Progressive Multifocal Leukoencephalopathy: Undiagnosed Risk Factors

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Background:

Progressive Multifocal Leukoencephalopathy (PML) is a degenerative neurological condition in which oligodendrocytes are destroyed due to JC virus reactivation. JC Virus infection is common and usually benign, but reactivation in context of immunodeficiency causes neurological infection. PML is most commonly seen in cases of cell mediated immunodeficiency such as HIV or lymphoma. PML usually presents with a combination of ataxia, cognitive impairment and dysarthria. Diagnosis is based on a clinical syndrome consistent with PML, Neuroimaging, and isolation of JC Virus from brain tissue or CSF.

Case

We present the case of SS, a 74-year-old woman who was admitted to Beaumont Hospital in 2023.

SS initially presented to St Columcille's Hospital with a 3 month history of a subacute cognitive decline, sleep cycle disturbance, difficulty with concentration and difficulty with activities of daily living. Over these three months, SS's memory significantly deteriorated and there was a decline in problem solving abilities. These symptoms progressed rapidly in the three weeks prior to presentation.

There was no history of recent infection, fevers, weight loss or bone pain, and SS's medical history was significant for transient global amnesia and breast cancer previously treated with exemestane, GCSF and subsequently tamoxifen.

During her stay in St Columcille's, A CT Brain demonstrated a potential multifocal glioma, which was subsequently investigated further with a MRI Brain (Figure 1). This demonstrated an ill-defined enhancing focus most extensive in the right frontal lobe, in addition to extension across the corpus callosum into the anterior left frontal lobe and posteriorly into the insula.

Following this scan, SS was transferred to Beaumont Hospital for Neurosurgical intervention. Biopsies were taken of the affected area, but a subsequent CT Brain (Figure 2) following clinical deterioration demonstrated right frontal lobe and basal ganglia haemorrhage, extensive acute subarachnoid haemorrhage and acute intraventricular haemorrhage.

Figure 1: MRI Brain

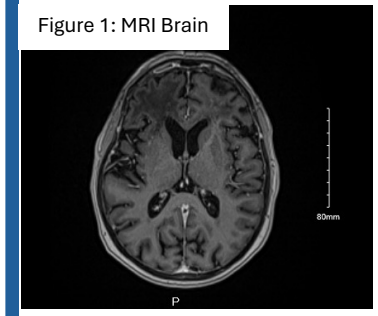
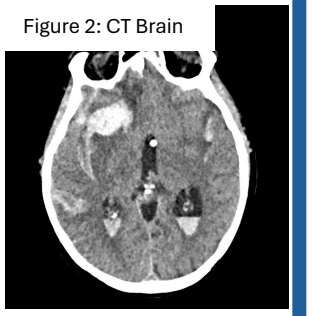


Figure 2: CT Brain



SS was transferred to ICU and subsequently investigations including a Lumbar Puncture, vasculitic, connective tissue disease and immunomodulatory screens were performed. These, including a CT TAP were all within normal limits.

An IgM Kappa band in the gamma region was demonstrated, which may have been in keeping with a possible myeloma or monoclonal gammopathy of undetermined significance (MGUS). Full blood counts were normal.
The brain biopsy which was taken stained positive for SV40 which is in keeping with PML.

While SS showed some interval improvement of haemorrhages on CT scans, there was a lack of clinical improvement, and the decision was made to pursue palliative measures. SS died two days following this decision.

Test	Result
HIV 1+2 Ag/Ab	Negative
HCV Ag/Ab	Negative
HBV sAg	Negative
HBV Core Total	Negative

LP Results	Result
CSF Total Protein	36mg/dL
CSF Glucose	4.4mmol/L
Erythrocytes	18,100/uL
Leucocytes	30/uL

LP Results	Result
IgG	<3.0g/L
IgA	<0.50g/L
IgM	20.44g/L

Other tests, including ANCA, anti-nucleosome antibodies, anti dual-strand DNA antibodies and ENA screen were all normal during these investigations. PCR for JC virus was not carried out on CSF or brain tissue.

Discussion

This case presents a situation in which an apparently immunocompetent 74 year old woman, which no history of other common predisposing factors such as HIV or lymphoma, can develop PML. While SS had a previous history of treatment for breast cancer with aromatase inhibitors and tamoxifen, in addition to the potential MGUS discovered during the course of investigations, these are not well documented risk factors for development of PML. To the best of our knowledge this is the first report of a PML secondary to MGUS.

PML carries a poor prognosis, and in many cases the importance of prompt recognition and diagnosis is in limiting the further progression. This case highlights the importance of early imaging in cases of patients with new neurological symptoms, including those with new cognitive and memory decline. Additionally, it is important to maintain a wide differential diagnosis in cases like these, even tough there may be a lack of risk factors identifiable from the history.

References

[1] Weber, T et al. "Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy." *The Journal of infectious diseases* vol. 176,1 (1997): 250-4. doi:10.1086/514032

[2] Joly, Marine et al. "Progressive multifocal leukoencephalopathy: epidemiology and spectrum of predisposing conditions." *Brain : a journal of neurology* vol. 146,1 (2023): 349-358. doi:10.1093/brain/awac237