Asymptomatic nodule in the right cheek in a 65-year-old female

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CLINICAL PRESENTATION

A 65-year-old African American female presented to the Harlem Hospital Center, Department of Oral and Maxillofacial Surgery, for evaluation of a persistent right buccal mass (Figure 1). The patient had incidentally discovered the lesion 3 months before presentation, and she denied any fluctuations in size or discomfort in the site. She reported no past medical history and was not taking any prescription medications at the time. Her substance history was positive for regular tobacco (4.5 pack-years) and alcohol (1−2 drinks per day) consumption, and she admitted to using marijuana and cocaine recreationally.

Review of her systems was unrevealing, and the patient denied any other recent symptomatology. Physical examination revealed a unilateral ovate mass overlying the right midcheek. The lesion measured 1 cm in the longest dimension and caused visible asymmetry of the lower third of the face. On palpation, the mass was firm, rubbery, and movable, and the patient denied any pain or tenderness on palpation. No palpable parotid, submandibular, or cervical lymphadenopathy was present. Intraorally, although the lesion could be felt through the right buccal mucosa, there was no visual evidence of mucosal ulceration or disturbance.

Facial computed tomography with contrast was performed to define the extent of the lesion. Imaging revealed a 12 × 13 mm, well-circumscribed, isolated, homogeneous, and lobulated soft tissue mass, with no discernible infiltration into the surrounding fat (Figure 2). In addition, no abnormalities were noted in any adjacent structures.

DIFFERENTIAL DIAGNOSIS

The clinical differential diagnosis for a subcutaneous lesion of the cheek may be broadly divided into dermal, lymphoid, and mesenchymal categories.[1] Commonly encountered dermal lesions at this site include the epidermoid/dermoid cyst[2] and the mixed tumor of skin (chondroid syringoma).[3] Lesions of lymphoid origin include reactive lymphoid hyperplasia and lymphoid neoplasms (lymphoma). Mesenchymal neoplasms, such as the lipoma, were also included in our differential diagnosis.[4]

Epidermoid cyst (EC), a keratin-filled cyst of the skin, arises from entrapped epithelial tissue. It constitutes approximately 80% of all follicular cysts and may arise either congenitally during embryologic development or be acquired from traumatic implantation or localized inflammation, which can cause infundibular epithelial proliferation.[2] Regardless of etiology, these lesions are histologically identical. When the lesion occurs on the face, the acquired EC arising from localized inflammation tends to involve acne-prone areas and appears as a nodular, fluctuant subcutaneous lesion. The sole pathologic distinction between EC and dermoid cyst is the presence of adnexal structures in the cyst wall of the latter on microscopic examination.[2] Dermoid cyst often occurs congenitally and has a different clinical presentation and distribution, often occurring on the floor of mouth midline.[2] Although EC was placed high on our list of differential diagnoses on the basis of frequency of occurrence, the clinical presentation of a firm, rubbery mass was not consistent with the usual texture of an EC.[5] Furthermore, the affected site lacked any yellow or white discoloration, which may be observed in areas underlying thin facial skin.

Although numerous adnexal tumors may present with clinical and radiographic features similar to those of the lesion observed in our patient, one of the more frequently encountered entities is the mixed tumor of skin, also referred to as *chondroid syringoma* (CS). CS is a benign skin appendage tumor that is most often reported in the head and neck region.[3,6] Originally described as a mixed tumor by Billroth in 1859, the

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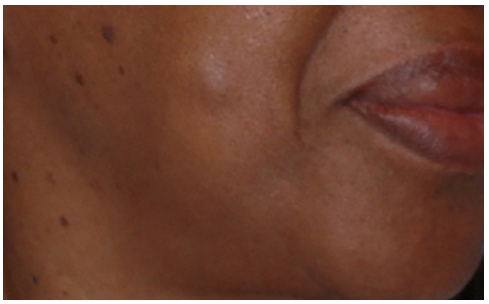

Fig. 1. Clinical image demonstrating a right facial mass deep to but not involving the skin surface. The area was firm, rubbery, and painless on palpation.

term *chondroid syringoma* was later coined by Hirsch and Helwig in 1961 because of the presence of sweat gland−like features within a cartilaginous stroma.[7] Although the overall incidence of CS has been reported as less than 1% of all skin lesions, a disproportionate number of these cases have involved the facial skin.[3,6] Clinically, CS presents as a slow-growing, painless, nonulcerated subcutaneous mass or nodule, with size usually ranging from 0.5 to 3.0 cm.[6] On microscopic examination, CS shares the histologic features of the benign mixed tumor of salivary glands (pleomorphic adenoma).[8] The clinical presentation of the lesion in question was consistent with that of a CS, and this entity was considered high among our differential diagnoses. The primary detracting factor for this diagnosis was that CS is most commonly seen in elderly males, and our patient was a middle-aged female.

The lymphoid lesions that were considered can be broadly divided into 2 subcategories: reactive and neoplastic.[9] *Reactive lymphoid hyperplasia* (RLH) refers to the benign and reversible enlargement of lymphoid tissue caused by an antigenic stimulus.[9] The type of hyperplasia may vary, depending on the particular offending agent, and can demonstrate an increase in the number of germinal centers (follicular hyperplasia), sinus distension and engorgement with histiocytes (sinus hyperplasia), partial or complete loss of the nodal architecture (diffuse hyperplasia), or a combination of the above processes. Clinically, a chronic RLH may present as a painful, rubbery, freely movable subcutaneous nodule.[10] One of the more common causes of RLH in the head and neck region is cat scratch disease, which results from infection by *Bartonella henselae* after an injury caused by a cat.[11] However, most of these cases are diagnosed in children and young adults, and our patient denied any recent contact with domestic animals. Some studies have reported head and neck RLH secondary to cocaine use;[12] however, many of the populations examined also had concurrent immunosuppression or human immunodeficiency virus infection, which may have been responsible for the detected RLH.[13] A prolonged history of illicit drug use could arguably place the patient into a higher risk category for RLH because of exposure to foreign antigenic stimulus. For this reason, RLH was included in the differential diagnosis.

Lymphoid neoplasms, such as non-Hodgkin lymphoma (NHL), were also considered in the differential diagnosis. Lymphomas can be broadly divided into 2 subtypes: Hodgkin lymphoma and NHL. Of these, NHL is more frequently encountered. *NHL* refers to a histologically diverse group of B-cell and T-cell malignancies. Most cases develop within lymph nodes; however, in approximately 20% to 40% of cases in the

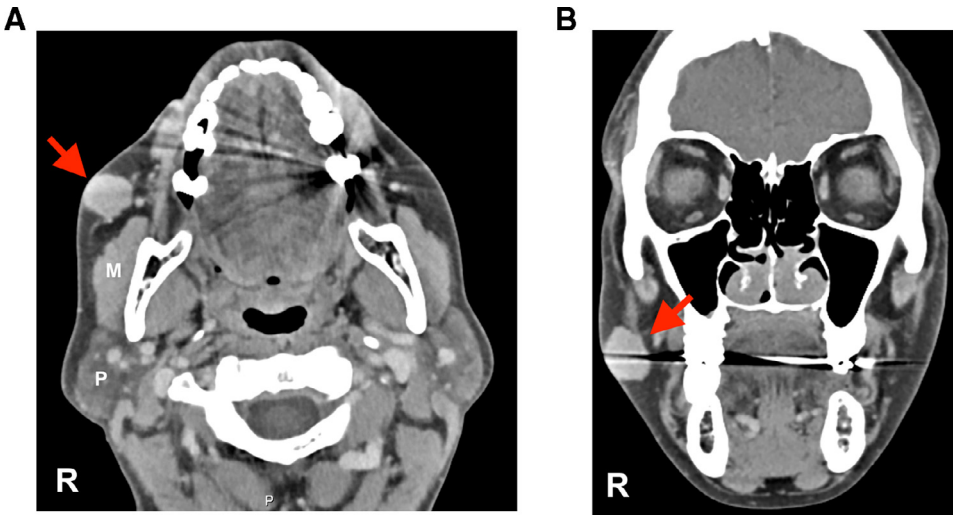

Fig. 2. Axial **(A)** and coronal **(B)** views demonstrating a 12 × 13 mm well-circumscribed, isolated, homogeneous, and lobulated soft tissue mass, as indicated by the arrows. The soft tissue mass is located anterior and superficial to the masseter muscle *(M)* and the parotid gland *(P)*.

United States, the tumors originate from extranodal sites.[14] Within the oral cavity, NHL usually presents as extranodal disease. Most often, it appears as a nontender, diffuse, boggy swelling affecting the palate, buccal vestibule, or gingiva.[15] NHL may also present clinically as a firm, variably painful mass, similar in appearance to chronic RLH.[14] For this reason, lymphoma was also included in our differential diagnosis.

Lipoma, a benign tumor of adipose tissue, typically involves the abdomen and the back. Lipomas infrequently involve the oral and maxillofacial region, and they represent only 1% to 4% of all benign oral lesions.[16] Buccal soft tissue represents the most susceptible area because of its proximity to the buccal fat pad.[4] Buccal lipoma is recognized as a soft, doughy, circumscribed, mobile nodule lying in the subcutaneous tissue. It is slow-growing and painless, with a mean duration of 3.2 years and a mean size of 1 to 3 cm at the time of examination. Affected individuals are often middle-aged males.[4] Magnetic resonance imaging visualization, particularly with T2-weighted magnetic resonance imaging, will clearly demonstrate a hyperintense, homogeneous image characteristic of fat neoplasms.[16] The classic lipoma is surrounded by a thin fibrous capsule that facilitates its local excision. Clinical and radiographic appearances of the lesion in question were consistent with those of a lipoma, and this entity was considered high among our differential diagnosis.

DIAGNOSIS AND TREATMENT

The patient underwent surgical excision of the lesion via a transoral approach to avoid facial scarring. The gross specimen consisted of a solitary tan mass measuring 1.0 × 1.0 × 0.8 cm in size (Figure 3). Histologic examination revealed diffuse sheets of small to intermediate-sized lymphocytes within a background of densely collagenized tissue (Figure 4A). In some areas, structures resembling follicles were identified. On high-power magnification, the lymphocytic infiltrate appeared monotonous, with little to no mitotic activity (Figure 4B).

Fig. 3. Gross image demonstrating an approximately 1-cm lesion, which was fully excised during surgery.

Immunohistochemistry (IHC) was performed to better classify the lesion. The neoplastic cells were positive for CD10 (Figure 4C), CD20, BCL-6, and BCL-2; staining with these markers highlighted the follicular pattern of the tumor. Staining with CD3, CD5, CD23, CD30, CD34, TdT, and BCL-1 was negative in the neoplastic cells. The ki67 proliferation index was low (10%). Fluourescence in situ hybridization detected a translocation between chromosomes 14 and 18 in the neoplastic cell population. On the basis of the location, morphology, IHC findings, and genetic profile, this lesion was diagnosed as a grade 1 extranodal B-cell follicular lymphoma (FL).

The patient was subsequently referred to the Hematology and Oncology service at Harlem Hospital for further workup. She underwent positive emission tomography, which revealed multiple hypermetabolic lymph nodes, both above and below the diaphragm. Both before and during her diagnosis, she reported no B-type systemic symptoms, such as unexplained weight loss, fatigue, fever, or night sweats. The patient's lymphoma was classified as stage IIIA, and after further evaluation, the hematology/oncology team deemed that her case was low risk with a favorable prognosis. She was recommended for a 3- to 6-month follow-up interval with no further treatment, provided her disease remained asymptomatic.

DISCUSSION

NHLs are a group of histologically diverse B-cell and T-cell malignancies. Most cases of NHL are diagnosed in the lymph nodes; however, extranodal lymphomas account for over a quarter of NHLs.[14] Extranodal lymphomas are most commonly seen in the gastrointestinal tract, and the head and neck region is the second most common site of occurrence.[17] Most patients diagnosed with extranodal head and neck lymphomas are in their fifth to seventh decades of life, and the tumor has a male predilection.[14] Despite their propensity for the head and neck, less than 5% of extranodal lymphomas arise primarily within the oral cavity and jaws.[17]

The clinical presentation of oral lymphomas is often non-specific and therefore nondiagnostic. Most patients present with vague signs and symptoms, such as local swelling, pain, discomfort, or ulcerations. Gnathic lesions tend to present as ill-defined unilocular radiolucencies. These patients can either be asymptomatic or may present with dull, nonspecific bone pain.[15] In many cases, clinical and radiographic findings may mimic those of oral squamous cell carcinoma, and a

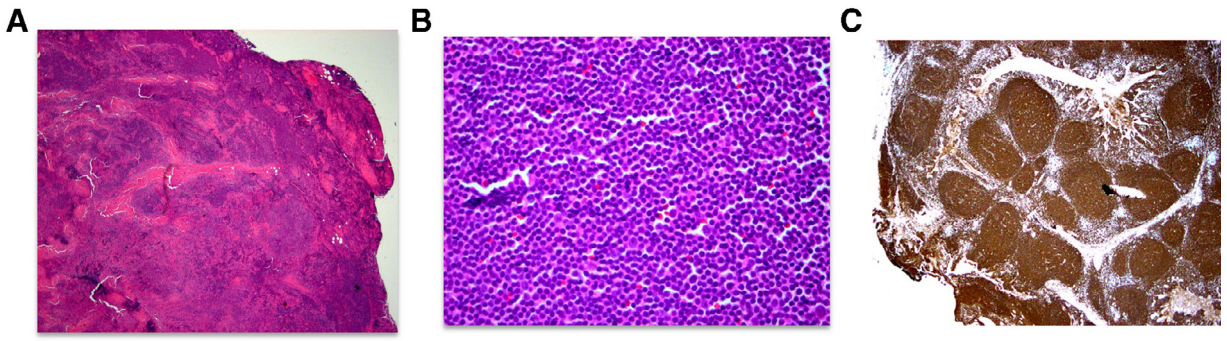

Fig. 4. **(A)** Low-power photomicrograph demonstrating diffuse sheets of small to intermediate-sized lymphocytes within a background of densely collagenized tissue (hematoxylin and eosin [H&E]; magnification × 40). **(B)** On high power, the lymphocytic infiltrate appeared monotonous, with little to no mitotic activity (H&E; magnification × 100). **(C)** The neoplastic cells were strongly positive for CD10 (CD10; magnification × 40). The cells were also positive for CD20, BCL-6 and BCL-2. *A high-resolution version of these slides for use with the Virtual Microscope are available as eSlides: VM05604 and VM05605.*

diagnosis of lymphoma is made only after biopsy and histologic analysis of lesional tissue.[17] Extranodal NHLs of the oral cavity have a predilection for the palatal mucosa and share some clinical features with salivary gland neoplasms.

FL is an NHL subtype that originates from germinal center B cells and represents the second most common form of NHL after diffuse large B-cell lymphoma. In 90% of FL cases, the neoplastic cells harbor a translocation between chromosomes 14 and 18 (t(14;18)), which causes upregulation of the BCL-2 protein and inhibition of apoptosis.[18] Despite their relative frequency, extranodal FLs within the oral cavity are extremely rare. After a review of extranodal oral lymphomas, Triantafillidou et al. found only 2 of 58 cases to be FLs.[19] Similarly, in a 15-year institutional review of oral lymphomas by Philipone et al., only 6 of 92 cases were confirmed to be FLs.[20]

Current World Health Organization guidelines for histologic grading of FL are based on the number of centroblasts present per high-power field. Grade 1 is given when fewer than 5 centroblasts are present; grade 2 when 6 to 15 are present; and grade 3 when greater than 15 are present. Grades 1 and 2 are considered low grade, and grade 3 is considered high grade and managed similarly to diffuse large B-cell lymphoma.

Staging is based on the Cotswolds-modified Ann Arbor system for lymphomas. This classification assigns stages I through IV based on the degree and location of lymph node involvement. As a general rule, stage III disease occurs when nodes above and below the diaphragm are involved. Modifiers are included with the stage to denote bulky disease (X), extranodal disease (E), and the presence (B) or absence (A) of B-type constitutional symptoms.

Stage, not grade, contributes to a patient's FL International Prognostic Index (FLIPI) score, which is an overall measure of prognosis. Poor prognostic factors that negatively impact the FLIPI score include age greater than 60 years, Ann Arbor stage III or IV, hemoglobin level less than 12 g/dL, elevated lactate dehydrogenase level, and 4 or greater affected nodes. The National Comprehensive Cancer Network practice guidelines recommend that low-risk and intermediate-risk patients with favorable FLIPI scores be monitored and high risk patients be treated with rituximab with or without additional chemotherapeutic agents.[21]

The histologic differential diagnosis of FL can be quite broad and requires exclusion of both reactive and malignant processes through IHC and molecular testing. Follicular lymphoid hyperplasia can be excluded on the basis of colocalization of CD10, BCL-6, and BCL-2 because reactive germinal centers stain positive for CD10 and BCL-6 but should not express BCL-2.[9] Colocalization is also helpful because CD10 and BCL-6 should not normally be expressed in primary follicles or mantle zone B cells.[22] Lymphocyte-rich variants of Hodgkin lymphoma can be differentiated from FL on the basis of positive staining with such markers as CD15 and CD30 in the former.[23] Positive staining with CD43 and lack of staining with CD10 would favor a diagnosis of mantle cell lymphoma or marginal zone lymphoma over FL.[24] Similarly, CD5 positivity in B cells would support a diagnosis of mantle cell lymphoma or chronic lymphocytic leukemia over one of FL.[25]

CONCLUSIONS

Extranodal FL, a rare manifestation of NHL, often presents with nonspecific clinical signs and symptoms making proper diagnosis difficult. For this reason, early biopsy of any suspicious or unexplained oral swellings is recommended to achieve an appropriate diagnosis and effective management.

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