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

Teja Kapoor, Pooja Mahadeshwar, Joyce Hui-Yuen, Kayla Quinannies, Nicholas Tattonetti, Yevgeniya Gartsheyn, Cathy Guo, Laura Geraldino-Pardilla, Anca D Askanase

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 x 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 13342 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, 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% azathiorpine and 2.03% rituxinmab). 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. No PML cases in pSLE were found.

Conclusion Among 7455 adult patients with SLE ICD codes, there were two PML cases, with only one confirmed case associated with severe lymphopenias 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. JC virus reactivation occurs during periods of immunosuppression: HIV infection, haematological cancers, organ transplantation and treatment of autoimmune diseases.

However, PML was also reported in rheumatic diseases in the absence of immunosuppressant treatments.

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 PML.
Lupus Science & Medicine

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

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

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

Table 2 NYP/CUMC immunosuppressants in patients with SLE codes

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

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

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 x 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.
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).

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>NYP/CUMC PML cases</th>
<th>Northwell Health PML cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases with PML ICD codes</td>
<td>n=2 (based only on ICD code)</td>
<td>n=1 (based only on ICD code)</td>
</tr>
<tr>
<td>SLE with PML ICD codes</td>
<td>n=1 confirmed PML</td>
<td>n=0 confirmed PML</td>
</tr>
<tr>
<td>SLE with HIV/AIDS ICD codes</td>
<td>0 out of 83</td>
<td>0 out of 35</td>
</tr>
<tr>
<td>SLE with renal transplant ICD codes</td>
<td>0 out of 212</td>
<td>0 out of 59</td>
</tr>
<tr>
<td>RA with PML ICD codes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HIV/AIDS with PML ICD codes</td>
<td>111</td>
<td>21</td>
</tr>
<tr>
<td>Renal transplant with PML ICD codes</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases; NYP/CUMC, New York- 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).

**Discusssion**

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. Of these patients with SLE and PML, 40% had minimal immunosuppression. A systematic review by Henegar et al estimated the PML incidence of 2.4 cases per 100,000 person-years. 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, 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.

Similarly, our confirmed patient with SLE and PML had a history of significant immunosuppression and absolute lymphocyte count <0.5 cells x 10⁹/L. CD4 T-cell lymphopenia is a common manifestation among active patients with SLE, with severe lymphopenia (<0.5 cells x 10⁹/L) occurring in 10% of patients with SLE. Multiple aetiologies of lymphopenia in SLE have been described, including lymphopoiesis impairment, lymphocyte sequestration, antilymphocyte antibodies, increased apoptosis and complement-mediated cytolysis.

All reported cases of SLE and PML are associated with severe lymphopenia. The suggested recommendation is to maintain a total count above 1.0 x 10⁹ cells/L. 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. 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 patients, suggesting a higher prevalence of PML in SLE than previously reported. 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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