Case report

Progressive multifocal encephalopathy after cyclophosphamide in granulomatosis with polyangiitis (Wegener) patients: case report and review of the literature

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ABSTRACT

Progressive multifocal encephalopathy (PML) is a rare demyelinating disorder targeting the central nervous system and resulting from JC virus reactivation. PML occurs in patients immunocompromised because of haematological malignancies, HIV infection or treatment with cytotoxic drugs. Herein, we describe PML occurring in 2 granulomatosis with polyangiitis (Wegener) patients treated with steroids and cyclophosphamide. The outcome was progressively favourable after immunosuppressant discontinuation for 1 patient and fatal for the other. Four previously reported GPA patients developed PML in the course of their disease. One of them improved gradually after immunosuppressant withdrawal. PML should be strongly suspected whenever unusual central neurological manifestations appear in this context. No effective treatment is available, but immunosuppressants should be discontinued if possible.

Introduction

Progressive multifocal encephalopathy (PML), a rare demyelinating disorder affecting the central nervous system (CNS), occurs in immunocompromised patients (1). Reactivation of JC virus, a polyomavirus that is latent in 70–90% of adults, causes PML, which is usually fatal. Although PML mostly occurs in severely immunodepressed HIV-infected individuals (2), it has been reported in patients taking immunosuppressants or immunomodulators (3) (mycophenolic acid, leflunomide, natalizumab or rituximab) to treat autoimmune diseases, like lupus (4) or rheumatoid arthritis (5). PML is extremely rare in granulomatosis with polyangiitis (Wegener) (GPA) (6–9). Herein, we describe 2 cyclophosphamide-treated GPA patients who developed PML.

Case 1

In 1997, a 60-year-old man in declining general health, with ear, nose and throat (ENT) manifestations (crusting rhinitis and sinusitis), alveolar haemorrhage (AH) and proteinuria was diagnosed with GPA. A nasal mucosa biopsy showed granulomatous angiitis. Tests for antineutrophil cytoplasm antibodies (ANCA) found c-ANCA, with a 1/200 titer and anti-proteinase-3 (PR3) specificity. He experienced successive flares (ENT signs and AH; then AH and rapidly progressive glomerulonephritis) over 8 years that were treated with steroids, IV then oral CYC and IV immunoglobulins, with azathioprine (AZA) during remissions. In September 2005, his cumulative CYC dose was 75g. When he developed Broca’s aphasia, apraxia and cerebellar dysmetria, he was taking prednisone (8 mg/d) and GPA was in complete remission. His total peripheral lymphocyte count was 740/mm³, with 177 CD4 T cells/mm³. Anti-PR3 ANCA were present (121 IU/mL). Cerebrospinal fluid (CSF) was normal; polymerase chain reactions (PCR) for JC virus and human herpesvirus-6 were negative, as were all the other microbiological tests. Magnetic resonance imaging (MRI) showed multiple subcortical hypointensity lesions in the left frontoparietal area, with no surrounding oedema (Fig. 1). Histological examination of these lesions found enlarged oligodendrocytes containing intranuclear inclusions and in situ hybridisation identified JC virus within the oligodendrocytes. PML was diagnosed. The outcome was favourable with steroid tapering and discontinuation of cytotoxic drugs. In 2012, the pa-
tient was alive, in complete remission, with minor cerebellar sequelae, and taking prednisone (7 mg/d).

Case 2
In 1993, a 63-year-old man was diagnosed with GPA characterised by poor condition, corneal ulcer and scleritis, and 2 lung nodules. Anti-PR3 ANCA were present. Treatment comprised 3 methylprednisolone pulses (725 mg/d), followed by prednisone until 1994, combined with IV CYC every 3 weeks (13 infusions) until November 1993, when his cumulative CYC dose reached 13 g; he was still taking prednisone (14 mg/d). He complained of ataxia, cognitive impairment, altered behaviour and a progressive decline of his functional and mental state. GPA was not active. During the past 3 months, his lymphocyte count had been between 1000/mm$^3$ and 500/mm$^3$; CD4 lymphocytes were not counted. ANCA were present. Electroencephalography showed slow delta waves in the frontal area. Computed tomography (CT) scan showed moderate hydrocephaly and basal ganglion lacunae. MRI suggested the diagnosis of PML. The patient died 4 months later.

Discussion
PML is characterised by JC-virus destruction of oligodendrocytes, causing progressive CNS demyelination. During immunocompromised states, the viral promoter in B lymphocytes can undergo trans-activation, travel via the bloodstream to the brain and infect oligodendrocytes. PML was first described in patients with chronic lymphocytic leukaemia or lymphoma (10), then in organ transplantees (11) and acquired immunodeficiency syndrome (12). A role for immunosuppressants was advanced to explain PML in patients with autoimmune diseases (3). PML affects the CNS and can cause visual disorders, motor loss and impaired cognitive function with subcortical dementia. Brain CT scan or MRI can suggest PML but PCR detection of viral DNA in the CSF or cerebral biopsy examination confirms the diagnosis (1). No specific antivirals are available. Most patients die within a few months. PML treatment comprises steroids and CYC, then maintenance AZA. More than the drugs used, it is the vasculitis-treatment-induced cellular immunodepression that is responsible for opportunistic infections (13), like Pneumocystis jiroveci pneumonia (14) or PML. All 4 previously reported patients were profoundly immunodepressed by massive immunosuppressant doses taken before PML onset. In 1989, Ettinger et al. reported a 62-year-old woman diagnosed with GPA since 1984 who had received 2 years of oral CYC (150 mg/d), stopped because of pancytopenia and replaced by cyclosporine for a GPA flare: 1 month later, and 5 months after stopping CYC, she developed (autopsy-confirmed) PML and died 2 months thereafter (6). The second case was a 59-year-old man diagnosed with GPA in 1988 who had taken prednisone and oral CYC for 3 years before developing PML (7). The third was a 60-year-old man diagnosed with GPA since 1991 who developed brain-biopsy-confirmed PML after 1 year of oral CYC (150 mg/d) (8). The last was a 71-year-old woman, diagnosed with GPA in 1990 who had been successively treated with steroids and pulse then oral CYC (neutropenia), mycophenolate mofetil (diarrhoea) and AZA; in 1999, she developed autopsy-confirmed PML (9). We describe 2 additional GPA patients who developed PML after CYC exposure (45 or 13 g). Apparently, all those massive exposures to CYC led to a profound immunodepression, which could facilitate PML.

PML is often fatal and does not respond to any antivirals. But for 10% of the cases, discontinuation of all immunosuppressants enhanced immune status and was followed by slow and usually partial clinical improvement (15). Morgenstern and Pards reported linear improvement over 2-years of follow-up once CYC was stopped and steroids tapered to 5 mg/d (8). Our case 1 also improved gradually after immunosuppressant withdrawal; he is still alive today with his GPA in remission without immunosuppressants.

GPA patients suffer profound long-term immunodepression, during which severe opportunistic infections are not rare (15); PML is one of them. Physicians must be aware of the risk of PML associated with CYC and rituximab, as reported in rheumatoid arthritis patients (5), especially because rituximab is expected to play an important future role in GPA treatment (16). PML should be strongly suspected whenever unusual central neurological manifestations arise in this context. A slow and partial recovery from PML is possible when the underlying disease allows discontinuation of immunosuppressants.
References