Malignant Epithelial Tumors of Sinonasal Tract

8

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8.1 Introduction

Malignant epithelial tumors of sinonasal tract have seen a major improvement in understanding of their pathogenesis due to advances in molecular pathology during the last decade or so resulting into introduction of many new distinct tumor entities.

WHO 2022 classification of tumors of nasal cavity and paranasal sinuses has integrated clinical, radiological, and molecular pathology features of each of these tumors (Table 8.1) for better diagnosis and management of patients [1].

Table 8.1 WHO 2022 classification of malignant epithelial tumors of nasal cavity and paranasal sinuses

Categories	Subtypes
Carcinomas	Keratinizing squamous cell carcinoma Non-keratinizing squamous cell carcinoma NUT carcinoma SWI/SNF complex (SMARCB1 and SMARCA4) deficient sinonasal carcinoma Sinonasal lymphoepithelial carcinoma Sinonasal undifferentiated carcinoma Teratocarcinosarcoma HPV-related multiphenotypic sinonasal carcinoma
Adenocarcinoma	Intestinal-type adenocarcinoma Non-intestinal-type adenocarcinoma
Neuroendocrine tumors	Well-differentiated epithelial neuroendocrine neoplasms/neuroendocrine tumors
Neuroendocrine carcinomas	Small cell carcinoma Large cell neuroendocrine carcinoma
Emerging entities	*DEK*::*AFF2* fusion associated squamous cell carcinomas *IDH*-mutant sinonasal undifferentiated carcinoma SMARCB1 deficient sinonasal adenocarcinoma

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8.2 Squamous Cell Carcinoma

Keratinizing squamous cell carcinoma (KSCC) is a surface epithelial malignancy with squamous differentiation and keratinization (Fig. 8.1).

About half of sinonasal (SN) tract malignancies are KSCCs. Genomically *p53*, *KRAS*, and *EGFR* mutations have been identified in them. *EGFR* exon 20 mutation has been detected in tumors arising from inverted papillomas. Human papilloma virus (HPV) infection is not implicated in pathogenesis of most of KSCC [1, 2].

Non-keratinizing squamous cell carcinoma (NKSCC) is another subtype of surface SCC with no or minimal keratinization (Figs. 8.2, and 8.3).

WHO 2022 classification subtyped NKSCC, based on molecular etiopathogenesis, into two subtypes: HPV-associated squamous cell carcinoma and *DEK*::*AFF2* carcinoma [1, 3, 4].

HPV association varies in different ethnicities being highest in Western countries and a low frequency in Asia [5]. Most of HPV negative NKSCC of SN tract have been shown to carry fusions between the *DEK* gene on chromosome 6p22.3 and the *AFF2* gene on chromosome Xq28 [6].

Morphologically, NKSCC show surface proliferation with downward pushing invasion of tumor cell nests without much desmoplasia [1].

Other variants of SCC such as acantholytic, adenosquamous, basaloid, spindle, and verrucous are rare in SN tract in comparison to other head and neck sites. Papillary subtype needs to be tested for HPV and *DEK*::*AFF2* fusion as these tend to show papillary exophytic growth pattern (Fig. 8.4).

The *DEK*::*AFF2* fusion carcinomas show bland cytomorphology with exophytic and endophytic proliferation. The tumor cells are oval to fusiform in some examples with monotonous appearance [4, 6] (Figs. 8.5, 8.6, and 8.7). Some reported cases show prominent neutrophilic infiltration which brings NUT carcinoma in differential; however, cytomorphology of NUT carcinoma is high grade.

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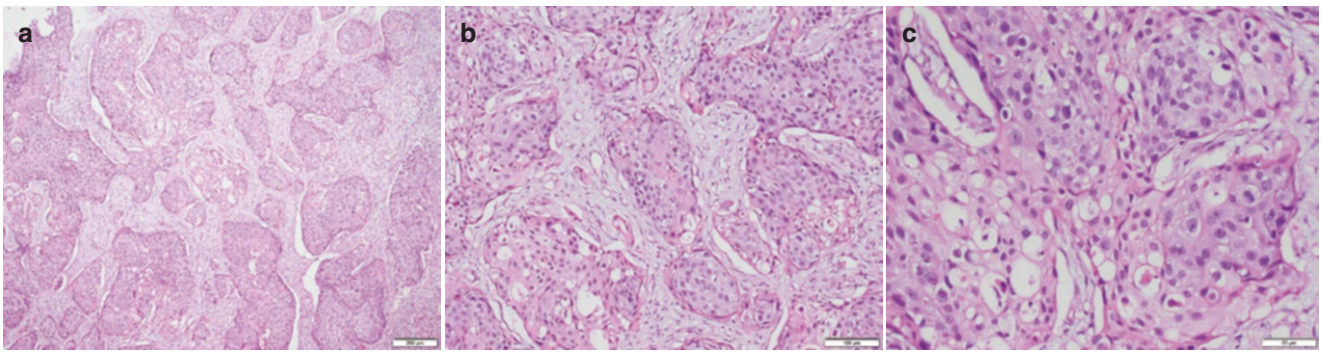


Fig. 8.1 Infiltrating nests and lobules of tumor with desmoplastic stroma (**a**). The tumors cells are polygonal and show intracellular keratinization (**b**). Cytoplasmic vacuolation and pseudoglandular spaces are evident (**c**). Tumor is positive for p40 (not shown here)

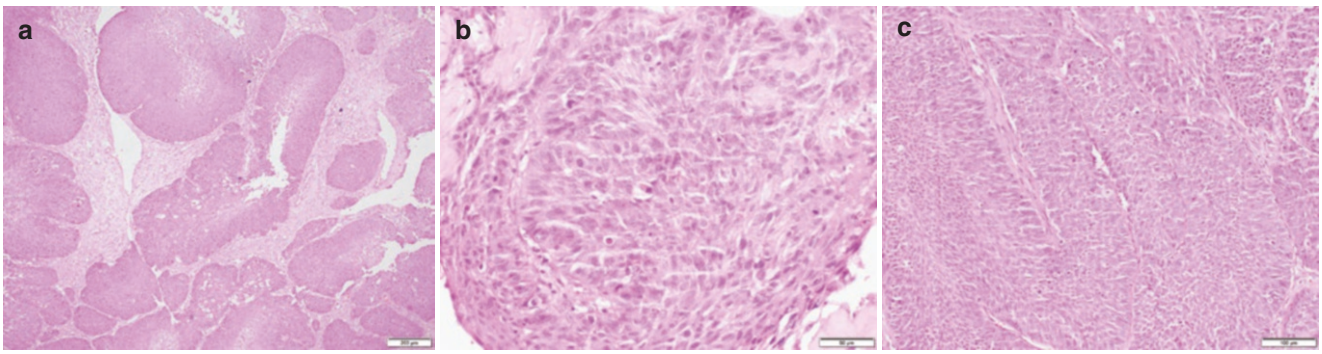


Fig. 8.2 Inverted papilloma with epithelial dysplasia (**a**), carcinoma *in-situ* (**b**) and interconnecting fronds of non-keratinizing squamous cell carcinoma (**c**)

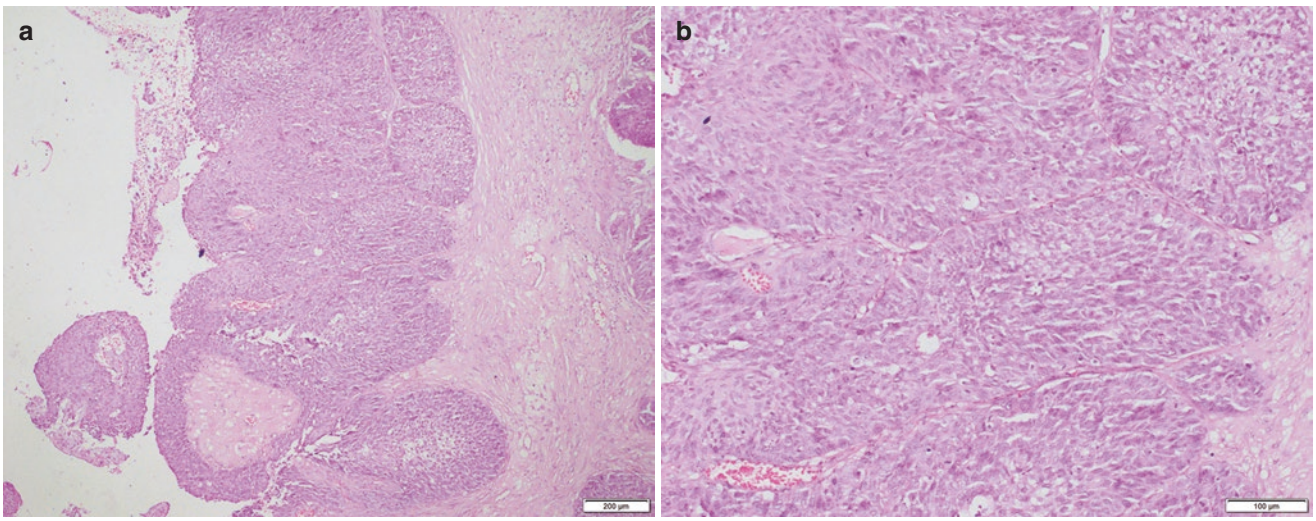


Fig. 8.3 The tumor nests at advancing edge show a smooth contour (**a**). Striking nuclear atypia and mitotic activity is noted (**b**)

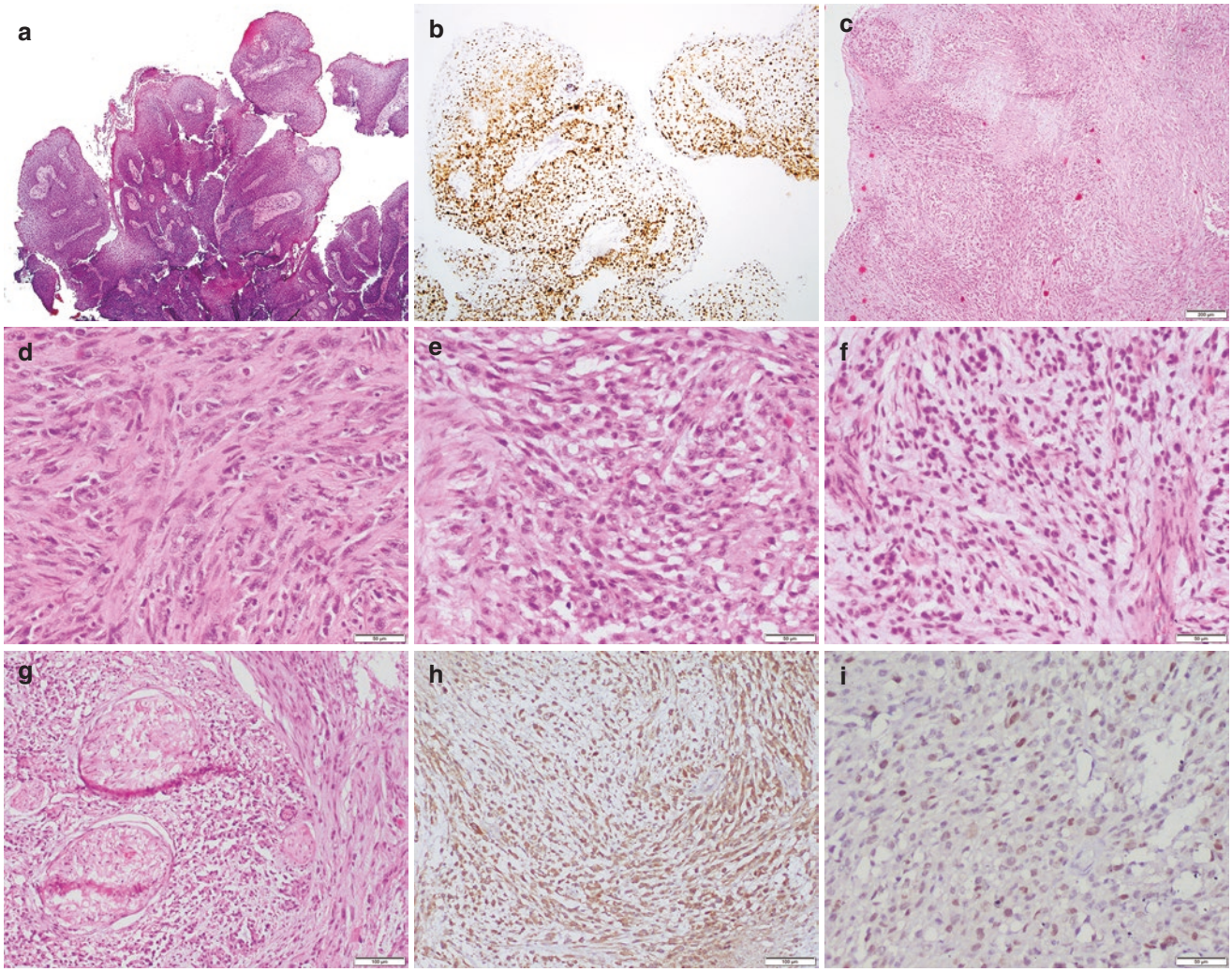


Fig. 8.4 Proliferating fronds of squamous epithelium with fibrovascular cores (**a**) positive for RNA *in-situ* hybridization for human papilloma virus (HPV) (**b**). Clinically, it was a soft tissue density mass in maxillary antrum with bone destruction. A case of spindle cell carcinoma with surface ulceration, geographic areas of necrosis and myxoid change (**c**). Pleomorphic epithelioid oval to spindle cells (**d**–**f**) show perineural invasion (**g**); positive for epithelial membrane antigen (EMA) (**h**) and p40 (**i**)

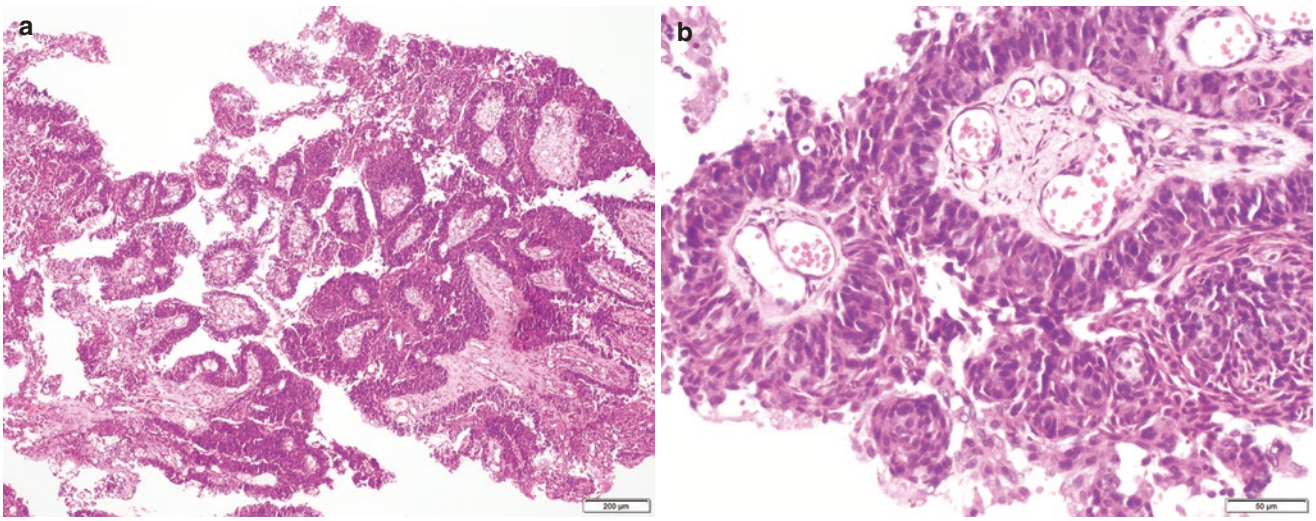


Fig. 8.5 (**a**) Low power view shows a complex papillary pattern of tumor which on higher magnification shows mild nuclear atypia (**b**)

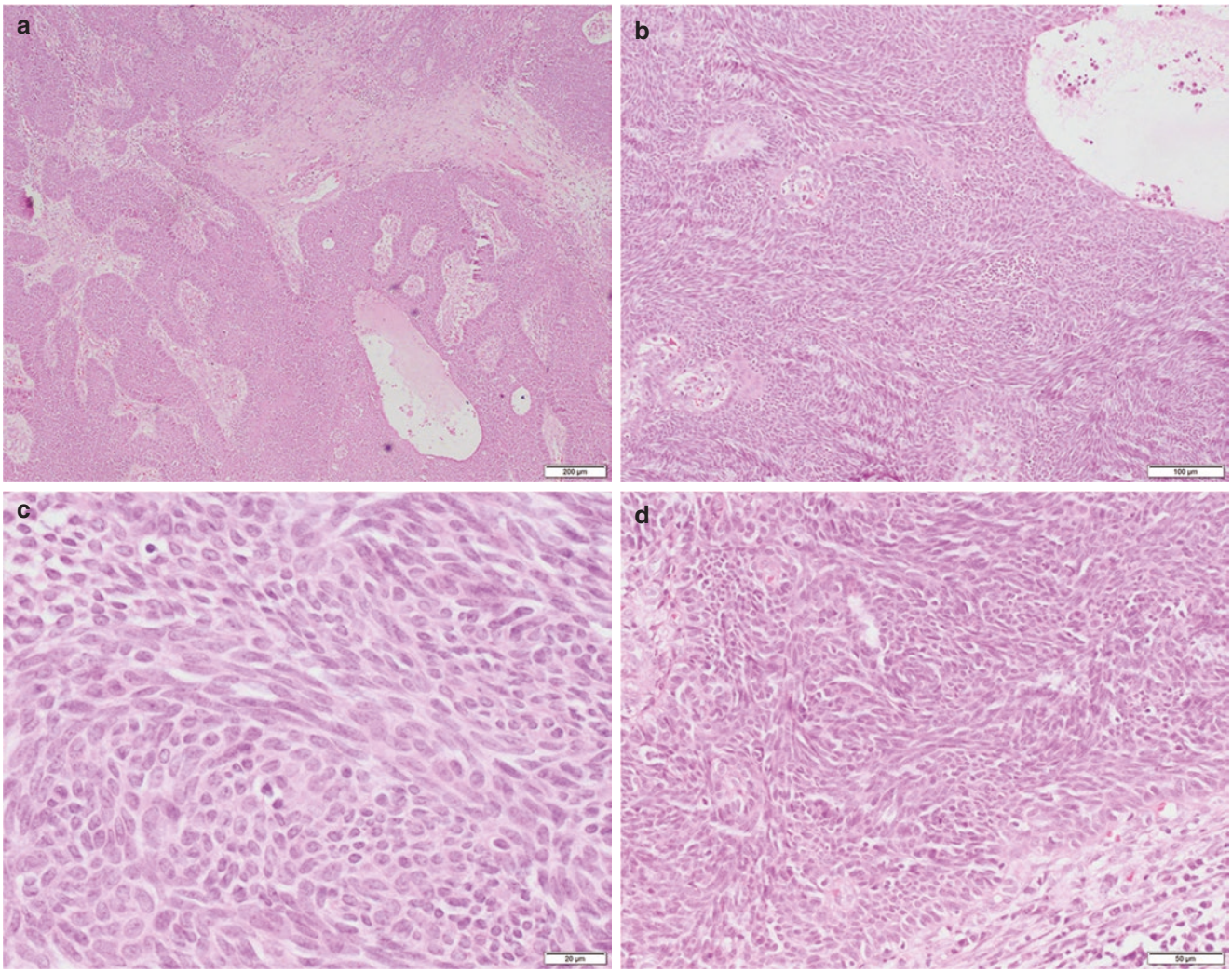


Fig. 8.6 Same case on recurrence shows predominantly endophytic growth with intercommunicating cords, nests, and papillae (**a**). Tumor cells appear transitional and have monomorphic oval to fusiform bland nuclei (**b**, **c**). Smooth transitioning to stroma is seen (lower right) (**d**)

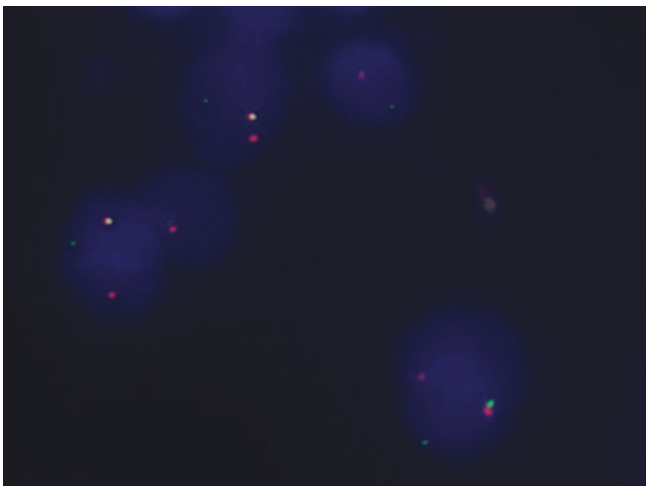


Fig. 8.7 *DEK* breakapart fluorescence *in-situ* hybridization shows break apart of *DEK* gene

Similar to squamous cell carcinoma of other body sites, all variants and subtypes are immunopositive for high molecular weight keratins, p40 and p63.

8.3 Sinonasal Lymphoepithelial Carcinoma

Sinonasal lymphoepithelial carcinoma (SNLEC) is an undifferentiated variant of squamous cell carcinoma, mostly occur in Asia in endemic form, associated with Epstein–Barr Virus (EBV) infection.

Tumor grows in syncytial appearance and tumor cells show abundant eosinophilic to amphophilic cytoplasm. The tumor cells show round nuclei with vesicular chromatin and prominent nucleoli. Although lymphoplasmacytic infiltrate

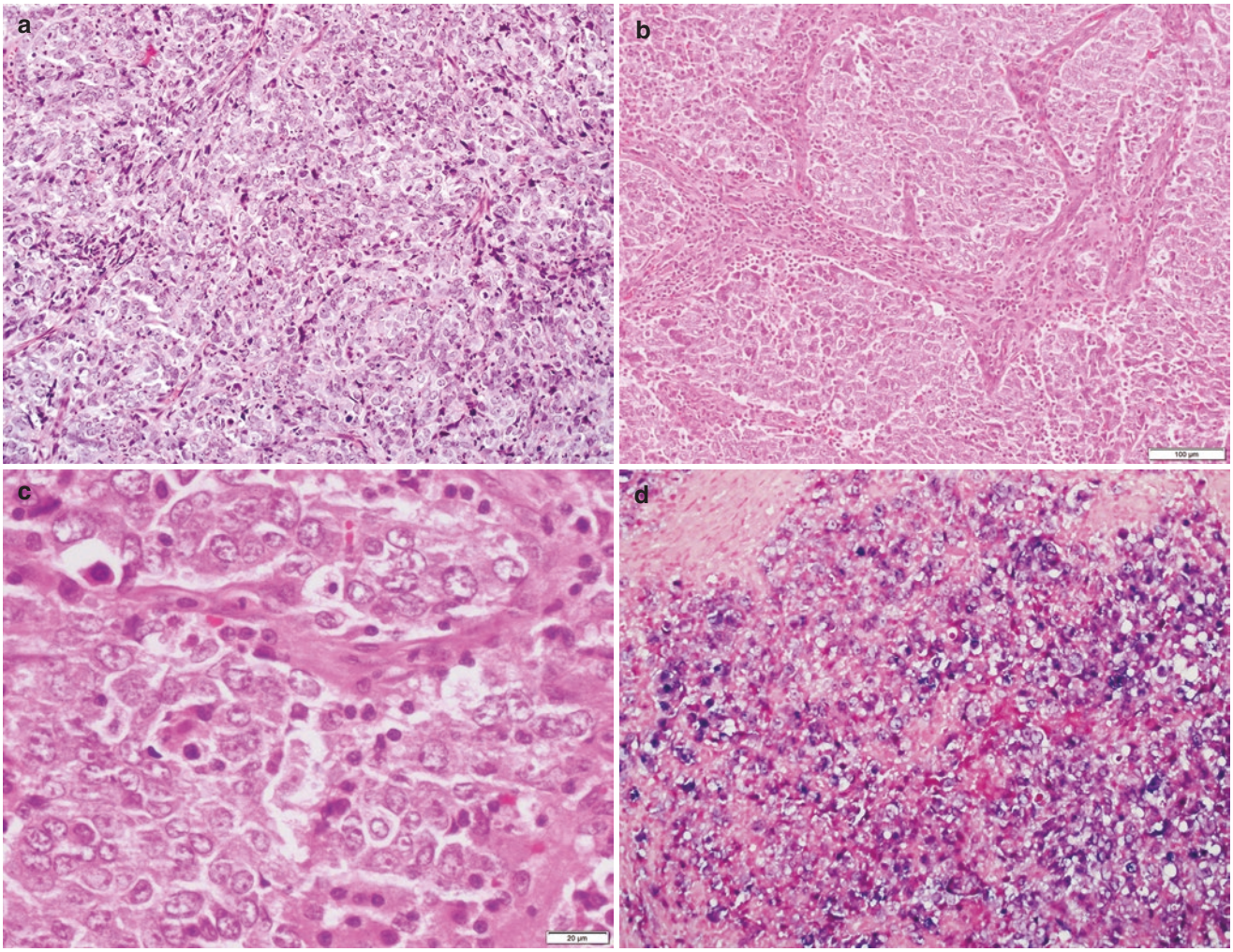


Fig. 8.8 (**a**–**c**) Syncytium of large undifferentiated cells with vesicular chromatin and prominent nucleoli. Prominent lymphoplasmacytic infiltrate is integral component of the tumor present within the stroma separating tumor lobules seen in (**b**). Tumor shows positive EBV-encoded small RNA (EBER) by *in-situ* hybridization (**d**)

is diagnostic, it is less prominent in SN tract in comparison to the nasopharyngeal counterpart (Fig. 8.8).

Keratin, p63, p40 and *in-situ* hybridization for EBV-encoded small RNA (EBER) is positive especially in endemic form [7, 8].

8.4 NUT Carcinoma

NUT (Nuclear protein in testis) carcinoma is a poorly differentiated carcinoma with squamous differentiation which is characterized by translocation/fusion involving the *NUTM1* gene on chromosome 15q14 with various partner genes, commonly BRD4 [t (15;19)], leading to formation of an oncoprotein [9].

NUT carcinoma is a high-grade tumor with "malignant small round blue" cell morphology comprising of sheets of primitive appearing undifferentiated cells. The cells possess uniform vesicular nuclei and prominent nucleoli. Foci of abrupt keratinization (keratinized squamous cells with or without keratin pearls and cytoplasmic clearing) are classical and can be seen in about a third of NUT carcinoma cases.

Immunohistochemistry with the NUT antibody is specific for the diagnosis only with diffuse (>50% of tumor cells) granular/speckled positivity. The tumor cells are immunopositive for pancytokeratin, p40 and p63 (more sensitive than p40) (Figs. 8.9, 8.10, 8.11, 8.12, 8.13, and 8.14). These tumors have an aggressive clinical course with a mean survival of 12 months [10].

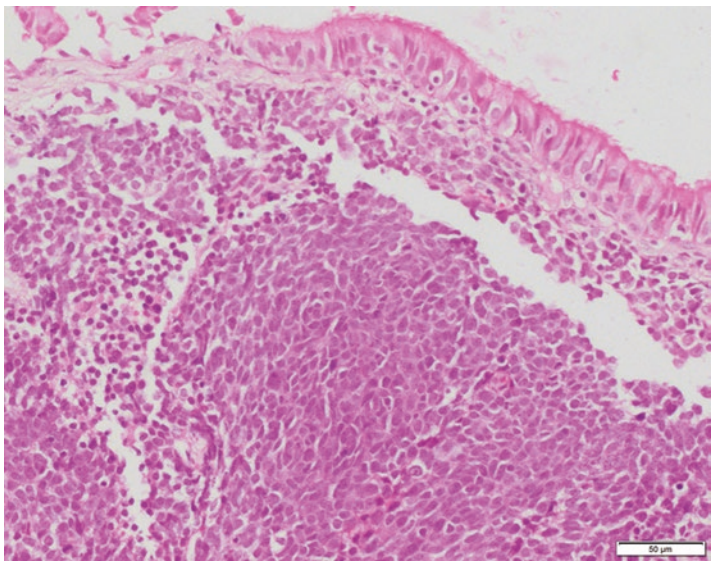


Fig. 8.9 A highly cellular tumor with overlying normal respiratory epithelium. Majority of tumor cells are round with hyperchromatic nuclei. Here the differential diagnoses cover spectrum of malignant small round cell tumors

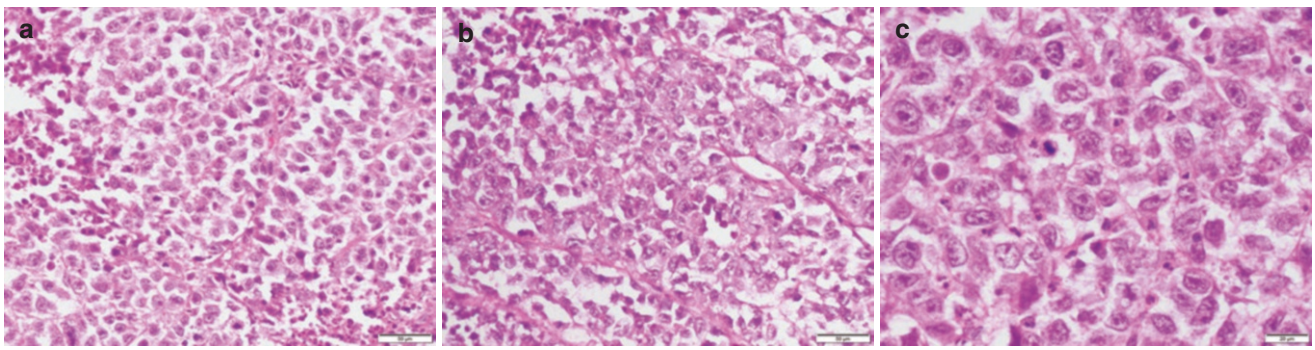


Fig. 8.10 (**a**–**c**) Another case on higher magnification shows perfectly round basaloid/undifferentiated tumor cells with stippled chromatin and prominent nucleoli. Necrosis and microabscesses are present (left upper and right lower-**a**)

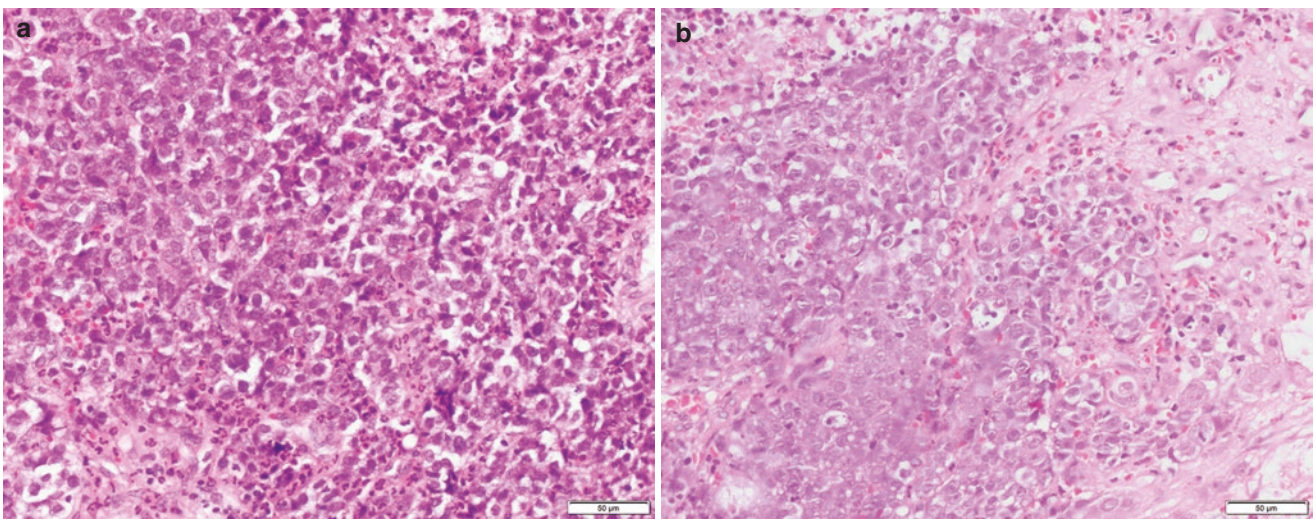


Fig. 8.11 (**a**, **b**) Tumor is heavily infiltrated by polymorphs (a helpful diagnostic clue of NUT carcinoma)

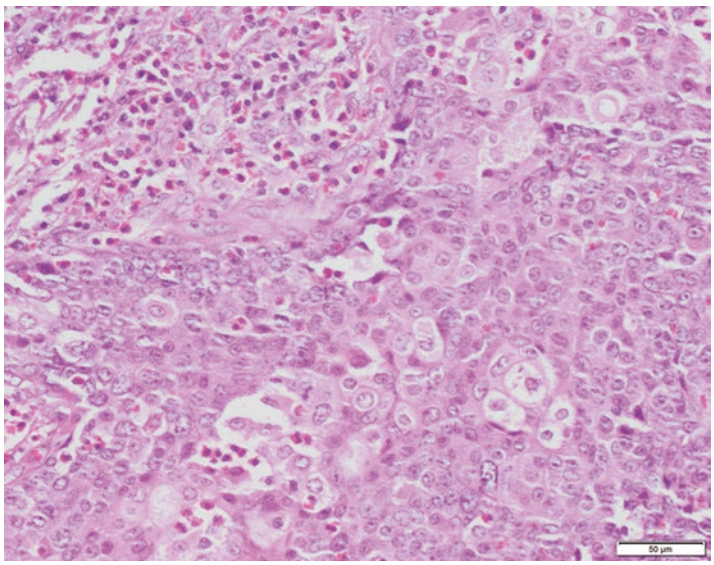


Fig. 8.12 This examples shows infiltration of tumor by eosinophils (possibly due to tumor released cytokines)

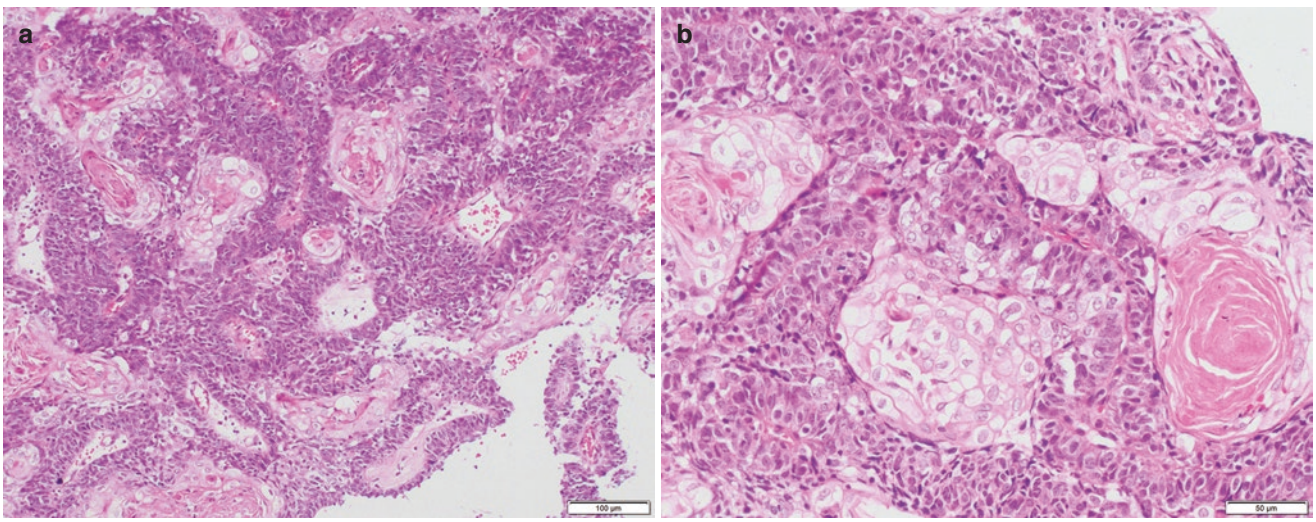


Fig. 8.13 (**a**, **b**) Abrupt keratinization with keratin pearls and surrounding clear squamous cells seen in about a third of NUT carcinoma, a diagnostic feature of NUT carcinoma

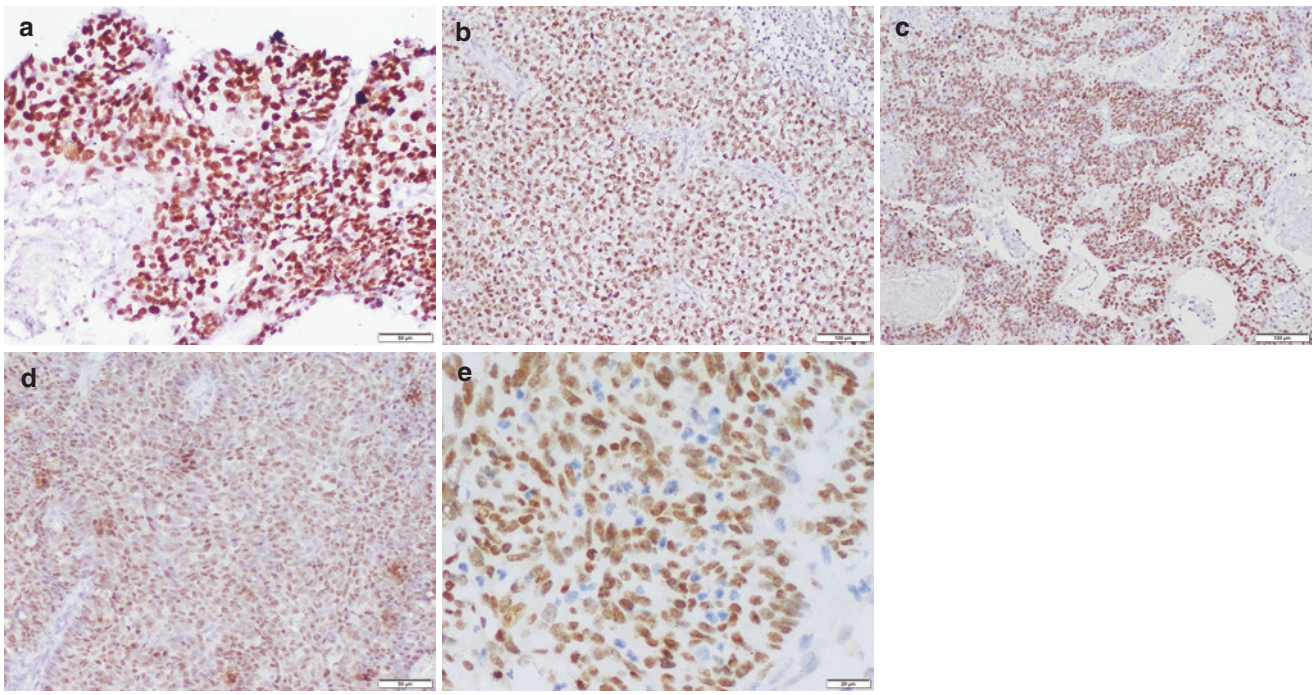


Fig. 8.14 p40 (**a**), p63 (**b**, **c**), and NUT immunohistochemistry (**d**, **e**) are diffuse and strong nuclear positive. p63 is more consistently positive than p40 in NUT carcinomas. NUT shows speckled nuclear pattern

8.5 HPV-Related Multiphenotypic Sinonasal Carcinoma (HMSC)

As the name indicates, this tumor is characterized by morphological and immunophenotypical characteristics of a salivary type carcinoma (ductal and myoepithelial differentiation) and squamous cell carcinoma. HMSC is limited to sinonasal tract.

Histology resembles solid to cribriform areas reminiscent of adenoid cystic carcinoma. The surface respiratory epithelium shows dysplasia. Immunohistochemistry shows p16 positivity, though HPV association needs to be confirmed by molecular methods. Transcriptionally active high-risk HPV type 33 is implicated in pathogenesis in most of the cases. The presence of high-risk HPV and absence of MYB gene fusion distinguishes it from the close differential of adenoid cystic carcinoma (Fig. 8.15, 8.16, 8.17, and 8.18).

These tumors behave indolently without much frequency of distant metastasis and tumor-related deaths [11].

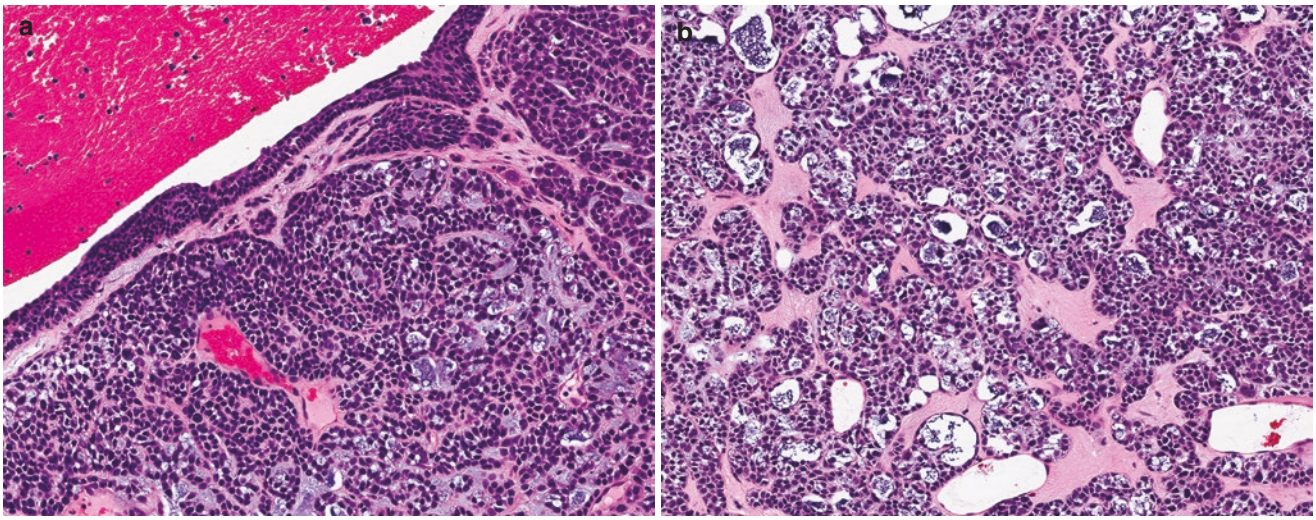


Fig. 8.15 A tumor with basaloid cells arranged in solid nests and cribriform pattern mimicking adenoid cystic carcinoma. Note the surface squamous epithelium with dysplasia (**a**). The cribriform spaces are filled with myxoid appearing basophilic material. The stroma is densely hyalinized (**b**)

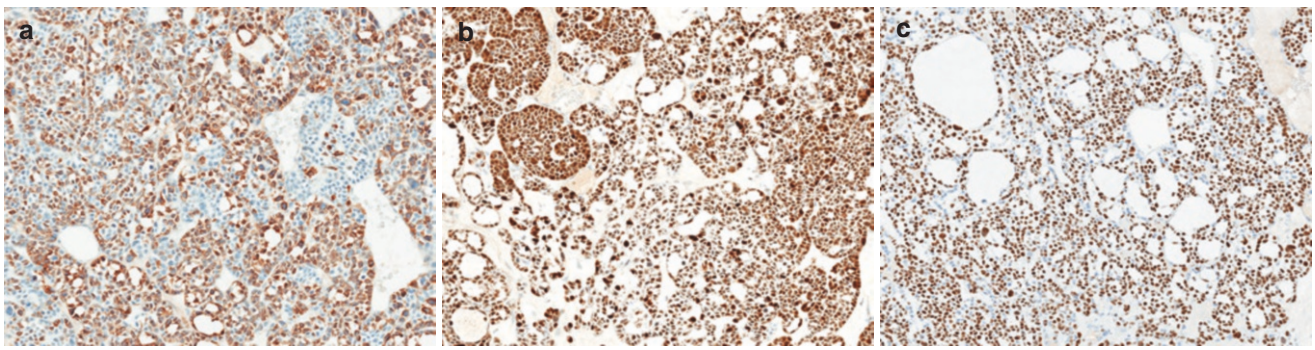
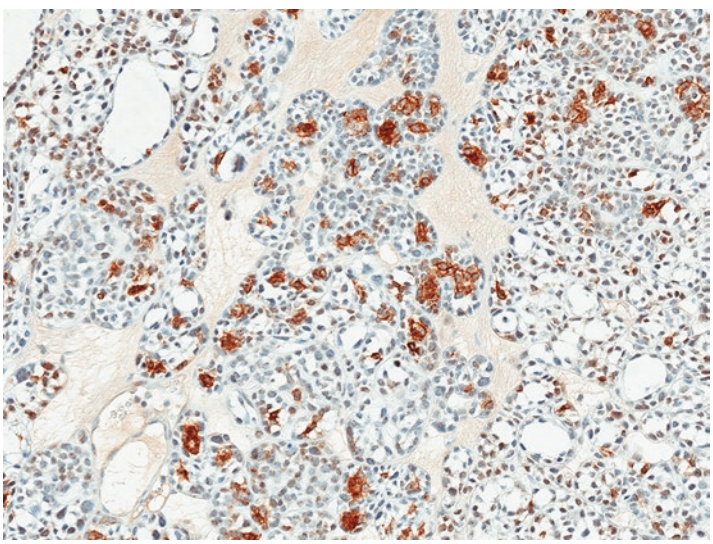


Fig. 8.16 One of the multiphenotypic lineage is myoepithelial cell differentiation which is shown by smooth muscle actin (cytoplasmic) (**a**), S100 (nuclear and cytoplasmic) (**b**), and p40 (nuclear) (**c**) staining in tumor cells

Fig. 8.17 CD117 highlights ductal differentiation; however, MYB gene rearrangement is negative in these tumors in contrast to adenoid cystic carcinomas



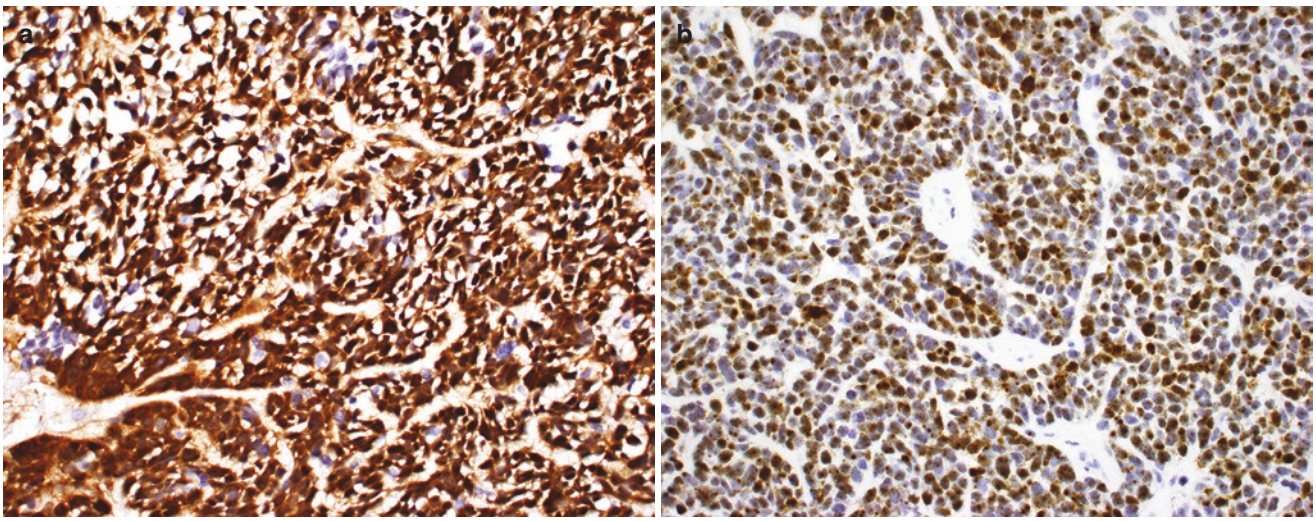


Fig. 8.18 Although p16 is a poor surrogate marker for HPV infection, it is consistently positive (diffuse, strong, nuclear, and cytoplasmic) (**a**). RNA *in-situ* hybridization for high-risk HPV is diffusely positive (**b**)

8.6 Adenocarcinoma

Sinonasal adenocarcinomas (showing glandular differentiation) can be salivary type (see Chap. 9) and non-salivary adenocarcinomas. The latter are further subdivided into intestinal and non-intestinal-type adenocarcinomas.

8.6.1 Intestinal-Type Adenocarcinomas (ITAC)

This group of tumors resembles the adenocarcinoma/adenoma of the intestine or rarely normal intestinal mucosa. ITAC originate from intestinal metaplasia of surface epithelium. Exposure to wood and leather dust are implicated occupational risk factors. These tumors commonly involve the ethmoid sinuses and nasal cavity.

Histologically, tumors range from well-differentiated papillary adenocarcinomas to poorly differentiated/solid and mucinous carcinomas (Figs. 8.19 and 8.20).

On immunohistochemistry, these tumors are positive for CK20, CDX2, SATB2, and villin and variably positive for CEA and CK7 [12].

Genomically, ITAC show frequent p53 mutations.

Clinical course is aggressive with frequent local recurrences, metastasis, and death.

8.6.2 Non-intestinal-Type Adenocarcinomas

This group includes tumors that does not show characteristics of minor salivary gland or intestinal-type adenocarcinomas. Unlike ITAC there are no known occupational risk factors. Nasal cavity and maxillary sinuses are commonly involved. These are further subdivided into low-grade and high-grade tumors.

On immunohistochemistry, these tumors are immunonegative for CK20, CDX2, and villin.

Markers of seromucinous differentiation, S100, DOG1, and SOX10, are expressed in the majority of non-intestinal-type adenocarcinomas [1, 13].

Low-grade non-intestinal-type adenocarcinomas show a back to back arrangement of uniform glands lined by single layer of cuboidal or columnar cells. Low-grade tumors may arise in association with benign lesions (sinonasal papillomas and respiratory epithelial adenomatoid hamartomas) [2] (Fig. 8.21).

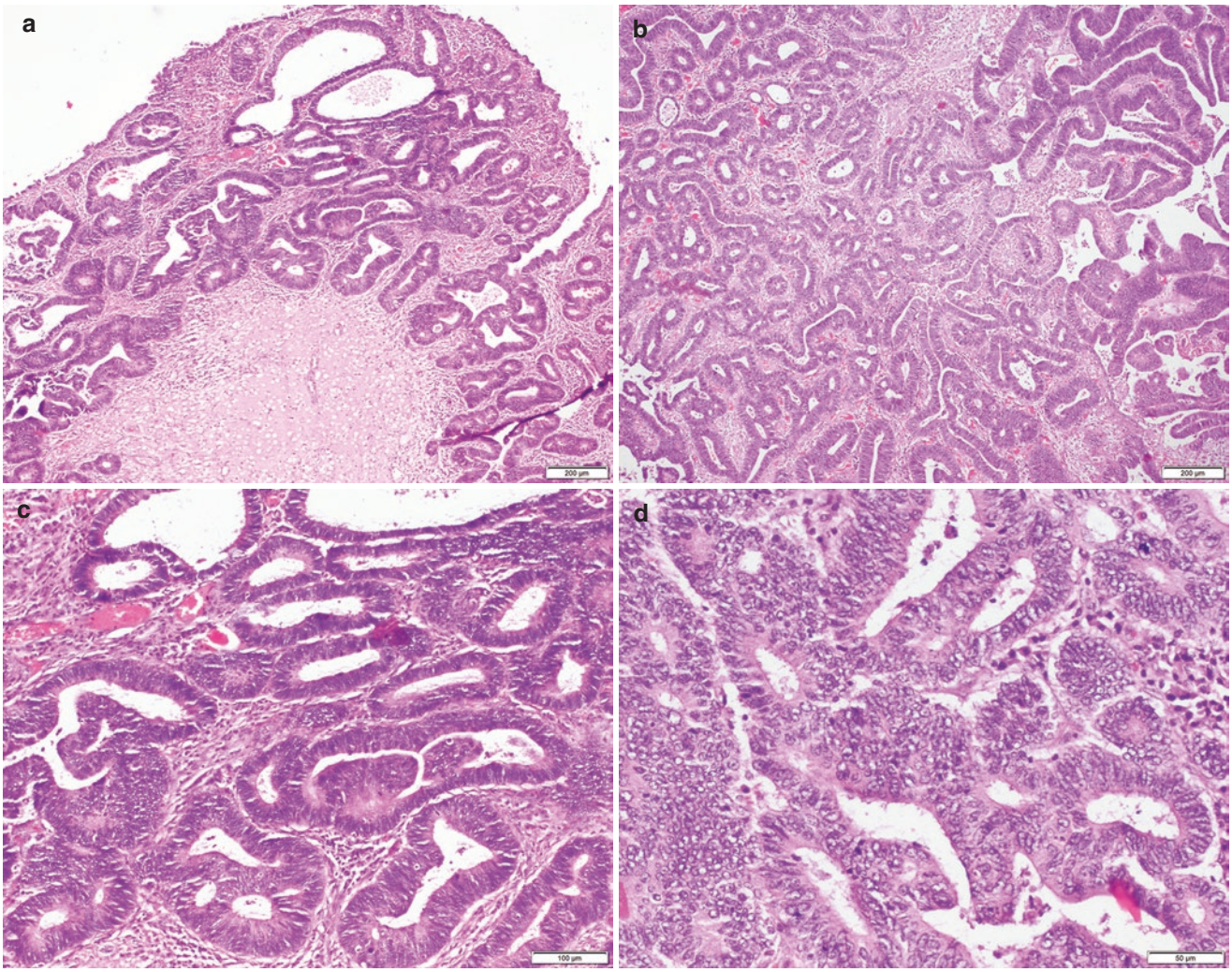


Fig. 8.19 A polypoidal tumor appears as a tubular adenoma of colon with overlying respiratory epithelium (**a**). This tumor shows complex tubulopapillary growth with branching and intercommunicating glands lined by tall columnar ("cigar shaped nuclei") epithelium (**b**). High-grade nuclear features are seen (**c**, **d**)

High-grade tumors show solid growth pattern with nuclear pleomorphism or malignant infiltrating glands with atypical mitoses in desmoplastic stroma [1, 2] (Fig. 8.22).

A subset of low-grade carcinomas show uniform population of cuboidal to columnar cells with glycogen-rich clear cytoplasm which is reminiscent of renal cell carcinoma and have been named as sinonasal renal cell-like adenocarcinoma. Renal cell-like adenocarcinoma expresses CK7, CAIX, and CD10, whereas negative for vimentin, RCCMa (renal cell carcinoma marker), and PAX8 (Fig. 8.23) (Table 8.2).

A subset of low-grade tumors carry ETV6::NTRK3/RET fusions. Interestingly, most cases of secretory carcinomas show same translocation involving ETV6 and NTRK3 genes. However, secretory carcinomas rarely involve sinonasal tract (Fig. 8.24). Rarely, CTNNB1 and BRAF mutations are reported [14].

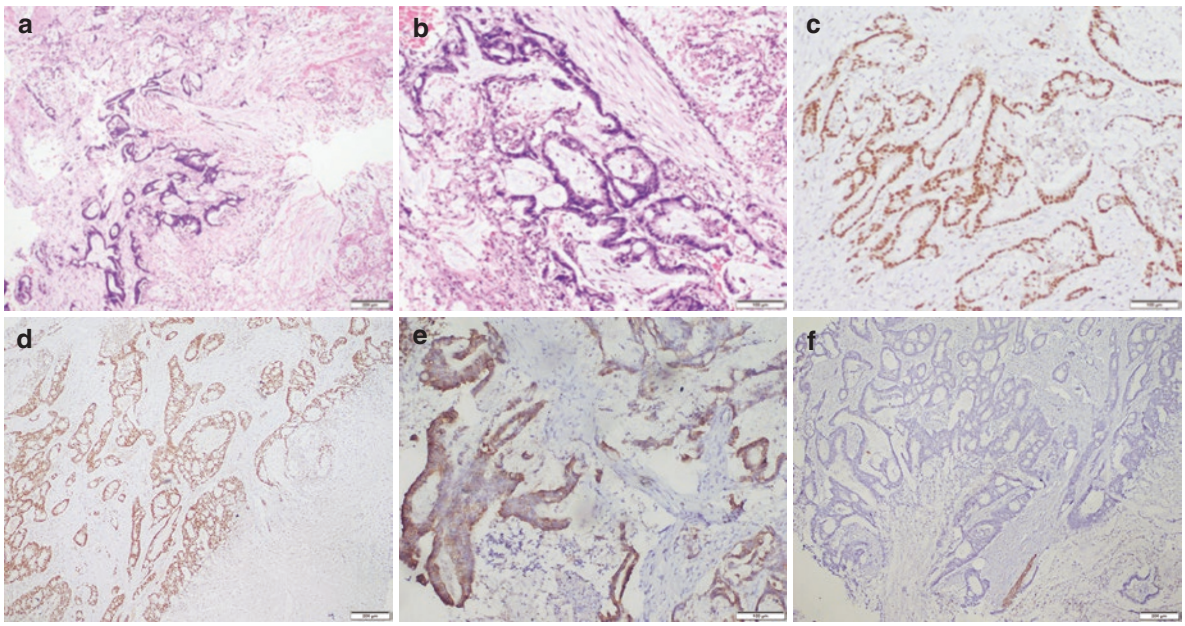


Fig. 8.20 Another example of ITAC shows abundant mucin, necrotic exudate, and abnormal malignant glands (**a**, **b**) which show nuclear positivity for CDX2 (**c**), SATB2 (**d**), and CK20 (**e**). CK 7 is negative (**f**)

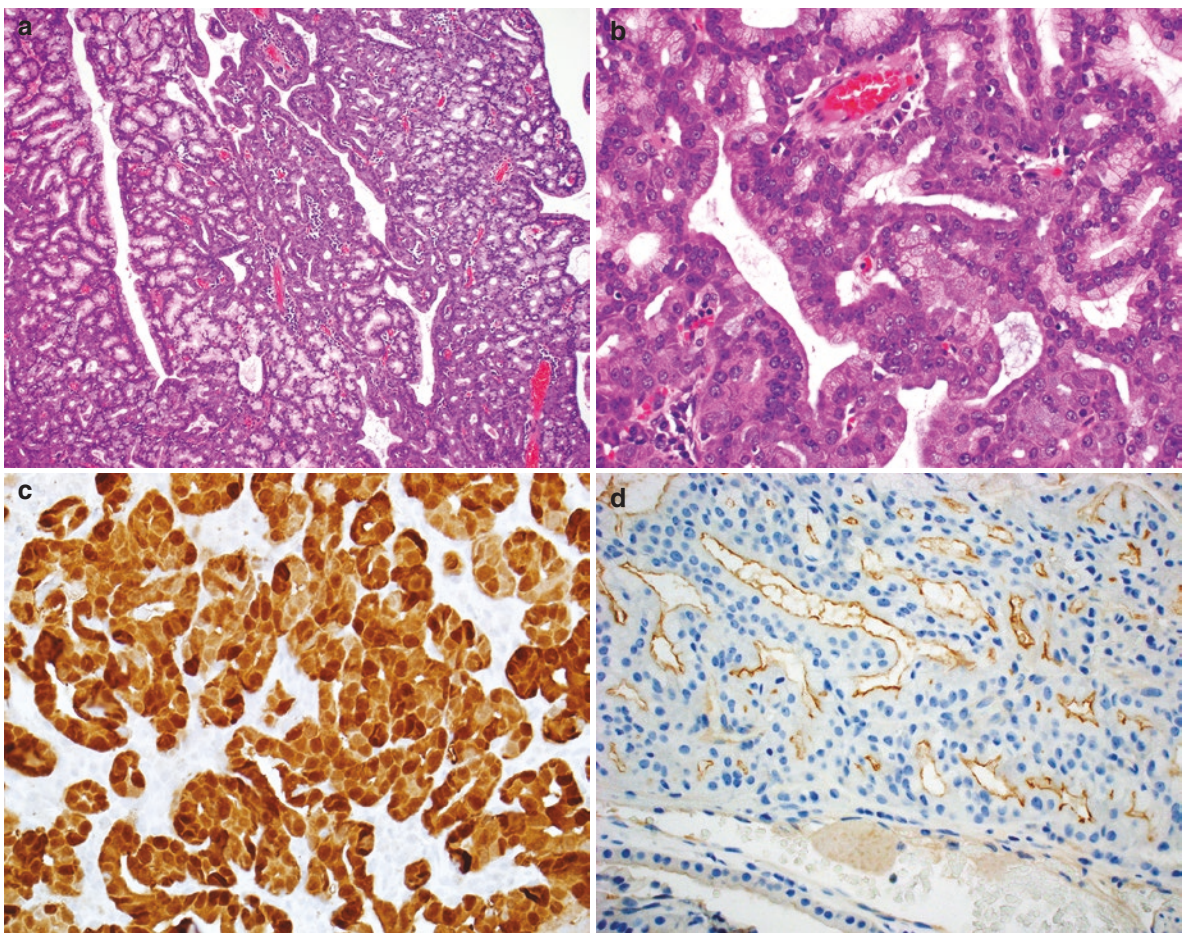


Fig. 8.21 (**a**, **b**) Low-grade non-intestinal adenocarcinoma: an exophytic tumor with tubulopapillary pattern where glands are placed back to back. The glands are low-grade seromucinous, lined by single layer of cuboidal epithelium with mild atypia. The tumor cells are diffusely positive for S-100 (**c**). DOG1 shows apical luminal staining (**d**)

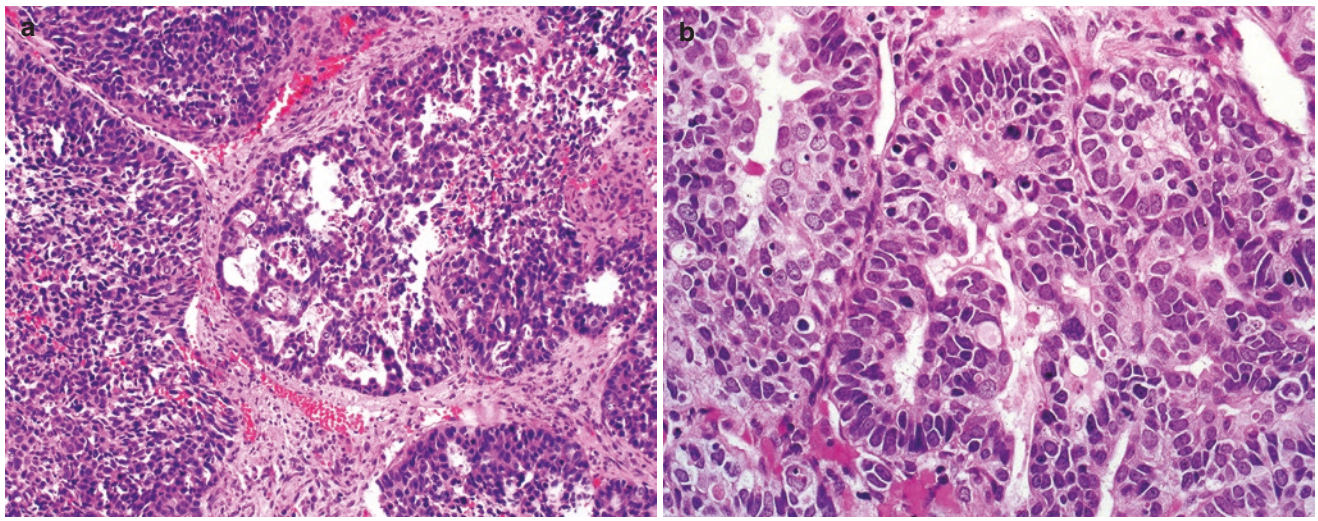


Fig. 8.22 (**a**, **b**) High-grade non-intestinal adenocarcinoma: Nested growth of an adenocarcinoma with solid and cribriform architecture. Note high-grade nuclear atypia (in comparison to Fig. 8.21b) with necrosis and mitosis

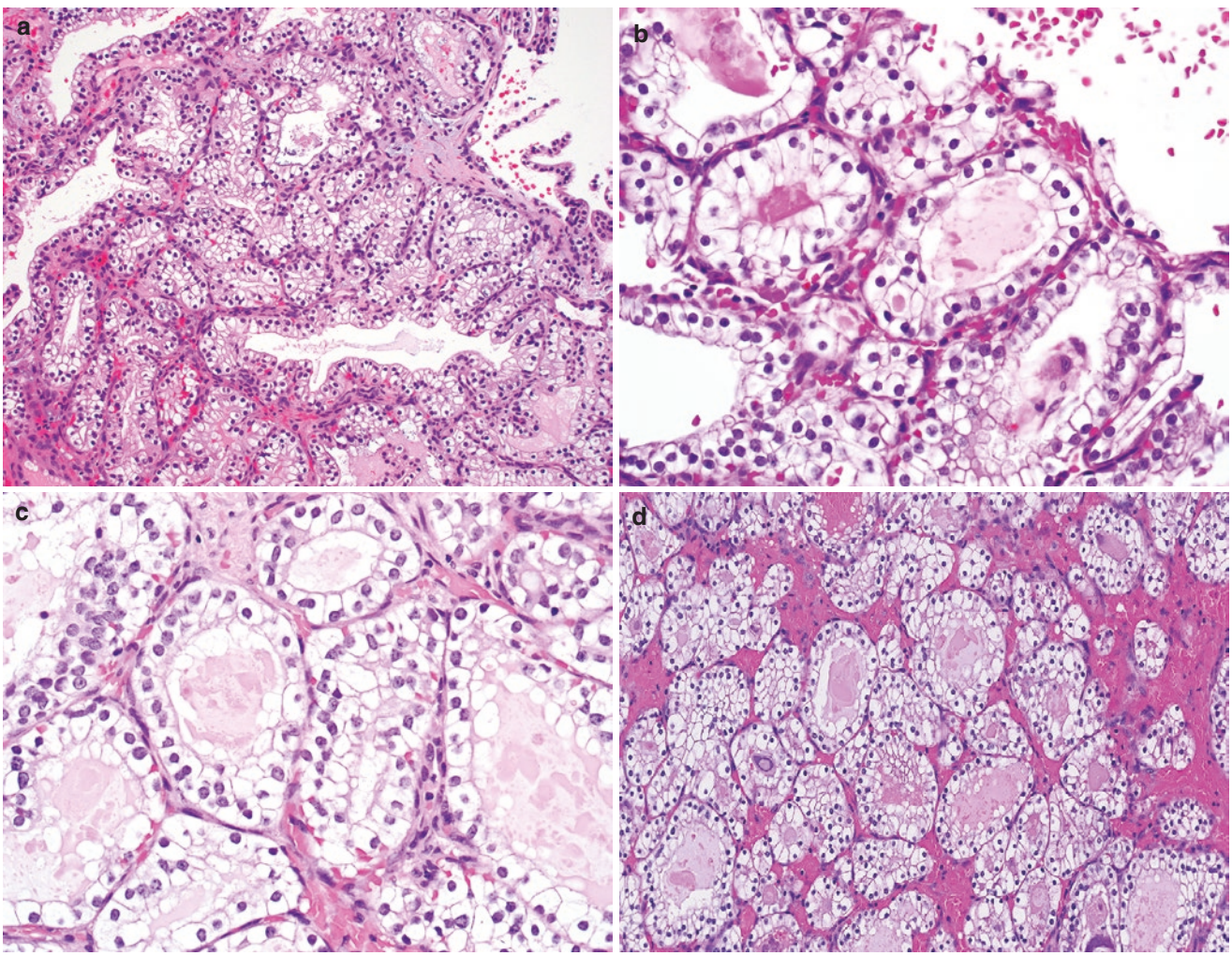


Fig. 8.23 (**a**–**d**) This variant shows remarkable degree of cytoplasmic clearing quite reminiscent of metastatic renal cell carcinoma. Like other low-grade sinonasal adenocarcinomas, some sinonasal renal cell-like adenocarcinomas are positive for S100 (**e**)

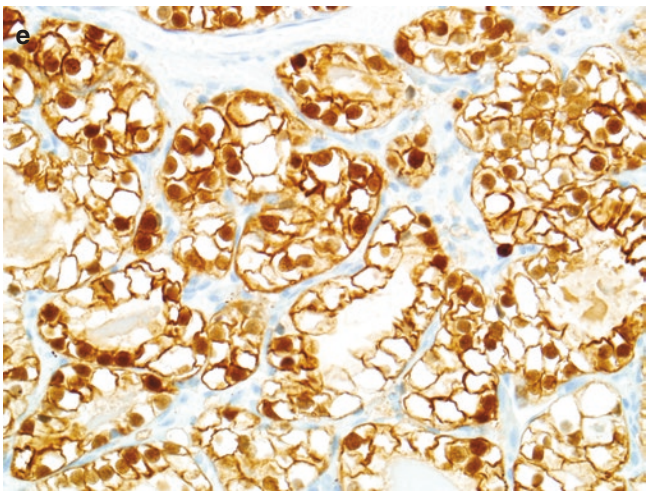


Fig. 8.23 (continued)

Table 8.2 Differences between sinonasal renal cell-like adenocarcinoma and metastatic renal cell carcinoma to sinonasal tract

Features	Sinonasal renal cell-like adenocarcinoma	Metastatic renal cell carcinoma
Location	Nasal cavity, paranasal sinuses, nasopharynx	Anywhere in the head and neck, including sinonasal tract
Histological features	• Acini and follicles of large polyhedral cells with abundant clear cytoplasm. • Follicles filled with thin eosinophilic material and sometimes hemorrhage. • Subtle nuclear atypia low mitotic rate, no necrosis.	• Alveolar and acinar pattern with prominent, arborizing capillary network. • Cells have optically clear abundant cytoplasm. • Nuclear pleomorphism, high mitotic rate, and necrosis are seen in high-grade tumors.
Immunohistochemistry	Positive for CK7, variably positive for S100 and CD10, negative for RCCMa, PAX8, and vimentin	Positive for PAX-8, RCCMa, CD10, and vimentin. CK7 is negative in clear cell type

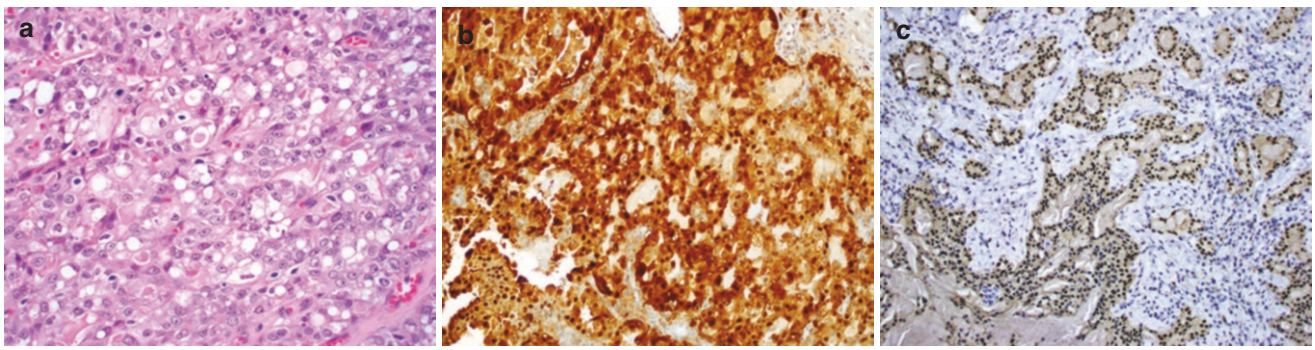


Fig. 8.24 The tumor is arranged in compact back-to-back tubules with intraluminal pink secretions. The tumor cells are round to polygonal in shape and have abundant eosinophilic to vacuolated cytoplasm. Nuclei are vesicular and show distinct nucleoli (**a**) S-100 (**b**) and pan-TRK (**c**) are diffusely positive. TRK expression suggests ETV6::NTRK rearrangement

8.7 SWI/SNF Complex Deficient Sinonasal Carcinoma

The SWI/SNF complex is a family of chromatin remodelling genes that function as tumor suppressors. Inactivating mutations lead to four distinct categories of tumors—SMARCB1(INI-1) deficient carcinoma, SMARCB1 deficient adenocarcinoma, SMARCA4 deficient carcinoma, and SMARCA4 deficient sinonasal teratocarcinosarcoma.

8.7.1 SMARCB1 Deficient Sinonasal Carcinoma

SMARCB1 (INI-1) deficient sinonasal carcinoma is a type of undifferentiated carcinoma with definitional inactivation of the *SMARCB1* gene on chromosome 22q11 due to biallelic deletion of *SMARCB1* gene in most of the cases. Monoallelic deletion or mutations occur in minority of cases. These tumors usually involve paranasal sinuses (ethmoids).

Histology shows mostly basaloid morphology with or without scattered rhabdoid cells. The other cytomorphologic subtype is oncocytoid/ plasmacytoid in which tumor cells possess abundant dense eosinophilic cytoplasm with central to eccentrically placed nuclei. This pattern can be present in solid sheets or complex tubuloglandular pattern which lead to diagnosis of SMARCB1 deficient adenocarcinoma. Rarely tumors show yolk-sac like patterns along with variable yolk-sac carcinoma immunophenotype in the form of SALL-4, glypican 3, and hep-par 1 positivity [14–16].

Immunohistochemistry for INI-1(SMARCB1) shows loss of expression in all variants while it is expressed in the nuclei of normal cells such as stromal fibroblasts, endothelial cells, and inflammatory cells. The tumor cells show immunopositivity for pankeratin with variable immunoreactivity for p63, p40, and neuroendocrine markers (Figs. 8.25, 8.26, and 8.27).

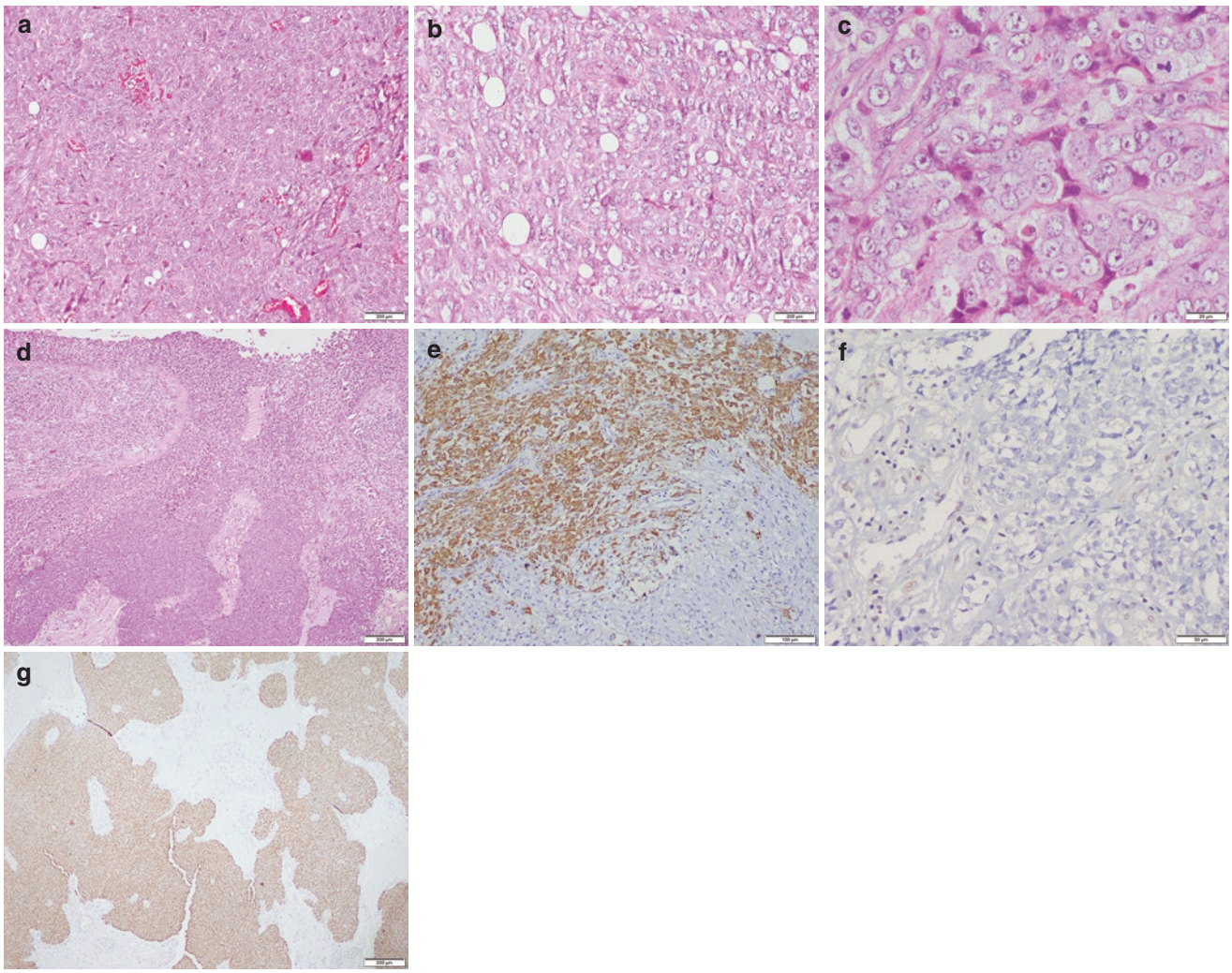


Fig. 8.25 Blue (basaloid) cell appearance. Cytologically monomorphic high-grade medium sized basaloid cells. Note empty vacuoles scattered throughout tumor (**a**, **b**). The nuclei have vesicular chromatin and pinpoint prominent nucleoli (**c**). The basaloid cells growing inwards from surface epithelium in expansile fashion mimicking inverted papilloma pattern. Entire epithelium is replaced by tumor cells (**d**). Tumor cells are diffusely positive for keratin (**e**) and show loss of SMARCB1 (INI1) protein in tumor cells (**f**). p40 shows positivity (**g**) (squamous markers show positivity in >50% cases)

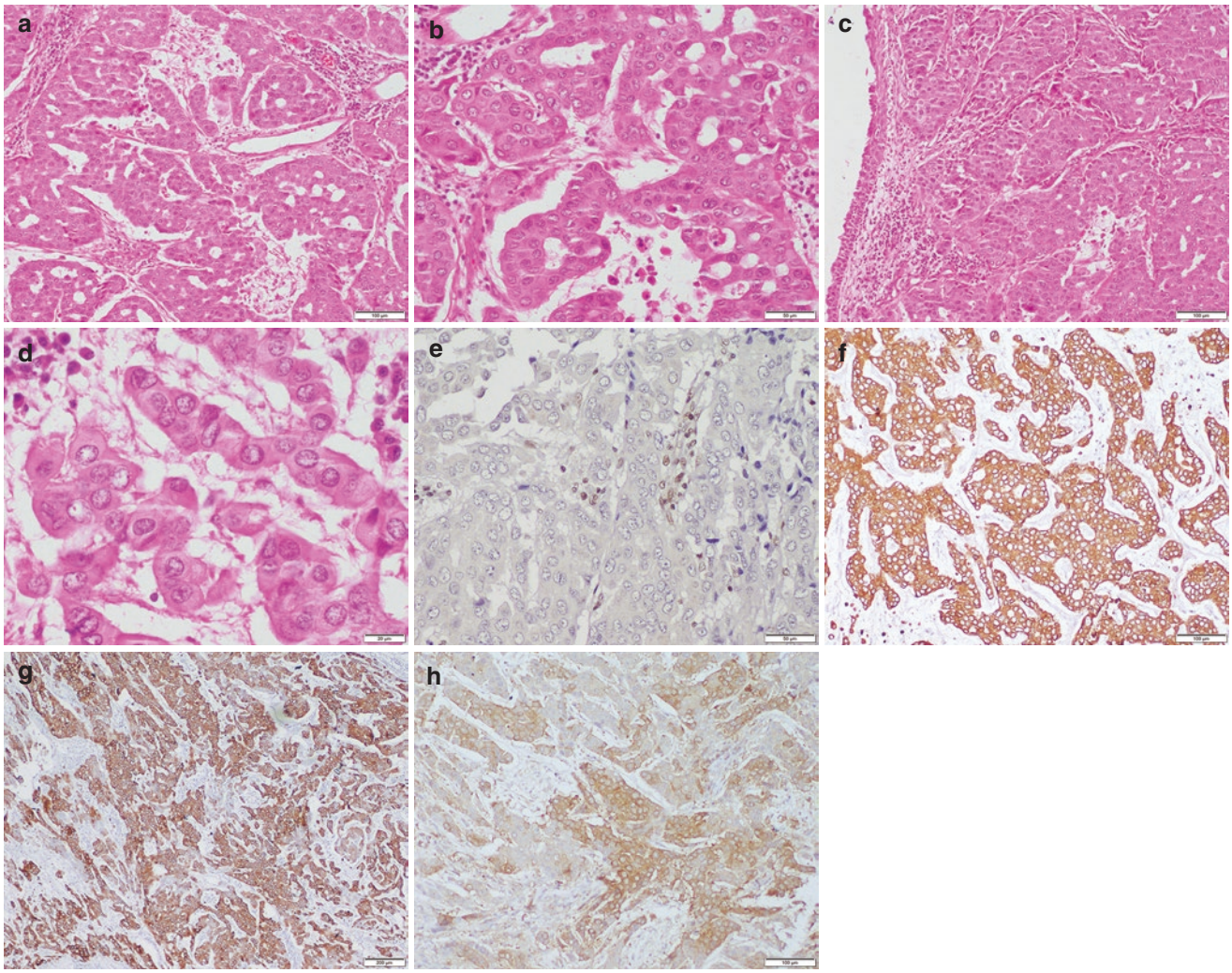


Fig. 8.26 Pink (oncocytoid) cell appearance. The tumor is arranged in complex tubular pattern with cribriforming suggestive of adenocarcinoma pattern. In contrast to basaloid variant, the cells have more cytoplasm which is dense eosinophilic throughout. The cellular monomorphism exists in this variant also. The nuclei are round and have fine chromatin (**a**–**d**). Overlying respiratory epithelium is identified which shows pagetoid spread of tumor cells in (**c**). The tumor here is arranged in solid sheets without glandular differentiation. The tumor cells show complete loss of SMARCB1 (INI1) protein from the tumor cells. Normal lymphocytes serve as control and retain brown nuclear staining (**e**). Keratin (**f**) and CK7 (**g**) are diffusely positive. Synaptophysin is also positive (**h**). About a third of tumors show positivity for neuroendocrine markers

8.7.2 SMARCA4 Deficient Sinonasal Carcinoma

The SMARCA4 gene is located on chromosome 19p13.2, inactivation of which leads to a group of aggressive carcinomas. SMARCA4 deficient SN carcinomas are also poorly to undifferentiated carcinomas with morphologic resemblance to neuroendocrine (NE) carcinomas. Similar to high-grade NE carcinomas, the tumor cells show nuclear molding, spindling, crushing, and stippled chromatin (small cell carcinoma phenotype). Some tumors show more cytoplasm, squared off edges, and prominent nucleoli and thus resemble large cell neuroendocrine carcinoma. Rare rhabdoid cells can be recognized on close search of tumor specimens. A characteristic cytologic monomorphism is maintained in these tumors also which is a diagnostic feature of all SWI/SNF family of tumors [17, 18] (Figs. 8.28, 8.29, 8.30, and 8.31).

A variation on this theme is identified in sinonasal teratocarcinosarcomas (TCS) which exhibit complete or partial loss of SMARCA4 (BRG1 protein) in about 70% of cases. SMARCA4 deficient or proficient tumors show *CTNNB1* mutations in a subset of cases. TCS are an admixture of carcinoma (epithelial), sarcoma (mesenchymal), and primitive neuroepithelium [19, 20] (Figs. 8.32, 8.33, 8.34, and 8.35).

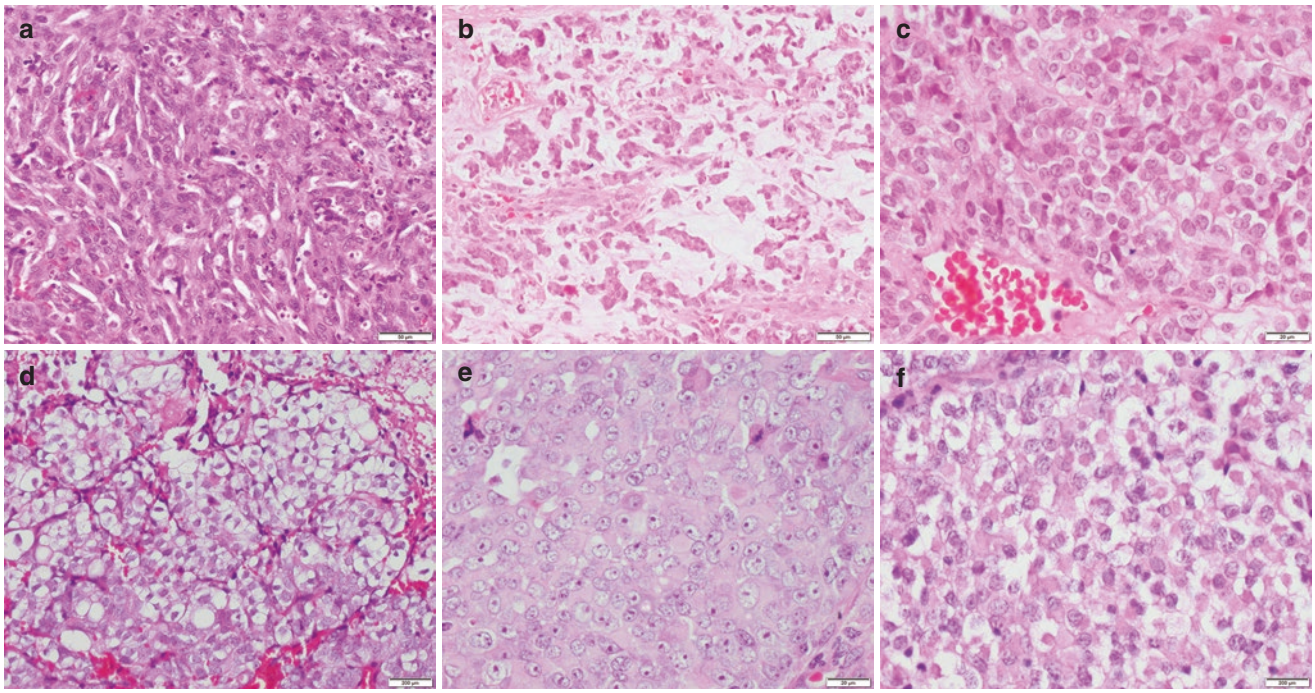


Fig. 8.27 Some tumors do not fall into strict basaloid or oncocytoid categories and show epithelioid tumor cells arranged in sheets with moderate amount of cytoplasm. Polymorphonuclear leukocytes are infiltrating into the tumor (right side) (**a**). Tumor cells in groups and nests are floating in myxoid stroma (**b**) and sometimes show abundant clear cytoplasm (**c**, **d**) and prominent rhabdoid appearance (**e**, **f**). Occasionally tumors show yolk-sac like morphology and immunophenotype (not shown here)

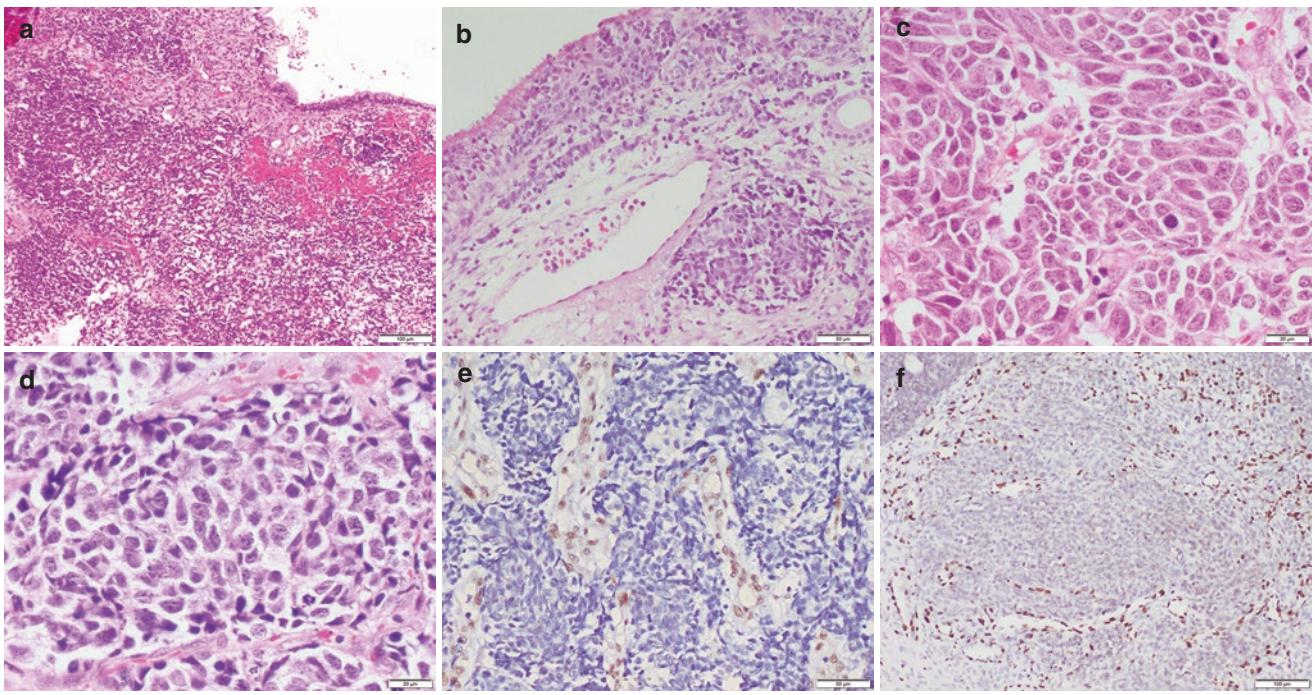


Fig. 8.28 Small cell carcinoma (SCC) phenotype: A highly cellular "blue" tumor present in sheets beneath respiratory epithelium. The tumor cells are round to fusiform and the stroma is richly vascular (**a**). Pagetoid spread of these undifferentiated tumor cells can be seen (upper part of **b**). The tumor cells are oval to fusiform with high N/C ratio, stippled "salt and pepper" chromatin and multiple chromocenters reminiscent of SCC. Frequent mitotic figures are seen (**c**, **d**). The tumor cells show loss of SMARCA4 (BRG1) protein against the background endothelial cells which retain normal immunoexpression of protein (**e**). This example demonstrates reduced (dim) expression of BRG1 in comparison to normal control of endothelial cells (**f**). Tumor cells spread through entrapped surface epithelium which retains BRG1 expression (**g**). Same is depicted by p40 stain which is negative in tumor cells (**h**). Retinoblastoma protein is retained (not lost as in SCC) in tumor cells (**i**). Chromogranin is focally positive (**j**)

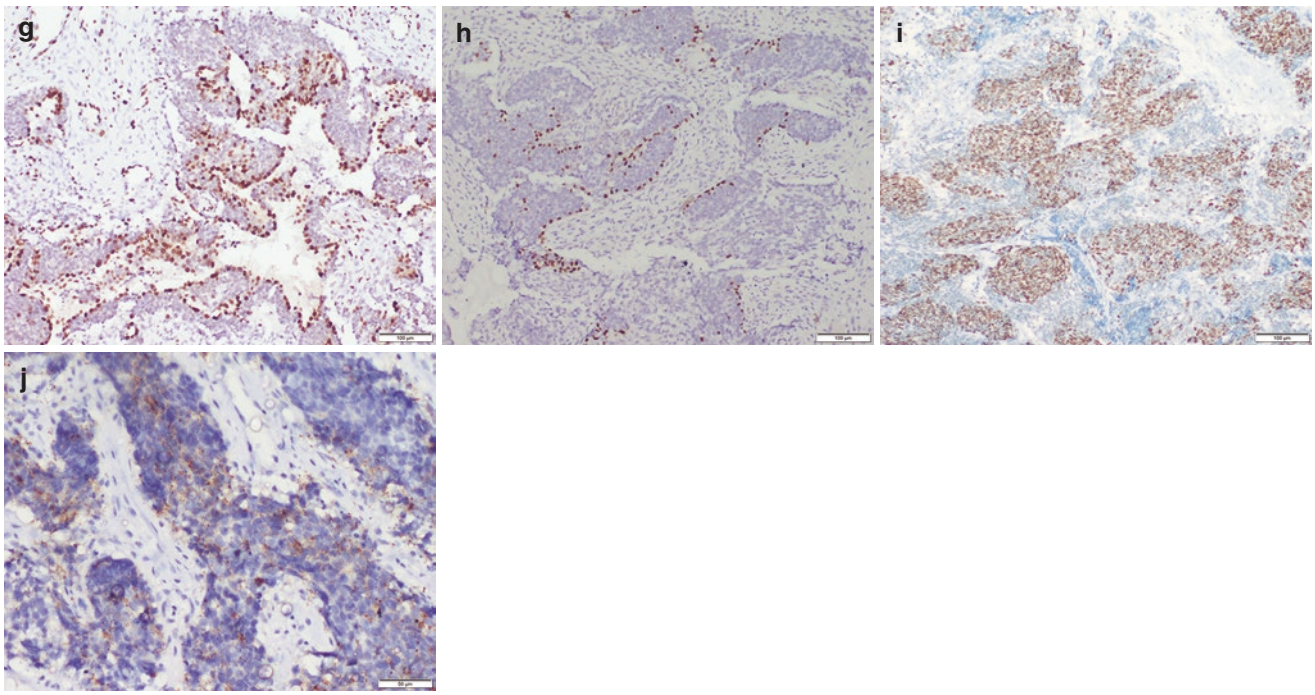
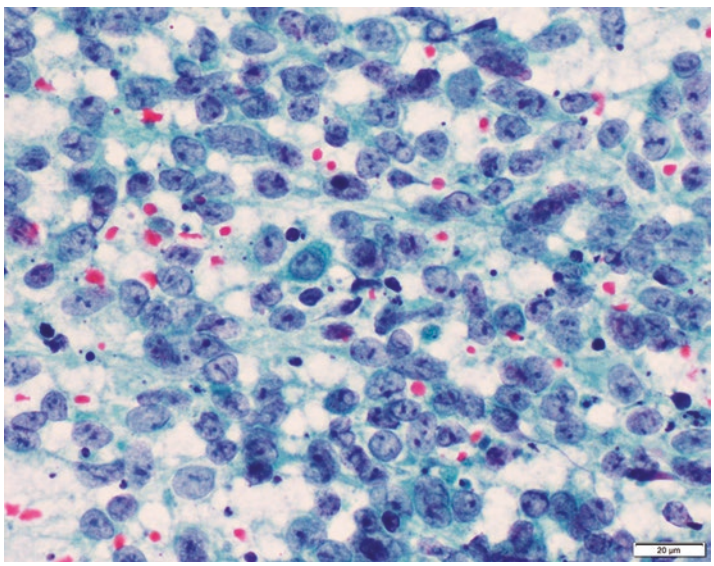


Fig. 8.28 (continued)

Fig. 8.29 Cytology of lymph node metastasis of a known case of SMARCA4 deficient carcinoma shows undifferentiated tumor cells mimicking small cell carcinoma



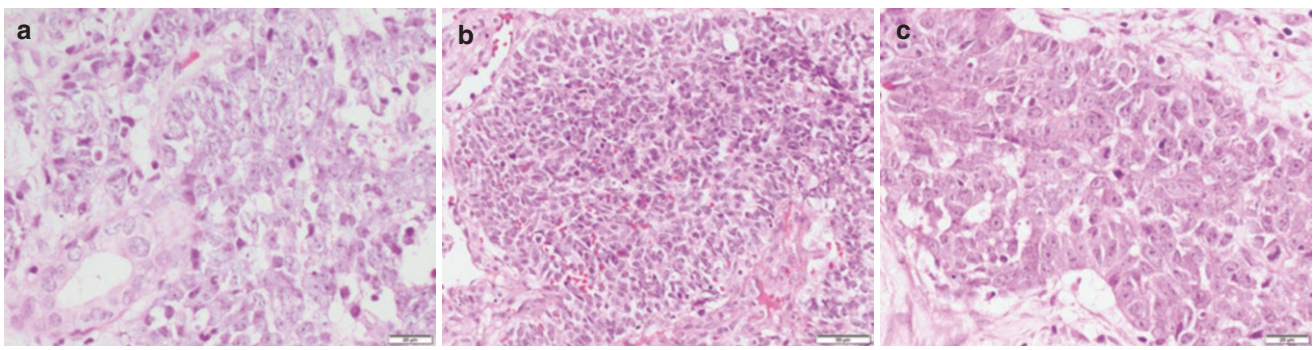


Fig. 8.30 Large cell neuroendocrine carcinoma (LCNEC) phenotype: The tumor cells show high nuclear/cytoplasmic ratio with finely stippled chromatin and conspicuous multiple nucleoli. A normal gland is entrapped in the tumor (left lower -**a**). A large tumor nest shows peripheral palisading. Note prominent nucleoli and moderate cytoplasm (**b**, **c**)

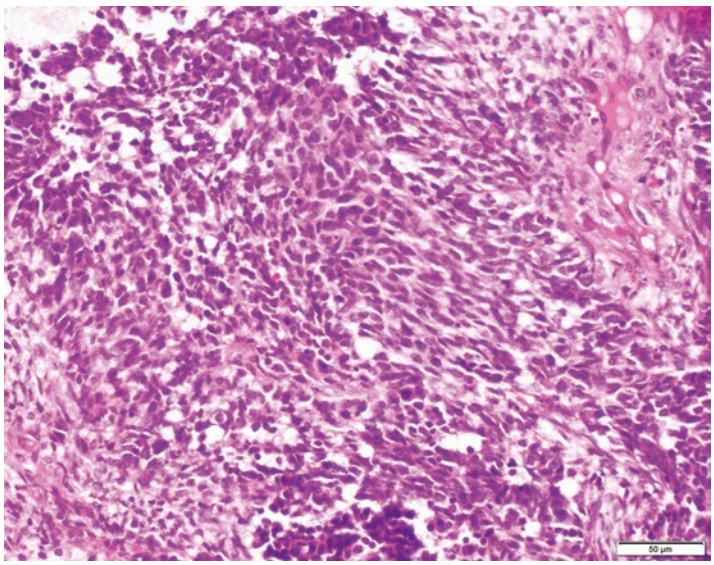


Fig. 8.31 Sometimes tumor shows prominent spindling

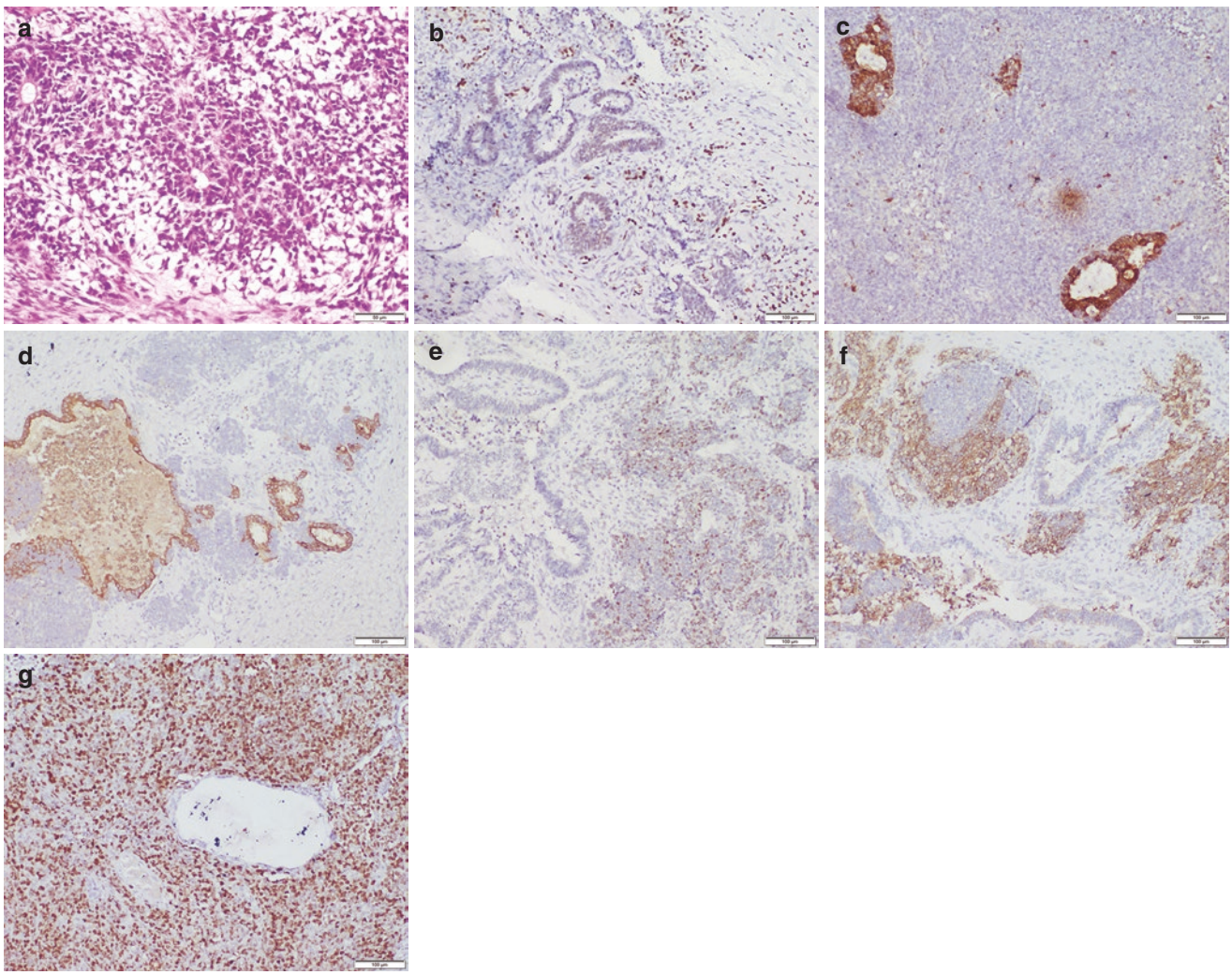


Fig. 8.32 A teratocarcinosarcoma shows primitive neuroepithelium (NE) arranged in rosettes. Malignant stromal cells are seen in left lower corner (**a**). BRG1 expression is reduced to absent in rosettes and background malignant stroma (**b**). Pan-Keratin (**c**) and CK7 (**d**) highlight glandular component of TCS while NE component is negative. On the other hand, INSM1 (**e**) and synaptophysin (**f**) are positive in NE component. These tumors are high-grade and show prolific KI67 labelling index (**g**)

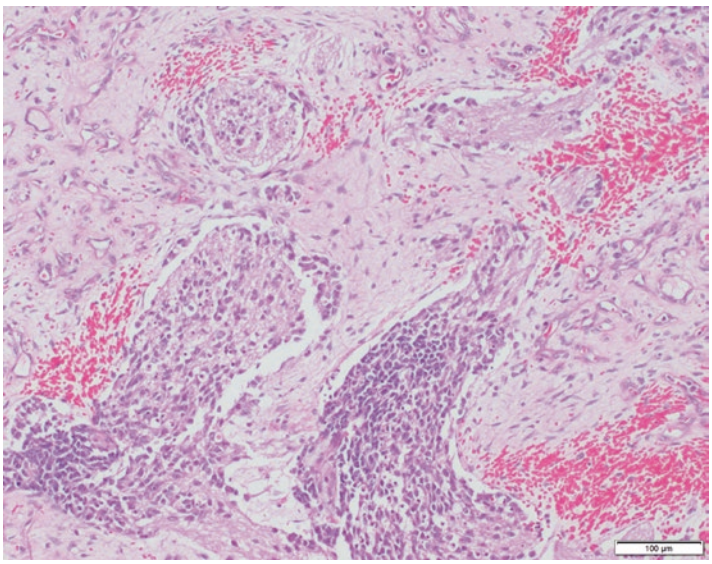


Fig. 8.33 Another case of TCS shows neurofibrillary background and undifferentiated primitive NE component

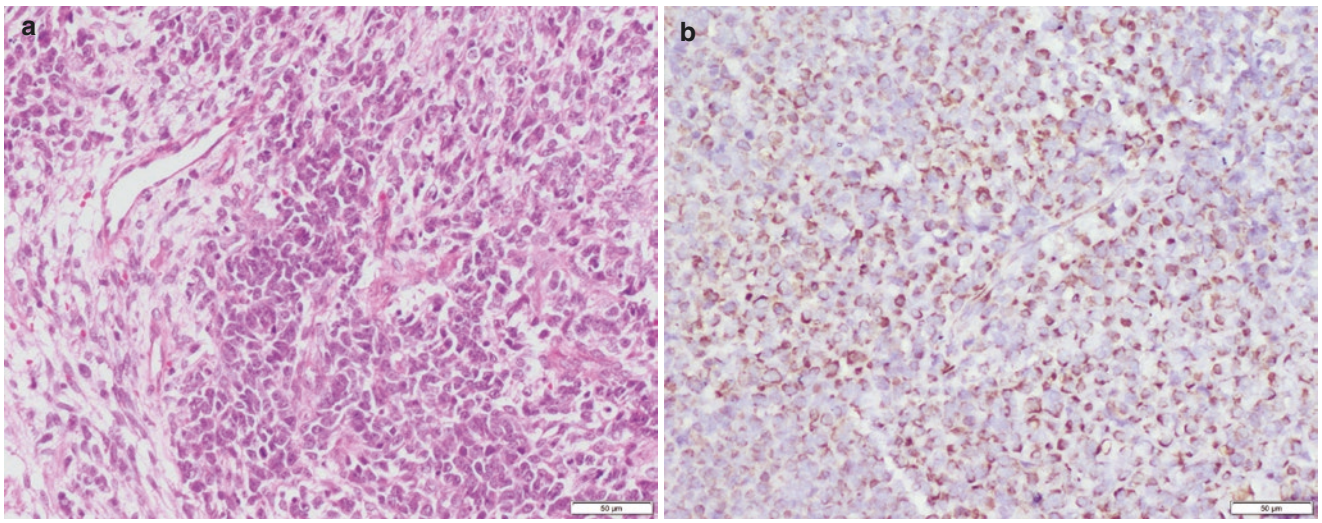


Fig. 8.34 TCS with rhabdomyoblastic differentiation (center) is seen in malignant stroma (**a**). Desmin is diffusely positive in stroma (**b**)

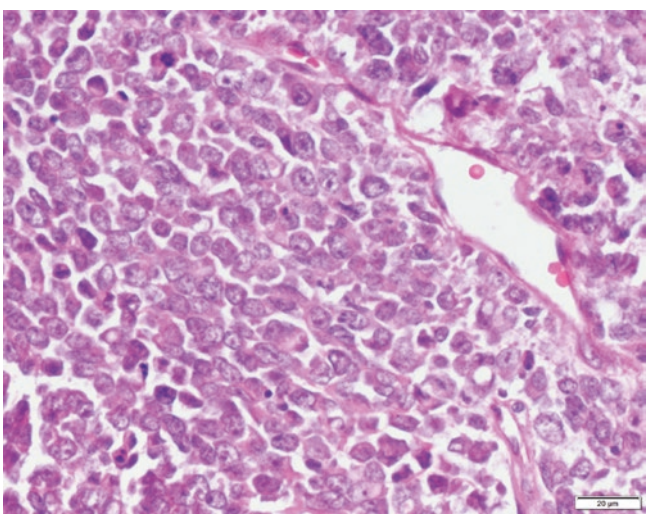


Fig. 8.35 This example of SMARCA4 deficient carcinoma shows high-grade morphology with prominent rhabdoid cells

IHC of SMARCA4 deficient carcinoma shows BRG1 loss with retention of other family proteins viz. SMARCA2 (BRM) and SMARCB1 (INI1). Focal reactivity to neuroendocrine markers is present.

TCS show positivity for keratins, p40 and p63 in epithelial component, NE markers in NE elements and mesenchymal component stains according to type of differentiation. When present, the degree of BRG1 loss may vary in the three components.

8.8 Sinonasal Undifferentiated Carcinomas (SNUC)

Sinonasal undifferentiated carcinomas are a diagnoses of exclusion where tumors do not show any lineage commitment either on morphology or on immunophenotyping.

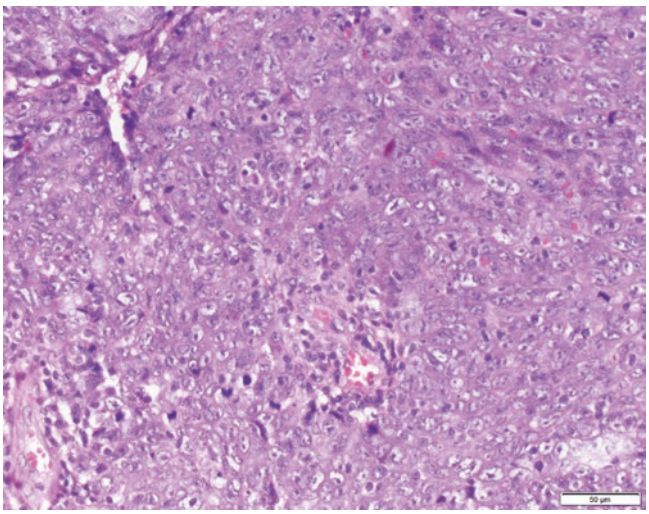


Fig. 8.36 Tumor nests show high-grade morphology with undifferentiated tumor cells. Immunophenotypically null cell type

Morphologically these tumors are undifferentiated high-grade tumors with frequent necrosis and mitosis (Fig. 8.36). Aside from simple keratins and epithelial membrane antigen (EMA), they do not show any consistent immunophenotype. No viral associations are reported. Differential diagnoses on morphology range from basaloid carcinoma, NUT carcinoma, SWI/SNF deficient tumors to high-grade neuroendocrine carcinomas [2].

Pathogenetically, *IDH2* hotspot mutations are identified in a significant number of SNUC cases (Fig. 8.37). Although IDH1/2 mutation-specific IHC is available, it is neither sensitive nor specific to identify all reported variants. Sequencing or PCR-based testing is suitable for mutation testing [21, 22].

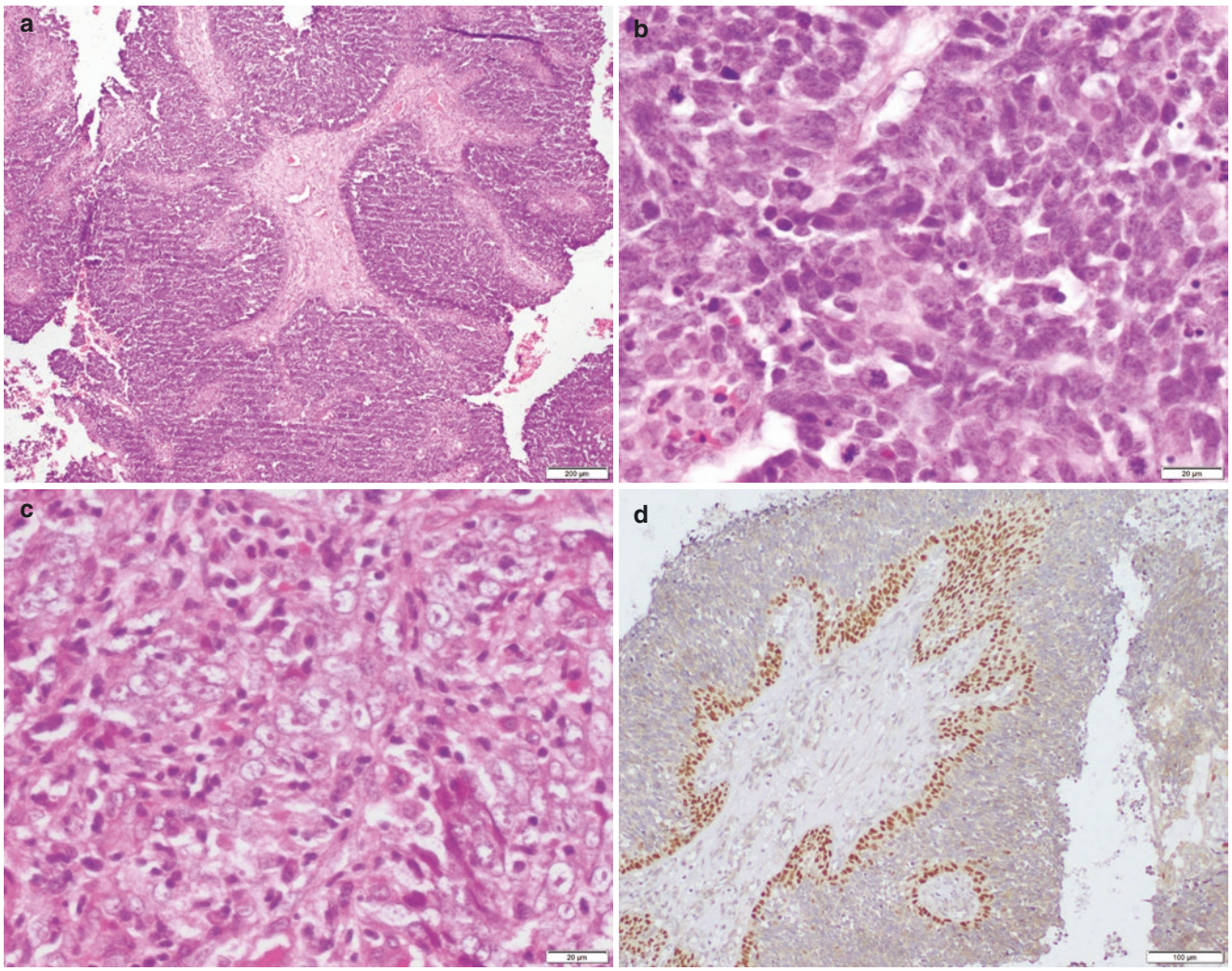


Fig. 8.37 Sheets and nests of undifferentiated tumor cells arising from epithelium and invading downwards with peripheral palisading reminiscent of inverted papilloma pattern (**a**) Higher magnification shows hyperchromatic nuclei with condensed chromatin (**b**) and vesicular nuclei with prominent nucleoli (**c**). Many mitotic figures are seen in (**b**). Tumor spreads through the entire thickness of epithelium with intact basal layer highlighted by p40 stain (**d**). IDH1/2 mutation specific IHC strongly positive in a IDH2 mutation positive case (**e**)

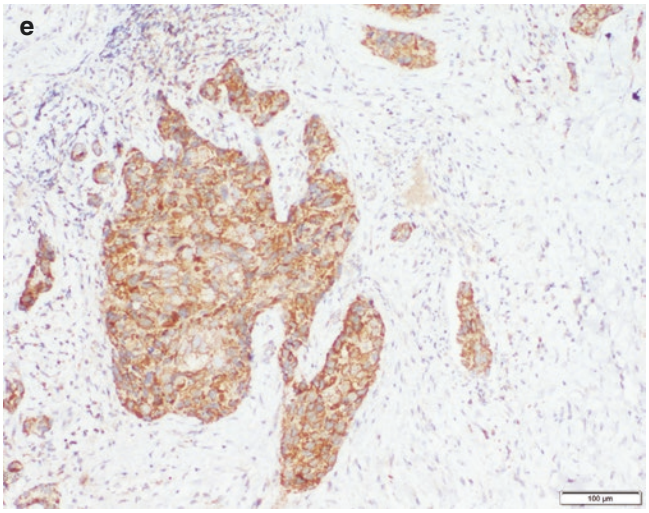


Fig. 8.37 (continued)

8.9 Sinonasal Neuroendocrine Tumors

WHO 2022 classification of head and neck tumors has unified the grading and nomenclature of neuroendocrine tumors at different sites. Sinonasal neuroendocrine tumors are subdivided into:

Grade 1: lack necrosis and have <2 mitoses per 2mm^2.

Grade 2: necrosis (often punctate or coagulative) and/or 2–10 mitoses per 2mm^2.

The use of Ki67 proliferation index is encouraged which is generally <20% in low-grade tumors. These tumors do not show abnormal p53 staining indicative of p53 mutation and retain rb (retinoblastoma protein) immunoexpression.

Neuroendocrine carcinomas can have small cell or large cell morphology with mitoses >10/2 mm2, and Ki-67 > 20% (Fig. 8.38).

Morphology of these tumors is same as at any other body site. It is important to exclude SMARCA4 deficient SN carcinomas if neuroendocrine markers are focal, weak and not consistent in an otherwise morphologically compatible NE carcinoma [1, 18].

Table 8.3 summarizes all basaloid (malignant blue cell morphology) appearing carcinomas of sinonasal tract.

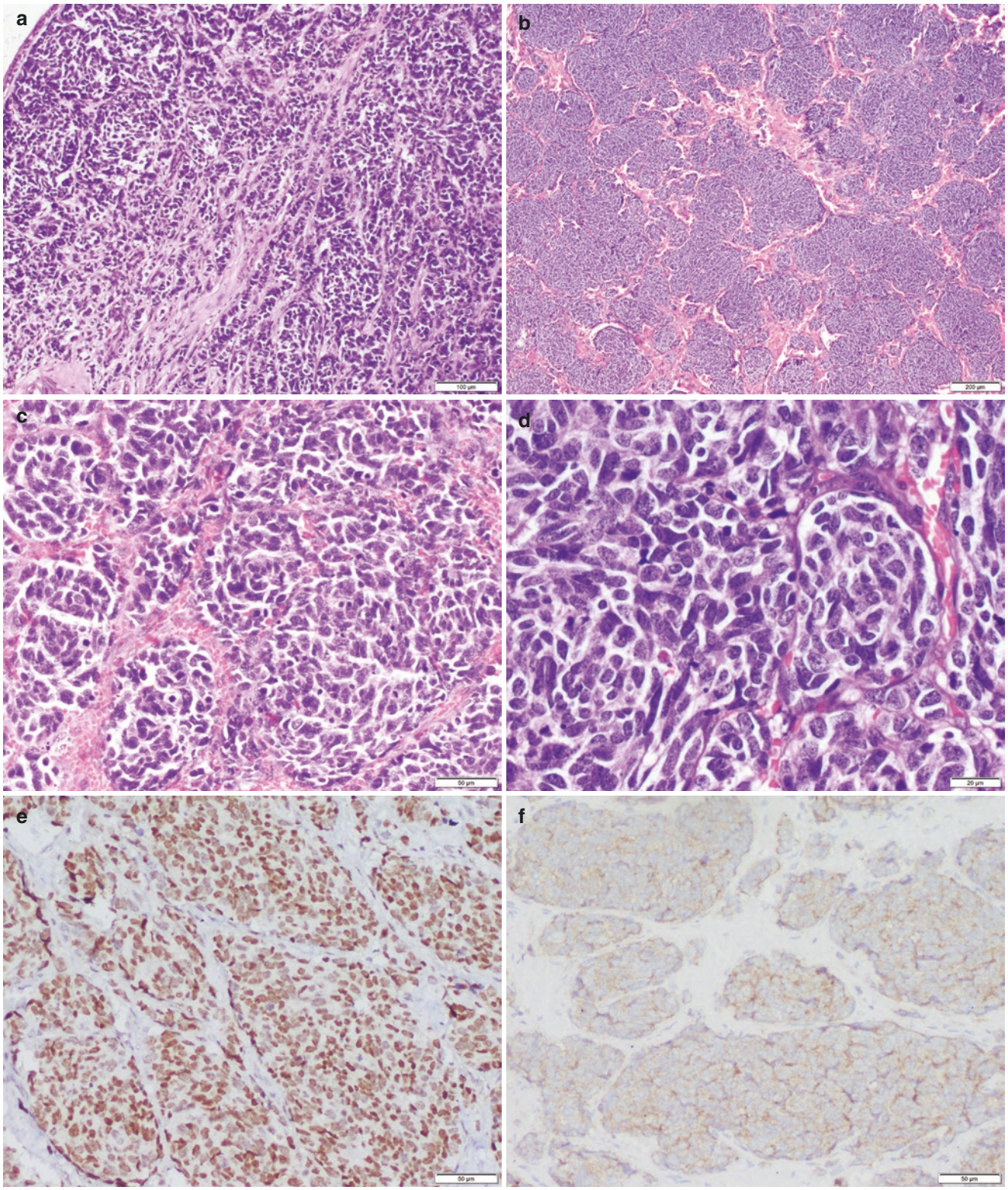


Fig. 8.38 A hypercellular "blue" tumor with overlying respiratory epithelium (left upper corner) (**a**). The tumor is arranged in swirling round nests and clusters (**b**). Individual cells are epithelioid round to oval shaped with stippled chromatin (**c**, **d**). Tumor is intensely positive for INSM1 (**e**) and synaptophysin (**f**). Retinoblastoma protein is lost in tumor cells. Normal endothelial cells around tumor nests serve as internal control (**g**)

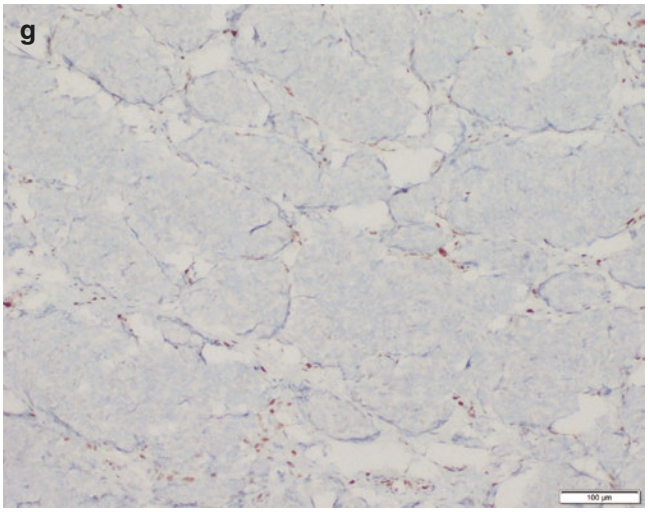


Fig. 8.38 (continued)

Table 8.3 Differential diagnoses of malignant "round blue cell" sinonasal carcinomas

	Morphologic hints	Initial IHC panel	Extended IHC panel	Other tests
Basaloid squamous cell carcinoma	Palisading of tumor nests, cohesiveness of tumor cells, subtle squamous phenotype	Keratin, p40 positive	NUT negative p16 ±	HPV ISH ±
NUT carcinoma	Undifferentiated cells with prominent nucleoli, neutrophils, abrupt keratinization	Keratin, p40, p63, NUT positive		NUT FISH, if available, positive for rearrangement
Lymphoepithelial carcinoma	Syncytium of cells, prominent nucleoli, stroma containing lymphocytes and plasma cells	Keratin, p40 positive, NUT negative	EBV LMP ±	EBER ISH positive
SMARCB1 (INI-1) deficient carcinoma	Basaloid cells, scattered rhabdoid cells, nondescript morphology not fitting in any other diagnoses	Keratin positive, p40, p63, NUT, NE markers negative[a]	INI-1 loss	
SMARCA4 deficient carcinoma	Small cell carcinoma or LCNEC morphology, rhabdoid cells	Keratin positive, NE markers focal, patchy, not consistent, p40, p63 negative	SMARCA4 (BRG1) loss, INI-1, SMARCA2 (BRM) and RB retained	
TCS (in biopsy specimens when only primitive neuroepithelial component is sampled)	Rosettes, nuclear molding, fine stippled chromatin	Keratin, CD99, NKX2.2 negative, NE markers positive	SMARCA4 (BRG1) loss	Repeat sampling if possible
Neuroendocrine carcinoma	NE phenotypic features	Keratin dot like (usually), NE markers positive	Rb deleted	
Solid adenoid cystic carcinoma	Solid basaloid cells, subtle basophilic secretions, cribriforming	Keratin positive, p40, p63 positive in myoepithelial cells	CK7, CD117 positive	*MYB* rearrangement
HMSC (in biopsy specimens if only solid component is sampled)	Surface dysplasia, subtle basophilic secretions, cribriforming	Keratin positive, p40, p63 positive in myoepithelial and squamous components	CD117, p16 positive	HPV ISH
SNUC	If no clue	Only keratin positive All other markers negative	IDH 1/2 ±	*IDH1/2* mutation testing by PCR based or sequencing methods

NE Neuroendocrine, *LCNEC* Large cell neuroendocrine carcinoma, *SNUC* Sinonasal undifferentiated carcinomas, *HMSC* HPV-related Multiphenotypic Sinonasal Carcinoma, *TCS* Teratocarcinosarcoma

[a] p40 and NE markers can come positive

8.10 Conclusion

Sinonasal carcinomas are an important category of tumors which needs thorough workup of cases to establish a correct diagnosis. Before labelling a case as SNUC, a battery of ancillary testing needs to be performed to provide a correct diagnosis as it has significant clinical implications.

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