Spontaneous Regression of Diffuse Large B-Cell Lymphoma Harbouring Epstein-Barr Virus: A Case Report and Review of the Literature

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We report an elderly patient with diffuse large B cell lymphoma harbouring Epstein-Barr virus that showed spontaneous regressions with subsequent relapses three times. The patient died of aspiration pneumonia without any anti-neoplastic treatment 5 years 10 months after the initial onset of lymph node swelling. In the literature, there are several reports of aggressive non-Hodgkin’s lymphoma cases that showed spontaneous regressions without relapse till the last observation. Over half of the cases were the extra-nodal type. The tendency toward regression of swollen lymph nodes detected by clinicians occurs within 2 weeks after biopsy. If the remaining lymph nodes show a tendency to decrease in size after biopsy without any anti-tumor therapies, the patient may develop spontaneous regression.

Keywords: diffuse large B-cell lymphoma, EB virus associated lymphoma, spontaneous regression

INTRODUCTION

Although spontaneous regression (SR) in patients with low-grade lymphoma has been reported to occur in 5 to 15 percents of patients¹,², aggressive non-Hodgkin’s lymphoma (NHL) cases showing SR are extremely rare³-¹⁶. We report here a case of diffuse large B cell lymphoma (DLBCL) harbouring Epstein-Barr virus (EBV) that showed SR in the absence of any anti-neoplastic treatment. EBV-associated lymphoproliferative disorders (LPDs) without immunodeficiency mainly occurs in elderly patients¹⁷. Recent studies suggested that EBV may be a causative factor for good prognosis of sporadic Burkitt lymphoma with granulomatous reaction¹⁸,¹⁹. Aggressive NHL cases showing SR are reviewed in the literature.

CASE REPORT

An 89-year-old man consulted to our hospital with a swollen left inguinal lymph node (LN) measuring 40 mm in diameter. The swollen LN was slightly tender. Physical examinations did not detect any other swollen LN or hepatosplenomegaly. Laboratory data including hematological and biochemical studies were unremarkable. The initial diagnosis was granulomatous lymphadenitis (GL). Postmorten immunostains of the first biopsy specimens were positive for CD20 and anti-Igκ antibody, but negative for CD3, CD5, CD10 and anti-EBV antibody. The anti-Igλ antibody was also negative. The pathological diagnosis of the first biopsy was corrected from GL to lymphoplasmacytoid lymphoma (Fig. 1). The swollen LN was removed by biopsy and there were no palpable LN for about 34 months (Fig. 2). Two years 10 months later, painful left inguinal and supraclavicular LN swellings were recognized, and measuring 20 x 40 and 40 x 40 mm, respectively. Serum M-protein appeared and the serum γ-globulin level was about 30%. Three years 2 months later, serum γ-globulin level increased to 45%. Extreme elevation of serum IgA (3,800 mg/ml), and normal levels of IgG (950 mg/dl) and IgM (95 mg/dl) were detected. Thrombocytopenia (70,000/µl) was observed. Bone marrow (BM) smears showed an increased percentage of plasma cells (11%) and hypoplastic megakaryocytes without adhesions of platelets. Laboratory data did not show any anemia and there were no abnormal findings on x-ray films of the whole body. Three years 8 months later, M-protein disappeared. Pathological examination of the second biopsy of the left inguinal LN demonstrated DLBCL with severe pleomorphism (Fig. 3). Lymphoma cells did not show a tendency of a differentiation to plasma cells. Immunohistochemical markers of LN cells were positive for CD20, CD30, MUM-1,
Oct-2, Bob-1 and EBV-encoded latent membrane protein-1, and negative for CD3, CD5, CD10, CD15, Bcl-6 and EBV nuclear antigen. RNA in situ hybridization with the EBV-encoded small nuclear early region-1 probe demonstrated that the lymphoma cells harboured EBV. Fifty-five days after the second biopsy, the swollen LNs decreased in size. After another five days, LN swelling disappeared completely. Thereafter, the right and left cervical, and right inguinal LNs became swollen for 2-3 months, then disappeared, respectively. The patient had advanced senile dementia, and aspiration pneumonias occurred repeatedly. Five years 10 months later, he died of severe aspiration pneumonia with disseminated intravascular coagulation syndrome. No anti-tumor agent, including prednisolone, had been administered. During the 31-month course from the initial diagnosis of DLBCL until death, there was an absence of palpable LN swelling for 20 of those months.

**DISCUSSION**

We present a case of DLBCL harbouring EBV and showing SR. Polyclonal or oligoclonal proliferation, but not monoclonal proliferation of EBV-positive large B-cells cannot be excluded, although the diagnosis of DLBCL was made.
The transient appearance of serum M-protein and increase of plasma cells in the BM may have been reactions to EBV infection. The thrombocytopenia probably occurred by the bone marrow suppression due to the viral infection. This infection may have been the cause of histological transformation in NHL in this case.

Cells from the first and second biopsied LNs were examined by polymerase chain reaction (PCR) to detect rearrangement of the same immunoglobulin gene. However, because the second biopsied specimen did not show rearrangement of the immunoglobulin genes, identification of cells from the two biopsied LNs could not be confirmed.

Gatti
er et al.20 reviewed 69 cases of diffuse type NHL retrospectively, and reported that 2 cases (2.9%) showed SR. However, clinicians generally start anti-neoplastic treatment immediately after establishing a pathological diagnosis of malignant lymphoma (ML). Since almost all patients with NHL were treated with irradiation and/or chemotherapies, the actual ratio of SR in NHL remains unclear. Table 1 shows 15 reported cases of SR in aggressive NHL except for the gastric type in patients without any anti-neoplastic treatments till relapse. Several gastric ML cases showing SR have been reported21-23. However, those cases were not included in table 1 because observations of those tumors require endoscopic examinations, and resection of gastric tumors is usually performed as the first therapy. Six of 15 cases (40%) have not shown relapse up to the respective last observation. Eight of 15 cases (53%) involved extra-nodal disease. Extra-nodal onset of lymphoma may be an important factor in SR. The tendency toward regression of tumors detected by clinicians occurs within 2 weeks after biopsy. If the remaining LNs after biopsy show a tendency to decrease in size without any anti-tumor therapies, the patients may show SR. In such cases, it may be a benefit for patients that “watchful waiting” is included in the list of ML therapies.

The leading hypothesis regarding SR in relation to NHL involves modulation of the host immune system to viral or bacterial infection and/or traumatic effects including biopsy7,11,13,23. Indeed, many cases in table 1 indicated that the trigger for reduction in the size of LNs was apparently biopsy alone, except in 2 cases developing measles shortly after diagnostic biopsy6 and our case. Schneider et al. reported regression of EBV-associated LPDs in 2 AIDS patients after therapy with an inhibitor of viral DNA polymerases24. Our patient might have had unstable immunocompetence due to his advanced age of about 90. It is probable that fluctuating increase and decrease of the patient’s immunocompetence affected the remissions and recurrences of DLBCL. In this case, the patient’s anti-tumor immunity which was activated by the EBV probably excluded the EBV infected lymphoma.

### Table 1. Spontaneous regression in aggressive non-Hodgkin’s lymphoma cases without anti-neoplastic treatments

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Location</th>
<th>Pathologic diagnoses</th>
<th>Starting of regression</th>
<th>Complete regression</th>
<th>Period of regression</th>
<th>Relapse</th>
<th>Last condition</th>
<th>EBV</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12/M</td>
<td>Submandibular</td>
<td>SNCML</td>
<td>1 day</td>
<td>ND</td>
<td>3 years</td>
<td>none</td>
<td>CR</td>
<td>Neg</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>67/M</td>
<td>Bone marrow</td>
<td>DLCL</td>
<td>7 days</td>
<td>21 days</td>
<td>16 months</td>
<td>none</td>
<td>CR</td>
<td>Neg</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>30/M</td>
<td>Chest wall</td>
<td>DLCL</td>
<td>8 days</td>
<td>12 days</td>
<td>9 days</td>
<td>present</td>
<td>Dead (AIDS)</td>
<td>ND</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>8/M</td>
<td>Orbita</td>
<td>Burkitt L</td>
<td>10 days</td>
<td>24 days</td>
<td>4 months</td>
<td>none</td>
<td>CR</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>58/F</td>
<td>S-LNs</td>
<td>Imm blast L</td>
<td>11 days</td>
<td>22 days</td>
<td>2 years</td>
<td>none</td>
<td>CR</td>
<td>Neg</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>63/F</td>
<td>Intracranial</td>
<td>DLCL</td>
<td>12 days</td>
<td>66 days</td>
<td>25 days</td>
<td>present</td>
<td>CR</td>
<td>ND</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>68/F</td>
<td>Thyroid gland</td>
<td>DLCL</td>
<td>ND</td>
<td>14 days</td>
<td>4.5 months</td>
<td>present</td>
<td>CR</td>
<td>ND</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>84/F</td>
<td>S-LNs</td>
<td>DLCL</td>
<td>ND</td>
<td>14 days</td>
<td>1.5 months</td>
<td>present</td>
<td>Dead</td>
<td>ND</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>78/M</td>
<td>Gingiva</td>
<td>DLBCL</td>
<td>ND</td>
<td>21 days</td>
<td>3 years</td>
<td>none</td>
<td>CR</td>
<td>ND</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>77/M</td>
<td>Soft palate</td>
<td>LCL</td>
<td>1 month</td>
<td>several weeks</td>
<td>12 months</td>
<td>present</td>
<td>CR</td>
<td>ND</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>54/F</td>
<td>Waldeyer’s ring</td>
<td>DLCL</td>
<td>1 month</td>
<td>8 months</td>
<td>4 years</td>
<td>none</td>
<td>CR</td>
<td>ND</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>54/F</td>
<td>S-LNs</td>
<td>DLBCL</td>
<td>1 month</td>
<td>7 months</td>
<td>3 months</td>
<td>present</td>
<td>Dead (ML)</td>
<td>Neg</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>48/M</td>
<td>Mediastinum</td>
<td>Anaplast T</td>
<td>ND</td>
<td>3 months</td>
<td>10 days</td>
<td>none</td>
<td>Dead (AIDS)</td>
<td>ND</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>82/F</td>
<td>Para-aortic LN</td>
<td>DLCL</td>
<td>ND</td>
<td>4 months</td>
<td>6 months</td>
<td>none</td>
<td>Dead</td>
<td>ND</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>91/M</td>
<td>S-LNs</td>
<td>DLBCL</td>
<td>55 days</td>
<td>60 days</td>
<td>16 months</td>
<td>present</td>
<td>Dead</td>
<td>Pos</td>
<td>Present case</td>
</tr>
</tbody>
</table>

cells, as in the recovery period of infectious mononucleosis. Haralambieva et al. and Schrager et al. indicated that EBV may be a causative factor for good prognosis of sporadic Burkitt lymphoma with granulomatous reaction. Recently, EBV-associated LPD in elderly people has been reported. Aging is another important factor in the oncogenesis of EBV-associated lymphoma.

The existence of these SR cases indicates the possibility of curing aggressive NHL by immunotherapy in the future.

REFERENCES