post ABVD showed progressive disease above and below the diaphragm, including mostly sub aortic node, some para aortic nodular involvement, and osseous marrow involvement (Deauville 5). A second vertebral biopsy was performed and found to be CD20 and CD30 positive. After reassessment, he was given a further 4 cycles of Rituximab, ifosfamide, carboplatin and etoposide (R-ICE). A post therapy PET scan was done and was read as a complete metabolic response (Deauville3). He was advised to have an emergency transplant but failed to follow through.

After 6 months, he presented with severe anemia and dyspnea. Consequently, the patient was transfused with blood and improved symptomatically. PET/CT was done and showed progressive disease (Deauville 5) with interval development of below diaphragm nodal disease in inguinal L iliac, aortic, celiac, superior mesenteric nodes and heterogonous marrow uptake. He was started on R-bendamustine and completed 3 cycles within the next 3 months. Ct/PET after R-benda showed a complete metabolic response (Deauville 2).

The patient was finally admitted to our hospital for an autologous bone marrow transplant planned for the same month. The BEAM conditioning protocol was delivered for 6 days. The patient tolerated them well. Patient harvesting was started and performed for 3 days and total CD34: 2.42 million cells were extracted with a cell viability of 86%.

Stem cells were transfused in the same week and engraftment was initiated. The post-engraftment patient remained stable and was subsequently discharged home with guidance regarding transfusions for low hemoglobin and neutropenic fever. On follow-up visits for the next 3 months, the patient remained stable.

He presented after 3 months with a complaint of intermittent fever and forgetfulness for 1 week. His CT showed T2 and FLAIR hyperintense signal lesions in bilateral periventricular and subcortical white matter of the frontal lobes, left frontoparietal lobe, left occipital lobe, and left thalamus (Figure 1); findings consistent with progressive multifocal leukoencephalopathy with disease progression and right frontal craniotomy were done for biopsy. The biopsy showed bizarre, pleomorphic, multilobate astrocytic nuclei in the background of histiocytes, which is a characteristic feature of PML (Figure2).

The Postop patient remained stable and was discharged with advice regarding wound care and home medications, which included a tapering dose of dexamethasone. The patient was also advised to follow up in OPD after 1 week, for which he didn’t show up.

**Discussion**

PML is a neuroinfectious disease caused by the John Cunningham (JC) virus, which belongs to the papovavirus family. PML cases markedly increased at the time of immunodeficiency from human immunodeficiency virus (HIV) infection and subsequently decreased with highly active antiretroviral therapy. Even though the vast majority of PML cases have been associated with HIV, there are other conditions that predispose to JC virus activation. There has been a resurgence in this condition with advances in immunomodulatory therapies. Treatment of multiple sclerosis with natalizumab received initial attention with regard to PML. Natalizumab has been reported to have, in addition to the known inhibitory effect on T cells, an inhibitory effect on B cell functioning and this may be the reason for the increased risk of developing PML. [1-4]

PML should be suspected in cases of rapidly progressing neurological symptoms and deterioration in immunocompromised individuals. Transplant recipients are at a small but significant risk of developing PML. They have the greatest risk of disease onset immediately post-transplantation. This risk decreases smoothly thereafter and eventually stabilizes and persists lifelong. [4,6] In our case, the patient developed neurological symptoms 3 months after the autologous bone marrow transplant. Regardless, PML must be suspected at all times during the post-transplantation period. [7]

Clinically, it is often difficult to establish the diagnosis of PML due to the broad spectrum of neurologic signs and symptoms. Since it may affect multiple areas of the brain and hence cause a broad range of symptoms; the most common clinical features are motor weakness, cognitive dysfunction, ataxia, visual symptoms, and speech disorders. In our patient, cognitive decline, particularly amnesia, was the predominant symptom along with fever. Additionally, typical radiological findings on brain CT or MRI support the diagnosis. In the present case, CT brain was done that showed T2 and FLAIR hyperintense signal lesions in bilateral periventricular and subcortical white matter of the frontal lobes, left frontoparietal lobe, left occipital lobe, and left thalamus. The findings suggest progressive multifocal leukoencephalopathy as the disease progresses. [8–10]

The high suspicion of PML in our case patient was based on clinical and imaging findings in the background of an immunocompromised state that prompted us to proceed to brain biopsy. It is reported as bizarre, pleomorphic, multilobate astrocytic nuclei in the background of histiocytes, which is a characteristic feature of PML. Brain biopsy typically shows demyelination and vacuolation with intranuclear inclusions of viral particles, which is characteristic of JC virus infection. Additional testing, including in situ hybridization testing, can be performed on biopsied tissue to confirm the diagnosis of the presence of JCV. [9–11]

Sometimes, the underlying diagnosis prompting transplantation, including Hodgkin's Lymphoma and other conditions, has been associated with the development of PML even in the absence of transplantation and immunosuppressive drugs [12]. Although PML can occur in hematological malignancies even in the absence of transplantation, as reported by Ström and colleagues [4], transplantation and immunosuppression, rather than the underlying disease, are the most important determinants for the development of PML [10-12]. Regardless, a history of pre-existing disease like lymphoma causes diagnostic confusion regarding the recurrence of primary disease versus PML, a rare condition. Regardless, a high clinical suspicion and low diagnostic threshold for PML are keys to early diagnosis. JC virus serology has low sensitivity with a false-negative rate of 37%, indicating that a negative antibody does not indicate an absence of JCV infection. [13] CSF analysis may help with the diagnosis. CTSF Since JC virus PCR is almost as sensitive and specific as a brain biopsy, it is considered the gold standard. [13–14]

**Conclusion**

Timely diagnosis of PML is important because the only way to stop the rapid decline of the patient's neurological status and improve survival rates is to try to restore the patient's immune status as soon as possible.

**List of abbreviations**

Progressive multifocal leukoencephalopathy (PML)

Adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD)

Rituximab, ifosfamide, carboplatin and etoposide (R-ICE)

**Declarations**

**Acknowledgment**

The Qatar National Library funded the publication of this article.

**Conflicts of interest**

All authors declared no conflict of interest.

**Sources of funding**

None

**Credit contribution**

IR, ZA, SR, IU, MI, AJN: Writing – original draft and Writing – review & editing

All authors read and approved the final manuscript

**Guarantor**

D. Ibad ur Rehman

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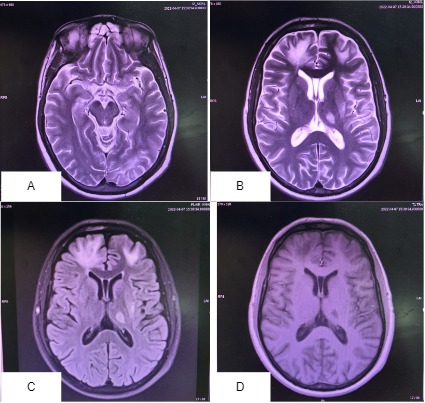


Figure 1. Multiplanar, Multi sequential MRI of brain with and without contrast in images A, B, C, D showing interval development of small t2 and FLAIR hyperintense signals noted in left peri-insular region (C and D) and in left medial temporal lobe (B).

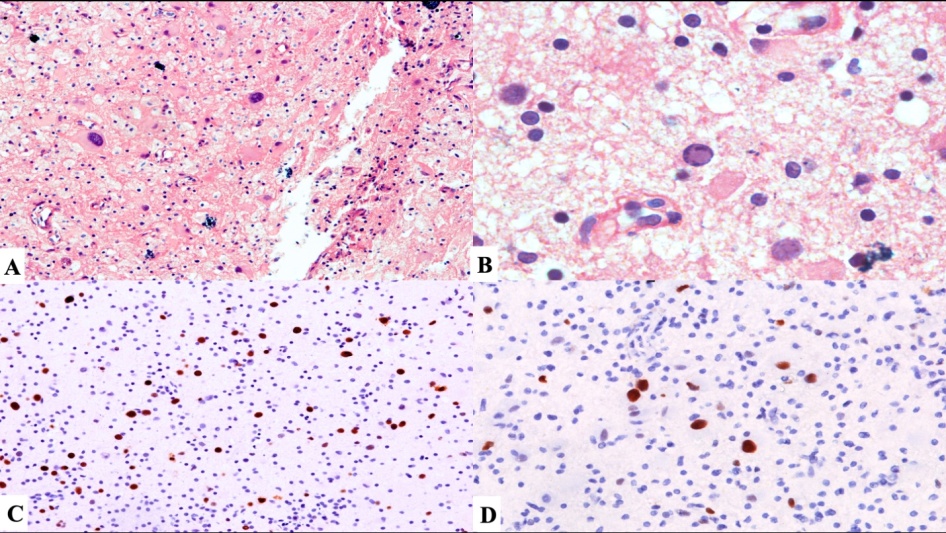


Figure 2. Progressive multifocal leukoencephalopathy (PML)

(A) Bizarre, pleomorphic multilobate astrocytic nuclei in the background of histiocytes is a characteristic feature of PML [H&E, 20×] (B) Inclusion-bearing, enlarged nuclei in virally infected oligodendrocytes with peripheral displacement of native nuclear chromatin [H&E, 40×] (C) SV40 viral protein immunohistochemistry demonstrates immunoreactivity in enlarged and small oligodendroglial nuclei [H&E, 20×] (D) Virally infected cells bind p53 and demonstrate nuclear immunoreactivity [H&E, 40×]