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Title Page

Title: SMARCB1 (INI1) -deficient sinonasal carcinoma: A series of thirteen cases with assessment of histological patterns

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Abstract

A significant proportion of sinonasal malignancies is comprised of poorly differentiated/undifferentiated carcinomas that defy accurate histological classification, and behave aggressively. Recent years have seen a refinement of this spectrum by inclusion of novel entities harboring specific genetic alterations, including SMARCB1 (INI1)-deficient sinonasal carcinoma (SDSC), characterized by inactivating alterations in *SMARCB1* gene, as demonstrated by loss of INI1 immunoexpression. Cyclin D1 is a cell-cycle regulatory protein downstream of INI1. Loss of INI1 leads to derepression of cyclin D1 transcription, suggesting its role as a putative therapeutic target. However, cyclin D1 expression has not been assessed in SDSCs.

We retrieved all sinonasal carcinomas, including sinonasal undifferentiated carcinoma (SNUC), undifferentiated carcinoma, poorly differentiated squamous cell carcinoma (PDSCC), and adenocarcinoma. Histopathological features were reviewed. INI1 immunohistochemistry was performed. Cyclin D1 was performed in cases showing INI1 loss. Loss of INI1 staining was seen in thirteen cases (5.8%), including 11 males and two females (age range: 11-65 years). Original diagnoses included SDSC (3/13), SNUC (3/13), adenocarcinoma (3/13), PDSCC (2/13), and poorly differentiated carcinoma (2/13). Tumors were predominantly basaloid in 6 cases, and plasmacytoid/rhabdoid in 5 cases. We identified two cases having oncocytoid cells arranged in gland-like pattern. Significant cyclin D1 immunoexpression was absent.

SDSC is a rare, emerging entity which resembles a poorly differentiated carcinoma. Histomorphologic spectrum of these tumors is evolving. In addition to basaloid and plasmacytoid/rhabdoid cells, oncocytoid/adenocarcinoma-like pattern can also be seen in SDSC and predicts INI1 loss. These histologic patterns can further be subjected to INI1 IHC for correct diagnosis.

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Key words: Sinonasal; carcinoma; basaloid; rhabdoid; plasmacytoid; oncocytic

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Introduction

The sinonasal tract plays host to a wide variety of epithelial neoplasms. While a proportion of them are the easily identifiable squamous cell carcinomas (SCC), the major chunk of these are poorly differentiated or undifferentiated carcinomas that defy accurate histological classification, and have variably aggressive biological behavior. In recent years, the spectrum of these neoplasms has been refined to a certain extent by the inclusion of newly described entities that harbor specific genetic alterations e.g. NUT midline carcinoma, or are caused by oncogenic viruses e.g. human papillomavirus (HPV)-related multiphenotypic carcinoma [1-4]. One such recently described entity is *SMARCB1* (INI1)-deficient sinonasal carcinoma (SDSC), which is characterized by inactivating alterations in *SMARCB1*, a tumor suppressor gene located on 22q11.2, as demonstrated by loss of INI1 immunoexpression, as well as morphological evidence of rhabdoid differentiation [5,6]. Less than 60 cases of this novel entity have been described in literature, with the largest series being of 39 cases, and including only one case reported from Asia, and none from the Indian subcontinent [5-8].

The initial description of SDSC by Agaimy et al was that of basaloid appearing tumors closely resembling basaloid SCC, with interspersed isolated rhabdoid appearing cells [5]. Bishop et al, apart from this typical morphological pattern, described cases in which rhabdoid cells or plasmacytoid-appearing cells made up the bulk of the tumor [6]. They also reported the identification of pseudoglandular spaces, but tubules/ glandular structures were not recognized in either of these initial reports. Subsequently, glandular architecture was reported in more recently identified cases [7,9]. Thus, as more cases are encountered, newer morphological patterns are being revealed.

Loss of INI1 in rhabdoid tumors of the nervous system i.e. Atypical teratoid/ rhabdoid tumor (AT/RT) has been associated with derepression of cyclin D1 transcription [10,11]. Cyclin D1 is a cell cycle regulatory protein, and its overexpression leads to progression of the cell cycle,

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with subsequent cell proliferation [10,11]. Thus, cyclin D1 is considered a putative therapeutic target in rhabdoid tumors [12]. Although cyclin D1 immunoexpression has been assessed in AT/RTs [13], its expression in SDSCs has not been evaluated. Therefore, we describe a series of cases of SDSC diagnosed retrospectively by INI1 immunohistochemistry, which is the first reported series of this enigmatic tumor from India, and report results of immunostaining for cyclin D1 in this tumor.

Materials and Methods

This study performed on archival patient tumor samples received approval from the Institute Ethics Committee. All cases reported as sinonasal carcinomas, including sinonasal undifferentiated carcinoma (SNUC), poorly differentiated carcinoma, undifferentiated carcinoma, poorly differentiated squamous cell carcinoma, and adenocarcinoma, between 2009 and 2017 were retrieved from our surgical pathology archives. Histopathological and immunohistochemical features were reviewed. Immunohistochemistry for SMARCB1 (INI1) was performed on formalin-fixed paraffin-embedded tumor sections, using a mouse monoclonal primary antibody (clone MRQ-27; Cell Marque, Rocklin, CA) in a dilution of 1:50. Sections from normal tonsil were used as positive controls; endothelial cell nuclei served as internal positive control. Cases with loss of nuclear staining for INI1 were interpreted as INI1- deficient. Immunohistochemistry for cyclin D1 (1:100; Biocare Medical, Concord, CA) was performed in all INI1-deficient cases, and a labelling index was calculated, as described previously [13]. Clinical details and follow-up of these cases were obtained, where available, by retrospective chart review and telephonic interview.

Results

Two hundred and twenty-five such cases of sinonasal carcinomas were identified from our archives, and were evaluated for INI1 expression. Thirteen cases (5.8%) showed loss of nuclear expression of INI1. Clinical details, treatment and follow-up of patients is

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summarized in Table 1. A biopsy as well as resection specimen were available for Patients 1 and 5, while the remaining patients had a single tissue sample. Patients ranged in age from 11 to 65 years (mean = 42 years; median = 40 years), and included eleven males and two females (M:F=5.5:1). Three cases (23.1%) had originally been diagnosed as sinonasal undifferentiated carcinoma (SNUC), three cases (23.1%) as adenocarcinoma, two (15.4%) as poorly differentiated carcinoma, and two (15.4%) as poorly differentiated SCC. Based on histopathological features of the initial biopsy from Patient 5, the diagnosis of SDSC was considered upfront, and was confirmed on INI1 staining. Patient 12 had undergone excision of a maxillary mass elsewhere one year prior to presentation at our institute; details of the procedure and histopathology diagnosis were not available for the same. We received a biopsy from the recurrent tumor in the maxillary antrum and medial wall, which was diagnosed upfront as SDSC (Fig 1). Patient 13 underwent a biopsy in Nepal, which was reported as olfactory neuroblastoma with rhabdomyoblastic differentiation, following which he was referred to our institute; the biopsy block was submitted for review, and was diagnosed as SDSC.

On histological examination, majority of the cases (6/13; 46.2%) showed basaloid morphology (Fig 2 a-f), with predominantly undifferentiated cells having scant cytoplasm arranged in sheets, nests and islands with minimal intervening desmoplastic stroma. Inverted papilloma-like downward growth was seen in one case (7.7%). Variable proportion of cells with rhabdoid morphology, having abundant eosinophilic cytoplasm and eccentric nuclei, was seen interspersed between the basaloid cells in all these cases. Tumor cells with a predominant plasmacytoid/ rhabdoid population of cells (Fig 2 g, h) accounted for 38.5% of cases (5/13). Clear, empty appearing cytoplasmic vacuoles were seen in six cases (46.2%), five with basaloid and one with plasmacytoid/ rhabdoid appearance. Palisading of cells at the periphery of nests and islands was seen in three cases (23.1%). Three basaloid appearing

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tumors showed focal presence of spindle shaped cells with ovoid to elongated nuclei; frank sarcomatoid features were, however, absent.

Two cases (Fig 3) were comprised of large cuboidal to polygonal cells with well demarcated cytoplasmic borders, abundant eosinophilic cytoplasm, and large round vesicular nuclei having variably prominent nucleoli. These oncocytoid, almost hepatoid-appearing, cells were arranged in nests, cords, trabeculae, and also displayed gland-like structures with well-defined lumina. Cells lining these glands showed cilia at the luminal aspect at places. Alcian blue – periodic acid-Schiff (AB-PAS) did not reveal the presence of mucin, either luminal or intracytoplasmic. Histopathological features of all the cases are summarized in Table 2.

Immunohistochemically, all cases were immunopositive for pancytokeratin. None of the cases showed p16, NUT or mic2 positivity. p40 staining, when present (two cases), was focal, staining nuclei at the periphery of tumor islands. Epithelial membrane antigen (EMA) highlighted the cytoplasmic empty vacuoles. Strong CD34 positivity was seen in Case 12 in approximately 75% of tumor cells (Fig 3h, 4). Among neuroendocrine markers, focal synaptophysin and chromogranin positivity was seen in one case each; CD56 was negative. Among the oncocytoid adenocarcinoma-like cases, one showed CK7 positivity, while the other was negative; CK20 was negative, as were organ-specific markers for adenocarcinomas viz. TTF-1, CDX2, and prostate specific antigen. On cyclin D1 IHC (Fig 4), faint nuclear immunopositivity for cyclin D1 was seen only focally in three cases, with labelling index in areas showing highest positivity ranging from 1-10%. None of the cases showed strong diffuse cyclin D1 immunostaining.

Follow-up was available for four of 12 patients (33%), which is a limiting factor of our study. Ours being the apex tertiary care centre in the country where health care is provided at markedly subsidized cost, patient load is high and there is a considerable waiting period for surgery as well as radiotherapy. Thus, the patient attrition rate is significant, as once a tissue

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diagnosis has been established, patients revert to regional cancer centres to receive treatment. Of the four, two patients (1 and 4) received platinum-based neoadjuvant chemotherapy, which led to reduction in tumor size in both. Patient 1 then underwent radical maxillectomy and received post-operative radiotherapy (PORT), leading to clinical remission. He was disease free at last follow up. Patient 4 was referred to his local hospital for surgery and PORT. Patient 5 underwent complete resection of the tumor, and received platinum-based chemotherapy, followed by PORT, after which there was no evidence of disease at 8 months. Patient 12 was to receive palliative CT following biopsy, but he expired due to excessive bleeding from the mass. Patient 13 has been diagnosed recently and is scheduled for NACT followed by craniofacial resection and post-op chemoradiation.

Discussion

Loss of expression of *SMARCB1*, a member of SWI/ SNF family of chromatin remodeling genes, is seen in several malignancies, including rhabdoid tumors of the central nervous system i.e. AT/RTs, kidneys and soft tissues, as well as in other tumors like epithelioid sarcoma, renal medullary carcinomas, epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, atypical chordoma [9,14]. INI1 immunohistochemistry serves as a valuable tool for identification of these tumors. Loss of *SMARCB1* in sinonasal tumors was first described almost simultaneously by two groups: Agaimy et al described a series of three cases of *SMARCB1* (INI1)-deficient basaloid sinonasal carcinoma, as did Bishop et al in their report of nine such cases [5,6]. These tumors occurred over a wide age range, showed a distinct growth pattern, with focal presence of rhabdoid cells, and showed absence of INI1 staining. Subsequently, around 60 cases of this unique neoplasm have been reported in the English literature, all from Western countries, barring one from China [7,9,14-17]. They have been found to account for 2.7% to 7% of all primary sinonasal carcinomas assessed [5,6,14]. These patients ranged in age from 16 to 89

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years with mean age in the sixth decade, and included an almost equal proportion of males and females [6,7,9,14,15,18]. Majority had previously been diagnosed as non-keratinizing SCC or SNUC [6,7]. Our results are similar to these; however, one of our patients was an 11-year-old child, the youngest patient to be reported. The gender distribution of our patients is, however strikingly different, with a definite male preponderance.

Although initial reports characterized SDSCs as poorly differentiated basaloid appearing neoplasms lacking evident squamous or glandular differentiation, since then the spectrum of morphological features of SDSC has gradually broadened [7]. Most SDSCs fall into the broad morphological categories of basaloid "blue cell" tumors or plasmacytoid/ rhabdoid "pink cell" tumors. Basaloid tumors are characterized by undifferentiated tumor cells with high nuclear: cytoplasmic ratio, scant cytoplasm and minimal nuclear pleomorphism arranged in sheets or nests in a desmoplastic stroma [6]. A variable proportion of plasmacytoid/ rhabdoid appearing cells with eccentric nuclei and eosinophilic inclusion-like cytoplasm, the morphological hallmark of INI1 deficient neoplasms, may be seen dispersed singly in basaloid tumors. "Pink cell" tumors, on the other hand, consist predominantly of such plasmacytoid/ rhabdoid cells arranged in sheets [7]. Other features that have been described include inverted papilloma- like downward growth, peripheral palisading, pagetoid spread into the overlying respiratory mucosa, presence of clear cells, and presence of non-specific empty vacuoles [5-7,17]. While most of our cases were diagnosed retrospectively, two cases were diagnosed prospectively based on the identification of occasional rhabdoid cells and empty vacuoles in a basaloid appearing neoplasm, and one case was composed predominantly of plasmacytoid/ rhabdoid cells, prompting INI1 IHC which showed loss of expression.

Two of our cases were composed entirely of "oncocytoid" cells with abundant glassy cytoplasm, having centrally placed, round vesicular nuclei with prominent eosinophilic

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nucleoli. Interestingly, both these cases showed the presence of well-formed tubular/ glandular structures, apart from nests and cords of tumor cells. This oncocytoid adenocarcinoma-like (mucin being absent) appearance has not been described previously. Due to their tubulo-glandular morphology, these cases had originally each been diagnosed as non-intestinal type adenocarcinoma and poorly differentiated adenocarcinoma. Agaimy et al. identified "oncocytic squamoid cells" with acantholytic appearance in three cases; however, these cases did not show the presence of gland-forming structures [7]. Glandular architecture leading to diagnosis of adenocarcinoma has rarely been described previously in five cases [7,9]. Two of these had predominant plasmacytoid/ rhabdoid appearance, while one had basaloid predominant appearance [7]; for the remaining two, these details were not available.

While SDSCs are consistently immunopositive with pancytokeratin, focal and variable positivity for HMWCK, p63, p40 and neuroendocrine markers has been described [6,7,15]. Unlike CNS and soft tissue rhabdoid tumors, SDSCs do not show a polyphenotypic immunoexpression profile, highlighting their distinctness from these clinical entities. Genetic analysis of SDSCs has shown that around three-fourths harbor either homozygous or heterozygous deletions of the *SMARCB1* locus as detected by FISH [6,7]. Associated monosomy 22q has also been identified [7]. It has been suggested that monoallelic or biallelic intragenic gene mutations, small deletions below the resolution of FISH, or epigenetic mechanisms are responsible for loss of INI1 expression in the remaining cases which do not show *SMARCB1* deletion [7].

Differential diagnosis includes poorly differentiated and undifferentiated carcinomas such as non-keratinized squamous cell carcinoma (NKSCC), small cell neuroendocrine carcinoma (SCNEC), NUT carcinoma, adamantinoma-like Ewing sarcoma, SNUC, and adenocarcinoma. NKSCCs exhibit greater nuclear pleomorphism than SDSC, and surface dysplasia is frequently present [17]. The former show diffuse, strong p63 and p40 staining,

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which is variable in the latter [15]. SCNECs have scant cytoplasm and nuclei lacking nucleoli, and display nuclear molding; they stain positively with at least two neuroendocrine markers, including synaptophysin, chromogranin and CD56, along with dot-like cytokeratin positivity [19]. While SDSC may show neuroendocrine marker positivity, staining is usually focal and not seen with all the markers [17]. NUT carcinomas are composed of undifferentiated basaloid cells; abrupt keratinization, though characteristic, may not always be present, especially in small biopsies [4]. Strong p40 and nuclear NUT staining help to distinguish it from SDSC. Adamantinoma-like Ewing sarcoma is comprised of p40/ p63-positive basaloid cells which show peripheral palisading, leading to overlap with SDSC. Membranous CD99 and nuclear FLI1 positivity, characteristic of the former, is not seen in SDSC [19]. SNUC is a diagnosis of exclusion and shows undifferentiated histomorphology and IHC profile similar to basaloid "blue" SDSC, and can be differentiated from the latter by INI1 staining only. SDSC with glandular architecture should be differentiated from sinonasal adenocarcinoma, both intestinal-type (ITAC) and non-intestinal type (non-ITAC). ITAC is composed of mucinous cells and goblet cells similar to colonic adenocarcinoma; strong CK20, CDX2 and villin positivity, along with variable CK7 staining and retained INI1 help differentiate from SDSC [20]. Non-ITACs contain intracytoplasmic or intraluminal mucin that is highlighted by PAS [21]. While non-ITACs share CK7 positivity with SDSC with adenocarcinoma morphology, as seen in one of our cases, INI1 is retained. Thus, INI1 is an extremely valuable adjunct in the differential diagnosis of poorly differentiated sinonasal carcinomas, and should routinely be incorporated into IHC panels for their evaluation.

Similar to *SMARB1*/ INI1 deficient tumors at other locations, SDSCs are aggressive tumors with uniformly poor prognosis, as most present with large, locally advanced, destructive tumors [6,9,15]. Although no defined management protocols are available, most patients have been treated with surgery followed by adjuvant chemoradiation [6,7,15]. Local recurrences

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and distant metastases are frequent following treatment, with 37% patients in the largest series developing distant metastases, and 33% of patients developing loco-regional recurrence [5-7,15].

Wasserman et al. reported good response to cisplatin-based neo-adjuvant chemotherapy (NACT) with significant reduction in tumor bulk, as also seen in two of our cases [17]. However, while NACT seems to help in preoperative reduction in tumor size facilitating complete excision, and in improving locoregional control, distant metastases to lung, pleura, bone, and liver have been reported following NACT and radical surgery [17].

Lack of effective treatment regimens for SDSC demands the identification of novel targeted therapeutic agents. The product of the INI1 gene interacts with several key cell-signaling molecules, thus regulating the transcription of downstream target genes and modulating cellular response to growth and differentiation factors. Cyclin D1 is one such critical downstream target gene to whose promoter INI1 binds, and thus regulates it expression [22]. Loss of INI1 expression leads to upregulation of Cyclin D1, resulting in cell cycle progression which is a requisite for neoplastic proliferation [11]. This derepression of cyclin D1 expression consequent to loss of SMARCB1 has led to exploration of cyclin D1 inhibitors for management of rhabdoid tumors, and positive results have been obtained in animal models [22,23]. We have previously demonstrated cyclin D1 overexpression in AT/RTs showing INI1 loss [13]. We therefore performed cyclin D1 immunostaining in our SDSC cases to identify cyclin D1 overexpression as a marker for tumors that might respond to treatment with cyclin D1 inhibitors. However, none of our cases showed strong immunoexpression of cyclin D1. As cyclin D1 is a component of many cellular pathways, it is likely that other genetic or epigenetic alterations may be preventing overexpression of cyclin D1 despite loss of SMARCB1, and further studies need to be undertaken to evaluate the same. Indeed, epigenetic alterations in the form of promoter methylation of RASSF1α

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gene have already been reported in SDSCs [14]. Occasional researchers have suggested that SDSCs be classified as rhabdoid tumors, based on SMARCB1 loss. This absence of cyclin D1 overexpression in SDSC as opposed to that in rhabdoid tumors highlights the differences in pathogenetic mechanisms of these two neoplasms, and serves to establish it further as a unique entity.

Conclusion

SMARCB1 (INI1)-deficient sinonasal carcinoma is a rare, emerging entity which has the morphological appearance of a poorly differentiated carcinoma. Presence of cells with basaloid, rhabdoid and oncocytoid morphology, with or without clear vacuoles, in an undifferentiated sinonasal tumor should prompt the use of INI1 IHC for its identification and differentiation from other poorly differentiated carcinomas, particularly SNUC, which is imperative bearing in mind the aggressive clinical course of the former.

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Figure legends:

Fig 1: Clinical and radiological features for Patient 12: External appearance at presentation (A). Endoscopic view of the tumor within the maxillary sinus (B). Coronal (C) and axial (D) CECT images showing a heterogeneously enhancing lesion arising from right lateral wall of nose, extending into nasal cavity, maxilla, masticator and buccal space (infratemporal fossa), and abutting masticator muscles and parotid gland. Superiorly, the lesion is extending into extraconal compartment of orbit and abutting inferior rectus muscle. Large cystic areas are seen in the masticator and buccal space (infratemporal fossa) with enhancement. Axial (E) and coronal (F) PET-CT images show a metabolically active soft tissue density mass arising from right maxilla with similar extensions, few enlarged right level 1b lymph nodes and right submandibular gland with increased FDG activity, suggestive of disease involvement.

Fig 2: Morphological features of SMARCB1 (INI1)-deficient sinonasal carcinoma: Basaloid appearing tumor with cells in nests (a; HE, x100) and sheets (b; HE, x200); tumor cells showing cytoplasmic empty vacuoles (arrow) (c; HE, x200), spindled nuclei (arrow) (d; HE, x400), peripheral palisading of nuclei (arrows) (e; HE, x200), and clear cytoplasm (f; HE, x400). Plasmacytoid/ rhabdoid predominant tumor composed of sheets of cells with abundant eosinophilic cytoplasm (g; HE, x200) and rhabdoid cells (arrow) (h; HE, x400). Tumor cells are immunopositive for pancytokeratin (i; IHC, x100), and show loss of INI1 (j; IHC, x200); p40 positivity in Case 2 (k; IHC, x200); EMA highlights empty vacuoles (l; IHC x200)

Fig 3: Oncocytoid adenocarcinoma-like pattern: Pink appearing tumor (a; HE, x100) composed of cuboidal cells with abundant eosinophilic cytoplasm and central round vesicular nuclei (b; HE, x400), gland-like structures (c; HE, x200), and prominent nucleoli (d; HE, x400); tumor cells lack mucin (e; AB-PAS, x200), show loss of INI-1 (f; IHC, x200), are positive for CK7 (g; IHC, x200), negative for CK20 (h; IHC, x100), and show high Ki-67 labeling (i; IHC, x200)

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Fig 4: Cyclin D1 and CD34 immunoexpression: Case 1 showing tumor cells devoid of cyclin D1 staining (a; IHC, x200); Case 5 showing focal faint cyclin D1 positivity (b; IHC, x200). Case 12 showing diffuse CD34 immunopositivity (c; IHC, x40; d; IHC x200)

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Table 1: Clinico-radiological data, initial histopathology diagnosis and clinical course of patients with *SMARCB1*-deficient sinonasal carcinoma

Case no.	**Age/ sex**	**Presenting complaints**	**Clinical and imaging findings**	**Initial diagnosis**	**Clinical course**
1	23/ M	Nasal stuffiness x 5 months; epistaxis x 4 months; upper jaw pain, loosening of teeth x 4 months; Diminished vision x 3 months	Soft tissue mass filling left nasal cavity, maxillary and ethmoid sinuses with destruction of bony walls and floor of maxillary sinus	SNUC	Biopsy followed by 2 NACT (cisplatin + 5FU) with significant reduction in size of mass; followed by radical maxillectomy and PORT 60gy in 30 fractions; achieved CR; NED at 17 months
2	60/M	N/a	Mass in left nasal cavity	SNUC	Biopsy only; no follow-up information available
3	40/M	N/a	Polypoidal mass in left nasal cavity	Sinonasal non-intestinal type adenocarcinoma	Biopsy only; no follow-up information available
4	11/M	Bilateral proptosis x 2 months; decreased vision in both eyes x 1.5 month; Progressive facial distortion x 2 months, epistaxis x 1 month.	8.5cm bilateral nasal cavity mass extending into ethmoid, maxillary sinuses, orbit, with destruction of lateral nasal walls, upper alveolus, clivus; infiltration into skull base, cavernous sinus, basifrontal and temporal lobes	PDCA	Biopsy followed by NACT (cisplatin + 5FU) with subjective reduction in size of mass; to be followed by surgery and PORT at referring local hospital
5	58/ M	Pain and epistaxis x 1 month	Polypoidal mass in left nasal cavity	SMARCB1 deficient carcinoma	Biopsy from left nasal cavity mass followed by left lateral rhinotomy excision, 7 cycles of cisplatin, and PORT 60gy in 30 fractions; NED at 8 months
6	65/F	Proptosis, vision loss x 1 month	Friable growth in nasal cavity	PDSCC	Biopsy only; no follow-up information available
7	31/M	Nasal obstruction x 1 month; vision loss x 15 days	Mass in right middle turbinate, middle meatus, orbit	PDCA	Biopsy only; no follow-up information available
8	40/M		Vascular mass in right nasal cavity	SNUC	Biopsy only; no follow-up information available

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9	47/F	Left nasal obstruction and discharge x 4 months	Mass in left nasal cavity	PDSCC	Biopsy only; no follow-up information available
10	64/M	Left eye pain x 15 days, diplopia	Fleshy mass filling nasal cavity, with intracranial extension on CT	Adenocarcinoma	Biopsy only; no follow-up information available
11	50/M	Left sided nasal obstruction, epistaxis x 5-6 months	Left nasal cavity mass	Poorly differentiated adenocarcinoma	Biopsy only; no follow-up information available
12	20/M	Right cheek swelling x 2 years; underwent surgery elsewhere 1 year ago; recurrent intractable nasal bleeding x 3 months	Nasal cavity, right maxillary mass extending to infratemporal fossa, skull base, orbit	SMARCB1 deficient carcinoma	Biopsy from maxillary antrum and medial wall; Planned for palliative chemotherapy, but expired due to excessive bleeding and tumor progression 2 months after diagnosis
13	37/M	Right nasal obstruction, right eye proptosis and decreased vision x 1 month	Right nasal cavity, right orbit, anterior skull base mass with intracranial extension to frontal lobe	SMARCB1 deficient carcinoma	Biopsy only; planned for NACT followed by craniofacial resection and post-op chemoradiation

Abbreviations: CR: clinical remission; 5FU: 5Fluoro-uracil; n/a: not available; NACT: Neoadjuvant chemotherapy; NED: No evidence of disease; PDCA: Poorly differentiated carcinoma; PDSCC: Poorly differentiated squamous cell carcinoma; PORT: Post-operative radiotherapy; SNUC: Sinonasal undifferentiated carcinoma

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Table 2: Histopathological features of cases of *SMARCB1*-deficient sinonasal carcinoma

Case no.	Predominant pattern	Architecture	Overlying mucosa	Empty vacuoles	Peripheral palisading	Clear cytoplasm	Ovoid nuclei	Nucleoli	Intracytoplasmic mucin	Inflammatory cells
1	Basaloid	Sheets	N/a	Present	Absent	Present	Present	Present	Absent	Lymphocytes
2	Basaloid	Inverted papilloma - like	N/a	Occasional	Present	Present	Absent	Absent	Absent	Absent
3	Oncocytoid adenocarcinoma - like	Nests, cords, glands	Normal	Absent	Absent	Absent	Absent	Present	Absent	Foamy histiocytes
4	Plasmacytoid/ rhabdoid	Sheets, nests	Normal	Absent	Absent	Present	Absent	Absent	Absent	Absent
5	Basaloid	Sheets, islands	Normal	Numerous	Present	Present	Absent	Present	Absent	Foamy histiocytes
6	Plasmacytoid/ rhabdoid	Sheets, islands	N/a	Absent	Absent	Present	Absent	Absent	Absent	Absent
7	Plasmacytoid/ rhabdoid	Nests, islands	Normal	Absent	Present	Absent	Absent	Absent	Absent	Lymphocytes
8	Basaloid	Sheets	N/a	Absent	Absent	Present	Present	Absent	Absent	Absent
9	Plasmacytoid/ rhabdoid	Islands	N/a	Absent	Absent	Present	Absent	Present	Absent	Absent
10	Basaloid	Sheets, nests, cords	N/a	Occasional	Absent	Absent	Absent	Present	Absent	Lymphocytes, neutrophils
11	Oncocytoid adenocarcinoma - like	Glands, nests, trabeculae	Normal	Absent	Absent	Absent	Absent	Present	Absent	Absent
12	Basaloid	Sheets	N/a	Present	Absent	Absent	Present	Present	Absent	Neutrophils
13	Plasmacytoid/	Sheets, lobules	Normal	Occasiona	Absent	Absent	Absen	Present	Absent	Lymphocytes, plasma

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rhabdoid	l	t	cells

Highlights

- SMARCB1 (INI1)-deficient sinonasal carcinoma is a newly described entity
- It is characterized by loss of INI1 immunoexpression in tumor cells
- Basaloid “blue cell” and plasmacytoid/rhabdoid “pink cell” patterns are described
- We report an additional morphological pattern: “oncocytoid adenocarcinoma-like”
- Presence of these patterns should prompt use of INI1 immunostaining for diagnosis

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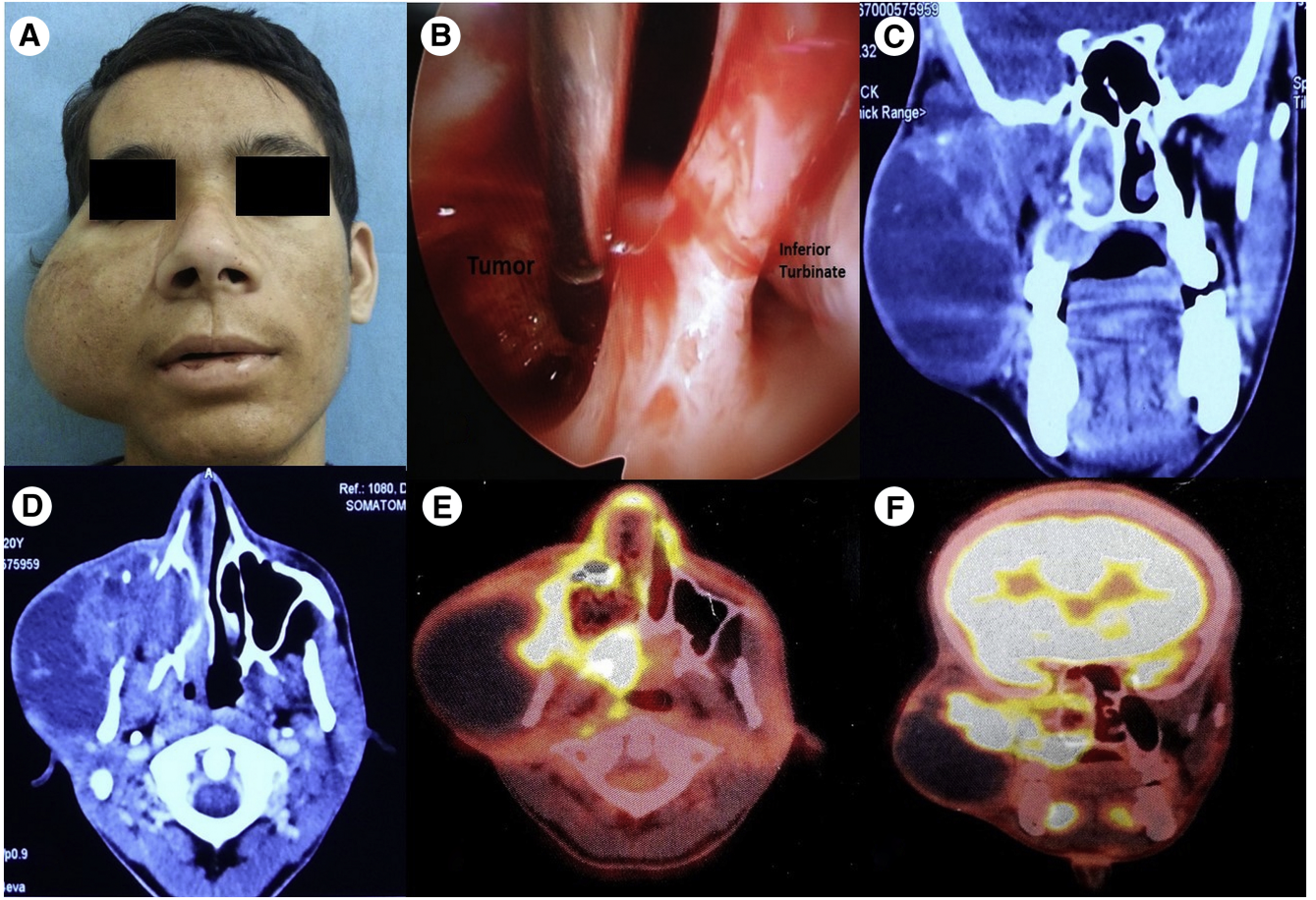

Figure 1

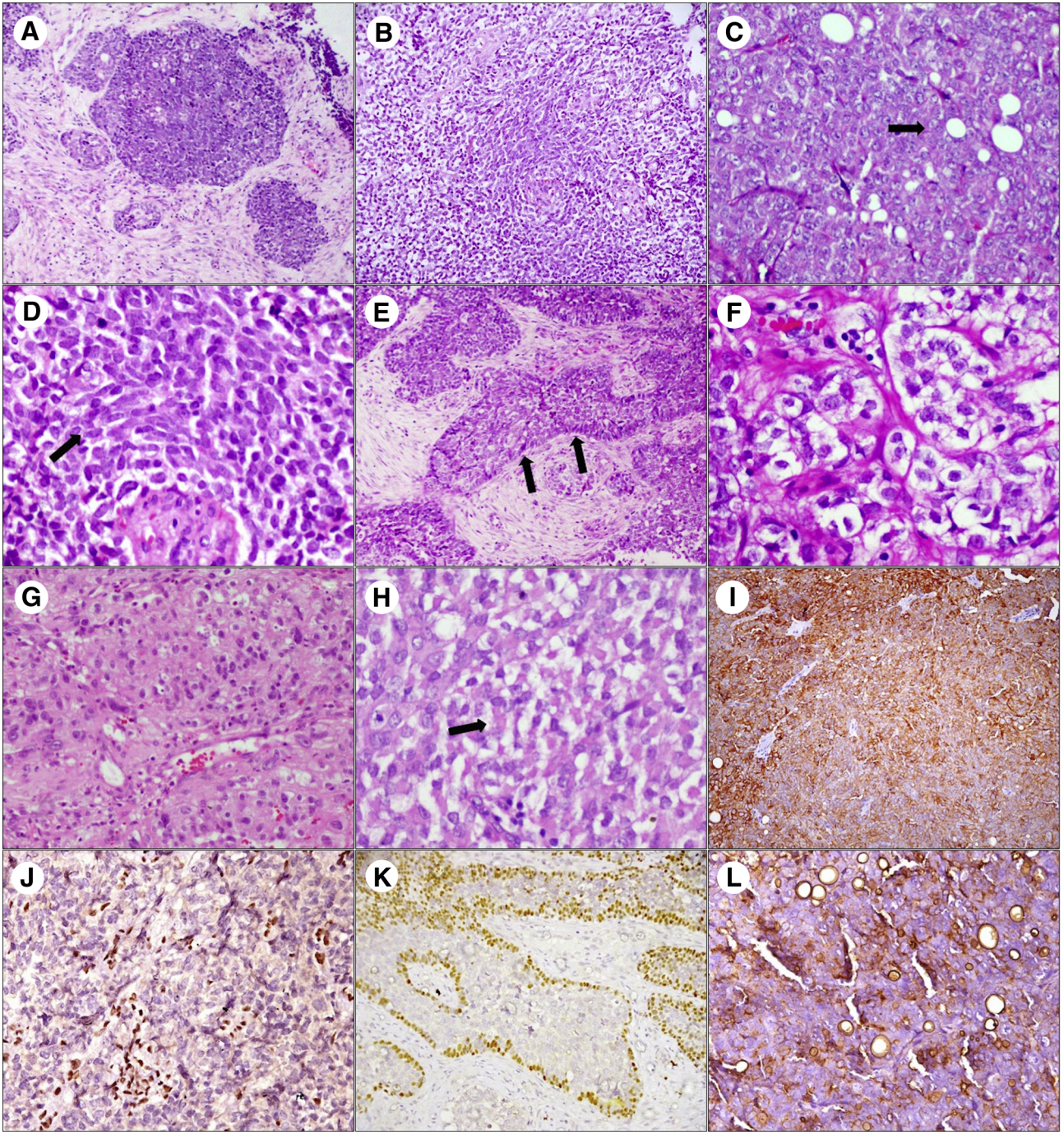

Figure 2

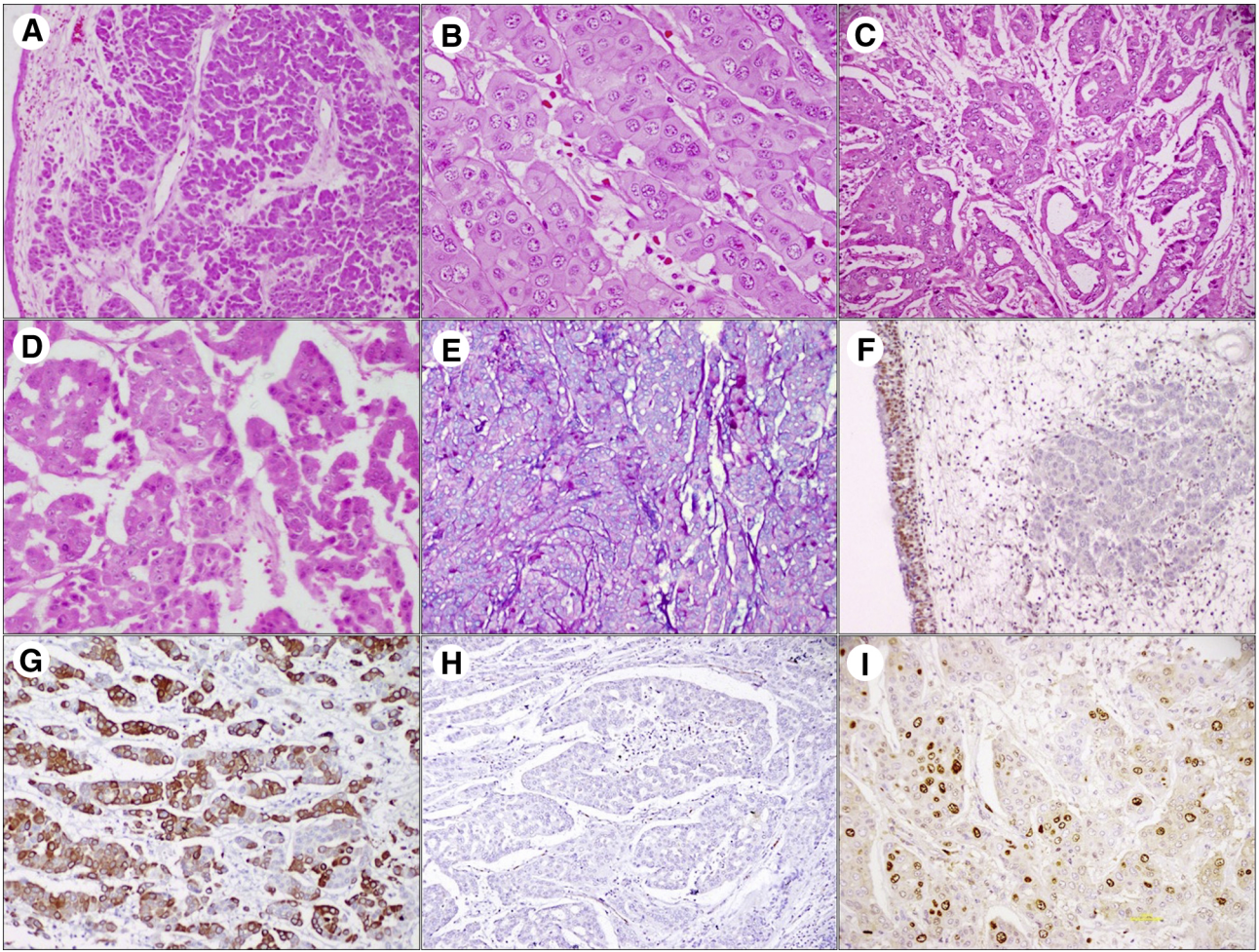

Figure 3

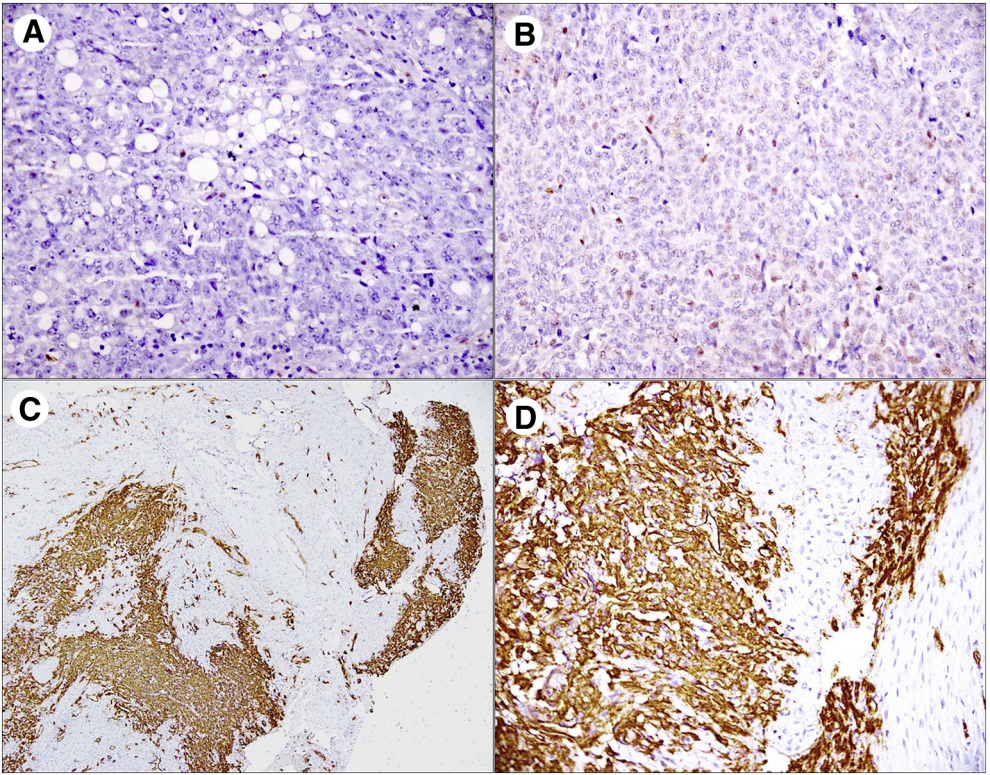

Figure 4