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Case Report

Marked Response to Chemoimmunotherapy in a Patient with Follicular Lymphoma of Huge Mesenteric Lymphadenopathy

Chia-Chen Li[1], Shan-Chi Yu[2,3,4], Sung-Hsin Kuo[1,5,6]*

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan
[2]Department of Pathology and Graduate Institute of Pathology, National Taiwan University College of Medicine, Taipei, Taiwan
[3]Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan
[4]Graduate Institute of Microbiology, National Taiwan University College of Medicine, Taipei, Taiwan
[5]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan
[6]Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan

Abstract

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphomas. We present the case of a 57-year-old woman who initially complained of abdominal fullness and unintentional weight loss. A computerized tomography scan disclosed a huge mesenteric mass and confluent lymphadenopathy in the paraaortic area, and the pathological diagnosis of a paraaortic lymph node biopsy showed histological Grade 1–2 FL. She received chemoimmunotherapy, including rituximab plus cyclophosphamide, vincristine, and prednisolone, for Ann Arbor Stage III FL disease accompanied by compression symptoms, and achieved a nearly complete remission after completing eight cycles of chemoimmunotherapy. She is currently receiving maintenance rituximab therapy.

Keywords: Chemoimmunotherapy, follicular lymphoma, huge mesenteric node

Introduction

The epidemiology of non-Hodgkin's lymphomas (NHLs) differs among geographic regions and ethnicities. The leading subtypes of NHLs include diffuse large B-cell lymphoma and follicular lymphoma (FL).[1,2] The incidence and prevalence of FL are higher in Western countries than in Asia.[3] Different primary anatomic sites have been reported to be prognostic in the early stage FLs.[4] Being an indolent disease, 30%–40% of FL patients undergo a high-grade transformation, present with different genetic alterations, and have poor survival outcomes.[5,6] While primary mesenteric neoplasms are relatively rare, FL neoplasms arising elsewhere with either direct invasion or lymphatic extension to the mesentery are more common. Mesentery nodal involvement of lymphomas has been reported.[7] Radiologically, mesenteric lymphoma may present with a hamburger or sandwich sign, also mimicking "thunders in the

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Address for correspondence: Dr. Sung-Hsin Kuo, Department of Oncology, National Taiwan University Hospital, No. 7, Zhongshan South Road, Taipei, Taiwan.
E-mail: shkuo101@ntu.edu.tw

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cloud."[7-11] Owing to its indolent nature, patients with FLs tend to be asymptomatic in the early stage and are subsequently diagnosed with more advanced disease.

In a randomized trial comparing rituximab added to the combination of cyclophosphamide, vincristine, and prednisone (R-CVP) with CVP in previously untreated patients with stage III to IV FLs, Marcus *et al.* showed that R-CVP provided a better overall response rate of 81% (30% with a complete remission [CR], and 11% with CR unconfirmed) compared to 57% for CVP (8% with CR and 3% with CR unconfirmed; $P < 0.001$) and a significantly prolonged median time to progression (32 months vs. 15 months; $P < 0.0001$).[12] In addition, they found that the addition of rituximab did not result in significantly increased toxicities compared to CVP, except for a higher incidence of Grade 3 or 4 neutropenia in the patients with R-CVP compared to those receiving CVP (24% vs. 14%). In addition, the results of a prospective randomized study of the German Low-Grade Lymphoma Study Group conducted by Hiddemann *et al.* demonstrated that rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) provided a better overall response rate (96% vs. 90%; $P = 0.011$) and a longer duration of response ($P = 0.001$) than CHOP for patients with untreated and advanced stage FLs.[13] These findings indicate that the addition of rituximab to the CVP or CHOP regimen can significantly improve the clinical outcomes in patients with previously untreated advanced FLs.

Here, we present a case of advanced-stage FL with huge mesenteric lymphadenopathy and obstruction symptoms who was successfully treated with conventional chemoimmunotherapy.

Case Report

This 57-year-old woman presented with abdominal fullness, poor appetite, and unintentional weight loss of over 3 kg. She had a history of hypertension which was controlled with medication, and she had otherwise been healthy until 1 month before this presentation. There were no changes in bowel habits or stool characteristics. She was initially found to have a huge mass in her left lower quadrant area through a physical examination and abdominal ultrasonography. A computerized tomography (CT) scan in August 2020, revealed a huge mesenteric mass in the left lower pelvic cavity with bowel wall involvement, outsizing the confluent lymphadenopathies from the upper abdomen through bilateral paraaortic areas [Figure 1a and d]. A fair hemogram profile was noted, with a leukocyte count of 7670/μL, hemoglobin level of 12.1 g/dL, and platelet count of 323000/μL. The biochemistry profiles were all within the normal upper limits, including a lactate dehydrogenase (LDH) level of 160 U/L, bilirubin 0.39 mg/dL, alanine aminotransferase 10 U/L, and serum creatinine 0.6 mg/dL. Due to the large tumor burden with an normal LDH level, an indolent lymphoma was suspected. A histopathological examination of the CT-guided biopsy showed Grade 1–2 FL. The atypical lymphoid cells were mostly small cleaved cells, which expressed CD20 and CD10. The representative photographs are shown in Figure 2. A positron emission tomography scan revealed involved lymph nodes above and below the diaphragm, with large mesenteric lymphadenopathy and Deauville score of 5 [Figure 3]. A bone marrow biopsy showed no morphologic evidence of lymphoma involvement. The patient was diagnosed with the WHO Grade 1–2 FL, Ann Arbor Stage III, international prognostic index follicular lymphoma international prognostic index Score 2, and Groupe d'Etude des Lymphomes Folliculaires criteria Score 4. Due to the advanced stage and high tumor burden, we prescribed antineoplastic therapy with a modified R-CVP regimen of rituximab 375 mg/m^2, cyclophosphamide 700 mg/m^2, vincristine 2 mg, and dexamethasone 10 mg/m^2/day for 5 days in September 2020. She tolerated the chemoimmunotherapy well except for an allergic reaction during rituximab treatment, and she achieved a good partial remission after four cycles of modified R-CVP chemotherapy (a follow-up CT scan disclosed markedly smaller lymphomas) [Figure 1b and e]. She also reported subjective relief of the compression symptoms, including softened abdominal tumors, less fullness sensation, and improved appetite. After eight courses of chemoimmunotherapy, she achieved a nearly CR of the lymphomas [Figure 1c and f]. She is currently receiving maintenance therapy with rituximab and has remained symptom-free. Throughout the whole treatment course, no adverse events such as leukopenia, opportunistic infection, or other severe adverse events were noted.

Discussion

FL is the most common subtype of indolent NHLs, and the incidence and prevalence of FLs in Western countries are higher than in Asia.[3] Although around 40% – 50% of patients with NHL present with mesenteric involvement,[7,14] the presence of huge lymphadenopathy is uncommon. Our case initially presented with a bulky abdominal mass, B symptoms, and compression symptoms, and she was diagnosed with advanced-stage FL with a high tumor burden. She underwent conventional chemoimmunotherapy with a reduced dosage considering her fragility and poor nutrition. The entire treatment course was accomplished uneventfully, and she achieved a radiologically nearly complete response despite the initial huge mesenteric lymphadenopathy at diagnosis.

The WHO classification uses a grading system based on centroblast count to grade FLs. Cases with 0–5 centroblasts/high-power fields are classified as Grade 1, 6–15 are classified as Grade 2, and >15 as Grade 3. This grading system has undergone many modifications. For instance, because the prognosis is not different between Grade 1 and Grade 2 patients, low-grade FL cases are recommended to be reported as Grade 1–2 FLs.[15]

Since the introduction of anti-CD20 monoclonal antibodies for patients with FLs,[12,13] it has become the standard of care

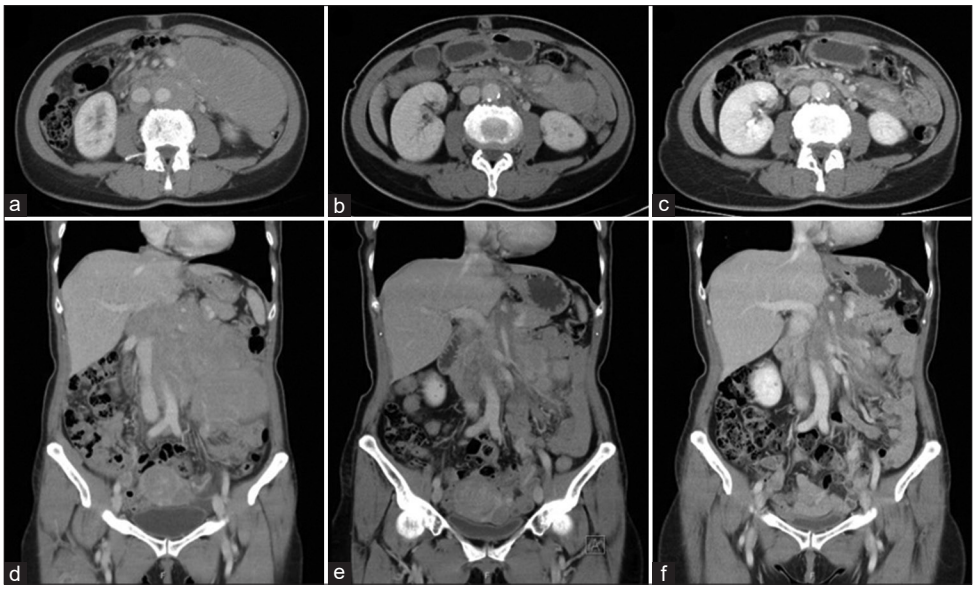

Figure 1: The treatment response of huge mesenteric lymphadenopathy. Serial computerized tomography scans disclosed huge confluent lymphadenopathy over the mesenteric area at baseline (a and d), after 4 cycles of chemoimmunotherapy with a marked response (b and e), and after eight 8 cycles of chemoimmunotherapy with a nearly total remission (c and f)

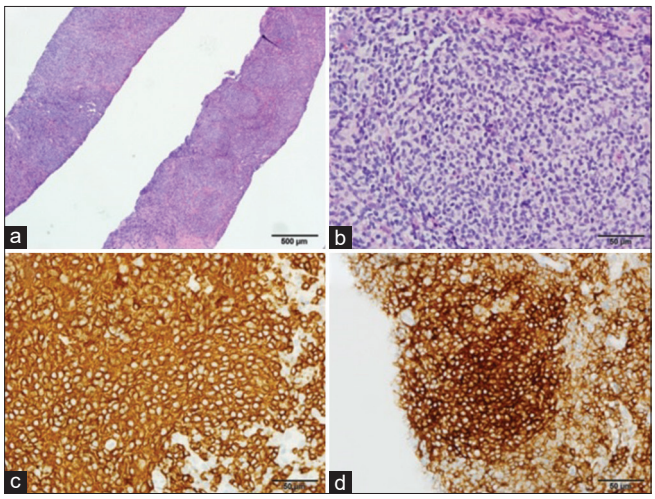

Figure 2: Histopathological features of a paraaortic lymph node. Hematoxylin and eosin stain showed nodular infiltrated of small cleaved atypical lymphoid cells (a and b). These atypical lymphoid cells were positive for CD20 (c) and CD10 in immunohistochemistry (d)

both in combination with backbone chemotherapy regimens, such as CVP, and as maintenance treatment. Maintenance treatment using rituximab alone was demonstrated to prolong progression-free survival (PFS) but not overall survival in patients with indolent lymphoma who received first-line chemotherapy with CVP in the randomized Phase III ECOG1496 study.[16,17] After the introduction of rituximab in a combined chemotherapy regimen, the response rate and clinical outcomes of patients with FL have improved. Along these lines of evidence, the (Primary Rituximab and Maintenance [PRIMA]) study enrolled patients with high tumor burden FL who initially received chemoimmunotherapy (including R-CHOP, R-CVP, or R-fludarabine, cyclophosphamide, and mitoxantrone) and achieved a complete response or partial response, and demonstrated that 2 years of maintenance treatment using rituximab every 8 weeks provided a better median PFS (10.5 years vs. 4.1 years; hazard ratio [HR], 0.61; $P < 0.001$) but no significant improvement in 10-year overall survival (80.1% vs. 79.9%; HR, 1.04; $P = 0.7948$) than those who did not receive rituximab maintenance therapy.[18,19] Importantly, the PRIMA study showed that more than 50% of the patients remained progression-free at 10 years, indicating that maintenance therapy with rituximab altered the relapse behavior of indolent FL. In this study, our case presented with high tumor burden FL and achieved a nearly CR after induction chemoimmunotherapy with R-CVP. She received rituximab maintenance therapy to increase the duration of remission according to the criteria and the encouraging results of the PRIMA study.

The optimization of anti-CD20 monoclonal antibody treatment appears to be a promising treatment option for FLs, such as obinutuzumab, a Type II anti-CD20 humanized monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity. The GALLIUM trial compared obinutuzumab plus chemotherapy with rituximab combined with different chemotherapy backbones, and Marcus *et al.* reported that obinutuzumab-based chemotherapy provided a better 3-year PFS (80% vs. 73%; HR, 0.66; $P = 0.001$) than rituximab-based chemotherapy for patients with FL. However, obinutuzumab resulted in more high-grade adverse effects.[20] Although the GALLIUM trial demonstrated a better 3-year PFS in the obinutuzumab arm than rituximab-based chemotherapy for patients with FLs, rituximab-based chemotherapy may be an appropriate frontline option for patients with FLs who have mild morbidities, because more high-grade adverse effects were observed in patients receiving obinutuzumab. In Taiwan,

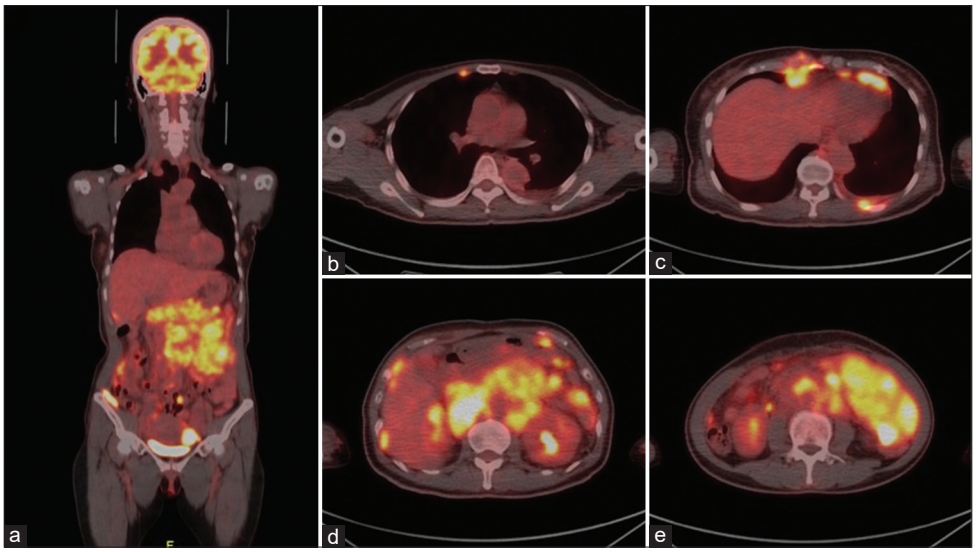

Figure 3: The positron emission tomography scan at diagnosis. There were lesions both above and beneath the diaphragm (a), including chest wall and pleura (b), rib (c), pancreas (d), paraaortic area and mesentery (e)

the National Health Insurance (NHI) system has granted reimbursement of rituximab for patients with previously untreated FLs, while obinutuzumab is only indicated for patients who are refractory or relapse from frontline rituximab-based therapy, as subsequent therapy. Therefore, our case was treated with first-line chemoimmunotherapy with R-CVP based on the higher response rate of R-CVP and reimbursement by the Taiwan NHI system.

The treatment schemes for FLs have evolved since the encouraging results obtained from the GALLIUM (obinutuzumab, trade name Gazyva, for the First-Line Treatment of [FL]), StiL-NHL 1-2003 (bendamustine plus rituximab [RB] vs. CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas, by study group indolent lymphomas), and BRIGHT (bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or mantle cell lymphoma) studies.[20-22] These three trials demonstrated that obinutuzumab or rituximab plus bendamustine provided a better PFS or response rate compared to traditional rituximab-based chemotherapy, such as R-CHOP or R-CVP. For patients with a high tumor burden of FLs, clinical physicians may tend to choose more intense chemoimmunotherapy regimens, such as R-CHOP or rituximab plus bendamustine, resulting in higher response rates despite the indolent disease nature. Our case had a huge tumor burden with a mesenteric mass and confluent paraaortic lymphadenopathy, but a normal LDH level and histology showing Grade 1–2 FL. Although intensive chemoimmunotherapy may have resulted in higher response of the tumor, a rapid response may have caused bowel perforation in our patient due to the huge mesenteric mass with bowel wall involvement. Therefore, she was treated with chemoimmunotherapy using R-CVP and achieved a nearly CR without severe adverse events.

Apart from anti-CD20 monoclonal antibodies, the introduction of bendamustine into the frontline chemotherapy backbone for advanced FL patients with selected risk factors resulted in increased PFS, response rate, and tolerable adverse event profiles compared with conventional chemotherapy regimens in the StiL-NHL 1-2003 and BRIGHT studies.[21,22] Of note, the use of bendamustine has also been associated with a higher risk of opportunistic infections after longer follow-up, especially in the fragile or elderly.[23] From real-world experience at our institute, the treatment scheme for advanced FLs in Taiwan has been largely influenced by the NHI program. Since RB has been granted by the Taiwan NHI as first-line therapy for advanced indolent NHL, the real-world practice has gradually been leaning to RB over other rituximab-based chemotherapies.

Besides the clinical trial results, real-world experience and the patients' preferences should all be taken into consideration when making comprehensive treatment plans. The modification of conventional regimens may provide efficacious treatment with less toxic effects for patients with potential morbidities and poor nutritional status. We hope our experience will highlight that this "wax and wane" disease may require more individualized treatment strategies.

Ethical approval and declaration of patient consent

This study was approved by the IRB of National Taiwan University Hospital (IRB approval project number: 202107104W). The patient informed consent was waived by the IRB.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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