CASE REPORT

Progressive multifocal leukoencephalopathy in a patient with chronic lymphocytic leukaemia treated with alemtuzumab

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SUMMARY

A 69-year-old Caucasian woman with a 15-year history of refractory chronic lymphocytic B-cell leukaemia (CLL), treated with alemtuzumab in the past 10 months presented with a subacute right foot drop. Initial evaluation with a brain CT scan, lumbosacral MRI, nerve conduction studies and LP was negative. In the following months, progressive right hemibody weakness and dysarthria developed. Brain MRI showed a bilateral parasagittal frontal lesion. Alemtuzumab treatment was withdrawn. Progressive multifocal leukoencephalopathy (PML) was confirmed by PCR. Attempted antiviral therapies proved fruitless. Inexorable clinical deterioration ensued and the patient passed away 10 months after the presentation. This case report intends to call attention for PML as a potential fatal complication of severe immunosuppression, including the possible role of new monoclonal antibodies (such as alemtuzumab) in its pathogenesis.

BACKGROUND

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the John Cunningham (JC) virus. It is a potentially fatal infection, first described in the 1960s in patients with lymphoproliferative diseases. Its incidence increased in the 1980s with the emergence of the HIV infection. Recently, some cases have been described in immunocompromised hosts treated with certain drugs, including monoclonal antibodies.[1]

B-cell leukaemia (CLL) is the most common leukaemia occurring in adulthood and is considered an indolent malignancy of the lymphoid tissue.[2]

Alemtuzumab is an anti-CD52 monoclonal antibody that causes a marked lymphocytic depletion lasting for several months (more pronounced on T lymphocytes). It is now well established in the treatment of refractory lymphoproliferative disorders and in bone marrow transplantation. The association of alemtuzumab and PML is scarce with only a few case reports in the literature of the past decade.

Since alemtuzumab had been recently under several promising phase III clinical trials in multiple sclerosis,[3 4] we found it important to present this case. To date and to our knowledge, there were no PML cases related to the use of this drug in those studies.

CASE PRESENTATION

A 69-year-old Caucasian woman presented to our neurology outpatient clinic with a 2-weeks progressive history of a right foot drop. She had a previous medical history of CLL, at that time on treatment with Alemtuzumab (30 mg alternate days TIW for 12 weeks) and oral prednisolone (20 mg daily). Since the CLL diagnosis, she had been previously and consecutively treated with chrolambucil+prednisone (5 cycles), fludarabine (7 cycles), COP protocol (cyclophosphamide, vincristine and prednisone, 2 cycles) and human immunoglobulin G (1 cycle). After a period of about 15 years of disease, she initiated a refractory response to chemotherapy with increasing leukocytosis, and was therefore proposed to begin treatment with alemtuzumab. There were no other personal or familiar medically relevant conditions.

At initial evaluation, the neurological examination was as followed: patient alert and oriented; no abnormal cranial nerves signs (except for a mild flattened right nasolabial fold), right foot drop (right foot extension: grade 4-in modified Rankin Scale (mRS) meaning "active movement against gravity and slight resistance"; right plantar flexion: grade 4), diminished right ankle reflex; no sensory, coordination or gait abnormalities.

INVESTIGATIONS

Initial evaluation with a brain CT scan and lumbosacral MRI was performed and no relevant lesions were found. Nerve conduction studies and LP were also normal. Nonetheless, in the following 3 months the patient also developed dysarthria and there was proximal weakness progression with a right crural paresis (grade 4). Brain MRI showed a bilateral frontal (mainly on the left side) parasagittal hyperintensity (figure 1A), with a mild cortical gyriform gadolinium enhancement. Another CSF study was undergone with normal cell count, protein, glucose, negative serologies (including HIV) and no evidence of neoplastic cells. The JC virus detection by PCR DNA was also negative. Oligoclonal bands were present on CSF (not in serum). Since there was no definitive aetiology, it was decided to perform a brain biopsy, which revealed only reactive astrocytosis (probably due to inadequate specimen). After discussion with the haematologist, alemtuzumab was withdrawn. Yet, the patient worsened in the following months with complete right-side haemiplegia and progressive aphasia, as it was shown by the correspondent increase of frontal MRI lesion on a

To cite: Isidoro L, Pires P, Rito L, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-201781

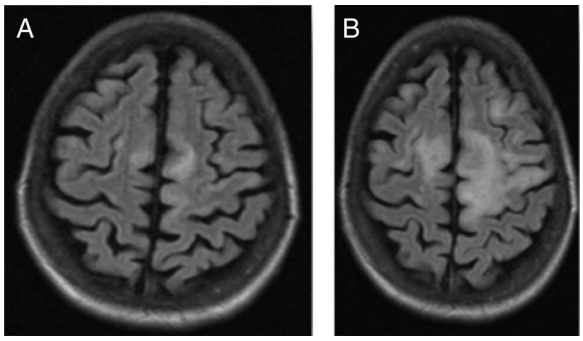

Figure 1 (A) Axial fluid-attenuated inversion recovery (FLAIR) MRI (3 months after presentation): bilateral, frontal parasagittal (mainly left) hiperintensity. (B) Axial FLAIR MRI (5 months after presentation): enlargement of initial parasagittal lesion with greater expansion on the left hemisphere.

later imaging (figure 1B). A third lumbar puncture was performed and the JC virus was identified by PCR amplification. PML diagnosis was finally made.

DIFFERENTIAL DIAGNOSIS

The routine investigation regarding frequent and benign causes of foot drop such as common peroneal palsy was held. There was no history of trauma, surgery, weight loss or frequent implicated habits such as leg crossing. Because of a significant history of leukaemia, it was decided to exclude causes as secondary cerebral involvement or infectious complications. Despite the initial negative results, due to the progressive nature of the symptom, the patient was strictly followed up and pursued investigation (repeating some tests inclusively) till the diagnosis was achieved.

Although a usual symptom such as a foot drop could have a simple and potential reversible cause such as a peripheral neuropathy, we found it fundamental to contemplate all diagnostic possibilities taking into account the patient history since they had considerable differences in relation to its investigation, treatment and prognosis.

TREATMENT

After the diagnosis of PML, it was decided to initiate treatment with cidofovir (275 mg/24 h intravenously) and human IgG (40 g/24 h for 2 days).

OUTCOME AND FOLLOW-UP

No neurological benefit was observed after antiviral therapy and the patient died 3 months later (about 10 months after the initial presentation). No autopsy was performed.

DISCUSSION

We found it important to report this case of PML because there is an increasing expectation regarding alemtuzumab therapeutic applications in areas such as multiple sclerosis. However, very few data about PML complicating treatment with this drug is available.

PML in the context of CLL treatment-naïve patients has lost preponderance, and since 1990, 90% of the cases of PML among patients with CLL occurred in those treated with purine analogues, especially fludarabine and cladribine.[2] With respect to alemtuzumab, after a review of the medical literature, we found reference to four published cases of PML under this monoclonal antibody treatment (three in patients with CLL and 1 in a lung transplant recipient).[5–7] According to the WHO Collaborating Centre for International Drug Monitoring Adverse Event Data Bank, there are 14 reported cases, with a mean latency from starting therapy drug to diagnosis of PML of 1 month and mean age at diagnosis of 58.2 years.[8] On the other hand, it is widely known and accepted the association of other monoclonal antibodies (such as natalizumab, efalizumab and rituximab) and the risk of PML development (regarding multiple sclerosis therapy with natalizumab, 372 cases worldwide as of June 2013, where 23% of them died[9]).

The physiopathological mechanism of this case still remains in discussion. Indeed, it could be associated with immunological dysfunction in relation with baseline haematological disease and/or the one resulting from the use of the alemtuzumab or even from previous treatments (namely fludarabine). Regardless of the precise cause, there is a common denominator underlying all these factors: severe downregulation of the immune system. We can only affirm the closest temporal relationship between PML appearance and alemtuzmab treatment course. As there is no current effective treatment for PML, it was first decided to stop undergoing immunosuppression and the usually proposed antiviral cidofovir treatment was attempted. However, no signs of improvement were seen and the patient ultimately died.

Physicians should be aware of the PML risk under aggressive immunosuppression. Tight clinical monitoring and surveillance as well as a high diagnosis suspicion (repeating diagnostic tests, including DNA analysis if necessary) are essential in patients undergoing this type of treatment.

Learning points

- Progressive multifocal leukoencephalopathy (PML) is a rare and potentially fatal infection of the central nervous system.
- PML is a condition most frequently observed in severely immunocompromised patients (such as those with lymphoproliferative disorders).
- The use of monoclonal antibodies (mainly natalizumab) is well associated with the risk of developing PML.
- There is scarce clinical literature regarding cases of alemtuzumab use and PML, although the increasing interest in this drug in certain areas such as multiple sclerosis therapy.
- Tight clinical monitoring and surveillance as well as a high diagnosis suspicion (repeating DNA analysis if necessary) are essential in patients undergoing this type of treatment.

Contributors LI and GC had the idea for the article. LI performed the literature search and wrote the article. GC gave expert opinion and reviewed the article. GC, PP and LR managed the case. All authors approved the final version of this manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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