**Background:** First classified in 2016, high-grade B-cell lymphoma (HGBCL) is a lymphoid neoplasm that is typically seen as an aggressive lymphoproliferative disorder (LPD). In most patients with HGBCL, various oncogene rearrangements present with advanced clinical features, such as central nervous system involvement. Patients with underlying autoimmune and rheumatologic conditions, such as rheumatoid arthritis, are at higher risk for developing LPDs, including highly aggressive subtypes of non-Hodgkin lymphomas such as HGBCL.

**Case Presentation:** We present a case of stage IV double-hit HGBCL with the presence of MYC and BCL6 gene rearrangements in an older veteran with rheumatoid arthritis treated with methotrexate. An excellent sustained response was observed for the patient’s disease within 4 weeks of methotrexate discontinuation. To our knowledge, this is the first reported response to methotrexate discontinuation for a patient with HGBCL.

**Conclusions:** Reducing immunosuppression should be considered in all patients with LPDs associated with autoimmune conditions or immunosuppressive medications, regardless of additional multiagent systemic therapy administration.

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**CASE IN POINT**

**EBER-Negative, Double-Hit High-Grade B-Cell Lymphoma Responding to Methotrexate Discontinuation**

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**CASE PRESENTATION**

A male veteran aged 81 years presented to the Raymond G. Murphy Veterans Affairs Medical Center (RGMVAMC) in Albuquerque, New Mexico, with an unintentional 25-pound weight loss over 18 months. Pertinent history included RA managed with methotrexate 15 mg weekly for 6 years and a previous remote seizure. The patient’s prior prostate cancer was treated with radiation at the time of diagnosis and ongoing androgen deprivation therapy. Initial workup with chest X-ray and chest computed tomography (CT) indicated loculated left pleural fluid collection with a suspected splenic tumor.

A positron-emission tomography (PET)/CT was ordered given his history of prostate cancer, which showed potential splenic and sternal metastases with corresponding fluorodeoxyglucose F18 uptake (Figure 1A). Biopsy was not pursued due to the potential for splenic hemorrhage. Based on the patient’s RA and methotrexate use, the collection of findings was initially thought to represent a non-Hodgkin lymphoma, with knowledge that
metastatic prostate cancer refractory to androgen deprivation therapy was possible. Because he was unable to undergo a splenic biopsy, an observation strategy involving repeat PET/CT every 6 months was started. The surveillance PET/CT 6 months later conveyed worsened disease burden with increased avidity in the manubrium (Figure 1B). The patient’s case was discussed at the RGMVAMC tumor board, and the recommendation was to continue with surveillance follow-up imaging because image-guided biopsy might not definitively yield a diagnosis. Repeat PET/CT 3 months later indicated continued worsening of disease (Figure 1C) with a rapidly enlarging hypermetabolic mass in the manubrium that extended anteriorly into the subcutaneous tissues and encased the bilateral anterior jugular veins. On physical examination, this sternal mass had become painful and was clearly evident. Additionally, increased avidity in multiple upper abdominal and retroperitoneal lymph nodes was observed.

Interventional radiology was consulted to assist with a percutaneous fine-needle aspiration of the manubrial mass, which revealed a dense aggregate of large, atypical lymphocytes confirmed to be of B-cell origin (CD20 and PAX5 positive) (Figure 2). The atypical B cells demonstrated co-expression of BCL6, BCL2, MUM1, and MYC but were negative for CD30 and EBER by in situ hybridization. The overall morphologic and immunophenotypic findings were consistent with a large B-cell lymphoma. Fluorescent in-situ hybridization identified the presence of MYC and BCL6 gene rearrangements, and the mass was consequently best classified as a double-hit HGBCL.

Given the patient’s history of long-term methotrexate use, we thought the HGBCL may have reflected an immunodeficiency-associated LPD, although the immunophenotype was not classic because of the CD30 and EBER negativity. With the known toxicity and poor treatment outcomes of aggressive multiagent chemotherapy...

**FIGURE 1** PET/CT Imaging Demonstrating the Progression and Regression of Disease

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Abbreviation: PET/CT, positron emission tomography/computed tomography. A, Initial PET/CT with fludeoxyglucose F18 uptake along sternum (orange) showed potential splenic and sternal metastases. B, After 6 mo a worsening hypermetabolic manubrial lesion (yellow/orange) is visibly larger. C, After 9 mo a rapidly enlarging hypermetabolic manubrial lesion with encasement of the surrounding structures (white/yellow) can be seen. D, Four wk after methotrexate discontinuation lesion (orange) is visibly reduced.
B-Cell Lymphoma

for patients with double-hit HGBCL—particularly in the older adult population—methotrexate was discontinued on a trial basis.

A PET/CT was completed 4 weeks after methotrexate was discontinued due to concerns about managing an HGBCL without chemotherapy or anti-CD20-directed therapy. The updated PET/CT showed significant improvement with marked reduction in avidity of his manubrial lesion (Figure 1D). Three months after methotrexate discontinuation, the patient remained in partial remission for his double-hit HGBCL, as evidenced by no findings of sternal mass on repeat examinations with continued decrease in hypermetabolic findings on PET/CT. The patient’s RA symptoms rebounded, and rheumatology colleagues prescribed sulfasalazine and periodic steroid tapers to help control his inflammatory arthritis. Fourteen months after discontinuation of methotrexate, the patient died after developing pneumonia, which led to multisystemic organ failure.

DISCUSSION

HGBCL with MYC and BCL2 and/or BCL6 rearrangements is an aggressive LPD.1 A definitive diagnosis requires collection of morphologic and immunophenotypic evaluations of suspicious tissue. Approximately 60% of patients with HGBCL have translocations in MYC and BCL2, 20% have MYC and BCL6 translocations, and the remaining 20% have MYC, BCL2 and BCL6 translocations (triple-hit disease).1

The MYC and BCL gene rearrangements are thought to synergistically drive tumorigenesis, leading to accelerated lymphoma progression and a lesser response to standard multiagent chemotherapy than seen in diffuse large B-cell lymphoma.1-3 Consequently, there have been several attempts to increase treatment efficacy with intense chemotherapy regimens, namely DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), or by adding targeted agents, such as ibrutinib and venetoclax to a standard R-CHOP (rituximab with reduced cyclophosphamide, doxorubicin, vincristine, and prednisone) backbone.4-7 Though the standard choice of therapy for fit patients harboring HGBCL remains controversial, these aggressive regimens at standard doses are typically difficult to tolerate for patients aged > 80 years.

Patients with immunosuppression are at higher risk for developing LPDs, including aggressive B-cell non-Hodgkin lymphomas such as diffuse large B-cell lymphoma. These patients are frequently classified into 2 groups: those with underlying autoimmune conditions (RA-associated LPDs), or those who have undergone solid-organ or allogeneic hematopoietic stem-cell transplants, which drives the development of posttransplant LPDs (Table).8-11 Both types of LPDs are often EBER positive, indicating some association with Epstein-Barr virus infection driven by ongoing immunosuppression, with knowledge that this finding is not absolute and is less frequent among

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**TABLE** Lymphoproliferative Disorder Comparison

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Rheumatoid arthritis-associated</th>
<th>Posttransplant</th>
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<tbody>
<tr>
<td>Common features</td>
<td>Immunosuppressive burden</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncontrolled B-cell proliferation</td>
<td></td>
</tr>
<tr>
<td>Distinct features</td>
<td>History of rheumatoid arthritis</td>
<td>Solid organ or allogeneic hematopoietic stem-cell transplants</td>
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<tr>
<td></td>
<td>History of methotrexate, azathioprine, or cyclosporine use</td>
<td>Usually within 1 y posttransplant (&gt; 85% cases)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Less common (30%-40%)9,10</td>
<td>More common (60%-80%), either primary infection or reactivation9,11</td>
</tr>
<tr>
<td>Treatments</td>
<td>Reduce immunosuppression</td>
<td></td>
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<tr>
<td></td>
<td>Antiviral medication</td>
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<td></td>
<td>Surgery</td>
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<td></td>
<td>Radiation</td>
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<td></td>
<td>Multiagent chemotherapy</td>
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</table>
B-Cell Lymphoma

For indolent and early-stage aggressive LPDs, reduction of immunosuppression is a reasonable frontline treatment. In fact, Tokuyama and colleagues reported a previous case in which an methotrexate-associated EBER-positive early-stage diffuse large B-cell lymphoma responded well to methotrexate withdrawal.13 For advanced, aggressive LPDs associated with immunosuppression, a combination strategy of reducing immunosuppression and initiating a standard multiagent systemic therapy such as with R-CHOP is more common. Reducing immunosuppression without adding systemic anticancer therapy can certainly be considered in patients with EBER-negative LPDs; however, there is less evidence supporting this approach in the literature.

A case series of patients with EBER-positive double-hit HGBCL has been described previously, and response rates were low despite aggressive treatment.14 The current case differs from that case series in 2 ways. First, our patient did not have EBER-positive disease despite having an HGBCL associated with RA and methotrexate use. Second, our patient had a very rapid and excellent partial response simply with methotrexate discontinuation. Aggressive treatment was considered initially; however, given the patient’s age and performance status, reduction of immunosuppression alone was considered the frontline approach.

This case indicates that methotrexate withdrawal may lead to remission in patients with double-hit lymphoma, even without clear signs of Epstein-Barr virus infection being present. We are not sure why our patient with EBER-negative HGBCL responded differently to methotrexate withdrawal than the patients in the aforementioned case series with EBER-positive disease; nevertheless, a short trial of methotrexate withdrawal with repeat imaging 4 to 8 weeks after discontinuation seems reasonable for patients who are older, frail, and seemingly not fit for more aggressive treatment.

CONCLUSIONS

For our older patient with RA and biopsy-proven, stage IV EBER-negative HGBCL bearing MYC and BCL6 rearrangements (double hit), discontinuation of methotrexate led to a rapid and sustained marked response. Reducing immunosuppression should be considered for patients with LPDs associated with autoimmune conditions or immunosuppressive medications, regardless of additional multagent systemic therapy administration. In older patients who are frail with aggressive B-cell lymphomas, a short trial of methotrexate withdrawal with quick interval imaging is a reasonable frontline option, regardless of EBER status.

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Ethics and consent
No informed consent was obtained from the patient; patient identifiers were removed to protect the patient’s identity.

References