

## Symptomatic Follicular Lymphoma: Complete Remission After Chemoimmunotherapy with Bendamustine–Rituximab

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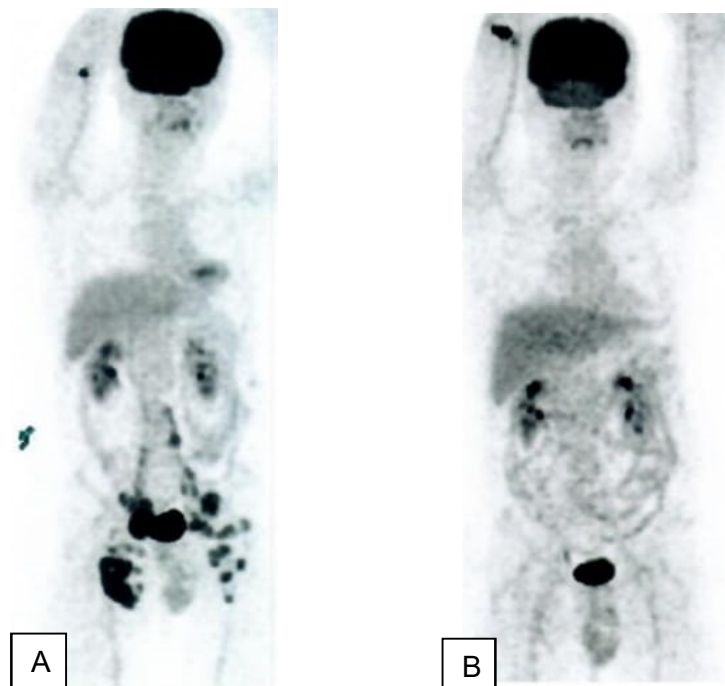
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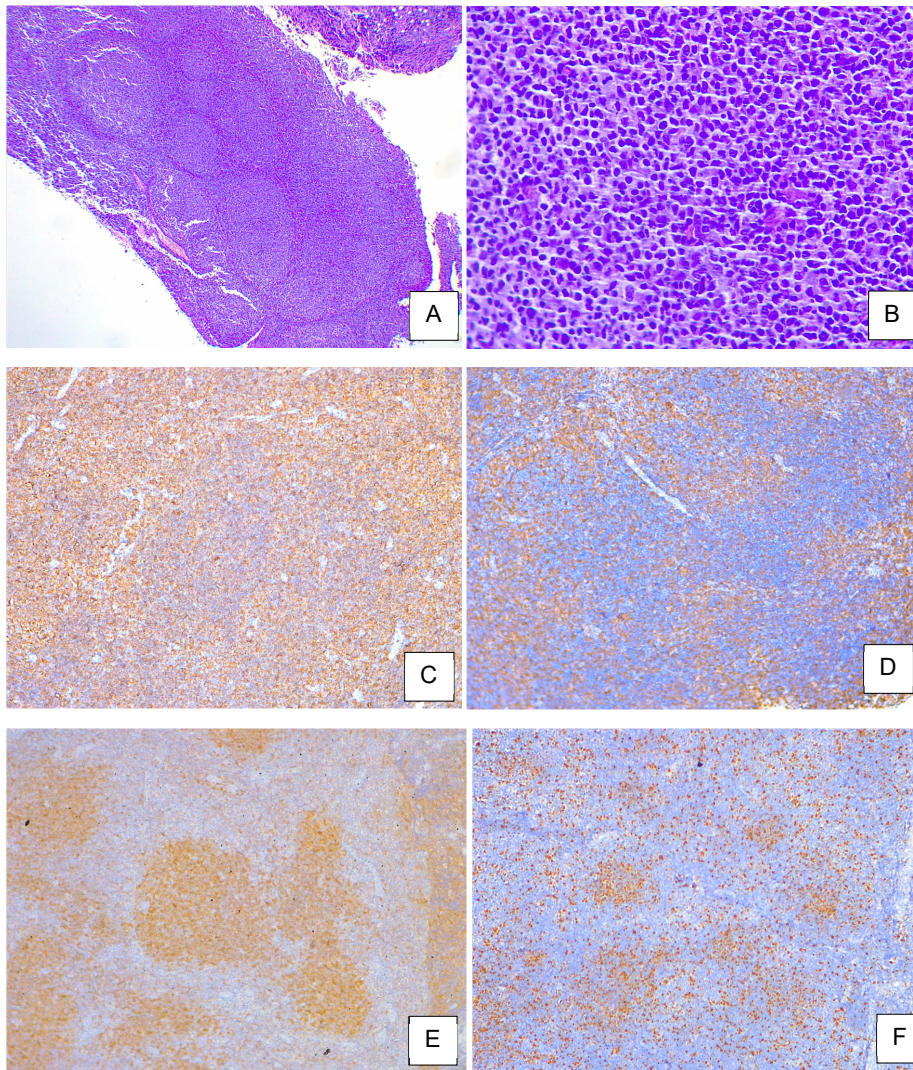
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**Figure 1.** A. Pretreatment FDG/PET CT on March 18<sup>th</sup>, 2023 showed enlarged hypermetabolic lymph nodes in the paraaortic (SUV 4.58), left iliac communis (SUV 5.58), presacral bilateral (SUV 4.29 and 4.20), conglomerated lymph nodes in the internal and external iliac (SUV 27.5 and 29.44), and bulky multiple lymph nodes in the right and left inguinal (SUV 8.83 and 5.97). B. Follow-up post-treatment FDG/PET CT on September 18<sup>th</sup>, 2023 showed complete remission of the disease.



**Figure 2.** A. Hematoxylin–eosin staining showing tumors arranged in a follicular pattern (40×). B. Tumors consisted mostly of centrocytes (400×). C. Immunohistochemistry staining showing CD20 positive (100×). D. CD3 was negative (100×). E. CD10 positive in the follicular area and spilled out to the interfollicular area (100×). F. Ki67 proliferation index was low (100×).

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma in Western countries after diffuse large B-cell lymphoma. However, the incidence of FL in Asia is low. The relative proportion reported in North America and Western Europe is 20%–33%; however, the relative frequency of FL has been reported to be approximately 10% in Asian countries.<sup>1</sup> Most patients with FL present with asymptomatic disease. When symptomatic, the clinical presentation is dominated by lymphadenopathy. The general “B” symptoms (recurrent fever  $>38^{\circ}\text{C}$ , drenching sweats, and weight loss  $>10\%$ ) associated with lymphoma only occur in approximately 20% of patients and should raise

the suspicion of histological transformation.<sup>2</sup> Survival rates have been rising over time mainly due to advancing therapeutic strategies. The advanced-stage disease is virtually incurable, but many treatment options are available with good results. In the first line, treatment is mostly based on chemotherapy combined with rituximab.<sup>3</sup> Herein, we report a case of a patient with FL who achieved complete remission after chemoimmunotherapy.

A 51-year-old male with a history of well-controlled diabetes mellitus treated with insulin presented to the outpatient clinic of hematology-medical oncology with worsening right inguinal lymphadenopathy for  $>3$  months.

He had no complaints of prolonged fever, night sweats, or weight loss. Initial physical examination revealed a healthy male with bulky right inguinal lymphadenopathy. The patient was then referred to a surgeon, and an excisional biopsy of the enlarged right inguinal lymph nodes was performed. The results of histopathology and immunohistochemistry from the specimen showed lymph nodes arranged in a follicular pattern with some centroblasts. Immunohistochemical staining showed that CD20, BCL 6, and CD10 were positive. The tumor was negative for CD5, cyclin D1, and CD23, compatible with low-grade FL.

FDG PET/CT showed enlarged hypermetabolic lymph nodes in the paraaortic (SUV 4.58), left iliac communis (SUV 5.58), presacral bilateral (SUV 4.29 and 4.20), conglomerated lymph nodes in the internal and external iliac (SUV 27.5 and 29.44), and bulky multiple lymph nodes in the right and left inguinal (SUV 8.83 and 5.97).

Therefore, stage II bulky symptomatic low-grade FL was established. We administered chemoimmunotherapy with rituximab and bendamustine every 3 weeks for six cycles. The patient tolerated the treatment well and completed six cycles of chemoimmunotherapy, and the follow-up FDG PET/CT showed complete remission of the disease.

FL is a nodal B lymphoid malignancy that originates from the germinal center of a lymph node.<sup>4</sup> The incidence rate of FL from 2000 to 2016 was 3.5 per 100,000, which was 1.2 times higher in men than in women. Compared with Western countries, FL accounted for a higher percentage of non-Hodgkin lymphoma (NHL) than Asia.<sup>5</sup> Although rare in Asia, evidence is accumulating that the FL incidence rate has been increasing in certain Asian countries. The proportion of FLs in Japan increased from 18.3% in 2000–2006 to 22.4% in 2007–2014.<sup>6</sup>

The diagnosis of FL should be based on surgical excisional lymph node biopsy, as performed on this patient. Diagnosing using fine-needle aspiration would not be adequate for a valid diagnosis. Even a core biopsy is only indicated for patients without an approachable lymph node.<sup>7</sup> The results of histopathology

and immunohistochemistry from the specimen showed CD20 and CD10 low-grade FL.

To determine the appropriate FL therapy, initial staging of the disease and risk assessment should be thoroughly performed. FDG PET/CT is recommended for routine staging and is a mandatory diagnostic modality for localized stage I/II disease before involved-site radiotherapy (ISRT). FDG PET/CT in this patient showed enlarged hypermetabolic lymph nodes in a few regions (paraaortic, left iliac communis, presacral bilateral, conglomerated lymph nodes in the internal and external iliac, and bulky multiple lymph nodes in the right and left inguinal); hence, the patient had stage II bulky symptomatic disease.

Treatment for FL is based on the advancement of the disease by staging and should be initiated upon the development of symptoms. This patient had stage II bulky symptomatic disease FL and was treated with chemoimmunotherapy using bendamustine–rituximab (BR) every 3 weeks for six cycles. This regimen was chosen because it prolonged progression-free survival and had less toxic effects compared with rituximab and cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (R–CHOP), as shown in the Study Group Indolent Lymphomas trial.<sup>8</sup> The BRIGHT 5-year follow-up study also concluded that BR demonstrated better long-term disease control than R–CHOP/R–CVP for patients with indolent lymphoma, including FL.<sup>9</sup>

Future assessment is still required for this patient to ensure the remission status of the lymphoma. To promptly identify unfavorable early recurrences, routine follow-up examinations should be performed every 3 months in the first 2 years after the end of therapy and every 6 months from the 3<sup>rd</sup> year.<sup>10,11</sup>

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