Richter transformation in the oral and maxillofacial area: report of 2 cases and literature review

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Richter transformation (RT) is a term used to refer to the development of an aggressive lymphoma, usually of diffuse large B-cell lymphoma type, in a patient with a history of chronic lymphocytic leukemia. It may present with heterogeneous manifestations, including the occurrence of tumors at extranodal sites. To date, only 6 cases of RT involving the oral and maxillofacial region have been reported. Here, we present 2 rare cases of lymphoma initially affecting the maxilla and the lower gingiva, respectively, of female patients with chronic lymphocytic leukemia and review the English language literature about RT manifesting in the oral and maxillofacial tissues. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e14–e20)

The term Richter transformation (RT) or Richter syndrome describes the development of an aggressive lymphoma in a patient with chronic lymphocytic leukemia (CLL). This is usually a non-Hodgkin lymphoma (NHL), more commonly a diffuse large B-cell lymphoma (DLBCL)1,2 and rarely Hodgkin lymphoma (HL–Richter),3 or another aggressive lymphoid malignancy, such as composite lymphoma,4 dendritic cell sarcoma,5 or plasmablastic lymphoma.6 Multiple myeloma may also develop in patients with CLL, although it is controversial whether this is coincidental or represents a Richter-like phenomenon.7

The prevalence of RT among patients with CLL varies from 0.7% to 23%.8 In a prospective cohort study,1 in approximately 2% of patients with CLL, DLBCL developed in 5 years, whereas the 10-year incidence of RT has ranged from 4.9%1 to 16.2%.9 RT is more common in males and median age is greater than 60 years.1,2 Predisposing factors include advanced-stage CLL,1,9; lymph nodes 3 cm or greater,9; expression by neoplastic cells of proteins ZAP70,1,9 CD38,1,9 or CD49d;1 nonmutated immunoglobulin heavy-chain variable region gene (IGHV);1 IGHV4-39 usage3; absence of del (13q14)9 and presence of del (11q22.3) or del (17p13)1; and prior treatment for CLL.1

We report here 2 cases of CLL in which DLBCL developed in the oral cavity and review the literature on oral and maxillofacial involvement by RT.

CASE REPORTS

Case 1
An 82-year-old female was referred by her dentist for evaluation of “poor soft tissue healing following periodontal scaling.” Five years earlier, the patient had been diagnosed with CLL stage I that did not necessitate any kind of treatment, and she was under regular follow-up by her hematologist. Complete blood count a month before presentation to us showed lymphocytosis (76%; normal range 44–44%) and increased lactate dehydrogenase (LDH; 326 units/L; normal range 122–214 units/L), as well as normocytic anemia (red blood cell [RBC] count 3,620,000/μL; normal range 4,200,000–5,400,000/μL); hematocrit [Hct] 35%; normal range 36–46%; hemoglobin [Hgb] 11.4 g/100 mL; normal range 12–16 g/100 mL; mean corpuscular volume [MCV] 97 fL; normal range 77–98 fL); and neutropenia (13%; normal range 35%–80%). These findings were considered consistent with the underlying disease by her attending hematologist. She was treated for rheumatoid arthritis with hydroxychloroquine and for chronic atrophic gastritis with monthly injections of B12. Her medical history also included hyperthyroidism, hypertension, and osteoporosis that were not being treated.

Clinical examination showed that the patient was edentulous, except for 4 teeth in the anterior mandible (Figure 1). The gingiva surrounding those teeth were enlarged, erythematous, and ulcerated. The rest of the oral mucosa was within normal limits. A panoramic radiograph showed limited alveolar bone loss around teeth, consistent with chronic periodontitis.

Because of the history of CLL, infiltration of the gingiva by the hematologic malignancy was suspected, and incisional biopsy was performed. Microscopic examination

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showed diffuse infiltration by small cells with morphologic characteristics of lymphocytes, mostly in the superficial lamina propria (Figure 2A), and large atypical mononucleated or binucleated cells with anaplastic characteristics in the deeper locations (Figure 2B). Abundant mitoses were also present. After a provisional hematoxylin and eosin–based diagnosis of lymphoproliferative lesion, further examination of the biopsy tissue was performed by an expert hematopathologist. Immunohistochemically, the small cells were CD20+, CD79a+, CD5+, OCT+, CD23−, CD30−, CD15−, CD3−, and multiple myeloma oncogene (MUM)−, whereas in situ hybridization for Epstein-Barr virus (EBV)–encoded RNA was negative. The large cells were CD20+ and CD79a+ (in equal numbers), CD23+, CD30+>CD15+, OCT+, MUM+, CD5−, CD3−, whereas EBV–encoded RNA was positive. Polymerase chain reaction was performed for the identification of immunoglobulin heavy-chain (IGHV) gene mutational status and proved a clonal relationship between the underlying and the present hematologic malignancy. The final diagnosis was gingival infiltration by a CD5+, CD23− B-cell lymphoproliferative lesion with small lymphocytic features, consistent with CLL, with transformation to a diffuse high grade EBV(+) B-cell lymphoma composed of large anaplastic CD30+>CD15+ cells, in the context of Richter syndrome.

The patient was treated with 6 cycles of chemotherapy with rituximab (500 mg), cyclophosphamide (1000 mg), vincristine (1.8 mg), and prednisolone (75 mg), as well as 30 cycles of radiotherapy (total dose 30 Gy). However, she was lost to follow-up.

**Case 2**

A 70-year-old female presented for the evaluation and management of a painless mass in the upper lip. According to her account, it had been first noticed approximately 3 years earlier, but in the past 3 weeks, it had enlarged and excreted pus-like material. Her dentist had ruled out a dental or periodontal origin. Her medical history was significant for CLL stage I, diagnosed approximately 8 years earlier. She had not received any treatment for CLL and was under regular follow-up by her attending hematologist. Blood tests
during this period showed CLL-associated leukocytosis and anemia managed with folic acid per os. LDH was within normal limits (377 units/L; normal range 230–460). The patient was also being treated for hypertension with amlodipine besylate, hypothyroidism with levothyroxine sodium, and osteopenia with risedronate sodium.

Clinical examination revealed a tumor in the middle of the maxilla and extending to the sulcus and the palate (Figures 3A and 3B). The tumor was covered by normal-appearing mucosa and was soft to fluctuant and painless on palpation. The involved teeth showed class II mobility. The rest of the oral mucosa was within normal limits. Cone beam computed tomography showed an ill-defined soft tissue density lesion in the anterior region of the maxilla, measuring approximately 3.5 × 3.0 × 2.5 cm, causing perforation of both the frontal and palatal cortical plates and extending to the floor of the nasal cavity (Figure 4).

Incisional biopsy was performed with the patient under local anesthesia, and histopathologic examination showed diffuse infiltration by large atypical neoplastic cells (Figure 5) with pleomorphic grooved nuclei and indistinct nucleoli. Mitoses, some of them atypical, were also detected. Additionally, small cells with phenotypic characteristics consistent with lymphocytes were distinguished focally, mostly in perivascular and perineural localization. Crush artifacts were observed. These features were consistent with NHL, and after further investigation by an expert hematopathologist, the immunoprofile of the tumor was shown to be positive for CD20, CD79a, bcl2, bcl6, CD23, and CD30 and negative for c-myc, CD10, MUM-1, CD5, and CD138; the Ki67 index was 80% to 90%. Based on the histologic and immunohistochemical examination, the diagnosis was diffuse large B-cell lymphoma with features not otherwise specified, probably originating from the germinatal center.

A full workup of the patient was undertaken, but no significant findings were revealed on chest and abdominal CT scans, the imaging features being similar to the latest evaluation performed 3 years ago.

The patient underwent 8 cycles of treatment with carfilzomib. Five months after commencement of therapy, her clinical condition and laboratory findings were satisfactory, and the maxillary lesion had regressed completely (Figure 6). Twenty-one months later no sign of recurrence was present.

**DISCUSSION**

We reported here 2 cases of DLBCL developing in the oral cavity of patients with CLL, which conformed to the diagnosis of RT. An English language literature review disclosed 6 previously reported cases of oral and maxillofacial RT, whose main features, along with those of the present cases, are summarized in Table I. Mean age was 65.1 years, and females were more commonly affected compared with males (female/male ratio 6:2). The latter finding is in contrast to the more common finding of more involvement in males by both RT and oral and maxillofacial lymphomas.

DLBCL, the most frequently encountered type of NHL in the oral and maxillofacial area and the most common lymphoma in RT, was diagnosed in the
majority of cases (6 patients), whereas in 2 patients, the diagnosis was plasmablastic lymphoma. Mean time between diagnosis of CLL and development of RT was approximately 5 years. The jaws were the most common site of involvement, with 6 of 8 cases (2 cases in the maxilla, 2 in the mandible, 1 with simultaneous involvement of both jaws, and 1 in an unspecified jaw), followed by the gingiva and the cheek, with 1 case each. This distribution is in agreement with the common and equal involvement of both jaws by NHL.16,17

Lymphomas in RT are, in most cases, clonally related to the pre-existing CLL directly—that is, lymphoma cells derive from the original CLL clone (linear evolution); or indirectly, both CLL and lymphoma cells derive from a common precursor cell (branching evolution).18 Clonal relationship should be established by IGHV-D-J rearrangement analysis.8,19 This is considered essential because of differences in the therapeutic management of clonally related and clonally unrelated RT, with the latter being treated in a similar fashion to de novo DLBCL.8,19 A clonal relationship between CLL and lymphoma was proved in one of our cases (case 1) and in that of Evans et al.14

In approximately 20% of NHL developing in patients with CLL, a clonal relationship cannot be established.20 In those cases, the biologic features and prognoses are more comparable with those of conventional NHL; therefore, they are considered to be de novo malignancies.8

Even though the exact molecular mechanisms of RT have not been fully elucidated, there are reports of genetic alterations in CLL cells that cause transformation to the clonally related lymphoma. Approximately 90% of RT cases exhibit genetic lesions in pathways that cause disruption of general cell regulators, such as tumor suppression, cell cycle, and cell proliferation (e.g., TP53, NOTCH1, MYC, and CDKN2A).18 Those genetic lesions are associated with the aggressive clinical behavior resulting from acquired features—resistance to chemotherapy and rapid disease progression.18

Previous therapy has also been suggested as a risk factor for the development of RT, although a mechanism has not been described.1 From another point of view, CLL requiring chemotherapy is usually an aggressive disease with poor biologic behavior, where the risk for the development of a lymphoma is, nevertheless, high.1 We reported for the first time 2 cases where RT developed in the oral cavity of patients with no previous treatment for CLL because in the previously reported 6 cases, different types of chemotherapeutic regimens had been applied.

RT in CLL-untreated patients is rarely EBV related, whereas in patients in immunosuppressive therapy, it is suggested that EBV reactivation may drive the development of the aggressive lymphoma.21 One of the cases presented here (case 1) is the first EBV-positive, clonally related oral RT in a previously untreated patient with CLL. Although the EBV status of the patient before RT was not known, it may be hypothesized that in this case, a secondary EBV infection drove the lymphomatogenesis.

Diagnosis of RT is based on clinical and pathologic examinations, as well as imaging. Severe deterioration in a patient with CLL manifesting fever, rapid lymphadenopathy, extranodal involvement presenting with tumors mostly of the gastrointestinal tract or bones, severe weight loss, hypercalcemia, and markedly elevated LDH are features that could raise the suspicion

![Fig. 5. A, B, Patient 2. Diffuse proliferation by large atypical basophilic cells with occasional mitoses, intermixed with smaller cells with morphologic features of lymphocytes (hematoxylin and eosin stain; initial magnification × 400). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05761.](image)

![Fig. 6. Patient 2. Complete response of the maxillary lesion 5 months after initiation of chemotherapy.](image)
Table I. Cases of Richter transformation with manifestations in the oral cavity or the jaws

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Age</th>
<th>Gender</th>
<th>Type of lymphoma</th>
<th>Time to RT</th>
<th>Site of involvement</th>
<th>Other manifestations</th>
<th>Clonal relationship</th>
<th>Prior treatment</th>
<th>Treatment for RT</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Trump et al.</td>
<td>66</td>
<td>F</td>
<td>DLBCL</td>
<td>7</td>
<td>Maxilla</td>
<td>Swollen ankles, wrist and knee, axillary adenopathy and hepatosplenomegaly</td>
<td>NI</td>
<td>Chlorambucil</td>
<td>Radiotherapy, CVP, BABV</td>
<td>8 months DOD</td>
</tr>
<tr>
<td>1983</td>
<td>Kendrick et al.</td>
<td>77</td>
<td>F</td>
<td>DLBCL</td>
<td>4, 5</td>
<td>Buccal area</td>
<td>Fever, liver and spleen enlargement</td>
<td>NI</td>
<td>Chlorambucil, radiotherapy</td>
<td>CHO</td>
<td>6 months DOD</td>
</tr>
<tr>
<td>2001</td>
<td>Robak et al.</td>
<td>61</td>
<td>F</td>
<td>PL</td>
<td>4</td>
<td>Mandible</td>
<td>Peripheral paresis of facial nerve</td>
<td>NI</td>
<td>2-CdA, prednisone</td>
<td>VAD, CHOP</td>
<td>6 months DOD</td>
</tr>
<tr>
<td>2013</td>
<td>Wiśniewska- Piątyska et al.</td>
<td>NM</td>
<td>F</td>
<td>DLBCL</td>
<td>NM</td>
<td>Mandible</td>
<td>Confusion, hypercalcemia, diplopia, ptosis as well as lytic lesions in the skull, humerus, scapula and ribs</td>
<td>NI</td>
<td>CC, R-CHOP, R-ESHAP, FMD, RB, radiotherapy</td>
<td>CHOP</td>
<td>DOD (unknown follow-up)</td>
</tr>
<tr>
<td>2015</td>
<td>Evans et al.</td>
<td>62</td>
<td>M</td>
<td>PL (from DLBCL)</td>
<td>4</td>
<td>Jaw (unspecified)</td>
<td>Lymphadenopathy</td>
<td>Yes</td>
<td>FCR, BR, ofatumumab, CHOP, flavopiridol and lenalimumide, ibrutinib</td>
<td>OFAR, XPO1, CTL019 (before PL) Radiotherapy (after PL development)</td>
<td>1 month DOC</td>
</tr>
<tr>
<td>2017</td>
<td>Bezinelli et al.</td>
<td>38</td>
<td>M</td>
<td>DLBCL</td>
<td>2</td>
<td>Maxilla and mandible</td>
<td>Lymphadenopathy, lytic lesions in the skull and iliac bone</td>
<td>NI</td>
<td>R-CHOP, FCR, AHSCT</td>
<td>R-ESHAP, methotrexate, cytarabine, dexamethasone</td>
<td>5 months CR</td>
</tr>
<tr>
<td>Current case 1</td>
<td></td>
<td>82</td>
<td>F</td>
<td>DLBCL</td>
<td>5</td>
<td>Mandibular gingiva</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Radiotherapy, R-COP</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Current case 2</td>
<td></td>
<td>70</td>
<td>F</td>
<td>DLBCL</td>
<td>8</td>
<td>Maxilla</td>
<td>None</td>
<td>NI</td>
<td>No</td>
<td>Carfilzomib</td>
<td>26 months CR</td>
</tr>
</tbody>
</table>

2-CdA, cladribine; AHSCT, allogeneic hematopoietic stem cell transplantation; BABV, bleomycin, adriamycin, vinblastine, and 1-3-bis (2-chloroethyl-1-nitrosourea); BR, bendamustine and rituximab; CC, cyclophosphamide and cladribine; CHO, cyclophosphamide, doxorubicin, and vincristine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, Complete response; CTL019, chimeric antigen receptor–modified T cells targeted for CD19; CVP, cyclophosphamide, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; DOC, died of complications; DOD, died of disease; F, female; FCR, fludarabine, cyclophosphamide, and rituximab; FMD, fludarabine, mitoxantrone, and dexamethasone; M, male; NI, not investigated; NM, not mentioned; OFAR, oxaliplatin, fludarabine, cytarabine, and rituximab; PL, plasmablastic lymphoma; RB, rituximab and bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-COP, rituximab, cyclophosphamide, vincristine, and prednisolone; R-ESHAP, rituximab, etoposide, cisplatin, cytarabine, and methylprednisolone; RT, Richter transformation; VAD, vincristine, doxorubicin, and dexamethasone; XPO1, inhibitor of exportin 1.
of RT development. In both cases presented here, the patients did not have any signs or symptoms other than swelling in the oral cavity. The most common signs in previously reported cases of oral and maxillofacial RT (see Table I) were lymphadenopathy in 3 cases, followed by hepatosplenomegaly and lytic lesions in bones other than the jaws in 2 cases each.

Histopathologic examination most commonly reveals diffuse infiltration by large atypical cells exhibiting pleomorphism and a centroblastic morphology. They are CD20 positive, with the markers CD5 and CD23 suggestive of CLL being expressed in 32% and 14%, respectively. RT cases most commonly show a nongerminall cell type DLBCL cases are rarer. When RT is suspected in the absence of clinically evident nodal or extranodal masses, imaging with F-18 fluorodeoxyglucose positron emission tomography is the diagnostic procedure of choice. The characteristics of the lesions detected, along with the standardized uptake value, exhibit a significant sensitivity and indicate whether biopsy should be performed, facilitating the diagnosis of RT.

RT treatment is challenging. Immunochemotherapy, stem cell transplantation, and novel targeted therapeutic agents have been tested with varying results with regard to patients’ response and overall survival. DLBCL in patients with RT acquires significant resistance to chemotherapy. Some of the chemotherapeutic regimens exhibit a low complete response rate (7%), with higher overall survival (21 months) and low treatment-induced mortality (5%), whereas others show a better response (complete response 38%) with a lower overall survival (10 months) because of the high toxicity of the chemotherapeutic agents. Allogenic and autologous stem cell transplantsations have been used. Overall 3-year survival of patients receiving allogenic stem cell transplantation and autologous stem cell transplantation is 36% and 59%, respectively, as indicated by a retrospective analysis. However, in most cases, stem cell transplantation is not an option because patients are unfit, either because of their age or because of insufficient response to initial chemotherapeutic treatment.

Novel agents that target the molecular pathways deregulated in patients with RT include the Bruton tyrosine kinase inhibitor ibrutinib, the B-cell lymphoma 2 antagonist venetoclax, the programmed cell death protein 1 antagonist pembrolizumab, and the exportin 1 inhibitor selexinor. The overall response rate varies from 33% for selexinor to 75% for ibrutinib, but the number of cases studied is too limited for any conclusions to be reached. Of the 8 cases presented in Table I, different immuno- or chemotherapeutic regimens were applied in 5 cases, combination of chemotherapy with radiation therapy in 2 cases, solely radiation in 1 case.

The median survival of patients with CLL with RT is approximately 2 years, with clonally unrelated cases exhibiting a behavior similar to that of de novo DLBCL, whereas clonally related cases have a significantly lower survival rate. Additional factors diminishing overall survival are LDH levels greater than 1.5 times the normal, tumor size greater than 5 cm, platelet count less than 100 $\times 10^9/L$, number of prior therapies greater than 1, Zubrod score greater than 1, TP53 deletions or mutations, and poor response to RT treatment. Five of the patients with oral and maxillofacial RT died either as a result of the spread of the lymphoma or because of chemotherapeutic toxicity, at a mean period of approximately 5 months, and 2 patients showed signs of remission at the 5-month follow-up.

CONCLUSIONS
Although first presentation of RT in the oral and maxillofacial area is extremely rare, clinicians should have a high level of suspicion when dealing with patients with CLL showing atypical lesions in the area because these lesions could be manifestations of an underlying RT.

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REFERENCES


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