CASE REPORT

A hitherto unrecognised case of progressive multifocal leukoencephalopathy

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SUMMARY

A 65-year-old man presented with a 6-week history of increasing confusion with associated cognitive decline. Empirical antibiotic cover for a urinary tract infection was prescribed with no response. After exhaustive radiological and pathological investigations were carried out, a diagnosis of John Cunningham virus encephalopathy was made. This case report describes the varied clinical presentation of symptoms and their management options, along with the latest clinical opinions behind them.

BACKGROUND

Progressive multifocal leukoencephalopathy (PML) occurs almost exclusively in severely immunosuppressed individuals. This is an unusual case of a patient with PML who had minimal or occult immunosuppression.

The incidence of PML is estimated at only 0.07% among patients with haematological malignancies, which again emphasises the rarity of this case.¹

This case report highlights the importance of early clinical suspicion of John Cunningham (JC) virus-related PML when making the diagnosis, which will be invaluable in supporting these immunodeficient patients.

CASE PRESENTATION

A 65-year-old man presented to the accident and emergency department with a 6-week history of increasing confusion and general malaise. His general practitioner had diagnosed the patient with a presumed infection, for which repeated courses of empirical antibiotics had been prescribed. However, the patient did not respond to the treatment.

He had previously been under follow-up by the haematology department for non-Hodgkin's follicular lymphoma for 2 years, with no preceding evidence of immunosuppression either clinically or biochemically. Owing to the indolent nature of his lymphoma, he was treatment naïve. During this time, he continued to remain clinically well and independently active.

On the current admission, however, the patient began to deteriorate significantly, especially cognitively, with aphasia and disorientation. Within the space of a few weeks, he deteriorated rapidly from being fully independent to remaining bedbound. Initially, the acute medical team diagnosed him with a stroke and he underwent intensive neurorehabilitation.

Figure 1 CT of the head—normal scan.

INVESTIGATIONS

A CT of the head (figure 1) showed small vessel gliosis and marked low attenuation in the right frontal region, consistent with previous infarction, with no abnormal enhancement, and, on review by a senior stroke consultant, the patient's clinical findings were deemed inconsistent with a diagnosis of stroke.

This was followed on with a CT scan of the entire body (figure 2), which demonstrated extensive retroperitoneal, retrocrural, pelvic and inguinal lymphadenopathy. The scan, however, showed no

Figure 2 CT of the chest/abdomen/pelvis—extensive retroperitoneal lymphadenopathy. Stable disease pattern.

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Figure 3 Age-matched normal CT of the chest/abdomen/pelvis (control).

significant change when compared with the previous CT scan. A normal age-controlled image is included for comparison (figure 3). MRI (figure 4) revealed bilateral subcortical diffusion restrictions, with no gadolinium enhancement. These findings were consistent with an unusual form of encephalopathy or an unusual distribution of subcortical small vessel vascular occlusive disease. A normal age-controlled image is included for comparison (figure 5).

A cerebrospinal fluid (CSF) sample was also sent for PCR tests, which all returned negative for meningitis and encephalitis. The CSF also returned negative for malignant cells.

DIFFERENTIAL DIAGNOSIS

- ▶ Encephalitis/viral meningitis
- ▶ Subacute stroke
- ▶ Central nervous system (CNS) lymphoma
- ▶ Paraneoplastic syndrome
- ▶ PML

TREATMENT

With all the investigations firing blanks, the patient continued to be treated with antibacterial and antiviral antibiotics, without any significant clinical improvement.

Figure 4 MRI of the head—bilateral subcortical diffusion restrictions. Findings could represent various forms of encephalopathy.

Figure 5 Age-matched normal MRI of the head (control).

The haematology department was then tasked with considering the possibility of a high-grade cerebral transformation lymphoma, but, as before, the CSF showed no malignant cells with MRI proving inconclusive.

The patient was subsequently referred to the neurological and infectious diseases team who raised the suspicion of either a paraneoplastic syndrome or the presence of JC virus, a polyomavirus that usually stays latent within the gastrointestinal tract or kidneys.

A CSF sample was then sent for further staining, which came back positive for JC virus. This clinched the diagnosis as PML secondary to JC virus.

This was highly unusual, as JC virus usually presents among the immunosuppressed patient group, and there was no apparent cause for immunosuppression in this particular patient with the status of his lymphoma remaining stable and a HIV screen returning as negative.

The prognosis of PML caused by JC virus remains poor, despite recent years of medical advances, with no definitive treatment for such a condition.

Following extensive literature searches and discussions within the multidisciplinary team, it was decided that mirtazapine, a tetracyclic antidepressant drug, was to be used as a bridge, to prevent further viral entry and replication within the glial cells, but with no definitive treatment options. Mefloquine was not given to this patient due to the potential of neuropsychiatric side effects in an already confused patient.

OUTCOME AND FOLLOW-UP

After a week of observation and monitoring, while on mirtazapine, there was no significant change noted in the patient's clinical symptoms, and the situation was discussed with both the patient and his family, and consensus was gained to discharge the patient home on palliative care.

DISCUSSION

Epidemiology and pathogenesis

John Cunningham virus, or JC virus, takes its name from the first patient who was diagnosed with it in the year 1965.¹ It is a

type of human polyomavirus, a double-stranded DNA virus that is genetically similar to BK virus and SV40.¹ JC virus stays latent in 70–90% of the human population, usually within the kidney, bone marrow and gastrointestinal tract,² and becomes reactivated and symptomatic in cases of immunodeficiency. The mechanism of transmission remains unknown, but it is believed that the virus crosses the blood–brain barrier and infects the oligodendrocytes and astrocytes via the 5-hydroxytryptamine (5-HT) serotonin receptors.³

During the 1980s, PML was a very rare disease, a ‘back of the textbook’ condition.⁴ With an increase in immunosuppression caused by the HIV and AIDS epidemic, it is postulated that this resulted in the reactivation of JC virus, with a corresponding increase in frequency of PML seen.⁴ Conversely, the development of immune reconstitution therapy, for example, antiretroviral medications, has stemmed this somewhat.

Interest in this disease has also recently increased in relation to the use of monoclonal antibodies such as immunomodulatory drugs for the treatment of lymphoma, multiple sclerosis and Crohn’s disease. When the immune system is suppressed in such situations, JC virus can potentially reactivate and proliferate in the nucleus of oligodendrocytes and astrocytes, causing destruction within the myelin sheath.⁵

Clinical symptoms

JC virus mainly infects the brain white matter, but grey matter involvements can also occur.⁵ The reactivation of JC virus in the CNS can cause JC virus-related inflammation, encephalitis and meningitis, but it most commonly causes PML.⁶ Thus there is a wide variety of clinical presentations, ranging from meningeal symptoms such as headaches, malaise, paralysis, vision loss and impaired speech, to cognitive deterioration. This is usually confusing for physicians as the symptoms are somewhat similar to CNS infections, stroke or multiple sclerosis.⁷ Diagnosis of PML is confirmed with the detection of JC virus in the CSF along with the exclusion of all other viruses.⁸

The likelihood of developing clinically active PML following persistent JC viraemia remains uncertain, and therefore the significance of pre-emptive detection of persistent JC viraemia is also unclear.^{7,8} However, this case demonstrates that early clinical suspicion of JC virus, preceding the development of PML symptoms or diagnosis, might be valuable in supporting the immunodeficient patient.^{7,8}

Prognosis and management of PML

The mortality rate of PML is between 20–50% within 3 months, hence highlighting this case as a priority.⁹ A recent nationwide cohort study performed by Engsig *et al* revealed that the median survival time among patients diagnosed with PML was 1.8 years.¹⁰

The prognosis for this condition may improve with reconstitution of the immune system, while medications such as mefloquine have mixed outcomes.^{11,12} This antimalarial agent had previously been used, as shown by Brickelmaier and colleagues and is thought to work by inhibiting the replication of JC virus within the cells.¹³ The evidence for this, however, is entirely based on case reports and case series.¹²

The use of mirtazapine, a tetracyclic antidepressant, has also been shown to be successful as it competitively inhibits the 5-HT serotonin receptors within the brain, preventing the entry of JC virus into unaffected glial cells.¹⁴

Case studies by Epperla *et al*¹² and Schröder *et al*¹⁵ have shown that the combination of mirtazapine and mefloquine, however, has been described as successful, though formal

case-controlled studies or trials have yet to prove a definite causal relationship.

In any clinical setting, however, the main focus in the management of PML should always be to avoid immunosuppression and to take a multidisciplinary approach, to decide the management options on a case-by-case basis.

Learning points

- ▶ Such a case should always be considered in individuals with indolent haematological malignancies.
- ▶ A heightened awareness of potential causes of immunosuppression and their investigation is essential in all haematological patients.
- ▶ Early referral to neurology or the infectious disease team might lead to earlier diagnosis and perhaps better prognosis.

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