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Abscopal Effect Following Orbital Radiotherapy in Refractory Diffuse Large B-Cell Lymphoma with Disseminated Cutaneous Relapse

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ABSTRACT

The abscopal effect refers to the regression of tumor lesions outside the irradiated field following localized radiotherapy and is thought to be mediated by systemic immune activation. Although increasingly reported in solid tumors, it remains rarely described in aggressive lymphomas. We report the case of a 72-year-old man diagnosed with advanced-stage diffuse large B-cell lymphoma (DLBCL). After achieving complete metabolic remission following first-line immunochemotherapy with R-mini-CHOP followed by R-CHOP, the patient experienced early systemic relapse with widespread cutaneous and subcutaneous lesions. Multiple salvage therapies, including R-GemOx, R-DHAOx, and lenalidomide plus rituximab, resulted in only transient responses with rapid disease progression. During this period, the patient developed right-sided ptosis, and imaging revealed an intra-orbital lymphomatous mass. Localized orbital radiotherapy was administered with palliative intent. Following irradiation, rapid regression of orbital symptoms was observed. Unexpectedly, a simultaneous and significant regression of diffuse cutaneous and subcutaneous lesions located outside the irradiated field also occurred, suggesting an abscopal effect. This case highlights the potential systemic immunomodulatory role of radiotherapy in lymphoma and underscores the need for further research exploring its therapeutic implications in relapsed or refractory DLBCL.

KEYWORDS

Diffuse large B-cell lymphoma, refractory lymphoma, Abscopal effect, Radiotherapy, Cutaneous involvement.

MAIN ARTICLE

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin lymphoma and is typically treated with immunochemotherapy. Radiotherapy is frequently used for local disease control, either as consolidation therapy in selected cases or for palliation of symptomatic extranodal involvement.

The abscopal effect, first described by Mole in 1953, refers to the regression of distant tumor lesions following localized irradiation. This phenomenon is thought to be mediated by systemic immune activation triggered by radiation-induced tumor antigen release and immune stimulation. While increasingly reported in solid malignancies—especially in combination with immunotherapies—abscopal responses remain rare in lymphomas.

Here, we report a case of refractory DLBCL with disseminated cutaneous involvement in which localized orbital radiotherapy was followed by rapid regression of widespread non-irradiated lesions, consistent with a possible abscopal effect.

CASE PRESENTATION

A 72-year-old man, a former heavy smoker, with no significant past medical history and no known hematologic disorder, was referred to our hematology department for the management of a newly diagnosed diffuse large B-cell lymphoma (DLBCL).

He initially presented with a one-month history of epigastric pain. Gastroenterological assessment revealed clinical and radiological tumor syndrome. He reported no B symptoms, including fever, night sweats, or weight loss, and denied pruritus or infectious manifestations. His general condition was preserved (ECOG/WHO performance status 1).

Physical examination identified multiple peripheral lymphadenopathies, including a left cervical lymph node measuring 4 cm, a right submental lymph node of 2 cm, and bilateral inguinal lymphadenopathies up to 2 cm. A large, painless, mobile median abdominal mass of approximately 15 cm was also palpable. There was no clinical hepatomegaly or splenomegaly. Neurological and dermatological examinations were unremarkable at diagnosis.

An ultrasound-guided biopsy of a right inguinal lymph node was performed. Histopathological evaluation with immunohistochemistry confirmed DLBCL, with tumor cells expressing CD20,

CD3, and MUM1 and showing a high proliferative index (Ki-67 approximately 85%), while CD10 expression was negative.

Baseline 18F-FDG PET/CT revealed extensive hypermetabolic lymphomatous involvement (Figure 1), with supra- and infra-diaphragmatic lymphadenopathies involving the coeliomesenteric, para-aortic, and pelvic regions, with partial nodal confluence. Splenomegaly measuring 15 cm was also noted, associated with infiltration of the intraperitoneal fat and minimal ascites.

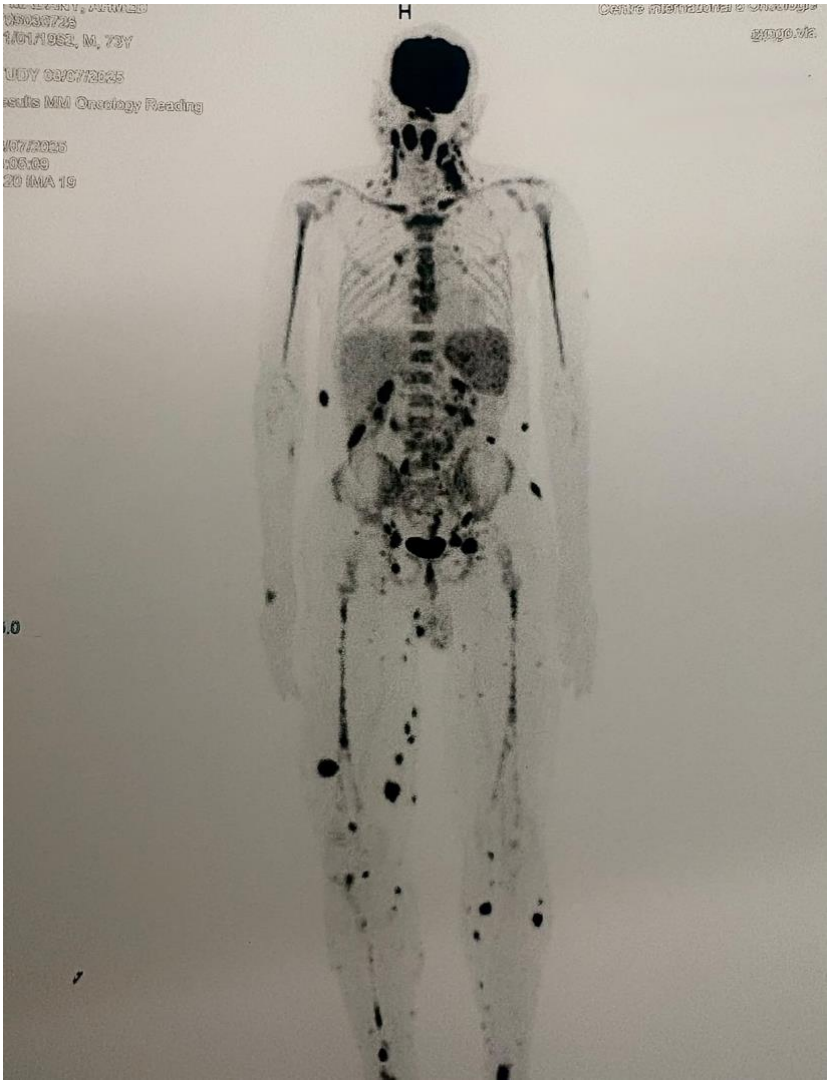

Figure 1.Baseline FDG PET/CT at diagnosis showing diffuse hypermetabolic lymphomatous involvement.

Baseline 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) revealed intense hypermetabolic activity within diffuse nodal conglomerates involving nearly all nodal stations above and below the diaphragm (SUVmax 3.1–13.2), diffuse splenic uptake suggestive of involvement, suspected gastric infiltration, multiple

hypermetabolic epiploic and mesenteric nodules, and diffuse bone marrow uptake. Bone marrow biopsy showed no lymphomatous infiltration.

The disease was staged as Ann Arbor stage IV, with an International Prognostic Index (IPI) score of 4, consistent with high-risk disease.

First-line therapy consisted of immunochemotherapy with R-mini-CHOP followed by standard-dose R-CHOP, for a total of six cycles. Treatment was overall well tolerated, except for transient episodes of uncomplicated chemotherapy-induced neutropenia. Interim PET/CT after four cycles demonstrated complete metabolic response, which was confirmed at the end of treatment.

Six months after completion of first-line therapy, the patient developed multiple painless subcutaneous nodules. Skin biopsy confirmed cutaneous relapse of DLBCL. PET/CT demonstrated early systemic relapse with widespread cutaneous and subcutaneous lesions, extensive nodal disease, diffuse osseous involvement, and bilateral testicular hypermetabolism.

Salvage therapy with R-GemOx yielded partial and transient improvement. The patient subsequently received R-DHAOx for five cycles, achieving initial tumor control. However, rapid disease progression was characterized by multiple cutaneous and subcutaneous lesions (Figure 2).

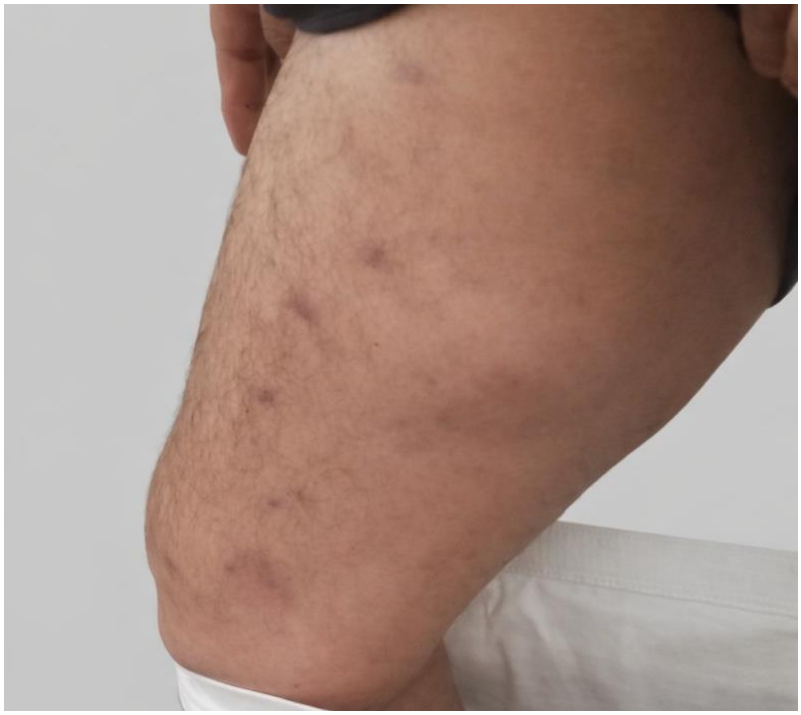

Figure 2. Multiple cutaneous and subcutaneous lesions during systemic relapse of diffuse large B-cell lymphoma.

Repeat biopsy confirmed persistent DLBCL. Treatment with lenalidomide plus rituximab was initiated, but after two cycles the patient developed marked progression of cutaneous disease with extensive lesions involving the trunk, back, buttocks, and both lower limbs.

During this period, the patient developed right-sided ptosis. Orbito-cerebral CT revealed a right intra-orbital mass consistent with lymphomatous involvement(Figure 3). In the context of symptomatic orbital disease, localized orbital radiotherapy was administered with palliative intent.

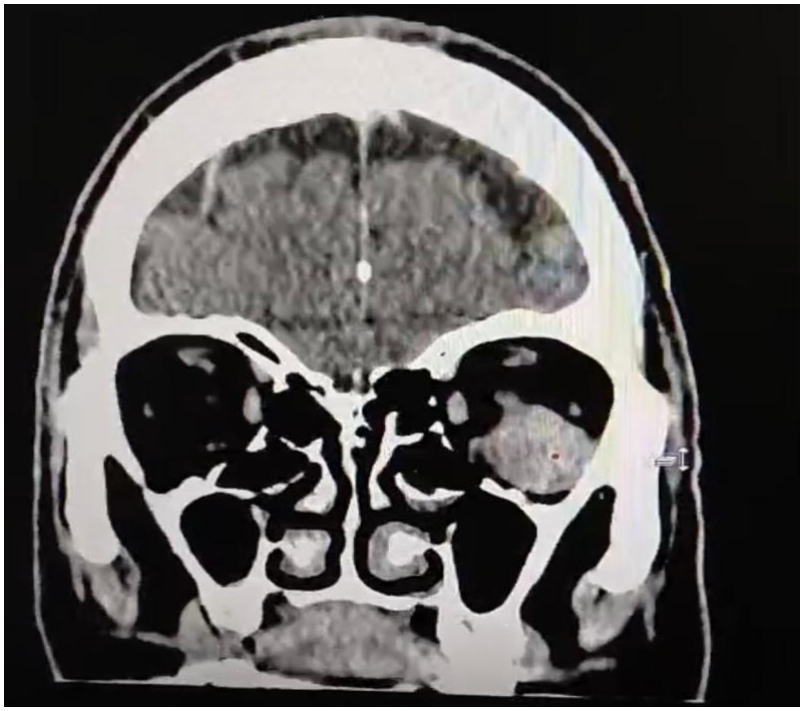

Figure 3.Coronal orbito-cerebral CT Demonstrating retrobulbar mass consistent with orbital lymphomatous involvement

Following irradiation, a rapid regression of orbital symptoms was observed. Unexpectedly, a concomitant and significant regression of diffuse cutaneous and subcutaneous lesions was also noted, including lesions located outside the irradiated field.

DISCUSSION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell non-Hodgkin lymphoma characterized by high chemosensitivity and significant radiosensitivity. Radiotherapy (RT) is widely used for local disease control or for palliation in cases of symptomatic extranodal involvement [1].

The abscopal effect, first described by Mole in 1953, refers to the regression of tumor lesions outside the irradiated field following localized radiotherapy [2]. Although this phenomenon was initially considered anecdotal, increasing evidence suggests that it is mediated by systemic immune activation triggered by radiation-induced tumor cell death [3,4].

Radiotherapy can induce immunogenic cell death, resulting in the release of tumor-associated antigens, inflammatory cytokines, and damage-associated molecular patterns (DAMPs), which can stimulate dendritic cell activation and promote systemic antitumor immune responses [3,5].

Through this mechanism, localized irradiation may function as an in-situ vaccine, enhancing T-cell–mediated antitumor immunity against distant tumor sites [6].

While the abscopal effect has been increasingly described in solid malignancies, particularly in combination with immune checkpoint inhibitors [4,6], it has only rarely been reported in hematologic malignancies. A limited number of clinical observations have described systemic tumor regression following localized radiotherapy in lymphoma patients [7].

In the present case, orbital radiotherapy was administered with palliative intent for symptomatic orbital involvement. Although regression of the orbital mass was expected, the simultaneous regression of multiple cutaneous and subcutaneous lesions outside the irradiated field was unexpected. The close temporal association between radiotherapy and systemic tumor regression strongly suggests an immune-mediated abscopal effect.

Cutaneous involvement in DLBCL generally reflects advanced-stage disease and is associated with poor prognosis. Orbital involvement represents an uncommon extranodal localization that may lead to visual impairment and therefore requires prompt local management [1].

Spontaneous regression of refractory DLBCL is extremely rare, and delayed responses to previously administered systemic therapies are unlikely in the setting of rapidly progressive disease. Therefore, the observed systemic tumor regression is most plausibly explained by a radiation-induced immune response consistent with the abscopal effect.

This observation highlights the potential role of radiotherapy not only as a local treatment modality but also as a systemic immune modulator in selected patients with relapsed or refractory lymphoma. Recent research suggests that combining radiotherapy with immunotherapy may enhance the likelihood of inducing clinically significant abscopal responses [6,8].

Nevertheless, the abscopal effect remains unpredictable and cannot currently be considered a therapeutic objective in routine clinical practice. Further studies are required to better understand the biological mechanisms underlying this phenomenon and to determine how radiotherapy might be optimally integrated with emerging immunotherapeutic strategies [8].

CONCLUSION

We report a rare case of systemic tumor regression following localized orbital radiotherapy in a patient with refractory DLBCL and extensive cutaneous involvement. The rapid improvement of non-irradiated lesions suggests the occurrence of an abscopal effect.

Although exceptional in aggressive lymphomas, this observation supports the hypothesis that radiotherapy may exert systemic immunomodulatory effects beyond local tumor control and highlights the need for further research exploring its potential therapeutic implications in relapsed or refractory DLBCL.

ACKNOWLEDGEMENTS

The authors declare no conflicts of interest.

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