Edentulous left maxillary ridge ulcerative swelling

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CLINICAL PRESENTATION

A 55-year-old male without cigarette-smoking, alcohol-drinking, or betel-quid -chewing habits was referred from a local dental clinic with the complaint of a swelling over the upper left edentulous ridge for the duration of 1 month. Other than a history of an extranodal diffuse large B-cell lymphoma on the upper left posterior gingiva, proven via histopathologic and immunohistochemical staining (Figures 1A to 1E), for which chemotherapy and radiotherapy had been administered 13 years ago, no other systemic diseases were noted. However, because of severe tooth mobility, the upper left posterior teeth had been extracted 6 months ago at another local dental clinic. After tooth extraction, the patient experienced pain over the left cheek and bloody tinged nasal discharge. For this reason, the patient visited the Department of Otorhinolaryngology at our institution 5 months ago for further examination; nasopharyngoscopy was performed, but no specific lesion was identified (Figure 2A), and a provisional diagnosis of chronic sinusitis was rendered. Then, after another month, the patient noted a swollen mass over the upper left edentulous ridge and sought treatment at the local dental clinic, and the dentist then referred the patient to the Department of Oral & Maxillofacial Surgery of our institution for further examination.

Intraoral examination revealed a painful, reddish, ulcerative, firm mass with an indurated border over the edentulous ridge of the upper left molar area, measuring about 2.5 × 2.0 cm (Figure 2B). Panoramic radiography showed an osteolytic lesion of the left posterior maxilla with an ill-defined border and discontinuity of the inferior and posterior borders of the left maxillary sinus (Figure 2C). Contrast maxillofacial computed tomography (CT) showed a destructive soft tissue mass involving the left buccal space, left posterior maxilla, left maxillary and ethmoid sinuses, and masticator space. Destruction of the left inferior orbital floor and borders of the left maxillary sinus and left posterior maxilla with involvement of the upper left gingiva was seen (Figures 2D to 2F), and some calcified foci within the lesion were also observed (Figure 2E).

DIFFERENTIAL DIAGNOSES

A painful ulcerative mass on the maxillary gingiva with widespread bony destruction in an adult elicits an extensive list of differential diagnoses. Because of the aggressive behavior of the lesion in the current case, the differential diagnoses focused on malignant neoplasms.

Oral squamous cell carcinoma (OSCC) is the most common epithelial malignancy in the oral cavity, accounting for greater than 90% of oral malignancies.[1] OSCC has varied clinical presentations, such as exophytic, endophytic, leukoplakic, erythroplakic, and erythroleukoplakic lesions. As in the current case, endophytic lesions appear clinically as irregularly shaped ulcers with a surrounding rolled border. Destruction of the underlying bones of the jaws is frequently observed as a moth-eaten radiolucency with ragged or ill-defined margins. However, the patient in the present case did not have cigarette-smoking, alcohol-drinking, or betel-quid-chewing habits, which have been reported to be the etiologic factors most commonly associated with OSCC in Taiwan.

Considering the past history of the patient, a recurrent diffuse large B-cell lymphoma was highly suspected. Oral lymphomas occur primarily in adults and most commonly involve the maxilla, mandible, tongue, palate, buccal mucosa, and gingiva.[2] Oral manifestations of lymphomas are nonspecific and are similar to those of many other diseases, such as advanced periodontal disease, osteomyelitis, or other malignancies encountered in the oral cavity. Clinically, the lesions appear as an erythematous or purplish swelling with or without an ulcerative surface. Such patients may have pain or paresthesia when the jaws are affected, which could be mistaken for toothache or a dentoalveolar

Statement of Clinical Relevance

Currently available data form a useful basis for clinical investigation and teaching regarding sinonasal carcinomas occurring in the oral cavity.

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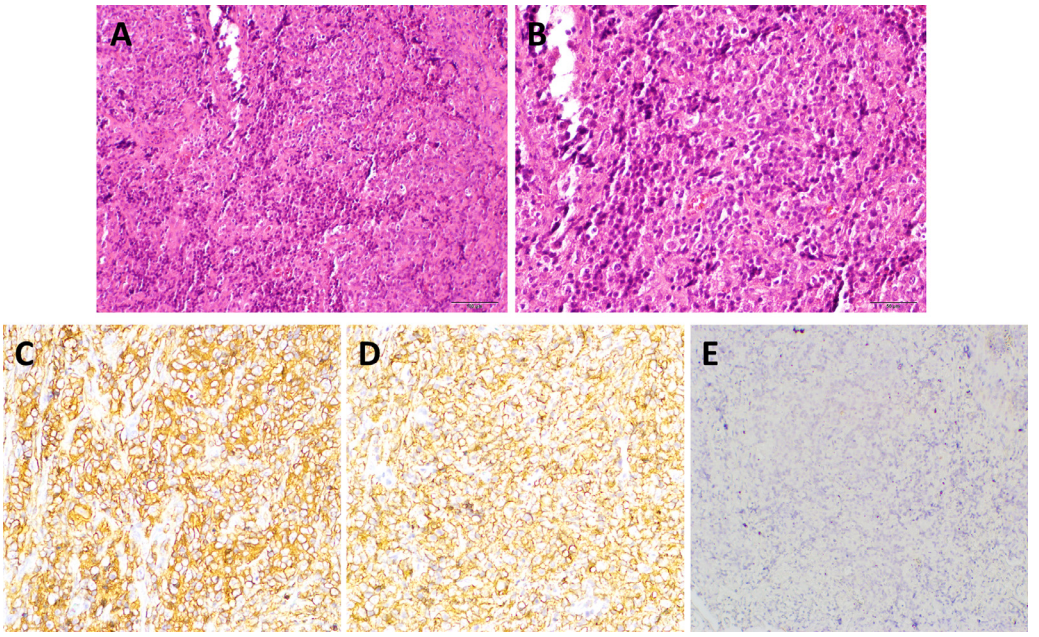

Fig. 1. **A, B,** Diffuse sheets of malignant lymphoid cells (**A,** hematoxylin and eosin [H&E], × 100; **B,** H&E, × 200). **C,** The tumor cells were positive for CD45 (× 100). **D,** Immunohistochemical staining for CD20 highlighted the neoplastic cells of B-cell origin (× 100). **E,** The tumor cells were negative for CK (AE1/AE3) (× 100).

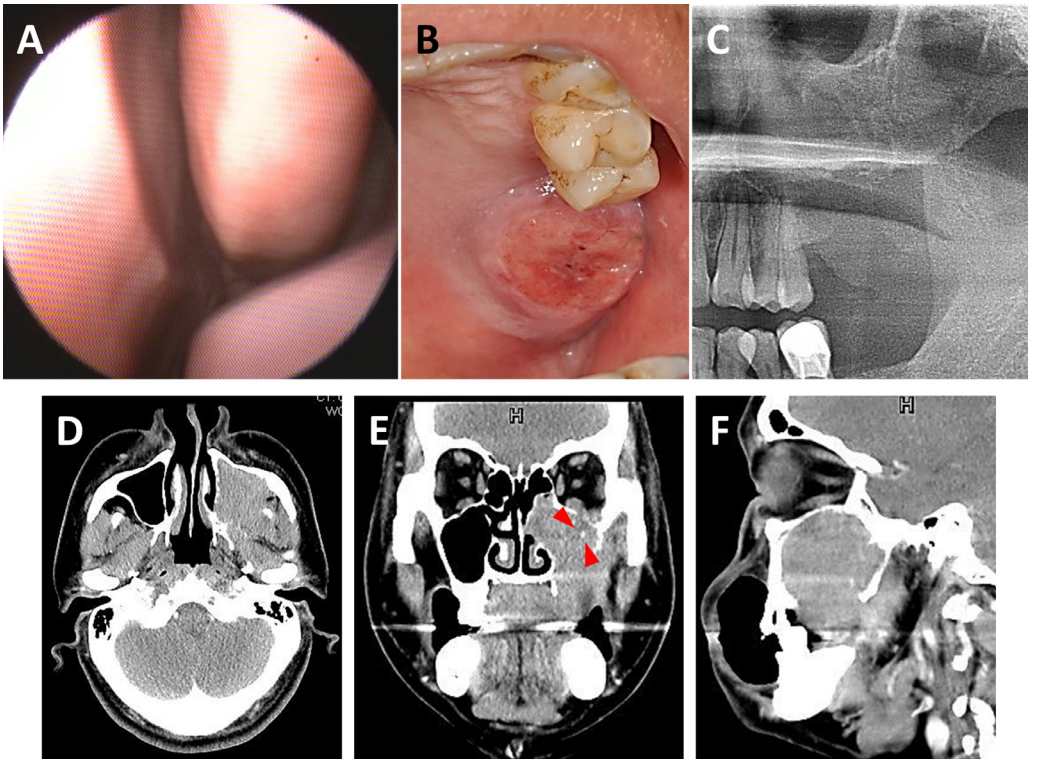

Fig. 2. **A,** No specific lesion was identified under nasopharyngoscopy. **B,** Reddish ulcerative mass with an indurated border over the edentulous ridge of the upper left molar area, measuring 2.5 × 2.0 cm. **C,** Ill-defined osteolytic lesion with an exophytic mass of soft tissue radiodensity of the left posterior edentulous ridge and discontinuity of the inferior and posterior borders of the left maxillary sinus. **D**–**F,** A destructive soft tissue mass involving the upper left gingiva, left posterior maxilla, left maxillary and ethmoid sinuses, and masticator space, with destruction of the left orbital floor and borders of the left maxillary sinus and the left posterior maxilla. Some calcified foci were observed within the lesion *(red arrow heads).*

infection. Radiographic examination usually reveals an osteolytic lesion with a poorly defined border.[2]

In the current case, the palatal mucosa was partially involved. The palatal mucosa is the most common site for minor salivary gland neoplasms;[3-5] therefore, palatal salivary gland malignancies were also included in our differential diagnoses. Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm, with a wide age range and a predilection for the female gender.[6] It usually presents as an asymptomatic red-blue swelling that could be mistaken for a mucocele. Ulceration is occasionally observed, as was seen in our case. Adenoid cystic carcinoma is the second most common salivary gland malignancy in the palate,[3,4,7] and most frequently occurs in middle-aged and older patients.[8] There is no apparent gender predilection in the case of palatal lesions. Clinically, these lesions usually appear as a slow-growing mass with a smooth or ulcerated surface, followed by the experience of pain. Lesions arising in the palate or maxillary sinus often display bony destruction on radiographic examination. Polymorphous adenocarcinoma exclusively occurs in minor salivary glands, and approximately 60% of cases involve the palatal area.[6,9] These lesions are most prevalent in the sixth to eighth decades, with two-thirds of cases occurring in women.[6] They most often present as a painless mass, occasionally associated with bleeding, discomfort, or ulceration.

In light of the extensive involvement of the left maxillary and ethmoid sinuses on radiographic examination, malignancy originating from the sinonasal tract wall was also strongly suspected. In terms of carcinomas arising from the aforementioned regions, despite some of the following disease entities being rare, keratinizing/nonkeratinizing squamous cell carcinoma (SCC), lymphoepithelial carcinoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, intestinal-type/non−intestinal-type adenocarcinoma, nuclear carcinoma of the testis (NUT), and SMARCB1 (INI-1)−deficient sinonasal carcinoma were included in the differential diagnoses. Other malignancies, such as rhabdomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, and Ewing sarcoma were also considered. Most of these malignant tumors share similar epidemiologic and clinical features, with frequent occurrence in the fifth to the seventh decades of life, or over a wide age range; however, there are some exceptions, in that the peak incidence of sinonasal rhabdomyosarcoma falls in the first decade of life, and angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, and Ewing sarcoma are more common in younger people.[6] The clinical presentations of these sinonasal malignancies are nonspecific; most appear as swollen masses, in combination with symptoms of nasal obstruction, discharge, epistaxis, pain, fullness, and eye-related symptoms, such as proptosis or diplopia.

DIAGNOSIS AND MANAGEMENT

An incisional biopsy was performed under local anesthesia. Microscopic examination with hematoxylin and eosin stain revealed a bisected gingival mucosa and fragmented sinus membrane. There were islands of epithelial neoplasm infiltrating the lamina propria of the gingiva (Figure 3A). These tumor cells displayed clear to vacuolated cytoplasm and nuclear hyperchromatism, pleomorphism, and abnormal mitotic figures (Figure 3B). No individual dyskeratosis or keratin pearl formation was observed. The morphology of the tumor cells under the respiratory epithelium was distinct from those in the oral mucosa. Sheets of tumor cells with an undifferentiated basaloid appearance were present in the stroma of the sinonasal mucosa (Figure 3C), and these cells showed enlarged blue round nuclei with inconspicuous nucleoli and scant cytoplasm (Figure 3D).

Corresponding to hematoxylin and eosin staining (Figure 4A, 5A and 6A), immunohistochemically, the tumor cells were diffusely positive for CK (AE1/AE3) (Figure 4B), p40 (Figure 4C), and p16 (Figure 4D); focally positive for CK5/6 (Figure 5B); and negative for CK7, CD3, CD20, SOX10, synaptophysin, chromogranin A, CD56 (Figure 5C), and NUT (Figure 6B). The tumor cells showed complete loss of nuclear SMARCB1 (INI-1) expression, with retained strong reactivity in the background inflammatory, stromal, and epithelial cells (Figure 6C). On the basis of these findings, the lesion was diagnosed as a SMARCB1 (INI-1)−deficient sinonasal carcinoma. As the tumor had invaded too extensively beyond being adequately resectable, the patient was referred to the Department of Oncology of our institution for further treatment. However, the patient sought a second opinion and treatment at another medical institution, and therefore, subsequent records of management and the prognosis of the patient were unavailable.

DISCUSSION

Sinonasal carcinomas comprise only 3% of malignancies occurring in the head and neck region[10] and are grouped into distinctive subtypes according to their clinical, histopathologic, immunohistochemical, and etiologic features. After reviewing the English language literature, to the best of our knowledge, SMARCB1-deficient sinonasal carcinoma is an uncommon sinonasal malignancy, fewer than 100 cases having been reported in the literature,[11] and the present report is the first detailing SMARCB1-deficient sinonasal carcinoma with involvement of the oral cavity. SMARCB1-deficient sinonasal carcinomas, first described by Agaimy et al.[12] and Bishop et al.[13], were categorized as a new entity of sinonasal carcinoma, distinguished by recurrent mutations in the *SMARCB1* gene and complete loss of the SMARCB1 (INI-1) protein. Currently, the etiology of SMARCB1-deficient sinonasal carcinoma is uncertain. In light of its rarity, it

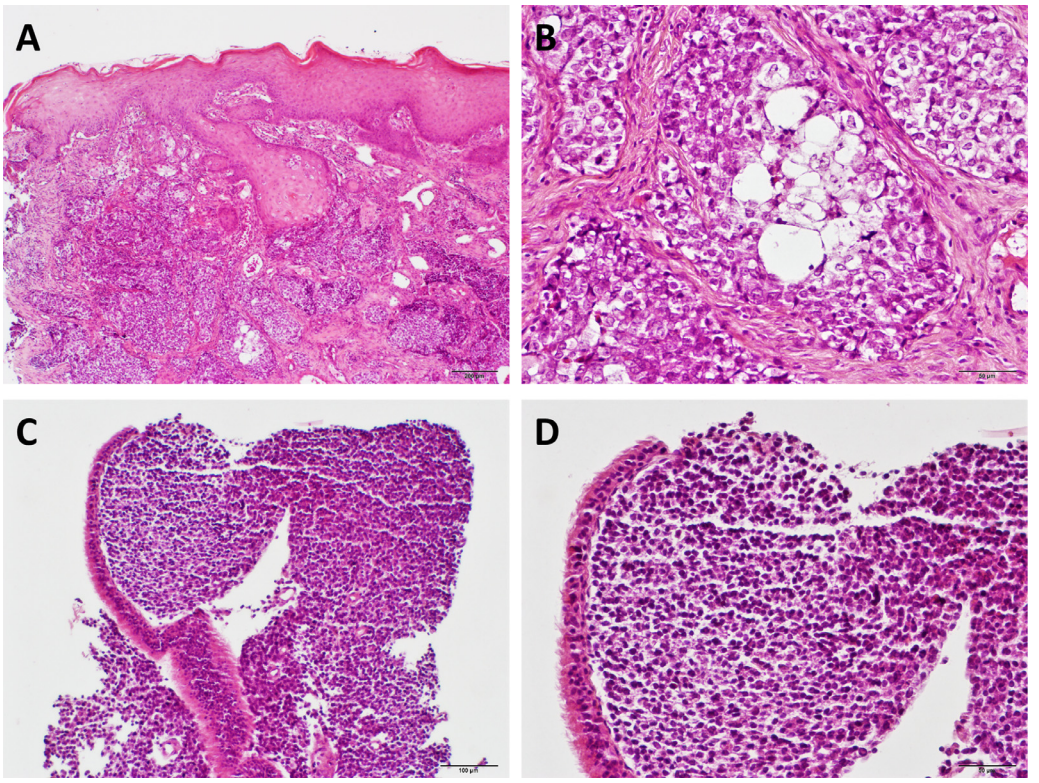

Fig. 3. **A,** Islands of epithelial neoplasm infiltrating the lamina propria of the gingival mucosa (hematoxylin and eosin [H&E], × 40). **B,** Tumor cells beneath the oral epithelium showed clear to vacuolated cytoplasm and nuclear hyperchromatism and pleomorphism (H&E, × 200). **C,** Tumor sheets with an undifferentiated basaloid appearance were present in the stroma of the sinonasal mucosa (H&E, × 100). **D,** Tumor cells under the respiratory epithelium revealed enlarged round nuclei with inconspicuous nucleoli and scant cytoplasm (H&E, × 200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05699.*

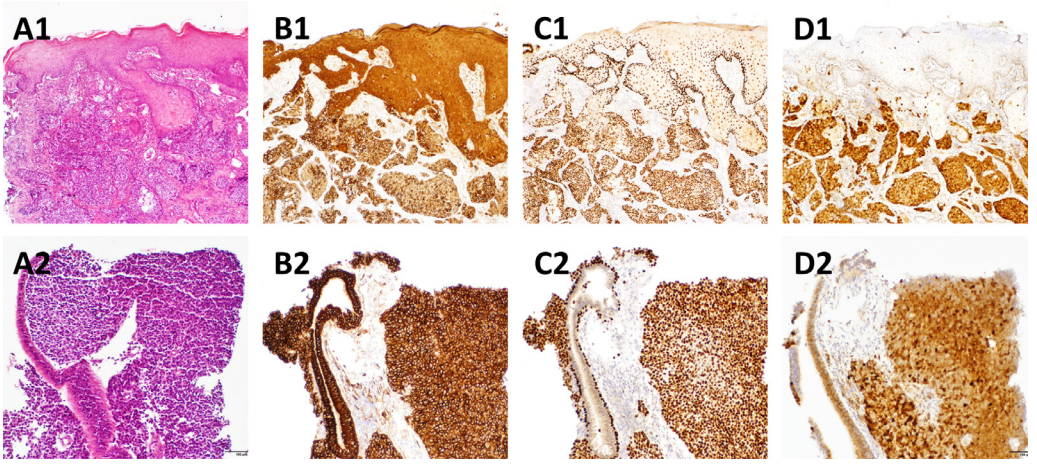

Fig. 4. **A,** Tumor cells of oral mucosa and sinonasal mucosa (hematoxylin and eosin [H&E], A1: oral mucosa × 40; A2: sinonasal mucosa × 100). **B,** The tumor cells had diffuse and strong cytoplasmic positivity for CK (AE1/AE3) (B1: oral mucosa × 40; B2: sinonasal mucosa × 100). **C,** The tumor cells exhibited nuclear positivity for p40 (C1: oral mucosa × 40; C2: sinonasal mucosa × 100). **D,** The tumor cells were diffusely positive for p16 (D1: oral mucosa × 40; D2: sinonasal mucosa × 100).

is difficult to define the specific causes of this newly described tumor. In the current case, the patient had undergone radiation therapy in the same region for diffuse large B-cell lymphoma 13 years ago. The subsequent SMARCB1-deficient sinonasal carcinoma could be speculated to be a radiation-induced secondary malignancy. However, more evidence is required to support the hypothesis that the development of the

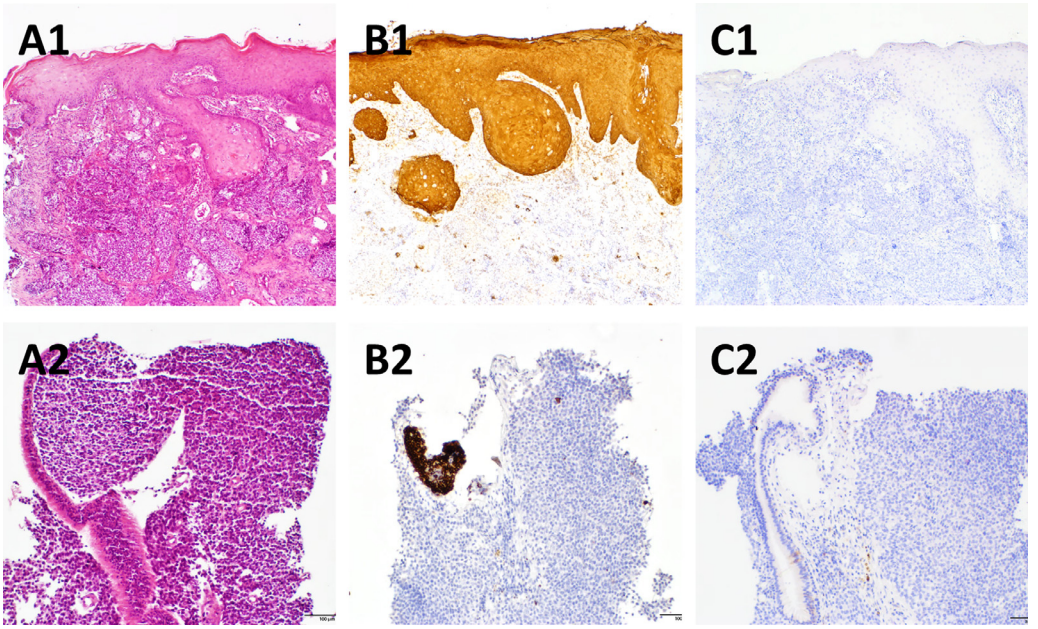

Fig. 5. **A,** Tumor cells of oral mucosa and sinonasal mucosa (hematoxylin and eosin [H&E]; A1: oral mucosa × 40; A2: sinonasal mucosa × 100). **B,** Most of the tumor cells were negative for CK5/6; only focal tumor cells were positive for CK5/6 (B1: oral mucosa × 40; B2: sinonasal mucosa × 100). **C,** The tumor cells were negative for CD56 (C1: oral mucosa × 40; C2: sinonasal mucosa × 100).

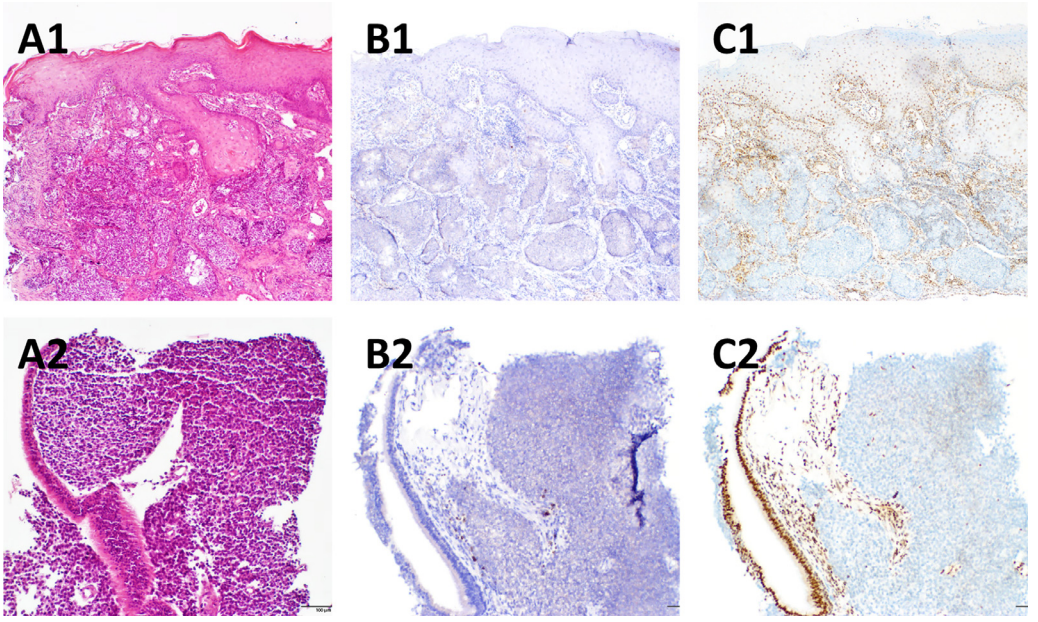

Fig. 6. **A,** Tumor cells of oral mucosa and sinonasal mucosa (hematoxylin and eosin [H&E], A1: oral mucosa × 40; A2: sinonasal mucosa × 100). **B,** The tumor cells showed negativity for NUT (B1: oral mucosa × 40; B2: sinonasal mucosa × 100). **C,** Complete loss of nuclear SMARCB1 (INI1) expression with retained strong reactivity in the background inflammatory and stromal cells was observed (C1: oral mucosa × 40; C2: sinonasal mucosa × 100).

SMARCB1-deficient sinonasal carcinoma was related to previous radiation therapy.

SMARCB1-deficient sinonasal carcinoma is encountered in patients across a wide age range (16−89 years), with a mild male predilection (male/female ratio = 3:2), and shows prevalence in the fifth to the seventh decades of life.[14-18] The most commonly affected sites are the nasal cavity and the ethmoid sinus, followed by the maxillary sinus, frontal sinus, and sphenoidal sinus.[14] Lesions may involve a single site or multiple sites of the

sinonasal area concurrently, and extension to adjacent structures, such as the orbit, skull base, intracranial area, and temporal fossa, is not uncommon. Clinical symptoms are nonspecific and resemble those of several benign or malignant tumors occurring in the sinonasal region. Patients may present with swelling, nasal congestion, epistaxis, rhinorrhea, or midfacial pressure. Eye-related symptoms, such as diplopia and exophthalmos, may also be found in patients with tumor involvement of the brain and the orbit, especially in cases where the tumor has invaded the superior nasal cavity and the ethmoid complex.[19] SMARCB1-deficient sinonasal carcinoma appears as a highly aggressive and infiltrative tumor on radiographs, with frequent skull/brain invasion. Calcifications are present in half the cases.[20] The clinical features of our patient were consistent with the above-mentioned features.

Microscopically, SMARCB1-deficient sinonasal carcinomas display various histopathologic appearances, which can be characterized into tw2o main patterns—basaloid and plasmacytoid/rhabdoid—and may be accompanied by focal squamoid or adenoid features.[14] The most common variant is the poorly differentiated basaloid pattern, which accounts for almost 60% of the tumors.[18] The tumor cells reveal uniform small to medium-sized rounded nuclei, a high nuclear-to-cytoplasmic ratio, variably prominent nucleoli, indistinctive cytoplasmic borders, and occasional nuclear palisading at the periphery of the tumor islands. Although a squamoid appearance may be observed in some cases, squamous differentiation or keratin pearl formation are absent. With regard to the second most common pattern, the tumors consist of plasmacytoid/rhabdoid cells with abundant eosinophilic cytoplasm and eccentric nuclei. These tumors may also display adenoid features. Because of the variety of microscopic findings, SMARCB1-deficient sinonasal carcinomas may be mistakenly diagnosed as basaloid SCC, nonkeratinizing SCC, sinonasal undifferentiated carcinoma, myoepithelial carcinoma, or poorly differentiated adenocarcinoma.[14]

The diagnosis of SMARCB1-deficient sinonasal carcinomas relies on the complete loss of SMARCB1 (INI-1) expression; however, these tumors demonstrate divergent immunoprofiles, significantly complicating their differential diagnosis. Almost all cases show diffuse, consistent expression of pancytokeratin and may exhibit focal expression of CK5, CK7, p63, and p40.[14,16-18] Focal expression of neuroendocrine markers, including CD56, synaptophysin, and chromogranin, has also been reported.[14,16,17] Similar to the present case, several other cases have shown focal or diffuse positivity for p16, but the results of further detection of human papillomavirus by a polymerase chain reaction−based method or RNA in situ hybridization did not indicate that SMARCB1-deficient sinonasal carcinoma is a high-risk human papillomavirus−related tumor.[14] Most cases are negative for myoepithelial markers, such as S100, smooth muscle actin, and calponin.[13,17,18] None of the previously reported cases was positive for the NUT protein.[14] According to the wide histomorphologic spectrum and immunophenotypic heterogeneity of SMARCB1-deficient sinonasal carcinoma, SMARCB1 should be included in the immunohistochemical marker panel for the workup of poorly differentiated epithelial malignancies that potentially originate from the sinonasal tract. Fluorescence in situ hybridization (FISH) was also applied to detect the deletion of *SMARCB1*. In that study, 78% of patients showing complete loss of SMARCB1 expression upon immunohistochemical staining displayed abnormal findings on FISH; however, the remaining 22% of the patients revealed normal signals of *SMARCB1* on FISH.[14] Therefore, the loss of SMARCB1 immunoexpression is not completely correlated with the results of FISH, and diagnosis of SMARCB1-deficient sinonasal carcinoma is based on the complete loss of SMARCB1 immunoexpression.

CONCLUSION

Although prognosis data for SMARCB1-deficient sinonasal carcinoma are limited, it is usually regarded as an aggressive malignancy. In the present case, no specific lesion was discerned via nasopharyngoscopy 5 months before the final diagnosis. The rapid onset and progression indicated its aggressive behavior. Almost two-thirds of patients die within 2 years of diagnosis,[14] and approximately one-third of patients experience postoperative local recurrence, regional lymph node metastases, and distant metastases.[14,18] For patients without distant metastases at the time of diagnosis, radical surgical resection with aggressive postsurgical radiochemotherapy is the recommended treatment modality.[14]

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