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Case report

Intra-oral small lymphocytic lymphoma

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Summary Small lymphocytic lymphoma (SLL) belongs to a family of low-grade malignant lymphomas. Its involvement in the oral cavity has not been reported previously. We describe the case of a 43 year-old male patient suffering intra-oral SLL. Microscopic examination of the incisional biopsy specimen revealed a diffuse and monotonous pattern of small lymphocytes with proliferation centers composed of prolymphocytes or para-immunoblasts. Immunohistochemical (IHC) staining demonstrated that these neoplastic lymphoid cells proved to be positive for LCA, CD5, CD20, CD79a, CD23, CD43, Bcl-2, Bcl-6, and negative for CD10, Bcl-1 (cyclin D1), CD3, CD30, as well as negative for CD68, and smooth-muscle actin, kappa and lambda. Based upon the histological features and the IHC assay pattern, a case of intra-oral SLL and its differential diagnosis using immunohistochemistry is reported here.

Introduction

Small lymphocytic lymphoma (SLL) is a low-grade malignant lymphoma characterized morphologically by a proliferation of small, mature-appearing lymphocytes.[1] From a review of the literature, it would appear to comprise around 7% of all non-Hodgkin's lymphoma cases in all geographic areas[2] but only 1% of all non-Hodgkin's lymphomas in Taiwan.[3] Microscopically, SLL shows a close resemblance to other small B-cell lymphomas such as mantle-cell lymphoma (MCL), follicular lymphoma (FL) and marginal-zone lymphoma (MZL).[4] Although SLL is primarily nodal, hepatic and splenic involvement may arise, and other extranodal tissues such as orbit,[5] lung,[6] skin[7] and stomach[8] may occasionally be involved. To our knowledge, its occurrence in the oral cavity has not yet been reported. Here, we report on a case of intra-oral SLL as well as the case's differential diagnosis using immunohistochemistry.

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Case report

A 43 year-old male patient was referred to our institution for further examination for the swelling of left face by a local dental clinic. Extra-oral examination revealed a painful swelling of the left cheek (Fig. 1A) whereas intra-oral examination demonstrated an ulceration, measuring about 1×1 cm in diameter, located over the left tuberosity and a painful swelling over the left buccal mucosa (Fig. 1B). Periapical radiography revealed an inconspicuous poorly defined radiolucence over the distal aspect of tooth 25 (Fig. 1C). Computerized tomography (CT) demonstrated massive soft-tissue lesions involving multiple tissue spaces and leading to the bony destruction of the maxilla, the wall of the maxillary sinuses and the mandibular ramus (Fig. 1D). Bilateral submandibular lymph-node involvement was suspected upon CT (Fig. 1E). No systemic symptoms such as fever, weight loss, or night sweats were reported, and no abdominal masses or tenderness, ascites, or hepatosplenomegaly were noted. A chest scan appeared to be normal. A peripheral blood smear revealed a normal white blood cell count. A bone-marrow aspiration demonstrated normal cellularity (43%) with an adequate level of megakaryocytes being noted to be present. Both myeloid (M) and erythroid (E) studies revealed normal maturation and differentiation with an M/E ratio of 3.6:1, there appearing to be no evidence of absolute lymphocytosis.

Incisional biopsies over the palatal and buccal lesions were then performed under local anesthesia. Microscopically, both specimens were chiefly composed of monotonous small lymphocytes, revealing a mature-appearance with clumped chromatin and slightly angulated nuclei (Fig. 2A). Under high-power, a few lymphoid cells featuring scanty cytoplasm were noted (Fig. 2A, inset a). Some neoplastic lymphoid cells exhibiting a rather pleomorphic appearance and demonstrating evidence of abnormal mitosis (Fig. 2A, inset b) were also occasionally noted. In addition, some larger, paler cells consistent with prolymphocytes could be seen (Fig. 2A, inset c), and in certain areas, a diffuse proliferation of small lymphoid cells with the preservation of a sinus was apparent (Fig. 2B). Significantly, we noted pale-staining areas of pseudofollicles (Fig. 2C) containing large paler

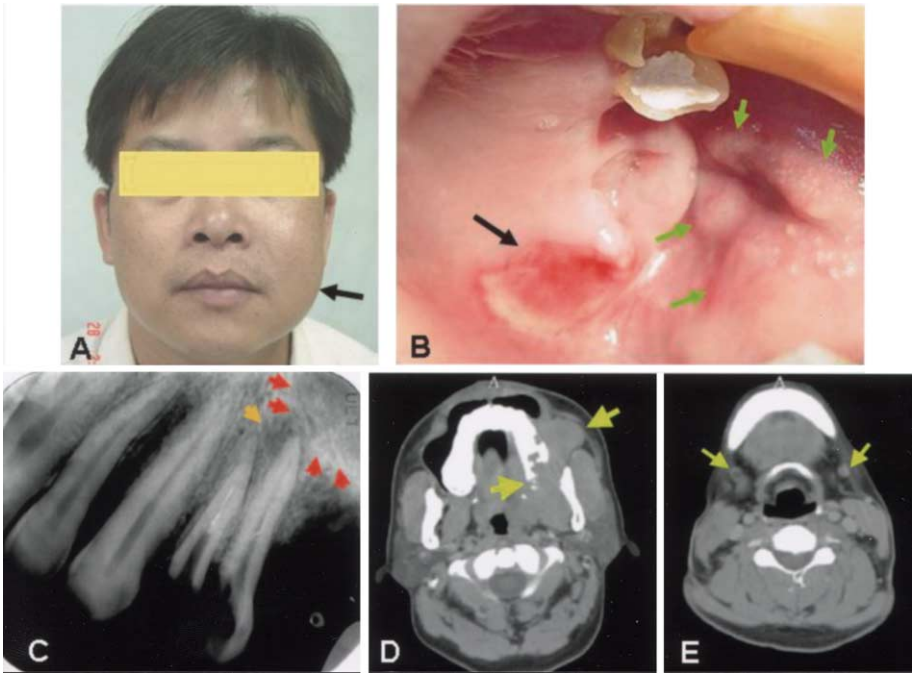

Figure 1 (A) A painful swelling was noted over the patient's left cheek (arrow). (B) An ulceration over the left tuberosity (black arrow) and a painful, tender swelling over the left buccal mucosa (green arrows) were also observed. (C) Periapical radiography revealed an apical lesion over residual root of tooth 25 (yellow arrow). An inconspicuous poorly defined radiolucence was found over the distal aspect of tooth 25 (red arrows). (D) Computerized tomography (CT) revealing extensive soft-tissue lesions involving the left nasopharyngeal space, maxillary sinus, infra-temporal fossa, oropharyngeal space, palate, parapharyngeal space and the buccal space and resulting in the bony destruction of the maxilla, the wall of the maxillary sinuses and the mandibular ramus (arrows). (E) Bilateral submandibular nodal involvement was suspected upon CT scan investigation.

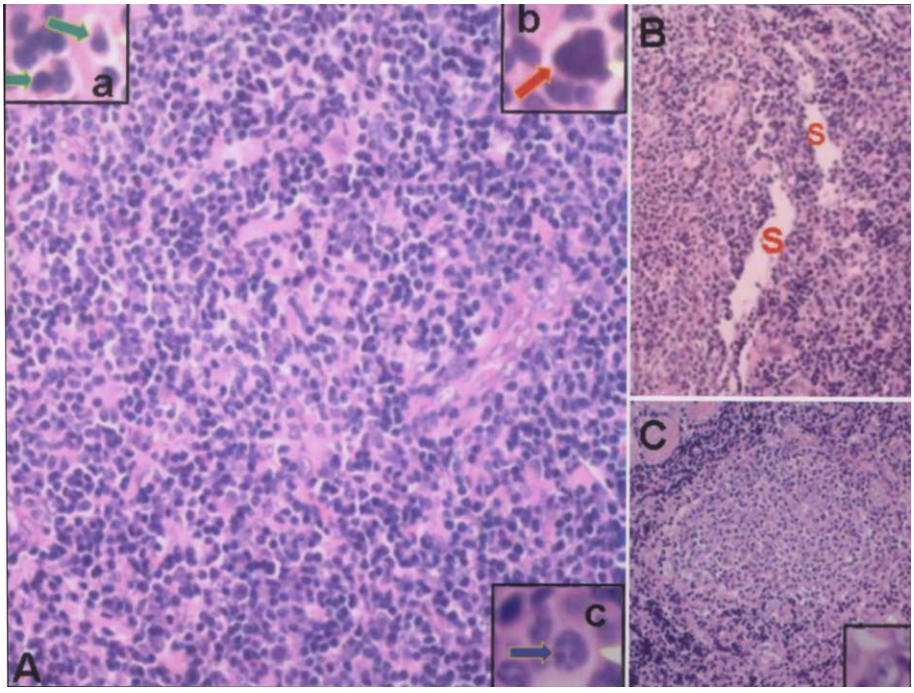

Figure 2 (A) The neoplastic lymphocytic infiltrates for both palatal and buccal specimens were chiefly composed of monotonous small, mature-appearance lymphocytes with clumped chromatin and slightly angulated nuclei upon low-power view (H-E stain × 40). A few lymphoid cells featuring scanty cytoplasm may also be noted (inset a, green arrows, H-E stain × 400). Some neoplastic lymphoid cells revealing a pleomorphic appearance, and demonstrating abnormal mitosis (inset b, red arrows, H-E stain × 400) may also be noted. Some larger, paler cells consistent with prolymphocytes may be seen (inset c, blue arrows, H-E stain × 400). (B) A diffuse proliferation of small lymphoid cells with preservation of sinus (S) is clearly apparent (H-E stain × 100). (C) Pale-staining areas of pseudofollicles containing large even paler cells (H-E stain × 100) containing oval nuclei, dispersed chromatin and a prominent nucleolus compatible with para-immunoblasts (inset, H-E stain × 400) may be noted.

cells with round to oval nuclei and dispersed chromatin and a prominent nucleolus compatible with para-immunoblasts (Fig. 2C, inset). These histological features raised the possibility of the present lesion being one variant of a family of low-grade B-cell neoplasm specific possibilities including SLL, MCL, FL and MZL.

Immunohistochemical staining (IHS) with various antibodies was then performed (Table 1). In summary, these neoplastic lymphoid cells were positive for LCA, CD5 (Fig. 3A), CD20 (Fig. 3C), CD79a, CD23 (Fig. 3D), CD43 (Fig. 3E), Bcl-2 (Fig. 3G), Bcl-6 (Fig. 3H), and were negative for CD10 (Fig. 3B), Bcl-1 (cyclin D1) (Fig. 3F), CD3, CD30 (Fig. 3I), as well as negative for CD68, smooth-muscle actin, kappa and lambda. Based upon these IHS results [CD5 (+), CD20 (+), CD23 (+), CD43 (+), Bcl-1 (−) and Bcl-2 (+)], a histological diagnosis of SLL was rendered. He refused to undergo any further treatment and was lost to follow-up. About 1 year later, the patient reappeared at our out-patient clinic to apply for the official pathological report. At this time, this patient's condition appeared to be stable following the completion of chemotherapy, which was performed in another teaching hospital in Northern Taiwan; however, the detailed treatment regimen for this was not able to be discerned.

Discussion

SLL is chiefly a disease of middle age and the elderly, with a median age at diagnosis of 55—61 years and very few SLL patients who are less than 40 years old.[9] The male-to-female ratio for SLL is approximately 2:1.[10] Our case was broadly consistent with those cases of SLL previously reported in the literature.[9,10]

To our knowledge, the clinical details of and prognosis for SLL in the oral cavity are not completely known. The modified Ann Arbor system[11] for cancer staging suggests that: stage I SLL indicates the involvement of some lymphoid structures or possibly a lymph-node region, whereas stage II exhibits the involvement of two or more lymph-node regions on the same side of the diaphragm; stage III disease denotes the involvement of

Table 1 Antibodies used for tissue identification, their predominant reactivity and results

Antibodies	Sources (dilution)	Predominant reactivity	Results
CD45	Dako (1:200)	Leukocyte common antigen	+
CD20	Dako (1:100)	Pan B-cell	+
CD79a	Dako (1:100)	Pan B-cell	+
CD10	Novocastra (1:80)	B-cell and granulocyte	−
CD5	Novocastra (1:80)	Pan T-cell and some B-cell lymphomas	+
CD23	Dako (1:200)	B-cell and dendritic cells	+
CD43	Novocastra (1:80)	T-cell and B-cell subset	+
CD3	Dako (1:200)	Pan T-cell	−
CD68	Dako (1:200)	Macrophage	−
Anti-kappa	Dako (1:200)	Kappa light chain	−
Anti-lambda	Dako (1:200)	Lambda light chain	−
Smooth-muscle actin	Chemical International (1:50)	Actin protein	−
S-100	Dako (1:200)	S-100 protein	−
Bcl-1 (cyclin D1)	Novocastra (1:80)	Cyclin D1 protein	−
Bcl-2	Novocastra (1:80)	Anti-apoptotic death protein	+
Bcl-6	Novocastra (1:30)	Bcl-6 putative transcription factor	+

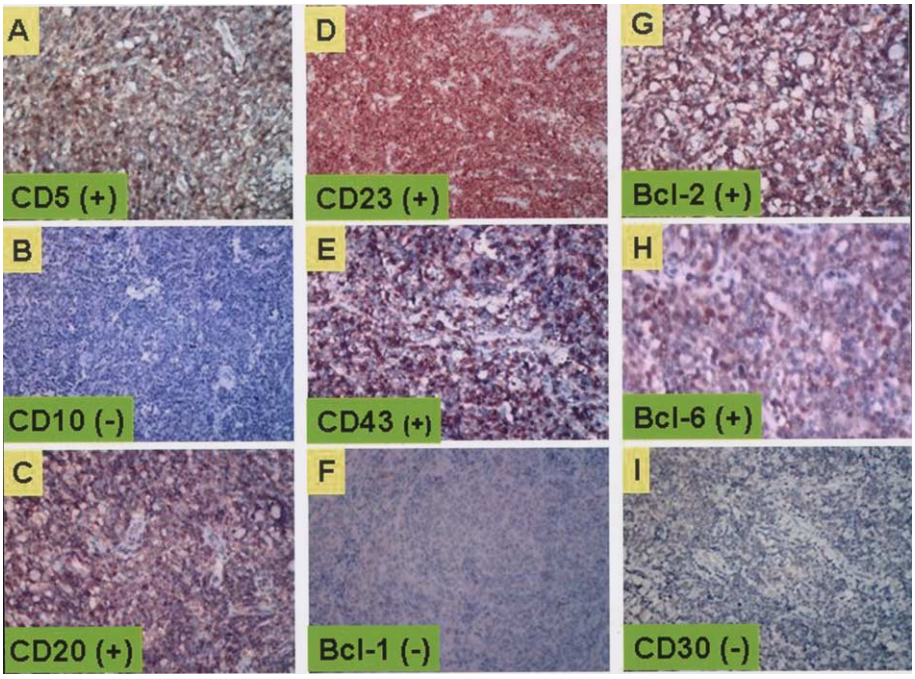

Figure 3 The neoplastic lymphoid cells proved to be positive for CD5 (A); CD20 (C); CD23 (D); CD43 (E); Bcl-2 (G); Bcl-6 (H), and negative for CD10 (B); Bcl-1 (cyclin D1) (F); CD30 (I) (×100).

structures or lymph-node regions on both sides of the diaphragm, whilst stage IV disease is represented by the diffuse, disseminated involvement of one or more extralymphatic organs, such as bone marrow, liver, or lung. Our patient appeared to suffer stage III SLL at initial presentation when classified with respect to the modified Ann Arbor system. The patient appeared to have experienced a good response to chemotherapy, however, long-term follow-up, which is necessary to determine the disease's entire course, was not available, but its conduct is strongly cautioned for all such cases.

Microscopically, both morphological and IHC findings of the neoplastic lymphoid cells of the present case share a close resemblance to those cases of SLL occurring in lymph nodes and extran-

odal sites.[1] The primary differential diagnoses of the current case comprise other small B-cell lymphomas including FL, MZL, and particularly MCL.

Histologically, MCL is characterized by a monomorphic lymphocytic infiltrate with a diffuse, vaguely nodular, or expanded mantle-zone pattern; the neoplastic lymphoid cells are small to medium, with nuclear contours ranging from slightly to markedly irregular.[12] Therefore, it appears clear that such a morphological picture shares some resemblance to the present case (SLL) and the distinction between these two entities, using morphological features alone, is frequently challenging and remains important because MCL has been recognized as a clinically aggressive lymphoma for which a modified treatment needs to be adopted accordingly.[2]

Immunophenotypically, the neoplastic lymphoid cells for MCL are usually CD5 (+), CD20 (+), and CD43 (+), Bcl-2 (+), but CD10 (−) or Bcl-6 (−).[12] The lymphocytic infiltrates are typically CD23 (−), but occasionally, they may be weakly positive.[12] Typically, all lymphocytic specimens are Bcl-1 (+), although for the rare specimen, the evidence may suggest CD5 (−).[13] This IHC pattern is very similar to that noted for SLL, i.e. [CD5 (+), CD20 (+), CD23 (+), CD43 (−), Bcl-1 (−) and Bcl-2 (+)],[1] such that Bcl-1 staining is very important to discriminate between MCL and SLL.[1] The IHC pattern revealed for the present case conformed fully to the criteria for a case of SLL.

For a typical case of FL, a nodular (follicular) pattern is usually observed with neoplastic lymphoid cells typically reflecting CD10 (+), CD20 (+), and Bcl-2 (+); CD5 (−), CD43 (−), Bcl-1 (−) and CD23 (−) [but occasionally CD23 (+)].[4] No nodular pattern of detected lymphoid cells appeared to have been expressed for the current case. In addition, an overt different IHC pattern was noted for this case [CD5 (+), CD43 (+) and CD10 (−), CD23 (−)] when compared to analogous results of typical cases of FC. MZL usually expresses an expanded marginal-zone pattern and contains a cascade of heterogeneous neoplastic lymphoid cells including centrocyte-like small cells, monocytoid lymphocytes, large transformed lymphocytes, plasmacytoid lymphocytes, and plasma cells.[4] Such histological features were obviously not demonstrated for the current case. The neoplastic lymphocytes typical of cases of MZL are usually CD20 (+); frequently Bcl-2 (+); occasionally CD43 (+); and CD5 (−), Bcl-1 (−), CD10 (−) and CD23 (−), thus, the IHC pattern revealed by this case was not indicative of cases of MZL.

For a palatal lymphoid lesion, the extranodal NK/T-cell lymphoma (nasal type) should also be included in the suite of potential diagnoses, as it is the most-common lymphoma involving the sinonasal region and hard palate.[14] This type of lymphoma is characterized by lymphocytic infiltrate revealing angiocentric invasion, prominent necrosis and vascular destruction as well as expressing markers for NK-cells (CD56) or T-cells (CD3), but not those of B-cells (CD20 and CD79a).[15] For the present case, the histological characteristics of angiocentricity, necrosis and vessel destruction were not observed, and furthermore, our case revealed positive staining for B-cell markers and negative staining for T-cell markers.

There has been a systemic counterpart of SLL reported previously, namely, chronic lymphocytic leukemia (CLL).[1] Discrimination between SLL and CLL may be difficult, and, typically, is based upon a blood examination; absolute lymphocytosis is indicative of involvement by CLL.[1] For this patient, no marrow and blood infiltration by neoplastic lymphoid cells was detected; therefore, a rather good prognosis would likely be able to be predicted.

Both SLL and CLL may be associated with second lymphoid malignant neoplasms, which may occur simultaneously or present up to 20 years later.[16] Approximately 3—10% of patients featuring CLL progress to cases of diffuse large B-cell lymphoma (so-called Richter's transformation).[16] Hodgkin's disease also may occur simultaneously or develop subsequently for CLL patients (a transformation called 'Hodgkin's disease variant of Richter's syndrome').[17] For the present patient, there was no evidence of Hodgkin's disease because neither Reed-Sternberg-like cells nor CD30-stained cells were able to be detected.

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