




Prevalence of progressive multifocal leukoencephalopathy (PML) in adults and children with systemic lupus erythematosus

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ABSTRACT

Objective To define the risk of progressive multifocal leukoencephalopathy (PML) in SLE.

Methods This is a retrospective observational study to evaluate PML cases in patients with SLE admitted to two large academic hospitals. Using electronic medical record (EMR) data, International Classification of Diseases (ICD) codes identified PML cases among patients with SLE, rheumatoid arthritis (RA) (controls), had renal transplant and with HIV. Medication exposure was reviewed.

Results A total of 5409 Columbia University Medical Center (CUMC) patients and 2046 Northwell Health patients were identified using one ICD code for SLE. Of 7455 patients, three had an ICD code for PML. On EMR review, however, PML was substantiated in only one fatal SLE case with significant immunosuppressant use and severe lymphopenia (<0.5 cells $\times 10^9/L$); one patient was evaluated for PML but cerebrospinal fluid (CSF) was negative for JC virus and improved with treatment of central nervous system (CNS) lupus. EMR data were very limited for the third patient and diagnosis could not be confirmed. None of the 13 342 patients with RA ICD codes had PML. Of the 5409 patients with an SLE ICD code at CUMC, 212 also had a renal transplant ICD code, and 83 had concomitant HIV/AIDS. Based on inpatient pharmacy records of 5409 hospitalised patients at CUMC, 59.2% were treated with steroids, and 16.09% with immunosuppressants (7.76% mycophenolate, 3.42% cyclophosphamide, 2.88% azathioprine and 2.03% rituximab). No patients with paediatric SLE (pSLE) ($n=538$) had PML. The combined prevalence of PML in hospitalised patients with SLE at the two hospitals was 13–27/100 000 patients.

Conclusion Among 7455 adult patients with SLE ICD codes, there were two PML cases, with only one confirmed case associated with severe lymphopenia and immunosuppressants, corresponding to a prevalence of 13–27 per 100 000 patients. No PML cases in pSLE were found. A high index of suspicion in patients with SLE and CNS manifestations is required for the prompt diagnosis of PML.

INTRODUCTION

Infections present a risk of major morbidity and mortality in SLE. Progressive multifocal leukoencephalopathy (PML) is a rare, potentially fatal, central nervous system (CNS) opportunistic infection of oligodendrocytes and astrocytes by John Cunningham virus (JC virus). Exposure is widespread; seroprevalence of JC virus antibodies is 33% in paediatric cohorts, and increases with age to 60%–80% in adults and 90% in the elderly.^{1 2} JC virus reactivation occurs during periods of immunosuppression: HIV infection, haematological cancers, organ transplantation and treatment of autoimmune diseases.^{3–6} However, PML was also reported in rheumatic diseases in the absence of immunosuppressant treatments.^{7–9}

The current study was initiated to evaluate PML cases in adult and paediatric patients with SLE at two large academic centres, compared with: (1) rheumatoid arthritis (RA) controls, (2) renal transplant recipients, and (3) patients with HIV/AIDS, in order to understand the role of immunosuppressant treatments in increasing the risk of PML in SLE.

METHODS

Data were obtained using the Observational Health Data Sciences and Informatics network at Columbia University, a network of electronic medical records (EMR) and claims databases. All patients included in this observational study were admitted at NewYork-Presbyterian/Columbia University Medical Center (NYP/CUMC) between 1986 and 2013. The database was queried using International Classification of Diseases, Ninth Revision (ICD-9) codes to identify patients with

Table 1 NYP/CUMC and Northwell Health adult inpatients with SLE and RA codes

Patients	NYP/CUMC (number of patients)	Northwell Health (number of patients)
Patients with SLE ICD codes	5409	2046
SLE with HIV/AIDS ICD codes	83	35
SLE with renal transplant ICD codes	212	59
SLE without HIV/AIDS or renal transplant ICD codes	5114	1952
Patients with RA ICD codes	10776	2566

ICD, International Classification of Diseases; NYP/CUMC, NewYork-Presbyterian/Columbia University Medical Center; RA, rheumatoid arthritis.

SLE, RA, HIV/AIDS and had renal transplant. Patients with SLE were identified using ICD-9 code 710.0 or 695.4, an alternative SLE diagnosis code, which has been verified with chart review.¹⁰ The use of an SLE ICD code from even a single hospitalisation allowed a higher sensitivity for identifying all patients with SLE and PML, with a 66% positive predictive value (PPV) for SLE in our cohort.¹⁰ A thorough chart review allowed for confirmation of SLE with PML diagnoses. Patients with HIV/AIDS were identified using ICD-9 code V08 or 042. Renal transplant recipients were identified using ICD-9 code 55.69 or 55.61. Patients with RA were identified using ICD-9 code 714.0. Cases of PML were identified using ICD-9 code 046.3.

Data from Northwell Health were obtained using the institutional EMR and claims databases, allowing for data extraction of diagnosis codes and medication use. All patients with SLE admitted at Northwell Health between 2013 and 2018 were included. The databases were queried as above, using the same ICD-9 codes and corresponding ICD-10 codes (after 1 October 2015). Patients with paediatric SLE (pSLE) were identified using the same ICD codes as above between 2003 and 2018. PML cases were identified

using ICD-9 code 046.3 and ICD-10 code A81.2. (See online supplementary material for more information.)

RESULTS

NewYork-Presbyterian/Columbia University Medical Center

A total of 5409 individuals with SLE codes admitted to NYP/CUMC from 1986 to 2013 were identified (table 1). Eighty-three patients had concomitant HIV/AIDS, and 212 patients had renal transplants. Only two had an ICD code for PML.

Out of the 5409 patients coded for SLE, 1996 were treated with glucocorticoids, 536 with mycophenolate mofetil, 185 with cyclophosphamide, 110 with rituximab, 156 with azathioprine, 545 with hydroxychloroquine, 156 with azathioprine and none with belimumab (table 2), based on a combination of active outpatient and inpatient medications.

PML cases description

Case 1

A 48-year-old woman presented with SLE and antiphospholipid antibody syndrome, diagnosed at age 42 with biopsy-proven photosensitive rash, necrotising mesenteric vasculitis with small bowel infarction s/p ileostomy with reanastomosis, CNS lupus vasculitis supported by CSF analyses and MRI with recurrent cerebrovascular infarctions, in association with deep venous thrombosis, pulmonary embolism, lymphopenia, ANA of 1:1280, positive Sjogrens Syndrome A (Ro) and Sjogrens Syndrome B (La) antibodies, low complements (C3 and C4) and lupus anticoagulant. The patient was treated successfully with 12 doses of intravenous cyclophosphamide, but had severe persistent lymphopenia with <0.5 cells $\times 10^9$ /L. Subsequently, 1 year later, she developed left hemiataxia and cognitive impairment requiring hospitalisation. She was empirically treated with pulse-dose intravenous steroids and underwent neurological evaluation. She was diagnosed with PML with confirmed JC virus in CSF and brain biopsy. Immunosuppression was withdrawn, but the patient expired 3 months after her PML diagnosis.

Table 2 NYP/CUMC immunosuppressants in patients with SLE codes

Immunosuppressant	NYP/CUMC inpatients with SLE codes (n=5409)	Northwell Health inpatients with SLE codes (n=2046)	Northwell Health outpatient paediatric SLE cohort (n=538)
Glucocorticoids	1996	979	477
Mycophenolate mofetil	536	260	366
Cyclophosphamide	185	85	147
Rituximab	110	40	41
Azathioprine	156	70	217
Hydroxychloroquine	545	616	475
Belimumab	0	17	3

NYP/CUMC, NewYork-Presbyterian/Columbia University Medical Center.

Table 3 NYP/CUMC and Northwell Health adult inpatients with PML codes

Patients	NYP/CUMC PML cases	Northwell Health PML cases
All cases with PML ICD codes	502	23
SLE with PML ICD codes	n=2 (based only on ICD code) n=1 confirmed PML	n=1 (based only on ICD code) n=0 confirmed PML
SLE with HIV/AIDS ICD codes	0 out of 83	0 out of 35
SLE with renal transplant ICD codes	0 out of 212	0 out of 59
RA with PML ICD codes	0	0
HIV/AIDS with PML ICD codes	111	21
Renal transplant with PML ICD codes	0	0

ICD, International Classification of Diseases; NYP/CUMC, NewYork-Presbyterian/Columbia University Medical Center; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis.

Case 2

The second case was managed by a rheumatologist at CUMC prior to comprehensive EMR use and thus complete records were unavailable to fully confirm the diagnosis. However, a PML diagnosis was made, immunosuppression was withdrawn and the patient was discharged.

Northwell Health

Out of a total of 2046 patients admitted to Northwell Health from 2013 to 2018 identified with an ICD code for SLE (table 1), 35 had concomitant HIV/AIDS, 59 had a renal transplant and 1 also carried the ICD code for PML. There were 23 patients with an ICD code for PML, 1 of whom had concomitant SLE code as noted above, 21 with concomitant HIV/AIDS and 1 with concomitant multiple sclerosis (table 3).

One Northwell Health patient with ICD codes for both SLE and PML had a presentation consistent with CNS lupus and not PML with CSF negative for JC virus, and clinical improvement with increased immunosuppression.

Of 2046 patients, 979 were being treated with glucocorticoids, 260 with mycophenolate mofetil, 85 with intravenous cyclophosphamide, 40 with rituximab, 70 with azathioprine, 616 with hydroxychloroquine and 17 with belimumab (table 2).

Paediatric patients with SLE

A cohort of 538 patients with pSLE followed in paediatric rheumatology clinics at Northwell Health from 2003 to 2018 was identified, none had been diagnosed with PML. Of these 538 patients, 477 were treated with

glucocorticoids, 366 with mycophenolate mofetil, 147 with at least one course of intravenous cyclophosphamide, 41 with rituximab, 217 with azathioprine, 475 with hydroxychloroquine and 3 with belimumab (table 2).

RA controls

Among the patients coded for RA, none were found to have PML (table 3).

DISCUSSION

In our study at two major academic institutions, we identified two cases of PML out of 7455 adult patients with SLE, with a suggested prevalence of 13–27 per 100 000 discharges. We describe one confirmed case of PML in detail. In addition, our Northwell Health outpatient cohort of 538 paediatric patients with SLE had no PML cases.

Molloy and Calabrese found the incidence of PML in rheumatic diseases to be 4 for SLE, 0.4 for RA and 2 for other connective tissue diseases per 100 000 discharges, compared with the rate of PML of 0.2 in the general population.⁹ Of these patients with SLE and PML, 40% had minimal immunosuppression.⁸ A systematic review by Henegar *et al* estimated the PML incidence of 2.4 cases per 100 000 person-years.⁷ Brandão *et al* identified two cases of PML in patients with SLE—one with significant immunosuppressant exposure including rituximab, yet the second case with no immunosuppressive treatment. However, both patients had profound CD4 lymphopenia,¹¹ suggesting severe lymphopenia regardless of aetiology was a significant risk factor for PML development. Thirty-five additional cases of PML have been reported, in which 3 had no immunosuppressant exposure at the time of PML diagnosis, 5 had minimal immunosuppression, 23 had severe immunosuppression and 4 were indeterminate.⁷

Similarly, our confirmed patient with SLE and PML had a history of significant immunosuppression and absolute lymphocyte count <0.5 cells $\times 10^9/L$. CD4 T-cell lymphopenia is a common manifestation among active patients with SLE, with severe lymphopenia (<0.5 cells $\times 10^9/L$) occurring in 10% of patients with SLE.¹² Multiple aetiologies of lymphopenia in SLE have been described, including lymphopoiesis impairment, lymphocyte sequestration, antilymphocyte antibodies, increased apoptosis and complement-mediated cytolysis.¹²

All reported cases of SLE and PML are associated with severe lymphopenia.^{13 14} The suggested recommendation is to maintain a total count above 1.0×10^9 cells/L.^{14 15}

Comparable to our findings, there have been no reported cases of PML in patients with pSLE. This suggests that paediatric patients may have a lesser risk for PML despite immunosuppression from medications or active SLE, compared with adult patients with SLE.

There were few limitations to this study. SLE codes from two or more hospitalisations have a higher PPV for the diagnosis of SLE (88%) compared with our method

of using one or more hospitalisations (66%). However, our method allowed a higher sensitivity for identifying all patients with SLE.¹⁰ The true prevalence of PML in SLE, RA, HIV and renal transplants therefore can only be estimated using this method to identify patients. In addition, given the retrospective nature of our study, patients with PML who were not clinically identified with the JC virus infection may not have been included. Finally, the differing time periods of the database queries for each institution might not have been comparable, but depended on the EMR database availability at each particular institution.

CONCLUSION

A retrospective review of patients with SLE admitted to two major academic centres identified two possible PML cases (with only one confirmed case) among 7455 patients with SLE ICD codes, with a proposed prevalence of 13–27 per 100 000 discharges, suggesting a higher prevalence of PML in SLE than previously reported.⁹ Importantly, severe lymphopenia and significant immunosuppressant use were identified as potential risk factors. Finally, no PML cases were identified in the paediatric patients with SLE.

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