A case of progressive multifocal leukoencephalopathy in a patient with sarcoidosis

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Case report

A 47-year-old caucasian man presented with a new visual field defect. He had been diagnosed with pulmonary sarcoidosis 15 years previously on the basis of mediastinal lymph node biopsy and chest imaging consistent with stage three disease. Other than an eruption of cutaneous sarcoidosis 5 years after initial diagnosis, his disease had been quiescent on maintenance medication of prednisolone 15 mg per day and hydroxychloroquine 200 mg per day. Several attempts to wean his steroids were unsuccessful. He had a documented long-standing T-cell lymphopenia, and at the time of presentation, his lymphocyte count was 488 × 10^6/l (T-cells 394 × 10^6/l, CD4 cells 131 × 10^6/l).

The patient was a hotel manager, had no other significant medical conditions and was a life-long non-smoker with moderate alcohol consumption. On routine annual ophthalmologic follow-up, perimetry demonstrated a new partial left superior quadrantanopia. On further questioning, the patient admitted to recent visual field problems, particularly during playing golf when he had a tendency to ‘lose’ the ball out to the left.

Pre- and post-contrast magnetic resonance imaging (MRI) of brain at this time demonstrated numerous high signal foci throughout both cerebral hemispheres including a lesion of the right geniculate-striate pathway as well as the right midbrain and upper pons. There was one isolated focus of enhancement in the left cerebellar peduncle. There was no meningeal thickening or enhancement (Figure 1). Analysis of cerebrospinal fluid including oligoclonal bands was within normal limits. Visual evoked responses were also normal.

The consensus opinion from ophthalmology, pulmonology, neurology and radiology specialties was that of neurosarcoidosis, and immunosuppression was escalated with an increase in prednisolone therapy to 60 mg per day for 6 weeks followed by a taper to 40 mg per day and the addition of azathioprine. Upon review 10 weeks after increasing immunosuppression, at which stage the patient was receiving prednisolone 40 mg per day and azathioprine 150 mg per day, he reported no improvement in his visual symptoms and complained of increased blurring of vision. Perimetry demonstrated progression of the visual field defect and clinical examination confirmed the development of a right infranuclear ophthalmoplegia and right conjugate lateral gaze paresis as well as a left seventh nerve palsy. Repeat MRI of brain demonstrated stability of the number and size of lesions however several foci within frontal lobes and left cerebellum now enhanced post-contrast (Figure 2).

Given the progressive nature of his condition despite advanced immunosuppression, consideration was given to alternative diagnoses. Serum samples were analysed for cryptococcal antigen, toxoplasma...
IgG and JC virus DNA, all of which were negative. HIV serology was performed which was negative. Lumbar puncture was repeated. On this occasion, protein was elevated at 0.72 g/l, glucose was 3.7 mmol/l, but with a white cell count of less than 1 per mm$^3$. There were no oligoclonal bands detected, and the cryptococcal antigen latex test was negative. JC virus DNA however, was detected on PCR analysis of CSF.

Stereotactic brain biopsies of one focus in the right frontal lobe was subsequently performed. The white matter demonstrated atypical astrocytes and oligodendrocytes with intranuclear inclusions.

Figure 1. (a) Axial FLAIR sequence at the level of the ventricles demonstrated punctate high signal in the deep white matter lesions of the left parietal lobe. (b) Axial FLAIR sequence at a higher level demonstrated further punctate high signal lesions in the right fronto-parietal deep white matter.

Figure 2. (a) and (b) Axial FLAIR sequences at levels corresponding to Figure 1a and b demonstrating stability of the number and size of previously identified lesions. (Several of the foci within the frontal lobes enhanced post contrast-not shown).
These inclusions stained positively with SV40 and SV80 consistent with a diagnosis of progressive multifocal leucoencephalopathy (PML) (Figure 3).

His immunosuppressive medication was weaned over the next few weeks. Cytarabine 2 mg/kg daily for 5 days and three treatments of Cidofovir 5 mg/kg at 2 weekly intervals were administered. Subsequently, maintenance treatment with mirtazepine 30 mg a day and mefloquine 250 mg weekly were also started. Follow-up perimetry at 2 months demonstrated further progression of visual field defects and repeat MRI of brain demonstrated an increase in size and confluence of several of the previously noted lesions (Figure 4). This clinical picture and radiological changes were felt to be consistent with immune reconstitution inflammatory syndrome as has been recently described in the natalizumab series.1–3

Over the forthcoming months he remained off all immunosuppressive therapies and treatment with mirtazepine and mefloquine was maintained. At 5 months from commencement of treatment for PML he had noticed significant improvement in his neurological symptoms. In particular his visual field defect had almost completely resolved which was confirmed on perimetry studies. Clinical examination also revealed improvement in his 6th-nerve palsy and facial weakness. Interval MRI imaging with contrast at 3 months demonstrated reduction
Discussion

Progressive Multifocal Leukoencephalopathy (PML) is a rare but devastating disease of the central nervous system (CNS) caused by reactivation of JC virus and subsequent haematogenous seeding to the CNS resulting in infection and demyelination of oligodendrocytes.4 PML typically only occurs in immunocompromised patients, most commonly HIV infection or AIDS, but it is also observed in association with haematological malignancies, chronic inflammatory/connective tissue diseases and transplant recipients.5 A number of immunosuppressive medications have been clearly associated with its development. Prolonged corticosteroid therapy has been well documented as an antecedent,6,7 while other drugs such as cyclophosphamide, azathioprine, methotrexate, cyclosporin, tacrolimus and mycophenolate have all been implicated.6,7 More recently, cases have been reported with the use of monoclonal antibodies such as natalizumab in patients with multiple sclerosis,3,8 and rituximab.9 Despite sporadic case reports of successful treatment of PML using medications such as cidofovir, cytarabine and mirtazepine, there is currently no recognized effective treatment for PML.10–15 Mefloquine has demonstrated some anti-JC virus activity in vitro16 and is currently being evaluated in a multicentre trial.17 The cornerstone of management however, is reversal of immunosuppression, either by institution of highly active antiretroviral therapy (HAART) in HIV cases which has been associated with stabilization of neurological symptoms and improved survival,14,18 or cessation of immunosuppressant drugs. The paradoxical worsening of neurological deficits due to the immune reconstitution inflammatory syndrome should be anticipated as a potential complication during reversal of immunosuppression, especially when instituting HAART.19 Prognosis of PML unfortunately remains extremely poor and the majority of non-HIV cases die within several months while only very few experience neurological stabilization or prolonged survival.20

PML is well described in sarcoidosis. Most commonly this occurs in the setting of immunosuppression with corticosteroids or other immunomodulating drugs.12,21–23 However, case reports have documented PML in sarcoidosis patients in the absence of immunosuppressive therapy.15,23,24 Indeed, there is extensive case reporting in the

in size and intensity of the previously identified lesions and there was no enhancement post contrast (Figure 5).

At 3 years since initial onset of symptoms and 2.5 years since withdrawal of immunosuppression, the patient remains in a stable condition having experienced resolution of his visual field defects and a significant improvement of his facial weakness and nerve palsy with continuing stability of MRI findings.
literature to suggest an increased risk of opportunistic infections, especially cryptococcal disease in patients with sarcoidosis.30,33–37 Several theories exist to explain this state of reduced immunocompetence. Peripheral T-lymphopenia is frequently seen in sarcoidosis27,28 which can be a consequence of either corticosteroid therapy, hypersplenism or bone marrow involvement.24 The most common mechanism however is thought to be the redistribution of T-cells, mainly CD4+ lymphocytes, to sites of disease involvement.27 Although not fully understood, it is generally accepted that there is significant T lymphocyte dysregulation in the setting of sarcoidosis resulting in intense inflammatory activity accompanied by a general state of anergy.29

PML is an important differential in the development of new neurological signs and symptoms in patients with sarcoidosis, especially those on long-term immunosuppressants. The exclusion of opportunistic infection in this setting is paramount before embarking on a treatment strategy of increased immunosuppression for presumed NS, however this is often challenging as the clinical presentation of PML and NS may be indistinguishable,7,30–34 and brain imaging may demonstrate similar findings.30,33–37

History and physical examination provides useful clues; review of four recent large case series reports on neurosarcoidosis found that optic nerve and spinal cord were involved with a mean frequency of 30 and 28%, respectively30–32,37 however these sites are almost never involved in PML7,33–34 and therefore provide strong evidence against this diagnosis. Clinical improvement is often observed in NS when immunosuppression is introduced or escalated28 whereas a rapid, relentless progression of disease typifies PML.7 The presence of mass effect or enhancement on MRI of the brain would suggest that PML is unlikely7,34,29 and that NS or other conditions should be considered, whereas detection of JC virus DNA on PCR of CSF would very much favour a diagnosis of PML, with a specificity close to 100% and sensitivity of 60–80%.2,7 Ultimately, however, the confirmation of diagnosis by brain biopsy may often be necessary before a definitive form of treatment is considered.

We report on a positive outcome in a patient who developed PML in the setting of pulmonary sarcoidosis and long-term immunosuppression. In this case, we feel that reversal of immunosuppression was key to the observed improvement. Maintenance therapy with mirtazepine and mefloquine may also have played a substantial role.

Conflict of interest: None declared.

References


