Systemic Abscopal Effect of Low-dose Radiotherapy (2 Gy × 2) against Palatine Tonsil Follicular Lymphoma

Kazuto Togitani¹, Tadashi Asagiri², Mitsuko Iguchi¹, Takuro Igawa⁴, Tadashi Yoshino⁴ and Kensuke Kojima¹

Abstract:
A 52-year-old man presented with palatine tonsillar swelling caused by follicular lymphoma. His tumor burden was low, but exacerbation of snoring and dysphagia was observed. Considering the first wave of coronavirus disease 2019 (COVID-19) pandemic, he received palliative 4-Gy irradiation to the tonsils in 2 fractions, which induced partial regression of tonsillar swellings and eradication of the circulating lymphoma cells. We suggest that low-dose radiotherapy triggered an abscopal effect of lymphoma, which allowed the patient time to receive COVID-19 vaccination before starting immunosuppressive chemo-immunotherapy.

Key words: low-dose radiotherapy, abscopal effect, CD5, follicular lymphoma

(intern med 61: 3107-3110, 2022)
DOI: 10.2169/internalmedicine.8968-21)

Introduction

Follicular lymphoma (FL) is the most common indolent B cell lymphoma. Although more than 90% of patients have advanced-stage disease at the diagnosis, most FL patients do not require immediate treatment unless they have symptomatic disease. At the time of treatment indication, rituximab-containing chemoimmunotherapy is usually recommended (1). However, therapy-induced impaired immunity can render patients vulnerable to infections, especially during the coronavirus disease 2019 (COVID-19) pandemic (2). As indolent B cell lymphoma, including FL, is extremely responsive to radiation therapy, there has been a recent trend in treating indolent lymphomas with low-dose radiotherapy of 4 Gy (2 Gy ×2) (3, 4).

Distant effects of radiotherapy at non-irradiated sites were reported anecdotally before the development of imaging equipment and were known as ‘abscopal effects’ (5, 6). The term ‘abscopal’ is derived from the Latin ‘ab’ for ‘away from’ and ‘scopus’ for ‘target’. Recently, the increased utilization of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has revealed the more frequent occurrence of abscopal regression, especially in FL (7), which has been recognized as an immunogenic tumor (5).

We herein report a case of palatine tonsil CD5+, CD10-, MUM1-, Ki-67™ FL treated with low-dose radiotherapy that showed not only effective local control but also distant circulating lymphoma cell clearance. Since CD5+, CD10-, MUM1-, Ki-67™ FL is rarely reported, we also discuss the characteristics of this unusual subtype of FL.

Case Report

In July 2020, a 52-year-old man was referred to us presenting with cough, snoring, and dysphagia. A physical examination revealed bilateral tonsillar enlargement. A blood count showed a normal hemoglobin (15.3 g/dL) level and platelet count (234×10⁹/L) and mild leukocytosis (11.9×10⁹/L) with 25% abnormal large lymphocytes (Fig. 1) and an immunophenotype of CD5+, CD10-, CD11c-, CD19+, CD20+, CD23-, CD25+, Igk+, CD200+, and ROR1-. A tonsillar biopsy revealed nodular proliferation of large lymphoid cells. Immunohistochemistry results indicated that the tumor cells were CD3-, CD5+, CD10-, CD20+, CD20+, BCL2+, BCL6+, MUM1-, cyclinD1-, SOX11-, and

¹Department of Hematology, Kochi Medical School, Kochi University, Japan, ²Department of Laboratory Medicine, Kochi Medical School Hospital, Kochi University, Japan, ³Department of Pathology, Kochi Medical School, Kochi University, Japan and ⁴Department of Pathology, Okayama University Graduate School, Japan
Received: November 8, 2021; Accepted: December 17, 2021; Advance Publication by J-STAGE: March 19, 2022
Correspondence to Dr. Kazuto Togitani, togitani@kochi-u.ac.jp
Peripheral blood smear showed circulating lymphoma cells.

A biopsy specimen of the tonsil showed follicle-like architecture with lymphoma infiltration. The cells were positive for CD20, BCL2, CD5, and LEF1; Ki-67<sup>+</sup> and negative for CD10 and MUM1. CD21-positive follicular dendritic meshworks were observed in follicular areas. HE: Hema-toxylin and Eosin staining

"Discussion"

We diagnosed this case as FL based on the finding of a
follicular growth pattern, comprising CD20-positive monoclonal B cells, despite an atypical immunophenotype and cytogenetics, including CD5+ CD10- immunophenotype, and the absence of t(14;18)(q32;q21). CD5-positive FL has been reported in several case reports (8-10). LEF1, a widely used marker for chronic lymphocytic leukemia/small lymphocytic lymphoma, was positive in our case. Interestingly, LEF1 has been reported to be positive in some patients with CD5+ FLs (11, 12). A large-scale series from MD Anderson Cancer Center revealed a 2.7% (88/3,286) incidence of CD5+ FL (9). In these previously reported cases of CD5+ FL, the characteristics included male predominance, Grade 3 histology, leukemic manifestation, expression of CD25, and absence of t(14;18)(q32;q21) (8-10), all of which were seen in our case. However, in contrast to these previous studies, our case was CD10-, MUM1-, and Ki-67 high, representing low-grade FL (13) despite a Grade 3 morphology. These clinical low-grade features may have afforded our patient time to achieve local and abscopal regression.

FL is extremely susceptible to radiation therapy, low-dose radiotherapy (2 Gy ×2) can be used for the palliation of patients who have symptoms related to a single disease site, with 57% Complete remission (CR) rates and an 82% overall response rate (ORR) (14). Due to concerns regarding immunosuppression during the COVID-19 pandemic, we used palliative low-dose radiotherapy (2 Gy ×2) for his symptomatic tonsillar disease. Although the response is not usually sustained, low-dose radiotherapy has been reported to have a high local control rate with few toxicities (15). There has been a recent trend in treating indolent lymphomas with low-dose radiotherapy because of the high radiosensitivity and tolerability (3, 4).

Abscopal regression of malignancy including FL after localized radiation therapy is defined as the disappearance or a reduction in the volume of neoplastic lesions located outside the irradiated volume in the absence of any other anticancer treatment (5, 6). In the instance of splenic irradiation for chronic leukemia, the abscopal effect in systemic bone marrow and blood smears may be explained by the direct radiation effect on circulating neoplastic cells passing through the irradiated spleen (6). Although this case seems consistent with circulating leukemic reduction after splenic irradiation, the long-lasting gradual reduction in circulating lymphocytes likely indicates the distant effects of radiation therapy rather than direct radiation damage to lymphoma cells passing through the tonsils during radiation, as radiation-induced direct cell killing occurs within hours or days and does not last for months (16, 17). In addition, tumor antigens or cytokines released from the irradiated tonsils may have elicited an anti-lymphoma immune response lasting for months (18-20). Finally, we cannot exclude the possibility that the circulating lymphoma clearance seen in our case represented coincidental spontaneous regression, as spontaneous regression occasionally occurs in FL (7, 21, 22).

Since hemato-oncology patients have been reported to have not only an increased risk of mortality from COVID-19 but also a diminished vaccine response (2, 23), low-dose radiotherapy may be an acceptable treatment choice to afford time for a patient to generate a response to COVID-19 vaccination.

A written informed consent was obtained from the patient for the publication.

Author’s disclosure of potential Conflicts of Interest (COI).
Kensuke Kojima: Research funding, Eisai, Daiichi-Sankyo, Kyowa-Kirin, Otsuka Pharmaceutical and Asahi Kasei; Honoraria, Janssen Pharmaceutical, AstraZeneca and AbbVie.
References

1. Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. Am J Hematol 95: 316-327, 2020.
2. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King’s College Hospital experience. Br J Haematol 190: e279-e282, 2020.
3. Cerrato M, Orlandi E, Vella A, et al. Efficacy of low-dose radiotherapy (2 Gy x2) in the treatment of marginal zone and mucosa-associated lymphoid tissue lymphomas. Br J Radiol 94: 20210012, 2021.
4. Saleh K, Michot JM, Schembri A, et al. Repeated courses of low-dose 2x2 Gy radiation therapy in patients with indolent B-cell non-Hodgkin lymphomas. Cancer Med 9: 3725-3732, 2020.
5. Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: a clinical review for the radiobiologist. Cancer Lett 356: 82-90, 2015.
6. Miyoshi H, Sato K, Yoshida M, et al. CD5-positive follicular lymphoma characterized by CD25, MUM1, low frequency of t(14;18) and poor prognosis. Pathol Int 64: 95-103, 2014.
7. Patil N, Durkin L, Bodo J, Hsi ED. Immunohistochemical expression of lymphoid enhancer binding factor 1 in CD5-positive marginal zone, lymphoplasmacytic, and follicular lymphomas. Am J Clin Pathol 153: 646-655, 2020.