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CASE REPORT

Low-dose radiotherapy for extranodal marginal zone B lymphoma of the lip: Case report and literature review

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Abstract
Non-Hodgkin lymphoma (NHL) of the lip is extremely rare. It is usually indolent and in early stages a local approach is often indicated. We present a case report of a patient with extranodal NHL of the lip treated with chemotherapy and low-dose radiation treatment (RT). The patient was affected by B-cell NHL of the marginal zone, Stage IAE. After a few months of observation with this progressive disease, the patient was submitted to two cycles of chemotherapy with no response. Therefore, he was treated with very low-dose RT consisting of two fractions of 2 Gy. Complete response was observed and after 1-year follow-up, persistent complete response was recorded. In cases of localized disease, especially in patients with comorbidities of poor performance status (PS), low-dose RT can be an appropriate approach with excellent outcomes in terms of effectiveness and low risk of toxicity.

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Introduction

Non-Hodgkin lymphoma (NHL) is very rare heterogeneous group of lymphoproliferative disorders originating from B-cells, T-cells, or natural-killer cells. According to estimates of the Italian Association of Tumor Registers (AIRTUM), every year in Italy ~5,600 and 4,600 new cases of NHL are diagnosed among men and women, respectively, while the deaths caused by this cancer approach 2,500 patients (equally divided between the two sexes). NHL develops mostly in people between 50 and 60 years old and occurs more frequently in males than females [1]. Furthermore, the incidence of NHL has increased in the past decade, probably attributable to human immunodeficiency virus or Borrelia virus and to antirejection drug therapy in patients who have undergone organ transplantation [2]. Immunosenescence is also considered as a potential mechanism of lymphoma etiology.

Marginal zone lymphoma (MZL) is a group of indolent B-cell malignancies which are thought to originate from B-lymphocytes that are normally present in the marginal zone of lymphoid follicles of lymph nodes, mucosal lymphoid tissues, and spleen [3]. This lymphoproliferative disorder accounts for ~5–17% of all NHL cases in adults [4]. According to the World Health Organization classification systems, MZL includes three subtypes depending on the site of lymphoma involvement: extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), splenic MZL, and nodal MZL [5]. Furthermore, the neoplastic elements share a similar immunophenotype: positivity for B-cell markers CD19, CD20, and CD22, and negative for CD5 and CD10 [6].

The most common sites of manifestation of nongastric MALT lymphomas are the salivary glands, thyroid, upper airways, lung, ocular adnexa, breast, liver, urothelial system, skin, dura, and other soft tissues. The development of this neoplasm in the head and neck region, except for the salivary glands, is very rare.

Besides a common cell of origin and some similarities among them, the clinical presentation is very different, with symptoms related to lymphoma location. MALT and splenic MZL present an indolent disease and are associated with long survival. Nodal MZL is a more aggressive disease and patients have a shorter disease-free survival [7]. Indeed, in patients with nodal MZL peripheral lymphoadenopathy is present in nearly all cases (95%); thoracic or abdominal lymph nodes may also be involved in ~50% of cases. Advanced-stage disease is observed in approximately two-thirds of newly diagnosed patients with nodal MZL [8].

The optimal approach for the three subtypes has yet to be defined; treatment options for MZLs are driven by the site of involvement, stage, and related symptoms. Given the frequently limited stage at presentation, antimicrobial therapy or local approaches, such as radiation therapy (RT), have been the mainstay of treatment; however, there are also systemic regimens available with excellent safety and efficacy profiles [9].

Here, we describe a rare case of MZL arising on the superior and inferior lip, treated with chemotherapy and subsequently very low-dose RT.

Case report

In May 2016, an 82-year-old man was referred to our hematological multidisciplinary team for persistent swelling of the lower lip in the previous few months. After a thorough examination, biopsy of the lip was performed. Immunohistochemical reactions showed diffuse infiltration of fibromuscular fragment by CD20+ small lymphocytes CD10− and CD5−, with small accompanying CD3+ and CD5+ lymphocytes, and Ki-67 value of 5% (Fig. 1). Morphological and phenotypic characteristics led to the diagnosis of B-cell NHL of the marginal zone. B symptoms were absent. Staging workup with computed tomography (CT) total body scan did not reveal any other site of disease. Complete blood cell (CBC) was normal. Bone marrow biopsy was not performed. The patient had stage IA E disease. At the beginning, no indication for cytoreductive therapy was given. A few months after diagnosis, clinical examination was again performed with evidence of progressive disease and a new small lesion of the lower and upper lip, respectively.

In September 2016, the patient received chemotherapy with 10 mg chlorambucil and 50 mg prednisone per day for 4 days. At diagnosis, the patient was not eligible for conventional treatment with rituximab and chlorambucil but with chlorambucil and prednisone, as he had received a recent diagnosis of prostate cancer treated with hormone deprivation with LH-RH analogous.

Despite the treatment with chlorambucil being well conducted, the patient had a progression of local disease that required a modification of the treatment. Therefore, many comorbidities radiotherapy were considered.

In November, the patient was submitted to a second course of chemotherapy which consisted of 10 mg chlorambucil and 25 mg prednisone for 1 week.

At the end of the planned chemotherapy, clinical examination recorded no measurable change in the lower lip lesion (stable disease) and further progression of upper lip disease, while restaging CT scan confirmed disease as a localized NHL.

In December 2016, given the nonresponse to medical therapy, the patient was referred to the Department of Radiation Oncology of Mauriziano Hospital.

In January 2017, RT was performed to upper and lower lip clinical target volume with 4 Gy in two fractions, using two opposite three-dimensional conformal 6-MV photons beam fields (Fig. 2A and B). The treatment was well tolerated, with mild erythema and oral mucositis. After 2 months from the end of RT, at the first follow-up evaluation, the patient achieved complete resolution of the tumor. RT toxicity was also completely resolved. The patient was submitted to follow-up visits with hematologists and radiation oncologists and to blood tests every 3 months. At the last examination performed in December 2017, persistent complete response was recorded.

Discussion

Most lymphomas arising from the head and neck region are B-cell NHLs and only 2% of these affect the oral cavity [10].

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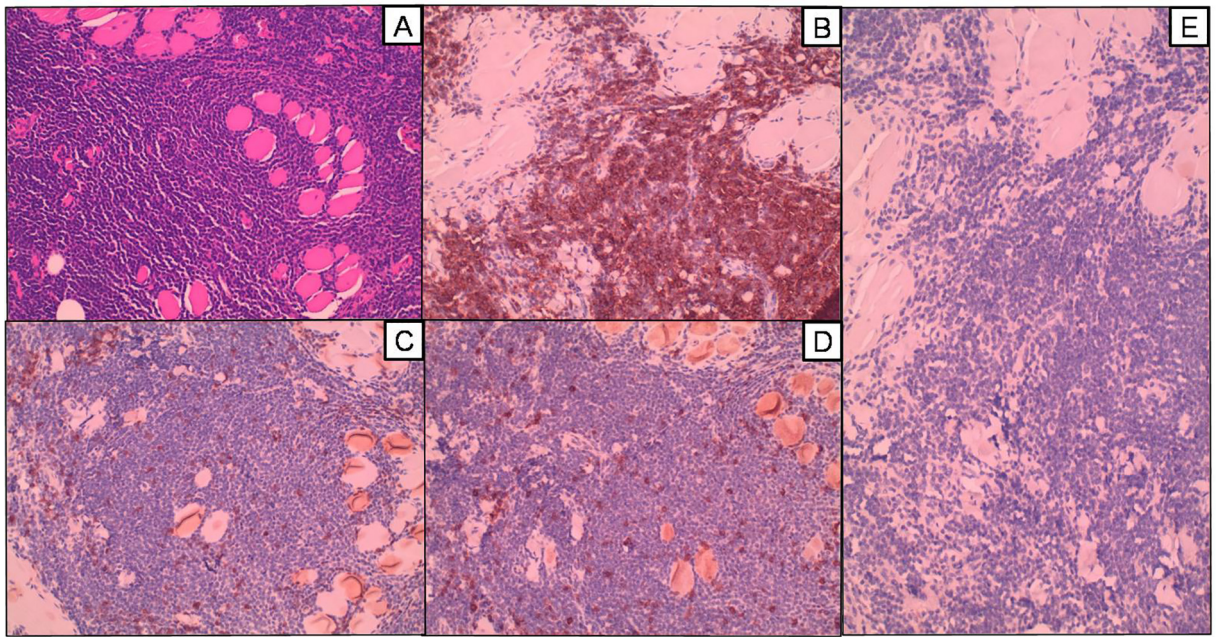

Fig. 1 Immunophenotype of patient (all pictures were taken with a 20× zoom). (A) Hematoxylin—eosin shows the growth pattern; (B) the diffuse positivity of CD20 B cells; (C) the accompanying T lymphocytes CD3+; (D) CD5 positivity in the T cells and negativity in the other B cells; (E) CD10 negativity.

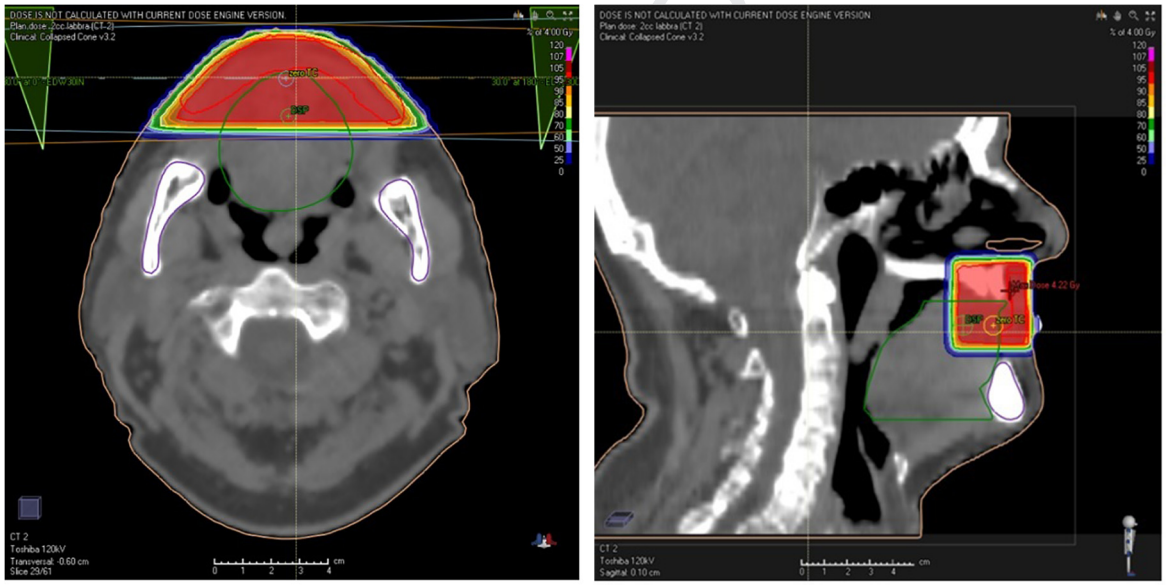

Fig. 2 Dose distribution from the radiation treatment plan using two opposite three-dimensional conformal 6-MV photons beam fields in (A) axial and (B) sagittal computed tomography images.

Lip region localization of NHL is very rare. In the Tumor Registry between 1969 and 1998, Epstein et al. [11] identified only three lip lymphomas among 391 cases in the oral and paraoral region; up to 2001, another three cases were reported by Sunaba et al., Yin et al., and Leong et al. [12—14] Afterwards, in a review of literature performed in 2011 by Shah et al. [15] analyzing extranodal NHL of the oral cavity, only 7/403 cases involved the lip. Finally, a recent analysis and review of English literature aimed to investigate NHL of the lip was published by Kaplan et al. [16] between 1996 and 2016, only 23 cases were identified, indeed they defined these lymphomas as ''a rare entity''. Regarding histology, in their review, extranodal marginal zone-B-cell MALT cases were predominant (78.2%). Of note, 40.9% of lip lymphomas were associated with Sjogren's syndrome [16]; indeed, the risk of lymphoma developing in

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patients affected by this disease is 44 times higher than for the general population [10], and autoimmune diseases in particular have been associated with higher risk of extranodal MZL [17].

Even our patient was diagnosed as having B-cell NHL of the MZ, reflecting this as the most frequent histological type among lymphomas of the lip.

The natural history of extranodal MZL is usually indolent. In recent literature, the 5-year overall survival rate is reported to be 88.7%, with a median overall survival of 12.6 years [17].

There is no consensus on the optimal systemic treatment of patients with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.

NHLs of the head and neck can be treated with chemotherapy, RT, or both. Different chemotherapeutic schemes have been used: in indolent NHL, the most frequently used chemotherapy schemes consist of chlorambucil with or without prednisolone, whereas aggressive diseases are treated with cyclophosphamide, vincristine, and prednisolone.

The final results of IELSG-19 demonstrated that rituximab in combination with chlorambucil demonstrated superior efficacy in mucosa-associated lymphoid tissue lymphoma; however, improvements in event-free-survival and progression-free survival did not translate into longer overall survival. Therefore, based on these results Zucca et al. [18] leaves room to consider the use of chlorambucil alone, but also provides evidence for the use of single agent rituximab to avoid the toxicity of chemotherapy.

RT alone is usually indicated in localized disease, whereas higher stages can be treated with a combination of chemotherapy and RT [15].

Regarding EMZL in particular, given the frequently limited stage at presentation, a local approach such as RT have been the main treatment, with excellent outcomes in terms of efficacy. In 2003 it was reported to lead to complete response in 99% and 5-year overall survival of 98%.

In patients with advanced-stage disease, watchful waiting can be the treatment of choice in asymptomatic cases and if there are severe comorbidities. Otherwise, chemotherapy or chemo-immunotherapy have been usually prescribed and MZLs are known to be chemo-sensitive tumors [17]. In these circumstances, RT can be very useful for palliation of local symptoms.

In previous years, standard RT prescription doses were usually between 20 Gy and 35 Gy; afterwards, lower doses were explored and in 1994, Ganem et al published the first experience of a total dose of 4 Gy in two fractions [15]. In that study, 27 patients affected by low-grade NHL were analyzed, the majority had advanced-stage disease. An objective response was observed in 24/27 cases, 37% and 52% had complete and partial responses, respectively. Furthermore, 8/27 responsive to the first course were submitted to at least another course of low-dose RT [19]. Other authors have subsequently reported on low-dose RT in patients affected by advanced indolent NHL, with response rates ranging from 81% to 92%. In 2012, Russo et al. [21] retrospectively reviewed 127 patients with NHL submitted to low-dose RT (4 Gy/2 fr); the total number of sites treated were 187. The overall response rate was 82%, with 57% cases of complete and 25% cases of partial response, respectively. There was no association between tumor size, site, age at diagnosis, or the use of previous chemotherapy and response. On the contrary, histology seemed to be the most significant factor in predicting response to treatment; in their clinical records, chronic lymphocytic leukemia was the only type to be associated with response. Therefore, the authors concluded that low-dose involved-field RT should be considered a palliative treatment option in patients with NHL [21].

In 2014, Hoskin et al. [22] published a randomized, unblinded, Phase III trial comparing standard dose of 24 Gy in 12 fractions to lower dose of 4 Gy in two fractions: 614 sites were treated from 2006 to 2011 in patients affected by follicular or MZL: 81% sites treated with 4 Gy had a complete or partial response compared with 91% in the group treated with 24 Gy, and progressive disease was reported in more patients treated with low-dose RT. In the low-dose RT group, complete remission was observed in >40% of sites and, as the authors stated ''that a dose as low as 4 Gy can achieve responses in a significant proportion of the populations remains remarkable"; furthermore, the incidence of acute Grade 3 or higher toxicity in the group treated with 4 Gy was approximately half in comparison. Therefore, they concluded that data supported the use of 4 Gy in two fractions for palliative treatment in the case of patients with poor performance status [22].

The definite explanation of how such a low dose of RT can be effective has not yet been given. Many studies have been performed, especially on follicular lymphoma, and many possible mechanisms of action have been recognized. Low-dose RT has been shown to induce apoptosis pathways of lymphoma cells and the correlation between in vitro RT-induced apoptosis and in vivo effects of 4 Gy RT has been demonstrated by Dubray et al. [23]. Many genes are involved in the apoptosis pathway, such as BCL2, P53, caspase-8, and caspase-9 [22]. Furthermore, low-dose RT was reported to induce up-regulation of macrophage activation-related genes and this activation of macrophages has been suggested to be subsequent to lymphoma cell apoptosis and so indirectly related to low-dose RT [24].

Reviewing literature, there are a few aspects of our case report that deserve attention: firstly, among cases of lymphoma of the lip, which has been defined as a ''rare entity" by others, the diagnosis of our patient was B-cell NHL of the MZ and so it was even more peculiar. In literature there is evidence of the effectiveness of low-dose RT in indolent lymphoma, but experiences of this approach performed in head and neck extranodal NHLs are very rare. Indeed, to our knowledge, the largest body of clinical data was reported by Pinnix et al. [25] who reviewed 22 patients affected by ocular adnexal B-cell lymphoma treated with 4 Gy RT. Therefore, this may be the first case of low-dose RT in extranodal MZL of the lip.

Secondly, low-dose RT has been primarily performed in the palliative setting, as it allows palliation of symptoms with a short duration of treatment, a very low risk of toxicity, and low cost of therapy, postponing the need for other approaches [25]. Furthermore, the total RT dose being extremely low, it can be repeated subsequently in case of recurrence. Despite this, our patient had localized disease and so he was treated with a radical intent rather than in order to provide palliation of the symptomatology. Indeed,

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Table 1 Review of literature with low dose of radiotherapy for localized low-grade non-hodgkin lymphomas.

Study	Age	Patients no.	Histology	Stage	CT	RT (Gy)	Median FU (Mo)	Time to progression (Mo)	Response rates (%)
Shah et al. [15]	42.6	15	Squamous	-	CHOP/CVP	45/25 fr	27	-	67
Ganem et al. [20]	50	27	-	II/IV	-	4 Gy/2fr	-	27	37
Russo et al. [21]	54	127	Follicular	I/IV	Yes	4 Gy/2fr	23.4	13.6	82
Hoskin et al. [22]	66	299	Follicular	I/IV	Yes	24/12fr	26	-	91
	66	315	Follicular	I/IV	Yes	4 Gy/2fr	26	-	81
Dubray et al. [23]	65	27	-	I/IV	-	4 Gy/2fr	10	-	71
Ganem et al. [24]	-	-	Follicular	III/IV	-	4 Gy/2fr	-	17	89
Pinnix et al. [25]	64.5	22	MALT/follicular	-	Yes, only 1	4 Gy/2fr	14.1	-	100
Rossier et al. [26]	73	43	-	I/IV	Yes	4 Gy/2fr	20	21	90

CT = computed tomography; MALT = mucosa-associated lymphoid tissue; Mo = month; RT = radiation treatment.

considering the age of our patient and the risk of toxicity related to different therapies such as chemotherapy or higher dose RT, low-dose RT seemed to be the preferable approach.

In literature, evidence of low-dose RT in a definitive setting is lacking: in the FORT trial, ~40% of cases were treated with curative intent and in fact in those patients, 4 Gy was inferior in terms of local progression compared to higher doses of 24 Gy [22]. In most other studies, low-dose RT has been prescribed in patients with advanced or recurrent disease and in palliative settings [20,21,26]. Therefore, in our opinion, it would be interesting to perform clinical trials to investigate efficacy of low-dose RT as radical treatment.

Several experiences with low dose radiation for MZL are reported in Table 1.

Conclusion

Extranodal MZL of the lip is an extremely rare neoplasm. In the case of localized disease, RT is an appropriate treatment. The case we have reported shows that in patients with comorbidities or poor performance status, low-dose RT can be an appropriate approach with excellent outcomes in terms of effectiveness. Our patient had a complete response to treatment with extremely low acute toxicity and, during a follow-up of almost 1 year, there was no need for other therapies.

Conflicts of interest

We declare that we have no conflict of interest regarding this study.

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