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In this issue

Certain medicines and progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy is a rare but serious disease associated with certain anti-neoplastic, immunosuppressant and immunomodulatory medicines.

Progressive multifocal leukoencephalopathy (PML) is a rare but serious disease of the central nervous system, caused by the John Cunningham Virus (JCV). Infection with JCV is commonly acquired in childhood, with up to 65% of individuals testing seropositive for JCV by the age of 17.[1]

Most infected individuals remain asymptomatic and will not develop PML. However, some individuals can develop the disease through reactivation of the virus when their immune system is weakened. A number of anti-neoplastic, immunosuppressive and immunomodulatory medicines have been linked to PML.

It is thought PML occurs following reactivation of JCV in the setting of severe cellular immune deficiency.[2]

Reactivation of JCV causes a lytic infection of oligodendrocytes and destruction of brain tissue. Development of PML occurs in immunosuppressed patients either because of an underlying medical condition which directly affects the immune system or through the use of medications that alter immune function.

PML can be a complication in those with HIV/AIDs, haematological malignancies (for example, lymphoproliferative disorders), organ or haemopoietic stem cell transplantation, and in those who are exposed to antineoplastic or immunosuppressive therapies such as fludarabine (Fludara), cyclophosphamide (Endoxan), azathioprine (Imuran), mycophenolate mofetil (Cellcept/Myfortic), tacrolimus (Prograf), everolimus (Certican) , sirolimus (Rapamune) and cyclosporine (Neoral); and monoclonal antibodies including natalizumab (Tysabri), rituximab (Mabthera), alemtuzumab (Mabcampath), vedolizumab (Entyvio), brentuximab vedotin (Adcetris) and Ofatumumab (Azerra).[1,2]

More recently, PML occurring in patients who were receiving immunomodulatory therapy, namely fingolimod (Gilenya) or dimethyl fumarate (Tecfidera) for the treatment of Multiple Sclerosis (MS) has also been reported.[3-5]

Clinical presentation of PML

Early neurological symptoms of PML may be non-specific or subtle, and are dependent on the initial focus of reactivation and infection in the brain.

Common presenting symptoms of PML include cognitive dysfunction (for example, confusion) or recent changes in behaviour or personality, motor symptoms (for example, weakness/gait disturbances), language or speech difficulties, sensory symptoms (for example, vision or hearing loss and paraesthesias) and seizures.[2]

As the clinical symptoms of PML are not pathognomonic, it may mimic other neuroinflammatory conditions, stroke or cerebral malignancies. In particular, it may be challenging to differentiate between the symptoms of PML and an exacerbation or acute relapse of MS. Often, MS

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is relapsing-remitting in nature, whereas PML is characterised by slowly progressive focal neurological deficits.[2]

PML can be diagnosed by MRI, cerebrospinal fluid (CSF) analysis for JCV and in some cases immunohistochemistry from a brain biopsy.[6]

MRI frequently shows focal, asymmetrical lesions involving periventricular and sub cortical white matter. Suspected cases of PML are confirmed by positive JCV DNA in the CSF via polymerase chain reaction (PCR) or detection of JCV in brain biopsy specimens.

Although the assay for JCV DNA via CSF PCR has a relatively high specificity (92-100%), sensitivity is variable and a negative CSF PCR does not necessarily exclude the diagnosis of PML in a patient with typical MRI lesions in the appropriate clinical setting.

Some risk factors have been identified in patients treated with natalizumab. These include positive anti-JCV antibody status, longer duration of therapy and prior treatment with immunosuppressant medications. The risk of developing PML is increased when one of more of these factors is present. Consideration should be given to testing patients for anti-JCV antibody status prior to commencing therapy or during therapy if antibody status is not known.[7]

It is important to note that patients who test negative for anti-JCV antibodies are still at risk of developing PML due to the potential for a new JCV infection or a false negative test result. Consideration should therefore be given to periodic re-testing of patients previously determined to be anti-JCV antibody negative.[7]

Australian PML cases

As of 16 November 2016, the TGA's Database of Adverse Event Notifications (DAEN) includes 30 reports of PML. It should be noted that not all of these reports document confirmed cases.

In many of these reports patients were also receiving chemotherapy and/or had concomitant or previous use of other immunosuppressive/ immunomodulatory medicines or had underlying immunosuppressive conditions. Some of the reports involved patients on treatment for MS.

The majority of reports were associated with use of monoclonal antibodies, in particular natalizumab and rituximab. There were 16 reports associated with rituximab and in 12 of these reports it was the sole suspected medication. There were 10 reports associated with natalizumab and in seven of these it was the sole suspected medication. In addition there were smaller numbers of reports that co-suspected multiple medications known to cause immunosuppression or to have previously been associated with PML; fludarabine (4), fingolimod (2), alemtuzumab (1), lefluonmide (1), azathioprine (1), mycophenolic acid (1) and tacrolimus (1).

Monitoring and treatment of PML

The risk of PML should be considered when making decisions regarding initiation of treatment with medicines that have been associated with PML.

Patients should be advised of the rare risk of PML and told to seek urgent medical attention if they develop new neurological symptoms.

Medical practitioners should monitor patients receiving medicines that have been associated with PML for any new neurological signs, consider PML in any patient receiving antineoplastic, immunosuppressant or immunomodulatory therapy that presents with new onset focal neurological signs or symptoms, and initiate prompt investigations in these patients to rule out PML.

Consideration should be given to testing patients for anti-JVC antibodies prior to treatment with medicines associated with development of PML or during treatment if antibody status is unknown.

Currently, there are no medications proven to be effective in treating PML. The only strategy is to treat the infection by allowing reconstitution of the patient's immune system. The development of PML-immune reconstitution inflammatory syndrome (PML-IRIS) is an unavoidable complication in most patients when immunosuppressive therapy is ceased or circulating antibodies are removed rapidly via plasma exchange.[6]

Frequently, paradoxical worsening in clinical status occurs due to an overwhelming inflammatory response to JCV and massive redistribution of immune cells to infected brain tissue. Treatment of PML-IRIS with high dose intravenous steroids has demonstrated clinical improvement in some patients.[8]

In MS patients afflicted by immunosuppressive therapy-induced PML, better patient outcomes depend on earlier PML identification and appropriate intervention. Increased clinical and radiological vigilance is therefore essential.

Key points

- Prescribers of anti-neoplastic, immunosuppressant or immunomodulatory medications should be aware of PML as a potential adverse event.
- Prescribers should consider PML in any immunosuppressed patient presenting with new onset focal neurological deficits.
- Prescribers should be aware that in MS patients, PML can sometimes be confused with an MS

relapse, which has the potential to delay PML diagnosis and treatment.

- Prescribers should monitor patients being treated with medicines known to be associated with PML for any new focal neurological signs or symptoms.
- Prescribers should consider testing for anti-JCV antibodies in patients prior to starting medicines that have been associated with PML or during treatment if antibody status is not known.
- If a prescriber suspects PML, immunosuppressive medications should be withheld and appropriate investigations ordered (gadolinium-enhanced MRI and CSF analysis for JC viral DNA are recommended).

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Aripiprazole and impulse control disorders

Health professionals are advised that the Product Information documents for aripiprazole have been updated to include additional information about impulse control disorders.

Aripiprazole is a novel antipsychotic medicine that is a partial dopamine agonist. It is marketed in Australia as Abilify (oral tablets) and Abilify Maintena (intramuscular injection), as well as various generic brands. Abilify is indicated for:

- the treatment of schizophrenia, including maintenance of clinical improvement during continuation therapy
- acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate
- maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy.

Abilify Maintena is indicated for the acute and maintenance treatment of schizophrenia in adults.

The Precautions and Adverse Effects sections of the Product Information (PI) documents for these medicines have been updated to include additional information about impulse control disorders.

Cases of obsessive-compulsive disorder, eating disorder and impulse-control problems, including gambling and hyper-sexuality, have been reported for patients being treated with aripiprazole.

The updated Precautions section of the PI warns that patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges reported were:

- increased sexual urges
- compulsive spending
- binge or compulsive eating
- other impulsive and compulsive behaviours.

Please note that impulse-control symptoms can be associated with the underlying disorder. However, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Patients may not recognise these behaviours as abnormal, therefore prescribers are advised to discuss these potential adverse events with patients and their caregivers. Prescribers should consider dose reduction or stopping aripiprazole if a patient develops such urges during treatment.

Vemurafenib and risk of radiation injury

Health professionals are advised that there have been overseas reports of radiation recall and radiation sensitisation in patients treated with radiation before, during or after taking vemurafenib.

Vemurafenib is a low molecular weight, oral inhibitor of some mutated forms of the BRAF serine-threonine kinase enzyme. It is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation. Vemurafenib is marketed in Australia under the brand name Zelboraf.

The risk of potentiation of radiation toxicity, such as radiation recall and radiation sensitisation, had been identified previously in the Product Information (PI) for vemurafenib. However the Precaution section of the PI was recently updated to strengthen this warning.

Radiation recall is an uncommon and unpredictable phenomenon that is characterised by acute inflammatory reactions confined to the previously irradiated area.

Radiation sensitisation refers to greater than expected severity of the reaction for local radiation injuries.

The PI now states that 'In the majority of [reported cases of radiation recall and radiation sensitisation], patients received radiotherapy regimens greater than or equal to 2 Gray/day (hypofractionated regimens).'

Prescribers are advised to use vemurafenib with caution when given concomitantly or sequentially with radiation treatment.

Most of the reported cases were cutaneous in nature, but some cases involving visceral organs had fatal outcomes.

As of 17 August 2016, the TGA had received no Australian reports of radiation injury associated with vemurafenib treatment.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to 02 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Pharmacovigilance and Special Access Branch on 1800 044 114.

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