Case Report

Lenalidomide-related Progressive Multifocal Leukoencephalopathy: A Case Report and Review of Drug-related Cases in Multiple Myeloma

Stephanie Anderson,[1] Matthew Kiernan,[2,3] P. Joy Ho[1,4]

Clinical Practice Points

- Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder caused by reactivation of John Cunningham virus. Prolonged treatment with immunosuppressive therapy is a risk factor for the development of PML, and cases have already been linked to agents used in the treatment of lymphoproliferative disorders such as rituximab, fludarabine, and brentuximab. However, literature on the epidemiology of PML in the multiple myeloma (MM) population and the risk associated with immunomodulatory agents or proteasome inhibitors is lacking.
- We present a case of PML in a 60-year-old female with immunoglobulin G MM on lenalidomide/dexamethasone for progressive disease post-autologous stem cell transplantation and discuss the causation, diagnosis, and management of PML in MM in the context of previous published reports.
- This report highlights the importance of considering PML in patients with MM who develop focal neurologic deficits. This is critical as early detection with cessation of causative chemotherapy is the only effective management strategy, yet it must be balanced against the risks of losing myeloma disease control. Such vigilance should not be limited to patients on immunomodulatory agents as our review identified cases linked to other drug classes including proteasome inhibitors. It should also be extended to newer agents, which are yet to be implicated, such as monoclonal antibodies.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system caused by reactivation of John Cunningham (JC) virus. Risk factors for the development of PML include infection with human immunodeficiency virus (HIV) or treatment with immunosuppressive therapy. This latter group, termed drug-associated PML, has been linked to rituximab, fludarabine, and brentuximab; all agents used in the treatment of lymphoproliferative disorders.[1] However, the literature remains scarce on the epidemiology of PML in the multiple myeloma (MM) population and the risk associated with immunomodulatory therapy. Unlike patients with lymphoproliferative malignancies, who may achieve long-standing remission with short but intense cycles of immuno-chemotherapy, patients with MM are often heavily treated over prolonged periods, with multiple generations of drug within a single class. Thus, an understanding of potential drug-related complications is particularly important in this group. Herein, we report the case of a woman with MM who developed PML after 47 months of lenalidomide/dexamethasone, administered for progressive disease post-autologous stem cell transplantation, and discuss the causation, diagnosis, and management of PML in MM in the context of previous published reports.

Case Report

A 60-year-old female was diagnosed with smouldering myeloma with lymph node plasmacytoma in 2013. She had an immunoglobulin G (IgG) lambda paraprotein of 25 g/L. Two months later, her paraprotein had risen to 64.3 g/L. A repeat bone marrow biopsy was performed, showing an increase in plasma cells from 50% to 90%. She was commenced on a 21-day cycle of bortezomib (1.3 mg/m^2), cyclophosphamide, and dexamethasone (CyBorD). Subcutaneous bortezomib 2.2 mg was administered on days 1, 4, 8, and

[1]Institute of Haematology
[2]Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia
[3]Brain and Mind Centre
[4]Bosch Institute, The University of Sydney, Sydney, Australia

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Address for correspondence: P. Joy Ho, MBBS, DPhil, FRACP, FRCPA, FFSc(RCPA), Institute of Haematology, Royal Prince Alfred Hospital, The University of Sydney, Sydney, Australia 2050
E-mail contact: joy.ho@sydney.edu.au

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11. Eight doses of oral dexamethasone 20 mg were given per cycle, together with oral cyclophosphamide 450 mg weekly.

The patient completed 4 cycles of CyBorD, then proceeded to a melphalan-induced autologous stem cell transplant. Her pretransplant paraprotein level was 36 g/L. Her first paraprotein level post-transplant was 18 g/L. She was commenced on maintenance oral thalidomide 200 mg daily and dexamethasone 40 mg/week. However, at 1 month, she demonstrated evidence of progression and was changed to lenalidomide 25 mg for 21 days in a 28-day cycle together with ongoing dexamethasone 20 mg/week. Two months later, owing to suboptimal response and the concerns for refractory disease, oral cyclophosphamide 300 mg weekly was added. Her paraprotein level decreased to 3 g/L and remained at this level. Owing to immune paresis with low total IgG (< 0.2 g/L) and recurrent chest infections, intravenous gammaglobulin was commenced at 7 months. Pegfilgrastim 6 mg was added at 8 months for each cycle to support neutrophils. Cyclophosphamide was ceased 27 months later.

After 47 months of lenalidomide and dexamethasone treatment, she presented with left-sided dyspraxia, expressive dysphasia, and incontinence. PML was suspected based on magnetic resonance imaging, which showed right frontal leukoencephalopathy with high T2 and low T1 signal. The lesion was hypometabolic on positron emission tomography. Cerebrospinal fluid was positive for JC virus DNA. Lymphocyte count was 2.0×10^9/L. HIV serology was negative. Immunosuppression was ceased, and oral mirtazapine 15 mg daily was commenced. The patient had progressive neurologic decline and died 4 months later. Autopsy was not performed.

Discussion

Lenalidomide is an oral immunomodulatory agent which has pro-apoptotic, antiinflammatory, and antiproliferative activity. It also exerts direct antitumor activity. Despite widespread use, there has only been 1 prior reported case of PML associated with lenalidomide. Brigo et al[2] described a dialysis-dependent male who developed neurologic deficits 9 months after initiating lenalidomide as first-line therapy for MM. The paraprotein level was not indicated in this report thus, how much the underlying MM contributed to the overall state of immunosuppression was not known. Our patient had a very low and stable paraprotein (3 g/L), suggesting lenalidomide was the principal factor. This was further supported by an absence of comorbidity, as opposed to the patient reported by Brigo et al, who had end-stage renal impairment. Although she required intravenous gammaglobulin, this had been introduced 40 months prior to the neurologic presentation.

There are only 7 other reports of PML in patients with MM in the literature (Table 1). Thalidomide, the precursor to lenalidomide, has been indirectly implicated in 2 cases. Fianchi et al[4] and Ripellino et al[3] both reported patients who developed PML post-autologous stem cell transplant. Both patients were treated with thalidomide prior to transplantation. There have been no published cases of PML associated with pomalidomide.

With regard to proteasome inhibitors, bortezomib has been implicated, but likewise only as a therapy prior to transplant.[5] The monoclonal antibodies, including daratumumab, have not been associated with PML, although the duration of their use in myeloma is still relatively short. Of the remaining cases, 3 occurred in patients treated with systemic chemotherapy.[7-9]

Restoration of the immune response is integral to the management of PML, and immunosuppressive therapy should be ceased when PML is suspected. However, despite this approach, the median survival in HIV-negative patients with PML is 3 months.[10] Such a poor response to our current treatment strategy highlights the importance of early recognition and the need to reassess the benefit of continuing high dose immunosuppression. Our patient had a small and stable paraprotein for 3 years prior to presentation. Although cessation of lenalidomide is not recommended in the

Table 1 Cases of Progressive Multifocal Leukoencephalopathy in Patients With Multiple Myeloma

Publication	Paraprotein	Lines of Therapy	Presentation	Site of Lesion (on MRI)	JCV DNA PCR (CSF)
Brigo et al (2017)[2]	Not specified	Lenalidomide	Left hemiparesis	Right subcortical occipito-parietal white matter	+
Ripellino et al (2011)[3]	IgG kappa	Thalidomide Tandem Melphalan AutoSCT	Left hemiparesis, ataxia, lower limb paraesthesias	Right fronto-parietal lobe and sub-cortical white matter	+
Fianchi et al (2010)[4]	Not specified	Thalidomide Dexamethasone AutoSCT	Dysarthria, left facial droop	Cerebellum and both cerebral hemispheres (multiple lesions)	− (+ on brain biopsy tissue)
Yokokawa et al (2016)[5]	IgG kappa	Bortezomib Cyclophosphamide Melphalan AutoSCT	Ataxia, dysphasia, left facial droop	Right frontal lobe	+
Mungunkhuyag et al (2014)[6]	IgA kappa	Prednisone Cyclophosphamide AutoSCT	Aphasia, right hemiparesis, memory impairment	Left parietal lobe and sub-cortical white matter	+
Akiyama et al (2010)[7]	IgD	Vincristine Doxorubicin, Dexamethasone	Disorientation, gait disturbance, logoclonia	Left frontal lobe	+
Mizutani et al (1984)[8]	Not specified	Cyclophosphamide Urethane Phenyl-alanine mustard	Gait disturbance, disorientation, memory impairment	Cerebral hemispheres (multiple lesions) (as per autopsy)	Not assessed
Bethlem et al (1964)[9]	Not specified	Urethane Steroid, unspecified	Aphasia, left hemiparesis	Cerebral hemispheres (multiple lesions)	Not assessed

Abbreviations: AutoSCT = autologous stem cell transplant; CSF = cerebrospinal fluid; Ig = immunoglobin; JCV = John Cunningham virus; MRI = magnetic resonance imaging; PCR = polymerase chain reaction.

treatment of relapsed refractory MM owing to the importance of maintaining disease control, dose reduction could have been considered, but is usually not undertaken owing to concerns of reactivation of myeloma, especially in cases such as this patient who exhibited early concerns of refractoriness to therapy.

Conclusion

This case highlights the importance of considering PML in patients with MM on immunosuppressive agents, such as lenalidomide, who develop focal neurologic deficits. It also illustrates the difficulties of balancing the importance of maintaining disease control by myeloma therapy versus a very rare but fatal adverse event. As withdrawal of immunosuppression remains the only effective treatment strategy in PML, early recognition is integral to limiting serious neurologic sequelae. Newer MM therapies, such as monoclonal antibodies, are yet to be associated with PML but should carry a similar degree of pharmacovigilance.

Disclosure

P.J.H. is an advisory board member for Amgen, Bristol-Myers Squibb, Celgene, Novartis, Janssen, and Takeda. The other authors have stated that they have no conflicts of interest.

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