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Contents

Thrice Monthly Volume 11 Number 32 November 16, 2023

EDITORIAL

7741 Efficacy of probiotics supplementation in amelioration of celiac disease symptoms and enhancement of immune system

Moawad MHE, Alkhawaldeh IM, Naswhan AJ

ORIGINAL ARTICLE

Retrospective Cohort Study

7745 Effect of enhanced recovery after surgery with multidisciplinary collaboration on nursing outcomes after total knee arthroplasty

Liu J, Zheng QQ, Wu YT

Retrospective Study

7753 Appropriate leucine-rich α-2 glycoprotein cut-off value for Japanese patients with ulcerative colitis

Yamazato M, Yanai S, Oizumi T, Eizuka M, Yamada S, Toya Y, Uesugi N, Sugai T, Matsumoto T

7761 Association between depressive mood and body image and menopausal symptoms and sexual function in perimenopausal women

Ling J, Wang YH

7770 Clinical study of NFNC in the treatment of acute exacerbation chronic obstructive pulmonary disease patients with respiratory failure

Chen X, Dai L, Ma JZ, Chu XX, Dai L, Liu JM, Guo SW, Ru XW, Zhuang XS

7778 Mortal condition in an unusual localization, analysis of isolated tongue and tongue base abscesses

Bal KK, Gür H, Demir I, Ismi O, Vayisoglu Y, Gorur K, Ozcan C, Unal M

7785 Adult-onset hypophosphatemic osteomalacia as a cause of widespread musculoskeletal pain: A retrospective case series of single center experience

Kim S, Kim SW, Lee BC, Kim DH, Sung DH

Prospective Study

7795 Efficacy and safety of laparoscopic *vs* open gastrectomy after neoadjuvant therapy for locally advanced gastric cancer

Yu CD, Zhang K

Randomized Controlled Trial

7806 Effect of anesthesia induction with butorphanol on postoperative nausea and vomiting: A randomized controlled trial

Xie F, Sun DF, Yang L, Sun ZL

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 32 November 16, 2023

Contents

Randomized Clinical Trial

7814 Efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke

Zhang JQ, Pan ZB

META-ANALYSIS

7822 Analysis of the effectiveness of cognitive rehabilitation for patients with chronic mental illness: A meta-analysis

Jang JS, Oh S, Kim G, Lee N, Song H, Park J, Lee Y, Kim M, Kwon M

SCIENTOMETRICS

7833 Emerging trends and hotspots of Nuclear factor erythroid 2-related factor 2 in nervous system diseases

Chang XQ, Xu L, Zuo YX, Liu YG, Li J, Chi HT

CASE REPORT

7852 Transcatheter embolization for hemorrhage from aberrant testicular artery after partial nephrectomy: A case report

Youm J, Choi MJ, Kim BM, Seo Y

7858 Persistent left superior vena cava in right hemiarch replacement under deep hypothermic circulatory arrest: A case report

Mi ZY, He G, Gao HL, Li C

7865 Type II Abernethy malformation with cystic fibrosis in a 12-year-old girl: A case report

Zhang LJ, Liu XY, Chen TF, Xu ZY, Yin HJ

7872 Glucocorticoid reduction induced chorea in pediatric-onset systemic lupus erythematosus: A case report

Xu YQ, Wang M, Zhang Y

7876 Primary pulmonary lymphoepithelioma-like carcinoma misdiagnosed as lung squamous cell carcinoma: A case report

Yin CJ, Wang GJ, Su XM, Li D

7881 Median arcuate ligament syndrome complicated with gallbladder stones: A case report

Dang JQ, Wang QQ, Yang YL, Shang L, Bian QT, Xiang HJ

7888 Uterine rupture due to adenomyosis in an adolescent: A case report and review of literature

Kim NI, Lee JS, Nam JH

7895 Multiple therapies relieve long-term tardive dyskinesia in a patient with chronic schizophrenia: A case report

Lv L, Guo P, Feng M, Fang Y, Wang SK, Chen HX

7900 Lung ultrasound for the early diagnosis of acute lung injury: A case report

Zheng X, Liu N

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 32 November 16, 2023

Contents

7905 New treatment for gastric duplication cyst: Endoscopic ultrasonography-guided fine-needle aspiration combined with lauromacrogol sclerotherapy: A case report

Bu YW, Han RQ, Ma WQ, Wang GN, Er LM

7911 Immunotherapy in SMARCB1 (INI-1)-deficient sinonasal carcinoma: Two case reports

Zhang L, Gao AX, He YL, Xu MJ, Lu HJ

7920 Interstitial pneumonia combined with nocardia cyriacigeorgica infection: A case report

Qi DD, Zhuang Y, Chen Y, Guo JJ, Zhang Z, Gu Y

7926 Intracranial infection accompanied sweet's syndrome in a patient with anti-interferon-γ autoantibodies: A case report

Zheng JH, Wu D, Guo XY

LETTER TO THE EDITOR

7935 Potential and limitations of ChatGPT and generative artificial intelligence in medical safety education

Wang X, Liu XQ

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 32 November 16, 2023

Contents

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AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

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CASE REPORT

Immunotherapy in SMARCB1 (INI-1)-deficient sinonasal carcinoma: Two case reports

Lu Zhang, Ai-Xin Gao, Yu-Lu He, Ming-Jin Xu, Hai-Jun Lu

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Abstract

BACKGROUND

SMARCB1/INI-1 deficient sinonasal carcinoma (SDSC) is a rare subset of sinonasal undifferentiated carcinoma with a poor prognosis. Here, we present two case reports of SDSC patients. We also review the literature on this tumor. This is the first published report of SDSC treatment with immunotherapy.

CASE SUMMARY

Here we present two patient cases of SDSC in which initial consultation and diagnosis were complicated but SDSC was ultimately diagnosed. One patient received a traditional treatment of surgery and adjuvant chemoradiotherapy, while the other patient received additional immunotherapy; the prognoses of these two patients differed. We review previous diagnostic literature reports and SDSC treatments and provide a unique perspective on this rare type of tumor.

CONCLUSION

SDSC is a rare, diagnostically challenging carcinoma with a consistently poor prognosis, early distant metastases, and frequent recurrence. Timely diagnosis and intervention are critical for treatment, for which the standard of care is surgery followed by adjuvant chemoradiotherapy, though immunotherapy may be an effective new treatment for SDSC.

Key Words: SMARCB1; INI-1; Sinonasal carcinoma; Gene deficient; Immunotherapy;

Surgery; Case report

Core Tip: SMARCB1/INI-1 deficient sinonasal carcinoma (SDSC) is a rare carcinoma with a poor prognosis and no standard treatment guidelines. Currently, the most effective treatment option is surgery followed by adjuvant chemoradiotherapy. Here, we present two SDSC patients with complicated consultation experiences. The patients differed in treatments and prognoses, and there was no indications of local recurrence or distant metastases in patient with immunotherapy. We also review the literature on SDSC treatment. This first report on immunotherapy in SDSC provides a unique perspective on treatments for this rare tumor.

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INTRODUCTION

Approximately 3%–5% of all sinonasal carcinomas are deficient in nuclear expression of SMARCB1, a tumor-suppressor gene on chromosome 22q11.2 that encodes INI-1 protein[1]. These SMARCB1-deficient sinonasal carcinomas (SDSC) are highly aggressive and malignant with poor prognoses[2-4]. SDSC was first described in 2014 by Agaimy *et al*[3] and Bishop *et al*[5], though the tumor is rare and remains classified by the World Health Organization only as a variant pattern of sinonasal undifferentiated carcinoma (SNUC)[6]. Patients are typically diagnosed with high-mortality locally advanced disease, but no standard guidelines are approved for disease management, and treatment options remain controversial[7]. Therapeutic approaches must be found to cure this disease with minimal side effects.

Developments in cancer molecular biology and immunology have provided immunotherapy treatments for other head and neck tumors, and many locally advanced and metastatic malignancies respond well to immunotherapy[8]. SDSC tumor progression is driven by the downregulation of the major histocompatibility complex and a tumor microenvironment that promotes immune escape, meaning that immunotherapy may be an effective intervention, though there is currently limited evidence of efficacy in treating SDSC[9].

In this report, we describe two cases of treatment progression in patients with SDSC who received a traditional treatment with surgery and adjuvant chemoradiotherapy, with one patient also receiving immunotherapy and remaining disease-free upon follow-up. Unlike most previously reported retrospective diagnostic cases, these two cases were prospectively diagnosed. To our knowledge, this is the first literature report of an SDSC patient responding well to immunotherapy; such cases set an important precedent for the treatment of this rare tumor.

CASE PRESENTATION

Chief complaints

Case 1: A 34-year-old man with a 20-pack-year smoking history presented with an intermittent left nasal obstruction with headache and loss of smell for about 1 mo.

Case 2: A 50-year-old man with a 10-pack-year smoking history presented with a swollen left eye for 4 wk.

History of present illness

Case 1: This patient presented to another hospital with an intermittent left nasal obstruction with headache and loss of smell for about 1 mo. Magnetic resonance imaging (MRI) of the nasopharynx revealed a mass in the left nasal cavity with invasion of the left axillary sinus, bilateral ethmoid sinus, and sphenoid sinus. He underwent a lumpectomy and was diagnosed with a poorly differentiated sinonasal carcinoma that did not exclude SDSC.

Case 2: Symptoms began 4 wk prior and were associated with episodic left-sided epistaxis.

History of past illness

Neither patient had past disease.

Personal and family history

Neither patient exhibited past personal or family history.

Physical examination

Case 1: Physical examination indicated hyperemia nasal mucosa, with the nasal septum deviated to the right and the left nasal passage showing changes after surgery.

Case 2: Physical examination revealed a centered nasal septum with no neoplasms and purulent discharge in both nasal passages.

Laboratory examinations

Case 1: Laboratory studies revealed a squamous cell carcinoma antigen concentration of 1.13 ng/mL (normal range ≤ 2.50 ng/mL), a carcinoembryonic antigen concentration of 1.07 ng/mL (normal range ≤ 3.40 ng/mL), and a cytokeratin 19 fragment antigen concentration of 1.75 ng/mL (normal range ≤ 3.30 ng/mL).

Case 2: Laboratory studies revealed a squamous cell carcinoma antigen concentration of 2.22 ng/mL (normal range ≤ 2.50 ng/mL), a carcinoembryonic antigen concentration of 1.56 ng/mL (normal range ≤ 3.40 ng/mL), and a cytokeratin 19 fragment antigen concentration of 1.62 ng/mL (normal range ≤ 3.30 ng/mL).

Imaging examinations

Case 1: This patient presented to our hospital for a follow-up examination on September 21, 2021. An MRI of the nasopharynx showed a heterogeneously enhancing mass in the anterior part of the left maxillary sinus that was considered a residual tumor (Figure 1A-C).

Case 2: Post-contrast MRI was performed and showed a large mass in the left ethmoid sinus and sphenoid sinus measuring 4.2 cm × 2.7 cm × 1.6 cm, extending into both the left orbit and cranial cavity without lymphadenopathy (Figure 1D-F).

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 1: The surgically resected tissue measured 3.5 cm × 2.4 cm × 1.2 cm and was grey-brown in color. Tumor cells were histologically nested (Figure 2A) with diffuse expression of creatine-kinase (CK); tumors were immunohistochemically negative for Vimentin, S-100, CD56, and thyroid transcription factor 1 (Figure 2B-E). Immunohistochemistry revealed a loss of INI-1 protein in the nuclei of the tumors and surrounding tissue. The Ki-67 proliferative index was approximately 70%.

Case 2: Pathological examination revealed diffuse expression of CK, CK8/18, and Nestin. Cells were partially positive for P40, P63, Syn, CD117, S-100, and epithelial membrane antigen, and were negative for CD56, leukocyte common antigen, CK7, H3K36M, and anti-smooth muscle antibody (Figure 3). The patient refused further pathological examination for INI-1 staining and was initially misdiagnosed with adenoid cystic carcinoma because of the glandular morphology (Figure 3B). Fortunately, an inter-institutional pathology consultation (Tongren Hospital, Beijing) demonstrated the loss of SMARCB1 (INI-1) expression in tumor nuclei.

FINAL DIAGNOSIS

These two patients were diagnosed with SDSC based on immunohistochemical staining and morphology. Tumors were diagnosed as pathological T4N0M0 stage IV using the tumor-node-metastasis staging system (American Joint Committee on Cancer, 8th edition).

TREATMENT

Case 1: The multidisciplinary care team proposed surgery followed by chemoradiotherapy. The patient underwent a complete excision of the tumor with resection of the bony wall of the ethmoid sinus, followed by adjuvant radiotherapy (60 Gy in 30 fractions, 5 d/wk for 6 wk) and chemotherapy (docetaxel plus cisplatin, administered in four cycles every 3 wk). The multidisciplinary team discussed this case again after surgery and chemoradiotherapy, and the patient and family decided to initiate immunotherapy with anti-PD1 (tislelizumab) that began in March 2022.

Case 2: This patient underwent complete resection of the tumor with frontal sinusotomy, total ethmoidectomy, and skull base reconstruction, and then finished subsequent radiotherapy (70.4 Gy in 32 fractions, 5 d/wk) and adjuvant chemotherapy (paclitaxel plus cisplatin, administered in four cycles every 3 wk).

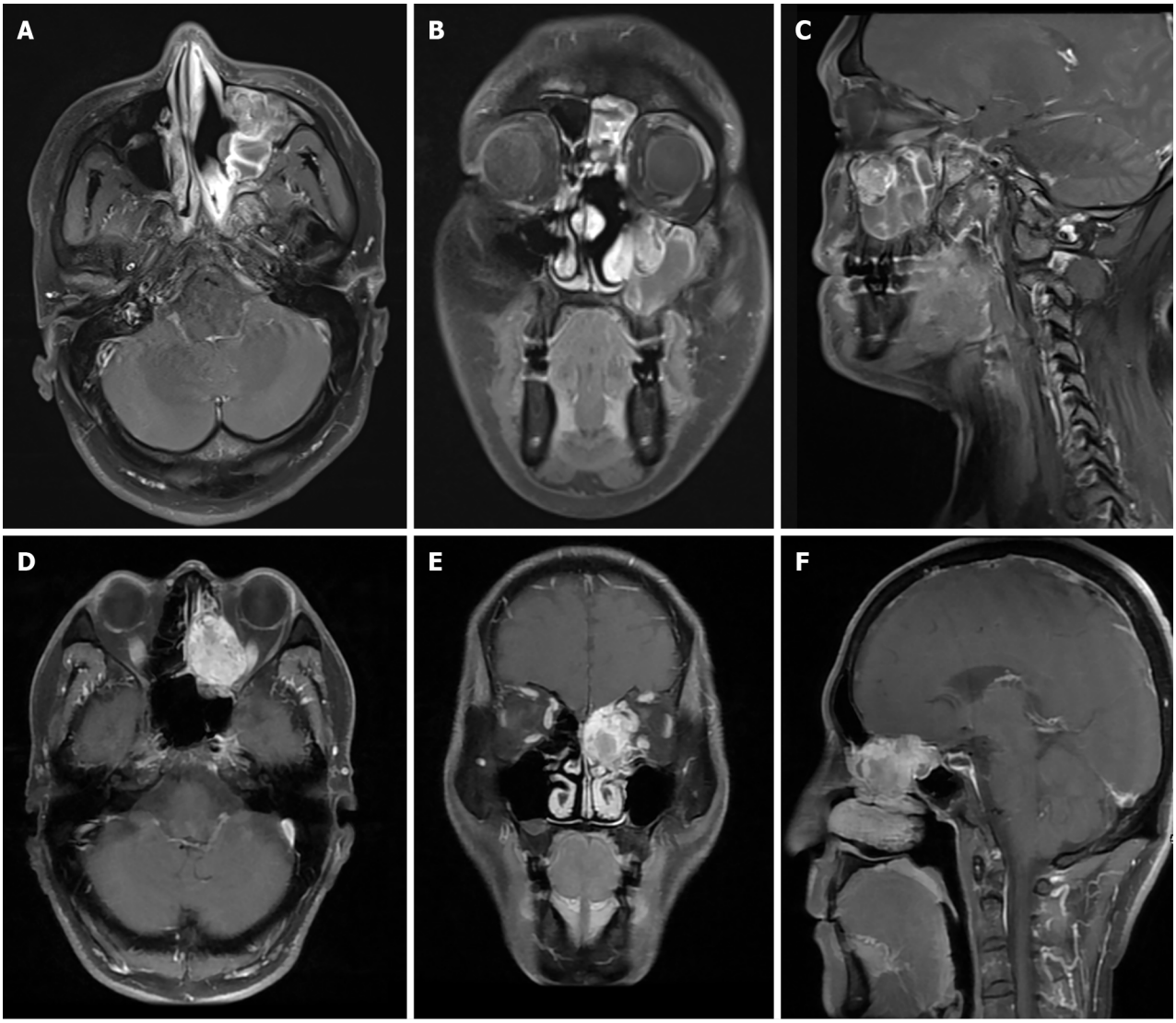

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Figure 1 Preoperative T1 post contrast magnetic resonance images of Case 1 and 2. A and D: Axial section; B and E: Coronal section; C and F: Sagittal section.

OUTCOME AND FOLLOW-UP

Case 1: After 2 years of follow-up, there were no serious adverse reactions, and laboratory/imaging tests indicated no local recurrence or distant metastasis. Figure 4 shows the timeline of this patient's clinical management and outcome.

Case 2: Through August 22, 2022, we observed no serious adverse reactions, regional recurrences, or distant metastases, though laboratory tests revealed elevated tumor markers that warrant a high degree of vigilance. The patient refused further image examinations. Figure 5 shows the timeline of this patient's clinical management.

DISCUSSION

SMARCB1/INI-1 is a tumor suppressor gene involved in epigenetic regulation of gene transcription[10]. The encoded INI-1 protein is a core subunit of the switch/sucrose nonfermenting (SWI/SNF) complex, which is ubiquitously expressed in healthy cell nuclei and participates in transcriptional regulation and many other cell functions (Figure 6)[11]. SDSC is a highly aggressive and rare subset of SNUC with poor prognosis that is characterized by loss of nuclear expression of SMARCB1. This tumor type has been well studied (Figure 7)[5,7], and the clinical manifestations, diagnosis, differential diagnosis, and treatment of SDSC have been systematically reviewed[12-16]. In this report, we describe two complex patient cases that were ultimately diagnosed correctly as SDSC. Below, we review the SDSC literature regarding clinical presentation, diagnosis, and treatment.

SDSC occurs mostly in middle-aged and elderly people (age range 19–89 years) and is slightly more common in males. Tumors are typically located in the nasal cavity and invade the adjacent paranasal sinus, fossa orbitalis, and cranial base

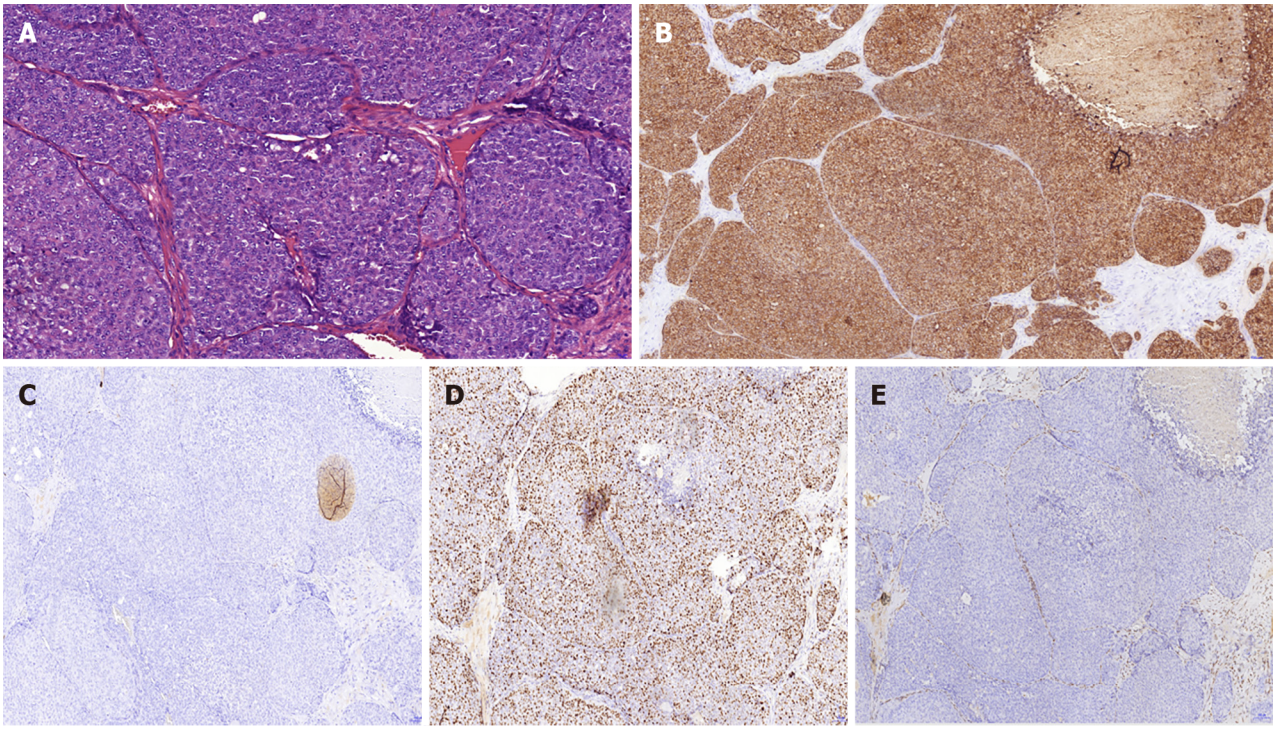

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Figure 2 Histopathological and immunohistochemical features of Case 1. A: Tumor cells grew as nested (hematoxylin and eosin staining, ×200); B and C: The tumor cells were positive for creatine-kinase (×100) and negative for S-100 (×100); D: The Ki-67 proliferative index was approximately 70% (×100); E: INI-1 expression was present in the nuclei of surrounding non-neoplastic cells but completely absent in the tumor cells (×100).

[17]. Patients mostly complained of different degrees of nasal obstruction, epistaxis, headache, or blurry vision[7,18]. SDSC patients generally present these nonspecific symptoms with massive and locally advanced tumors, with > 60% staged as T4 with lung metastases. Imaging often shows a mass with infiltrative growth and low or moderate MRI signal. Here, we report a 34-year-old man and a 50-year-old man who presented with a nasal obstruction and eye swelling, respectively; both were diagnosed with stage T4 tumors. MRI images are mentioned above.

Clinically, SDSC is a misunderstood malignancy[18,19]. A systematic review has showed that 72.5% of patients were first misdiagnosed initially[16]. SDSC should be differentiated from a variety of poorly differentiated or undifferentiated sinonasal tumors. Two studies have compared SDSC with INI-1-positive SNUC; SDSC has a lower recurrence rate (17%-53%) than other sinonasal malignancies (53%-60%), while SNUC patients experience disease-free survival for approximately four times longer than SDSC[14,20]. Thus, differentiating SDSC from SNUC is essential for selecting appropriate targeted therapies. SDSC has various morphologic features but no clear differentiation; Agaimy *et al*[7] found that most tumors display either a predominantly basaloid (61%) or plasmacytoid/rhabdoid (36%) morphology. In the latter, tumor cells have abundant eosinophilic cytoplasm with inclusion bodies, eccentric nuclei, and glandular differentiation. This glandular morphology was observed in case 2 (Figure 4B), which led to the initial misdiagnosis as adenoid cystic carcinoma. Using microscopic morphology alone, SDSC is difficult to diagnose, so undifferentiated tumors should be examined immunohistochemically for INI-1[3,5].

As a highly aggressive and rare malignancy, timely intervention is critical. No standard guidelines are currently approved for the management of this rare carcinoma[21]. The most effective treatment option for SDSC is a multimodal approach with surgery and subsequent adjuvant chemoradiotherapy, though few retrospective studies are available.

One retrospective study demonstrated that comprehensive surgical treatment can prolong recurrence-free survival (RFS), while non-surgical systemic therapy was an independent poor prognosis factor[16]. Moreover, surgery combined with chemoradiotherapy had a better overall-survival (OS) and RFS than surgery alone; surgical treatment alone often resulted in early relapse and metastatic disease. As Agaimy reported, over 77% of patients underwent surgical resection with adjuvant chemoradiation and currently remain tumor-free after follow-up[7]. Therefore, adjuvant radiation therapy or chemoradiotherapy is required to improve prognosis; neoadjuvant chemoradiation with cisplatin also reduced tumor volume and morbidity relative to surgical resection alone[18,22]. Wasserman *et al*[22] and Kakkar *et al*[18] found that tumor volume was dramatically reduced by pre-surgical neoadjuvant treatment, which facilitated complete surgical resection and improved patient OS. Therefore, neoadjuvant therapy may be a suitable treatment for large tumors prior to surgical excision.

Recurrence and mortality rates, however, are still typically high. A systematic review of 82 cases revealed that most SDSCs are diagnosed at an advanced stage, resulting in a poor prognosis (average mortality 45.3%), a median OS of 22 mo, and a high frequency of distant metastases (49.3%)[15]. Immune escape is enabled by the downregulation of major histocompatibility complex molecules[9], but the upregulation of preferentially expressed antigens in melanoma and breast cancer type 1 (BRCA1) may pave the way for immunotherapy[23]. Immunotherapy may reduce relapse and

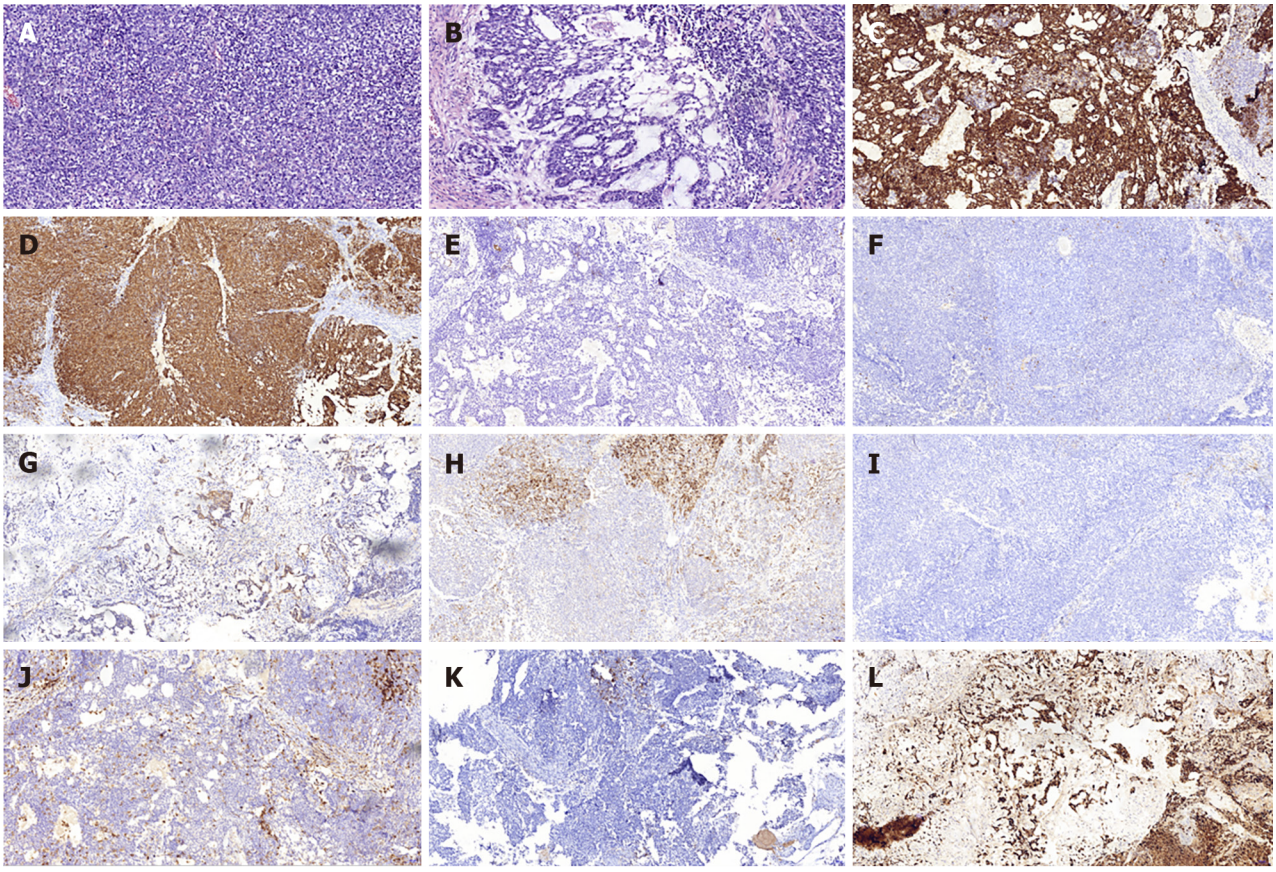

Figure 3 Histopathological and immunohistochemical features of Case 2. A and B: Tumor cells had no clear differentiation, glandular morphology and mucoid interstitial substance could be observed in some areas. (Hematoxylin and eosin staining, ×200); C-J: The tumor cells were diffuse positivity for CK(x100), CK8/18 (×100), partial positivity for P40 (×100), P63 (×100), S-100 (×100), Syn (×100), and negativity for CK7 (×100), LCA (×100); K: Tumors had a PD-L1 combined positive score of one (×100); L: The Ki-67 proliferative index was approximately 70% (×100).

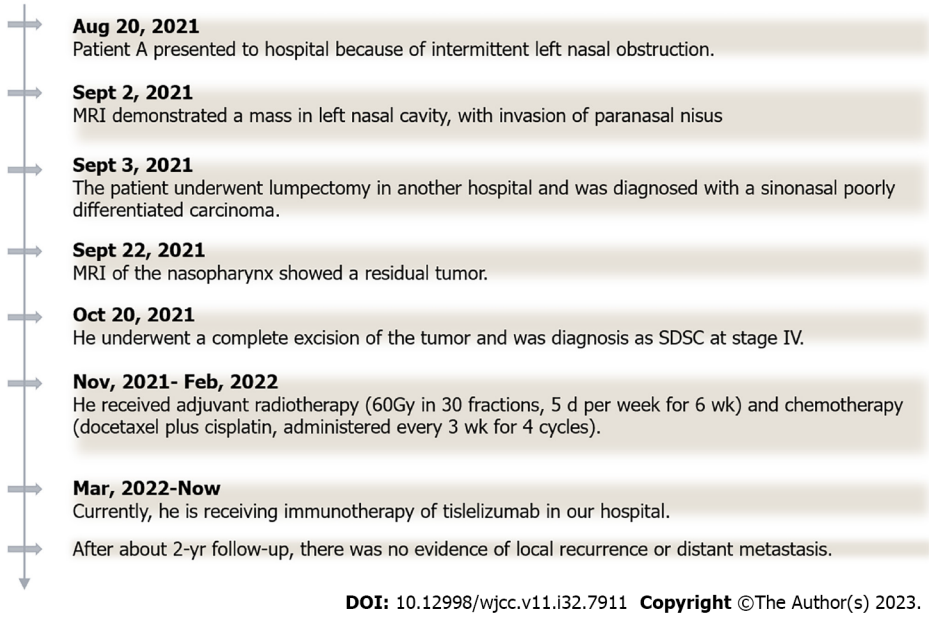

Figure 4 Timeline of Case 1's clinical management and outcome. MRI: Magnetic resonance imaging; SDSC: SMARCB1-deficient sinonasal carcinomas.

Aug 1, 2021
Patient B presented in our hospital with 4-week swollen left-side eye and episodic left-sided epistaxis.

Aug 4, 2021
Post contrast MRI showed a large mass in the left ethmoid sinus and sphenoid, extending into both left orbit and cranial cavity without lymphadenopathy

Aug 6, 2021
He underwent complete resection of the tumor with frontal sinusotomy, total ethmoidectomy and skull base reconstruction.

Aug 15, 2021
This patient was diagnosed as T4NOMO SDSC at stage 4 finally.

Aug, 2021- Dec 2021
Then he finished subsequent radiotherapy at a prescribed dose of 70.4Gy in 32 fractions given on 5 d per week and adjuvant chemotherapy with paclitaxel plus cisplatin per 3 wk for 4 cycles.

Aug 9, 2022- Dec 26, 2022
Laboratory tests reveal elevated tumor markers.

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Figure 5 Timeline of Case 2's clinical management and outcome. SDSC: SMARCB1-deficient sinonasal carcinomas.

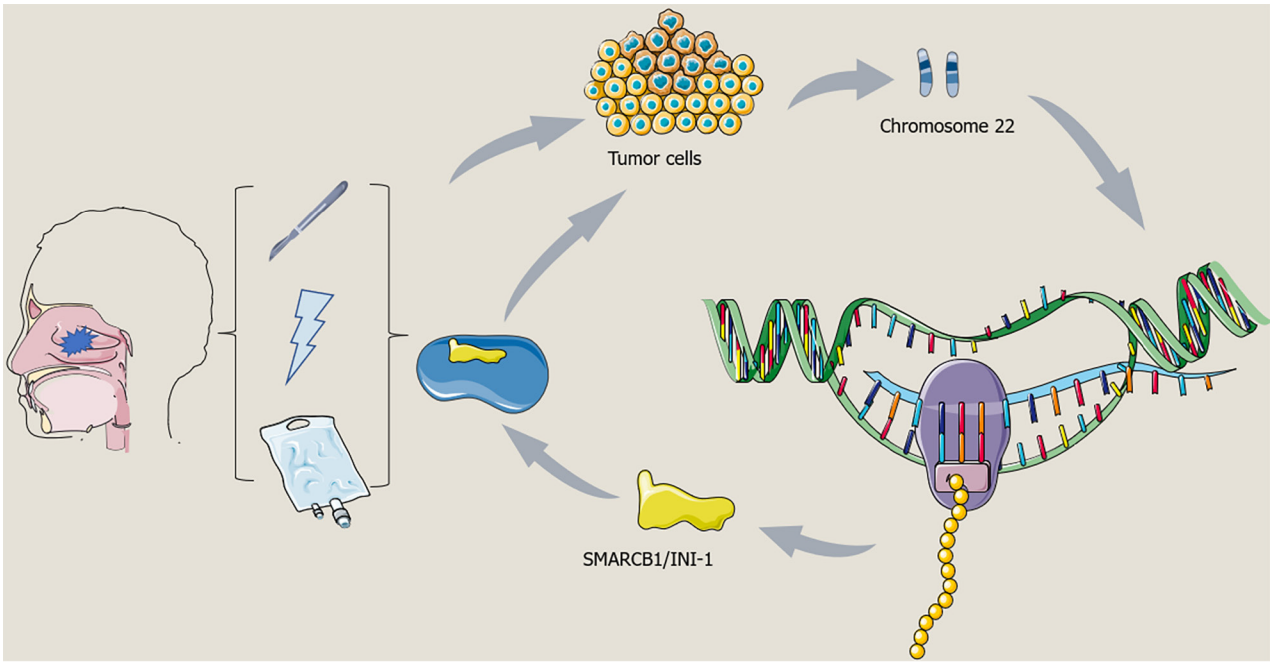

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Figure 6 SMARCB1 is a tumor suppressor gene located at chromosome 22q11.2. The protein encoded by this gene is a core subunit of the switch/sucrose nonfermenting complex, which can be ubiquitously expressed in the nucleus of all normal cells and can participate in regulating transcription and many other functions of cells.

mortality in the treatment of SDSC.

Clinical data on SDSC immunotherapy are lacking; fewer than five cases of sinonasal cancer treatment with immunotherapy have been reported[24,25]. In one reported SNUC case, a young man received triple modality treatment (chemotherapy, surgery, and radiation) and showed a long-lasting response to immunotherapy[25]. SDSC may also respond well to this treatment. In this report, we compared two SDSC patients with or without immunotherapy, thus providing the first published report of SDSC treatment using immunotherapy. Immunotherapy produced a long-lasting progress-free survival that sets a new precedent for immunotherapy in SDSC. However, several limitations exist for using immunotherapy with SDSC patients, and more clinical evidence and mechanistic studies are required.

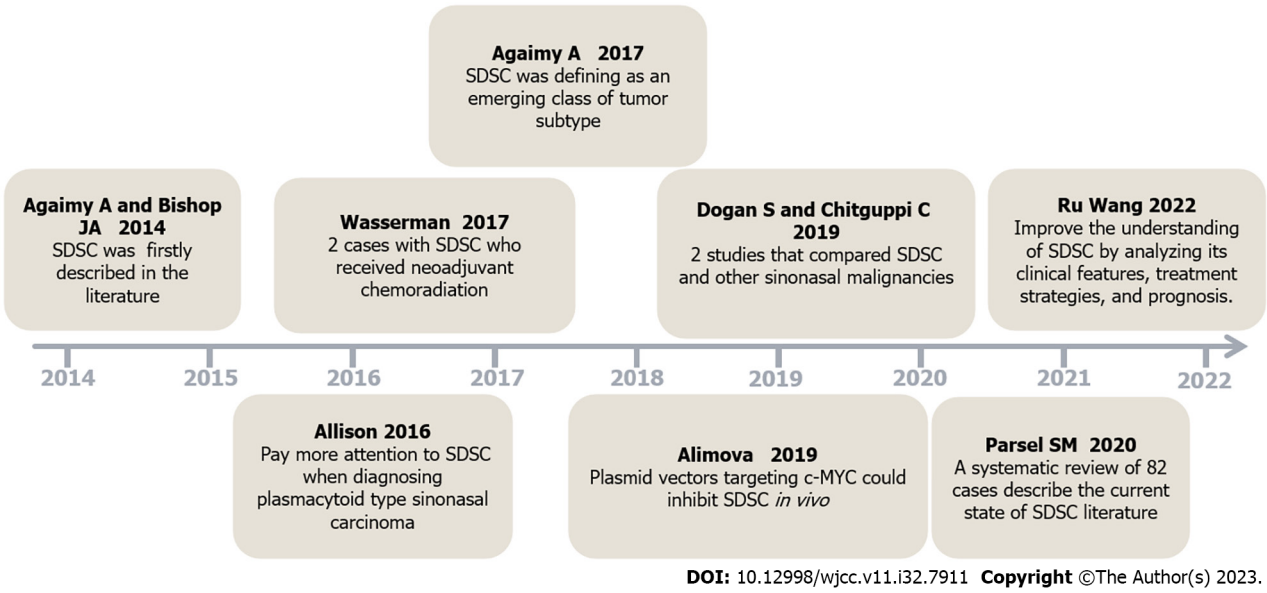

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Figure 7 Selected publications further studied SMARCB1-deficient sinonasal carcinoma. SDSC: SMARCB1-deficient sinonasal carcinomas.

CONCLUSION

In this report, we describe two SDSC patients with different prognoses. SDSC is a rare carcinoma with early distant metastases and a poor prognosis. The patient who underwent traditional treatment showed elevated tumor markers at the 1-year follow-up, while the patient who received immunotherapy experienced a long-lasting progress-free survival. This is the first report of immunotherapy treatment in SDSC patients and provides a valuable reference for the clinical treatment of this rare tumor.

FOOTNOTES

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