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Small round blue cell tumors of the sinonasal tract: a differential diagnosis approach

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One of the most challenging diagnostic categories within tumors of the sinonasal tract is the small round blue cell tumors. Biopsies are usually small and limited, resulting in considerable diagnostic difficulty for practicing surgical pathologists. These tumors share several overlapping histologic and immunophenotypic findings while also showing considerable variation within and between cases. Specific tumor site of origin, imaging findings, and clinical findings must be combined with the histology and pertinent ancillary studies if the correct diagnosis is to be reached. Discrimination between neoplasms is critical as there are significant differences in therapy and overall outcome. It is important to have a well developed differential diagnosis for this category of tumors, where each of the diagnoses is considered, evaluated, and either confirmed or excluded from further consideration. In an undifferentiated tumor, showing a small round blue cell morphology, using the mnemonic 'MR SLEEP' helps to highlight tumors to consider: melanoma, mesenchymal chondrosarcoma, rhabdomyosarcoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma (including NUT carcinoma), small cell osteosarcoma, lymphoma, esthesioneuroblastoma (olfactory neuroblastoma), Ewing sarcoma/primitive neuroectodermal tumor, pituitary adenoma, and plasmacytoma. A panel of pertinent immunohistochemistry studies, histochemistries and/or molecular tests should aid in reaching a diagnosis, especially when taking the pattern and intensity of reactions into consideration.
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Introduction

The sinonasal tract is affected by a wide variety of reactive and neoplastic conditions. The anatomy of the region is complex and difficult to visualize, even when radiographic images are employed. Biopsies are usually small and limited, resulting in considerable diagnostic difficulty for practicing surgical pathologists. Diagnoses are sought on smaller and smaller biopsies, many of which require additional studies to confirm the diagnosis or render management decisions (prognostication). There is a major emphasis on getting a definitive diagnosis on as little material as possible, with several overlapping histologic and immunophenotypic findings along with considerable variation within and between cases, making interpretation a daunting challenge, especially for pathologists who may not be as familiar with the diagnostic entities of these anatomic sites.

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One such area is the 'small round blue cell' tumor category. This group of tumors encompasses a wide diversity of both benign and malignant neoplasms. The separation and distinction between tumors is critical as some are managed by conservative medical therapy, others by local surgery, a different group by primarily radiation, some by chemotherapy only, whereas others are managed by exenterative surgery and multimodality therapies, which can leave the patient potentially disfigured for life. It is, therefore, important to have a well developed differential diagnosis for this category, where each of the diagnoses is considered, evaluated, and either confirmed or excluded from further consideration. The major considerations are highlighted in Table 1, but this should be viewed as a guide, supplemented by good histology and appropriate dialogue with the treating clinicians. Although this approach is one I have found useful, there are several excellent reviews on this topic,[1–6] the combination of which should help the reader in determining an approach that works for them.

Approach

In an undifferentiated tumor, showing a small round blue cell morphology, I find the mnemonic

Table 1 Features to consider in a small round blue cell tumor evaluation

Symptom duration	Unique/specific symptoms	Exact tumor location
Bone destruction by imaging	Evidence of metastatic disease	Laboratory findings
Surface origin; pagetoid spread; junctional activity; ulceration	Dominant pattern of growth (lobular, ribbon, trabecular, sheets, organoid, diffuse, fascicular, alveolar)	Tumor necrosis; geographic necrosis; apoptosis
Perineural invasion	Destructive bone invasion	Lymphovascular invasion
Pleomorphism *vs* monotony	Cell size	Nuclear to cytoplasmic ratio
Cytoplasmic quality (clear, eosinophilic, amphophilic, pigmented (melanin, lipofuscin, hemosiderin), basophilic, vacuolated, granular, globules, inclusions)	Cytoplasm location (even, plasmacytoid, rhabdoid)	Intercellular bridges, borders
Keratinization, dyskeratosis, squamous pearls/eddies	Mucin vacuoles	Glycogen granules
Chromatin pattern/distribution	Nuclear molding	Nuclear cleaves, grooves, folds
Intranuclear cytoplasmic inclusions	Nucleoli (prominent, small, absent)	Nuclear viral inclusions
Background matrix	True rosettes (Flexner–Wintersteiner)	Pseudorosettes (Homer Wright)
Neural matrix	Desmoplasia/reactive fibrosis	Inflammatory infiltrate

'MR SLEEP' or 'MRS LEEP' to be helpful, as it highlights a series of tumors that must be considered in the differential diagnosis: melanoma, mesenchymal chondrosarcoma, rhabdomyosarcoma, sinonasal undifferentiated carcinoma (SNUC), squamous cell carcinoma (including NUT carcinoma), small cell osteosarcoma, lymphoma, esthesioneuroblastoma (olfactory neuroblastoma), Ewing sarcoma/primitive neuroectodermal tumor, pituitary adenoma, and plasmacytoma (Table 2). There are obviously tumors that are more common than others, and these should be more carefully excluded. It is important to select a panel of immunohistochemistry studies during the initial evaluation in order to avoid misclassification; the antibodies may include an epithelial marker (pancytokeratin such as AE1/AE3, epithelial membrane antigen (EMA) or OSCAR), a neuroendocrine marker (synaptophysin, chromogranin, or CD56), a muscle marker (desmin, myogenin, MYOD1), S100 protein, and CD45RB. The patterns of reactivity would then help to guide additional studies, as suggested by the histologic features, combined with the clinical and imaging findings. The following is a brief discussion of the pertinent findings of each of the major tumors in this site that can show a small round blue cell morphology.

Specific tumors

Melanoma

Mucosal melanoma arises within the sinonasal tract from melanocytes within the mucosa, representing about 4% of all sinonasal tract tumors.[7–9]

Clinical. With an equal sex distribution, there is a wide age range but more common in elderly (7th decade) patients (Table 2).[7,9] Symptoms are non-specific, with melanorrhea (black flecked secretions) uncommon. A mass usually affects the sinonasal cavity (septum) more often than the paranasal sinuses.[10]

Histopathology. When surface involvement or pagetoid spread is present (Figure 1a and b), a mucosal melanoma is much easier to diagnose. However, there is frequently surface ulceration, precluding junctional assessment. A peritheliomatous distribution of slightly dyscohesive cells is quite characteristic at low power (Figure 1c), but it is not specific. Tumor necrosis is common, as are easily identified and increased mitoses. The morphologic features are protean, but usually some of the cells will show eccentric nuclei, intranuclear cytoplasmic inclusions, prominent nucleoli, and/or cytoplasmic pigmentation (Figure 1d). The variable morphologies within a single tumor may help with the diagnosis, with cells ranging from undifferentiated to epithelioid, spindled, plasmacytoid, and rhabdoid, all in the same tumor.

Special studies. When pigmentation is absent, immunohistochemistry becomes helpful, with S100 protein and SOX10 usually strongly and diffusely reactive, whereas other melanocytic markers (HMB45, tyrosinase, melan A, MITF) are expressed to a variable degree, often based on tumor morphology;[6,7,11,12] in undifferentiated tumors, scant cytoplasm may result in focal or negative reactions, requiring careful high-power examination. Cross-reactivity with neuroendocrine markers is rare.[12] In general, *RAS* and then *KIT* mutations (mutually exclusive) are detected at a distinctly higher rate than cutaneous melanomas, with *BRAF* mutations rarely detected.[13–15]

Outcome and management. Theoretically, cutaneous primary melanoma may present with sinonasal mucosal metastasis, but practically are vanishingly rare, with melanoma in the sinonasal tract considered primary. In spite of multimodality therapy (including targeted treatments), due to high stage at presentation, there is an overall poor survival of $< 30\%$ at 5 years.[7,11,16–18] Depth of invasion and tumor thickness do not apply in sinonasal tract tumors.

Table 2 Immunohistochemical reactivity of small, round, blue cell tumors of the sinonasal tract (in mnemonic order: MR SLEEP)

	Mucosal melanoma	*Rhabdomyosarcoma*	*Sinonasal undifferentiated carcinoma*	*NUT carcinoma*	*Neuroendocrine carcinoma*	*Extranodal NK/ T-cell lymphoma, nasal type*	*Olfactory neuroblastoma*	*Ewing sarcoma*	*Pituitary adenoma*
Pattern	Protean, solid, organoid, fascicular	Sheets, alveolar	Sheets, nests	Sheets, nests	Syncytial, islands, ribbons sheets	Diffuse	Lobular	Sheets, nests	Sheets, rosettes, trabecular
Morphologic features	Large, polygonal, epithelioid, rhabdoid, plasmacytoid, spindle cells; pigment, pleomorphism, high mitotic count, limited necrosis, rare vascular invasion, surface involvement, no neurofibrillary matrix	Round, strap, spindled, rhabdomyoblasts, primitive cells, pleomorphism present, variable mitoses, limited necrosis, rare lympho-vascular invasion, no neurofibrillary matrix or rosettes	Medium cells, inconspicuous nucleoli, pleomorphism, high mitotic count, prominent necrosis, lympho-vascular invasion, no neurofibrillary stroma, pseudorosettes usually absent	Medium cells, monotonous, high nuclear to cytoplasmic ratio, abrupt keratinization or squamous differentiation, high mitotic count, tumor necrosis	Small cells, with high nuclear: cytoplasmic ratio, nuclear molding, nuclei crushed, moderate pleomorphism, inconspicuous nucleoli, high mitotic count, necrosis, no neurofibrillary matrix, pseudorosettes may present	Polymorphous, small to large cells, folded, cleaved and grooved nuclei, pleomorphism, high mitotic count, necrosis, lympho-vascular invasion, no neurofibrillary matrix or rosettes	Salt-and-pepper chromatin, small nucleoli (grade dependent), limited mitoses, scant necrosis, neurofibrillary matrix present, pseudorosettes and true rosettes	Medium, round cells, vacuolated cytoplasm, fine chromatin, scant pleomorphism, easily identified mitoses, necrosis, limited to absent lympho-vascular invasion, no neurofibrillary matrix, rosettes often present	Small cells, no perineural or vascular invasion, may have pleomorphism, limited mitoses, necrosis can be seen, no neurofibrillary matrix
CK-pan (AE1/AE3)	N	S (up to 10%; weak; punctate/ dot)	P	P	P (dot/punctate)	N	R, focal and weak	R (< 30%)	P (80%; dot/ punctate)
CK5/6	N	N	N	P	R (dot/punctate)	N	N	N	N
CK7	N	N	P (~50%)	S (40%)	R	N	N	N	R
EMA	R	R (< 1%)	P (~50%)	S (30%)	P	N	R (focal only)	R (< 20%)	N
CAM5.2	R	S (up to 50%, focal, weak)	S	P (50%)	P (dot/punctate)	N	R (focal only)	R (focal to diffuse, 20%)	P
p63	N	N	S (20%)	P	R (weak)	R	R	S	N
p40	N	N	N	P	N	N	N	N	N
Synaptophysin	N	R (up to 30%, weak)	S (< 15%)	S (< 15%)	P	N	P (may be weak)	S (focal)	P
Chromogranin	N	R (up to 20%, weak)	S (< 10%)	S (< 15%)	P	N	P (may be weak)	R (2%, focal)	P
CD56	N	P	S (< 5%)	N	P	P	P (membrane)	R (10%, focal)	P
NSE	N	R (up to 8%)	P	n/r	P	N	P	P	P
CD99	N	R (up to 20%)	S (< 10%)	S (30%)	N	R	N	P	S (~30%)
p16	N	R (< 10%)	P	P	P	N	N	P	N
FLI-1	P	R (focal)	n/r	n/r	R (focal)	n/r	R	P (~75%)	n/r

Table 2 (Continued)

	Mucosal melanoma	*Rhabdomyosarcoma*	*Sinonasal undifferentiated carcinoma*	*NUT carcinoma*	*Neuroendocrine carcinoma*	*Extranodal NK/ T-cell lymphoma, nasal type*	*Olfactory neuroblastoma*	*Ewing sarcoma*	*Pituitary adenoma*
Calcitonin	N	N	N	N	R	N	N	N	S (20%)
S100 protein	P	R	R	R (focal, weak)	R	N	P (sustentacular only)	S (up to 30%, focal)	R (focal, weak)
SOX10	P	N	N	N	N	N	P (sustentacular only)	N	N
HMB45	P	N	N	N	N	N	N	N	N
GFAP	N	N	N	N	N	N	P (sustentacular only)	R (up to 20%, focal)	N
Calretinin	R	N	N	n/r	S	R	P	R (up to 15%, focal)	P
CD45RB	N	R (< 5%)	N	N	N	P	N	N	N
Vimentin	P	P	N	S	S	P	R	P	N
Myogenin	N	P	N	N	N	N	N	N	N
CD117	S	R (< 15%)	P	N	P	N	N	S (~35%)	S (50%)
Pituitary[a]	R (hormones)	N	N	N	N	N	N	N	P
TTF-1	N	N	N	R	P	N	N	R	N
EBER (ISH)	N	N	N	N	N	P (~100%)	N	N	N
NUT IHC	N	N	N	P	N	N	N	N	N

Abbreviations: N, negative; NEC, neuroendocrine carcinoma; n/r, not reported; ONB, olfactory neuroblastoma; P, almost always positive; R, rarely positive; RMS, rhabdomyosarcoma; S, sometimes positive; SNUC, sinonasal undifferentiated carcinoma.
[a]Pituitary hormones and/or pituitary transcription factors, but may include or peptides and hormones (ADH, oxytocin).
Based on data aggregate in part from Bahrami *et al*,[36] Bell *et al*,[51] Bishop *et al*,[74] Bourne *et al*,[143] Chapman-Fredricks *et al*,[88] Folpe *et al*,[151] Hafezi *et al*,[150] Hicks *et al*,[30] Nikitakis *et al*,[166] Thompson *et al*,[7] Thompson *et al*,[124] Thompson *et al*,[159] and Wooff *et al*.[57]

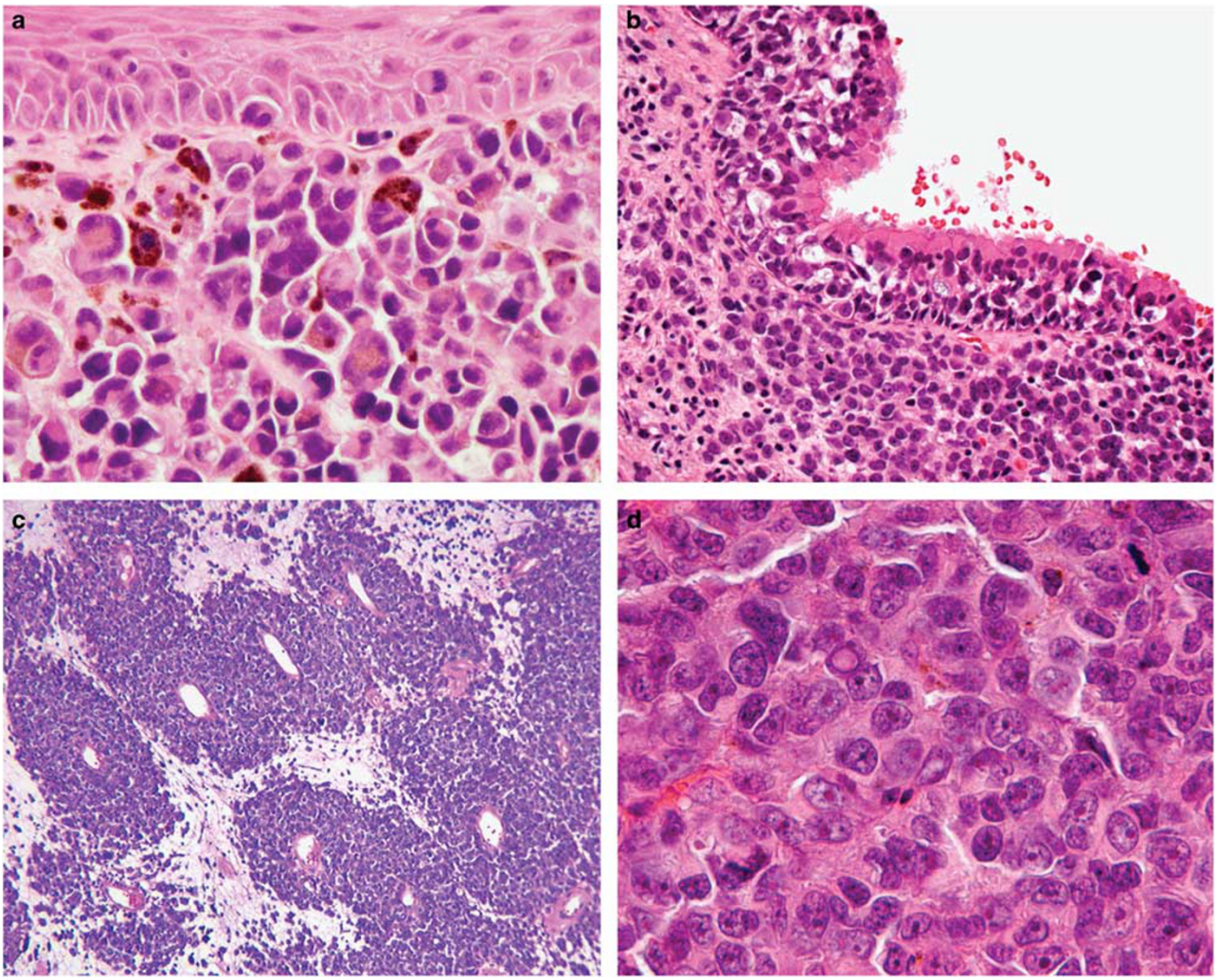

Figure 1 Mucosal melanoma. Surface involvement by neoplastic and pleomorphic, pigmented melanocytes (a) are much easier to diagnose than the small round blue cell pattern often seen (b), although surface involvement is helpful. A peritheliomatous distribution of slightly dyscohesive cells (c) is a characteristic finding. The cells are large, with prominent nucleoli, intranuclear cytoplasmic inclusions and focal pigmentation (d).

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a rare malignancy with a biphasic small round blue cell proliferation associated with islands of differentiated hyaline cartilage. The proportion of cartilage may be exceedingly limited, requiring careful evaluation of all tissue, sometimes with multiple serial sections or deeper levels required.

Clinical. With an equal sex distribution, tumors present most commonly in the 2nd to 4th decades, with craniofacial bones frequently affected (about 13%), although usually jaws, often with soft tissue extension.[19–22]

Histopathology. The tumor always shows the small blue round cell component, although the proportions of cells to differentiated cartilage varies (Figure 2). The cartilage must be neoplastic rather than native cartilage of the sinonasal tract being destroyed by the tumor. The cells are arranged in solid sheets, frequently around a prominent, hemangiopericytoma-like vascularity. The small cells have ovoid, hyperchromatic nuclei with scant cytoplasm, although they often show a spindled morphology. Tumor necrosis is uncommon, but mitoses, including atypical forms are easily identified and increased.

Special studies. The neoplastic cells are positive with antibodies to CD99, CD56, NSE, variably with glial filament acidic protein (GFAP), desmin, and synaptophysin, whereas non-reactive with keratins and S100 protein. One of the most helpful markers is strong nuclear expression for SOX9, a regulator of chondrogenesis, non-reactive in the other small round blue cell tumors.[23,24] Further, about 80% of tumors show *HEY1-NCOA2* fusions by FISH.[25]

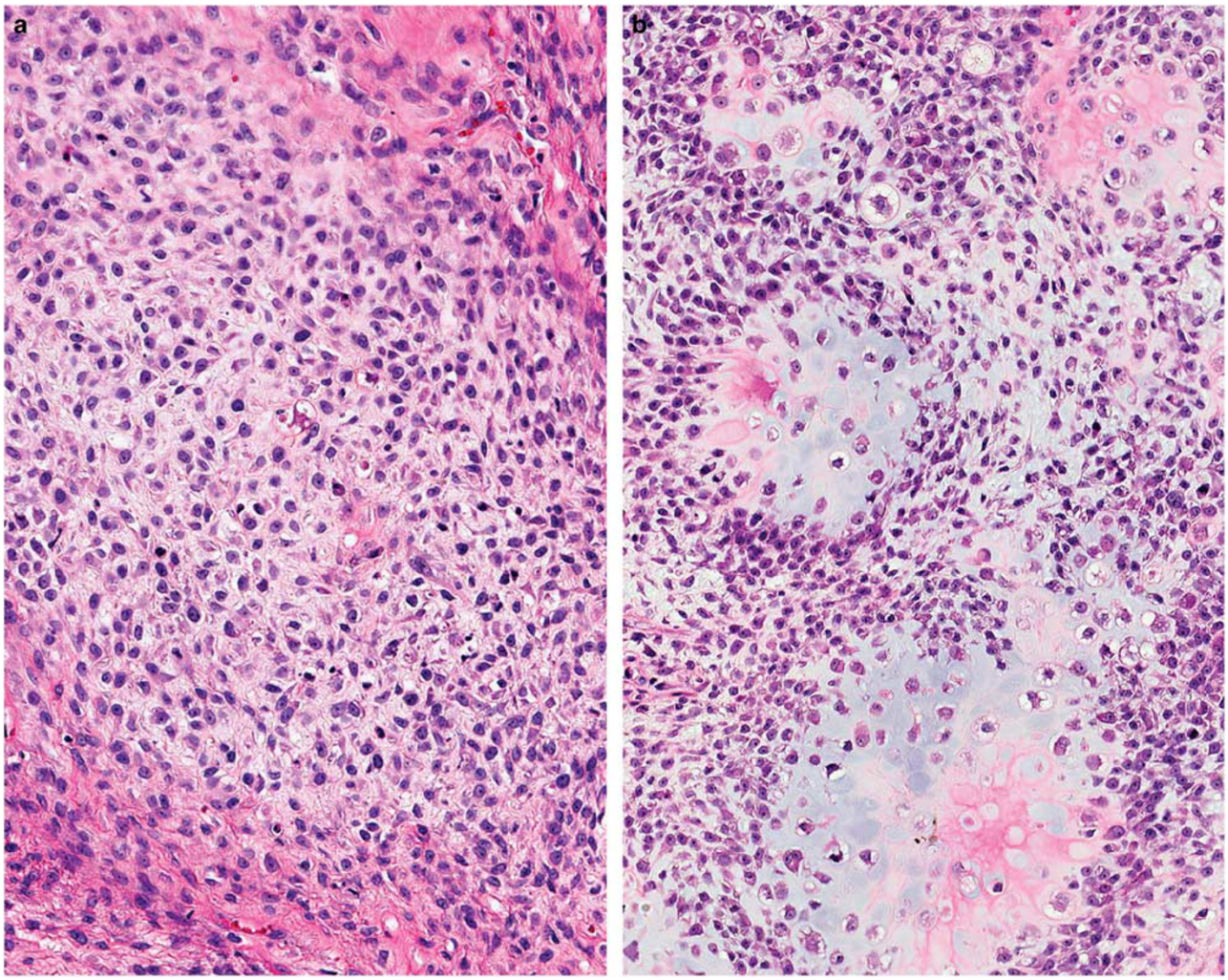

Figure 2 Mesenchymal chondrosarcoma. There is a small round blue cell to spindled appearance without well-developed cartilage (a), although neoplastic hyaline cartilage is surrounded by a small round blue cell component in this sinonasal tract tumor (b).

Outcome and management. Complete resection and chemotherapy yield an excellent median overall survival (17 years), whereas metastases at presentation has the strongest negative impact on survival. Mandatory long-term follow-up is required due to late recurrences.[21]

Rhabdomyosarcoma

Sinonasal rhabdomyosarcoma are rare malignant tumors showing skeletal muscle differentiation. Although several subtypes are recognized, the alveolar type is included specifically in the small round blue cell differential.[26–28]

Clinical. Rhabdomyosarcoma, although uncommon, is still the most common sinonasal sarcoma,[29–31] with a slight female to male predilection (1.2:1).[32] In adults, alveolar rhabdomyosarcoma is the most common subtype in the sinonasal tract. Syndrome association (Li-Fraumeni, Costello, and neurofibromatosis type 1) may be seen in children.[33] Symptoms are non-specific, with polyps, obstruction, facial swelling, proptosis, and epistaxis (Figure 3a). The paranasal sinuses are affected most commonly, with extension into the nasal cavity, orbit and skull base.[27,34,35]

Histopathology. Most lesions present as polyps, with a tan-grey cut surface. The embryonal type is the most common in the sinonasal tract, but in the small round blue cell differential, the alveolar type is considered. Fibrovascular septa separate the tumor into nests of small to medium round cells, which aggregate in the center, showing a clinging dilapidated appearance at the fibrous septa (Figures 3 and 4). Apoptotic, degenerated cells coalesce in the center of the alveolar spaces, often associated with tumor necrosis. A characteristic plasmacytoid-rhabdoid appearance, with eccentric, eosinophilic cytoplasm strongly suggests ribbon or strap-type

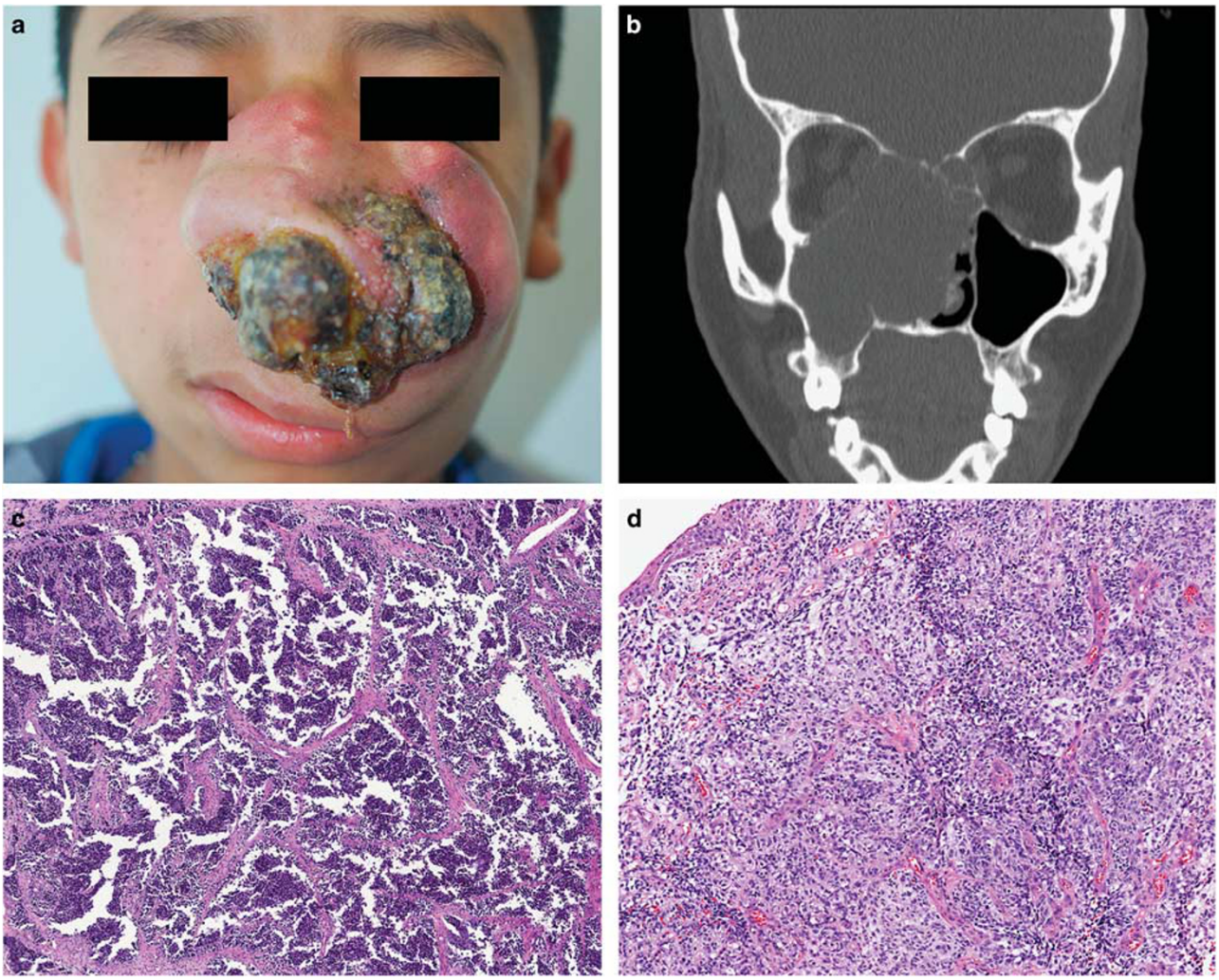

Figure 3 Rhabdomyosarcoma. (a) A large destructive mass of the nasal cavity, expanding into the soft tissues (photo courtesy Dr R Carlos). (b) A large destructive midline mass on computed tomography, expanding into the maxillary sinus. The low-power alveolar pattern with fibrous septa (c) helps in the differential diagnosis of this tumor. A slightly more epithelioid pattern is seen in this rhabdomyosarcoma (d).

rhabdomyoblasts (Figure 4c and d). Nucleoli are inconspicuous. Mitoses are usually easy to identify.

Special studies. The neoplastic cells are usually positive with desmin and myogenin (Myf-4; Figure 5a and b), with Myo-D1 and muscle-specific actin less frequently positive; smooth muscle actin is only detected in about 10% of cases.[30] Co-expression of CD56, synaptophysin (Figure 5c), cytokeratins (up to 10%; Figure 5d), EMA, NSE, and CD99,[30,36–38] must be taken into account in differential diagnosis, especially when choosing a panel of immunohistochemistry studies to perform. A FISH break-apart probe for *FOXO1* (13q14) may help to confirm the commonly identified fusion with *PAX3* or *PAX7* genes in alveolar rhabdomyosarcoma.[38,39]

Outcome and management. Rhabdomyosarcoma is considered a systemic disease, managed with multimodality therapies including surgery, chemotherapy and radiation,[40] frequently associated with adverse late sequela of treatment.[41] There is an overall poor prognosis of sinonasal tract alveolar rhabdomyosarcoma (5-year survival 30–40%),[29,35,41–44] with patients frequently showing regional and/or distant metastases, although young patients (5-year survival 62.5%) tend to have a better prognosis.[28,32,43]

Sinonasal Undifferentiated Carcinoma (SNUC)

SNUC is a rare tumor, lacking glandular or squamous features, and is not otherwise classifiable. Thus, it is a tumor of exclusion, comprising 3–5% of all sinonasal tract carcinomas.[45–47]

Clinical. Affecting a wide age range, the tumor is most common in 50–60 year olds, with men affected much more frequently than women.[45–49] Often with a rapid clinical presentation, obstructive symptoms

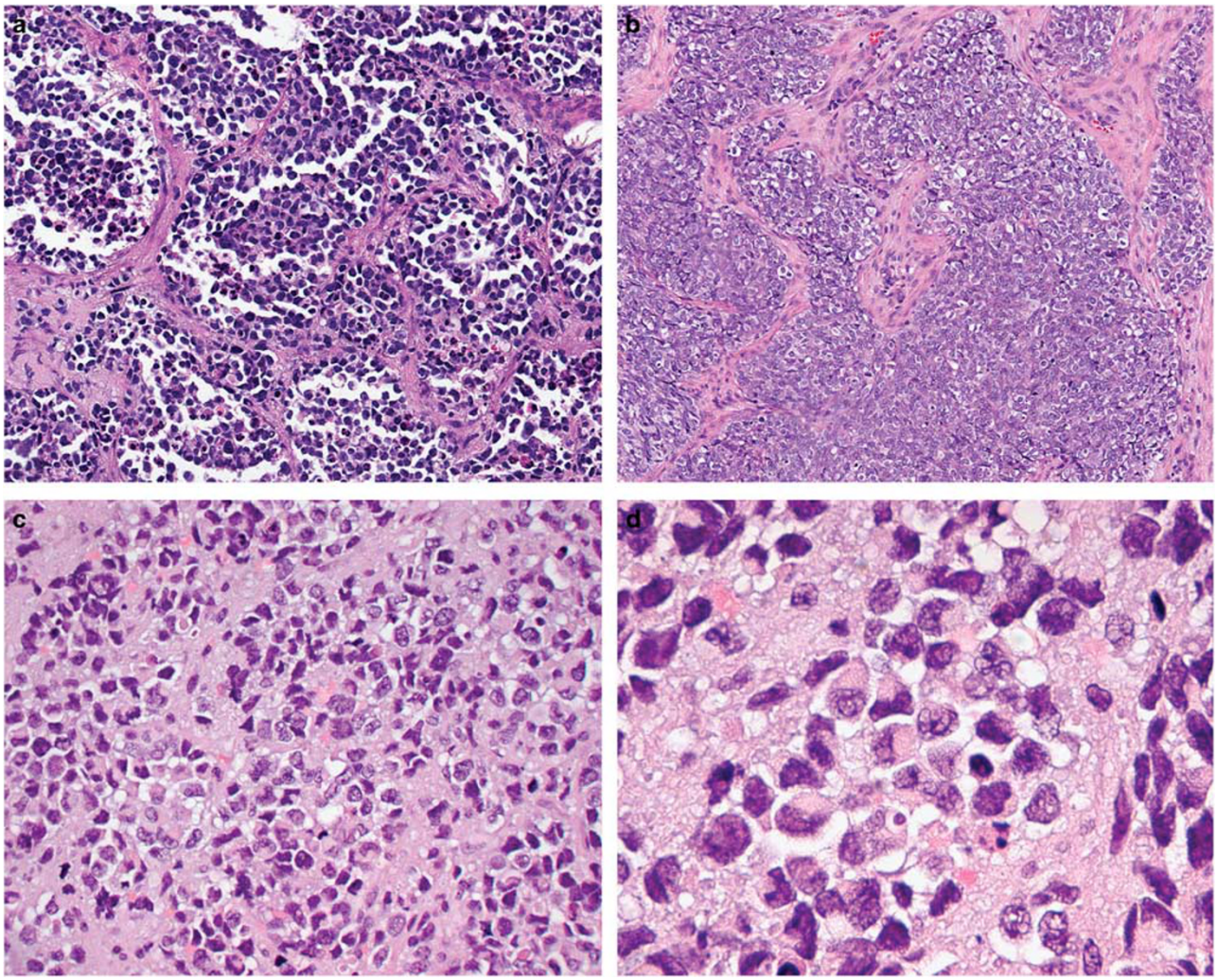

Figure 4 Alveolar rhabdomyosarcoma. Alveolar spaces (a) with dyscohesive dilapidated cells in the center, with clinging cells on the fibrous septa. A more solid appearance (b) may be seen in rhabdomyosarcoma. The neoplastic cells show a plasmacytoid (c) to rhabdoid appearance. There is moderate to severe nuclear pleomorphism (d), with well-developed rhabdoid/plasmacytoid cells noted.

are related to tumor presentation as large, midline widely destructive masses, starting in the nasal cavity, but rapidly expanding into adjacent sites (60% have orbit or skull base extension).[48–50]

Histopathology. Tumors are usually large (>4 cm) at the time of initial clinical presentation, showing ulceration, bone destruction, lymphovascular invasion, perineural invasion, and extensive necrosis. The cellular tumors are arranged in sheets, lobules, and trabeculae of atypical, but monotonous polygonal cells, showing round to irregular nuclei, well-defined cell borders and ample cytoplasm (Figure 6). The nuclear chromatin is vesicular to open with prominent nucleoli. Neuroendocrine morphologic features are absent. Apoptosis and increased mitoses are easily identified. By definition, squamous or glandular differentiation is absent, but in some cases surface dysplasia or carcinoma *in situ* may be seen. Rosettes may be present.[4,45,49–53] When more basaloid growth and rhabdoid features are present, the lack of *SMARCB1* (INI-1) protein by immunohistochemistry may suggest a different tumor type.[54,55]

Special studies. There is a strong and diffuse expression of epithelial markers (AE1/AE3, CK7, OSCAR, CAM5.2, EMA; Figure 6), consistent p16 and CD117 reactions, and only focal, patchy nuclear reaction with p63, whereas CK5/6, p40, CEA, EBER, CD34, desmin, S100 protein, and calretinin are consistently negative.[53,56–61] Focal, patchy, and/or weak reactions with neuroendocrine markers (NSE, synaptophysin, chromogranin, CD56) may be present, but there is no corresponding neuroendocrine morphology.

Outcome and management. The overall prognosis is poor, but with aggressive multimodality therapy,

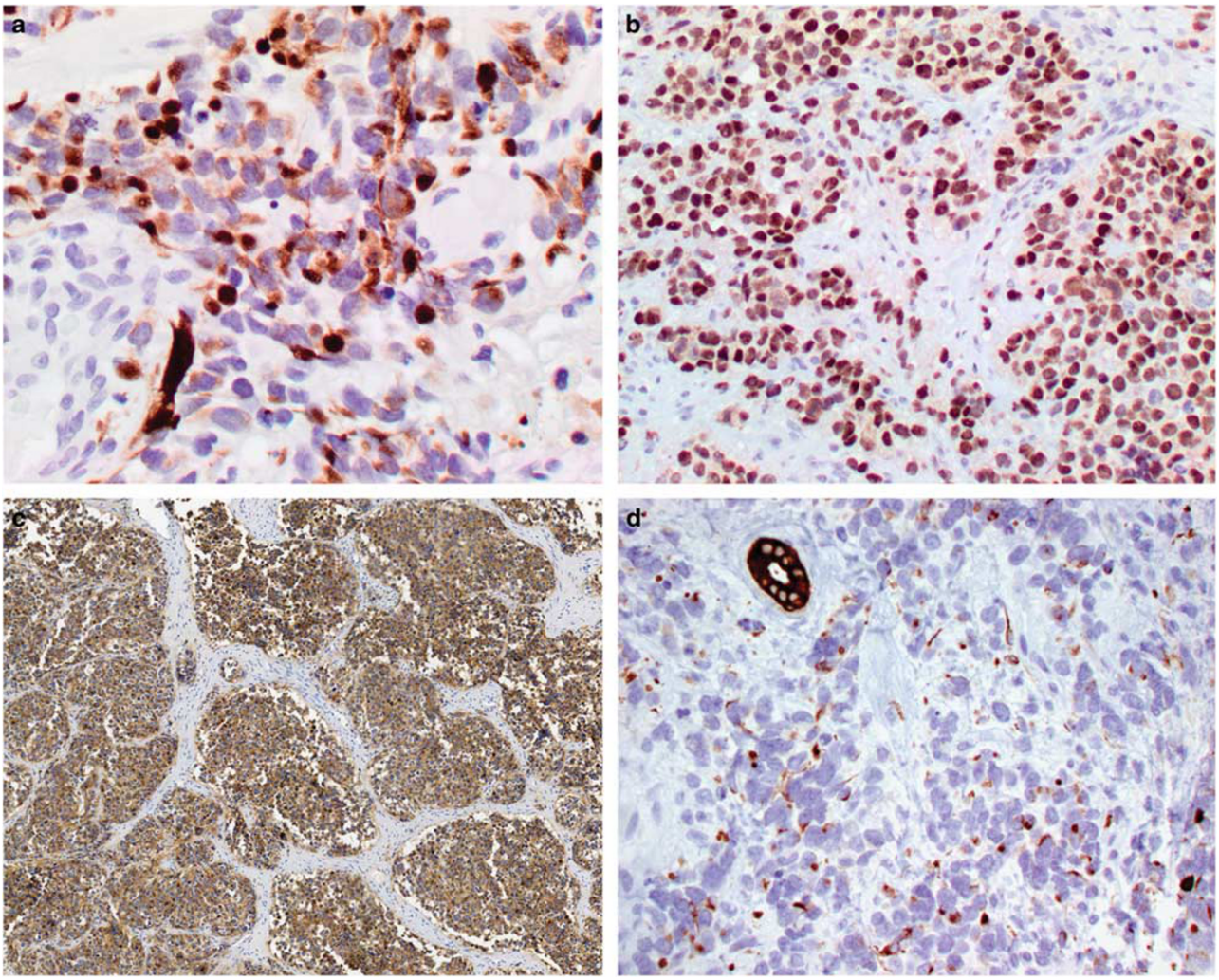

Figure 5 Alveolar rhabdomyosarcoma. The neoplastic cells show positive reactions with desmin in the cytoplasm (a), myogenin in the nuclei (b), although synaptophysin (c) and pancytokeratin (d) may be aberrantly expressed.

including primary surgical resection, 5-year survival rates or 35–63% are achieved, but with a median overall survival of about 2 years.[46–49,53,60,62–66] Local recurrence is common, but nodal metastases are relatively uncommon, although distant metastases are frequent.

NUT Carcinoma (Squamous Cell Carcinoma)

NUT carcinoma is a poorly differentiated carcinoma that shows abrupt evidence of squamous differentiation, defined by the presence of *NUTM1* gene rearrangement (nuclear protein in testis). This very rare malignancy is suggested morphologically by the abrupt keratinization but can only be confirmed by *NUTM1* detection.

Clinical. Sinonasal tract involvement by NUT carcinoma is much less common than mediastinal disease, but most head and neck cases affect the nasal cavity and paranasal sinuses (65%), with a median presentation in the 20 s, showing a slight female predominance.[67–73] There is no known etiologic association. Patients present with a rapidly-growing, extensively destructive mass, often with orbital involvement, and lymph node metastases in about 50% of patients.[70,73,74]

Histopathology. The tumors invade as sheets of monotonously undifferentiated cells, frequently showing bone invasion and tumor necrosis (Figure 7). The undifferentiated cells have moderate cytoplasm (occasionally clear) surrounding round to oval nuclei with vesicular chromatin and distinct, but small nucleoli. Characteristically, there are areas of abrupt keratinization or squamous differentiation (Figure 7), occasionally showing more extensive squamous features. Usually, careful, high-power review is required to see these areas. Rarely,

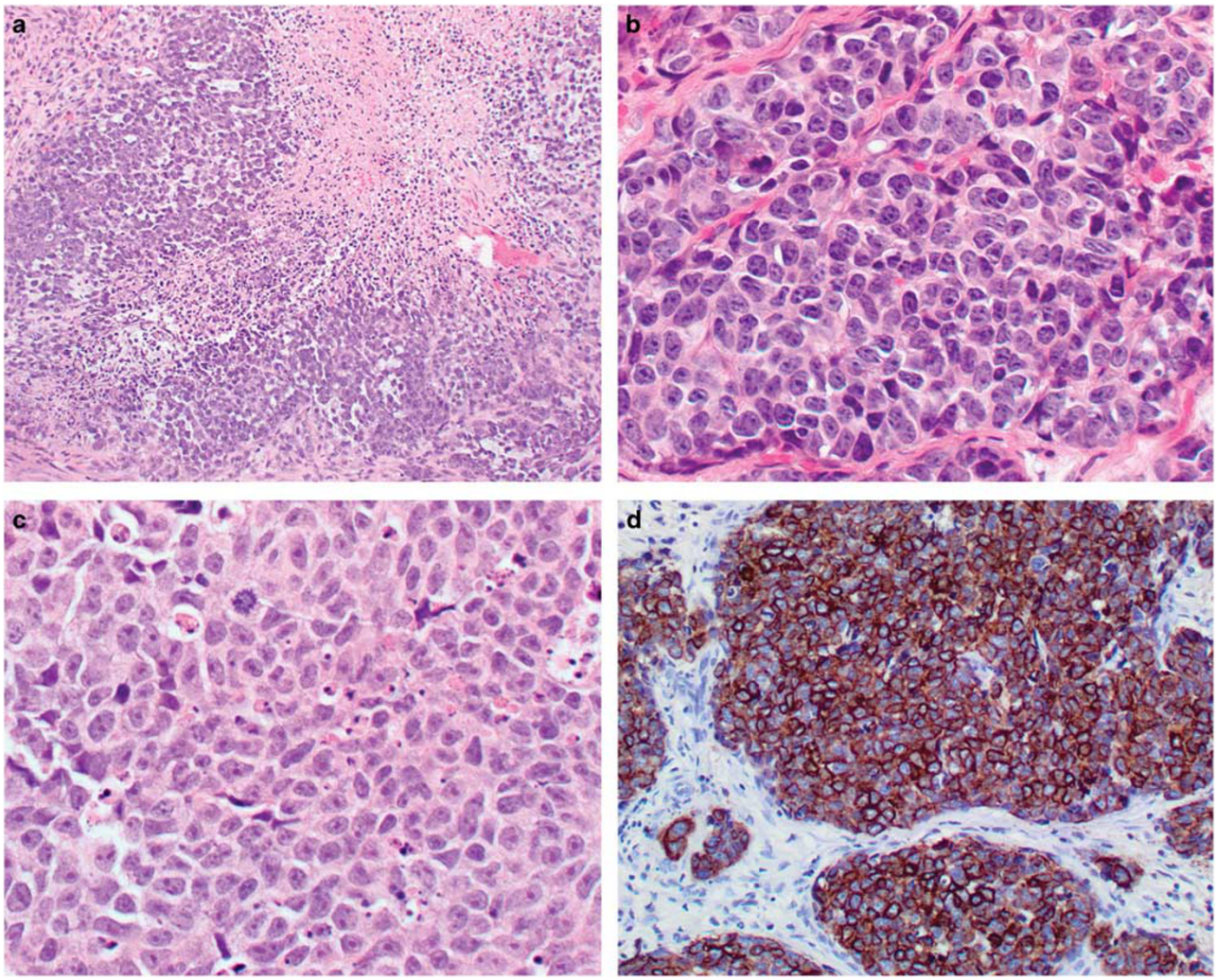

Figure 6 Sinonasal undifferentiated carcinoma. The neoplastic cells are medium, associated with tumor necrosis (a). The cells are arranged in sheets and nests (b), comprised of cells that have a high nuclear to cytoplasmic ratio, vesicular to open nuclear chromatin, and often prominent nucleoli (c). Mitoses are easily identified. The neoplastic cells are strongly reactive with pancytokeratin (d).

glandular or mesenchymal differentiation may be present. Acute inflammation within the neoplasm can be quite brisk.

Special studies. The neoplastic cells will be positive with pancytokeratin (AE1/AE3), along with CK5/6, p63 and p40,[69,70,75] frequently with CD34 (55%)[76], and uncommonly with neuroendocrine markers, p16 and TTF-1. By definition, *NUTM1* rearrangement must be documented, which can be achieved by strong, diffuse (>50%) nuclear staining with the NUT monoclonal antibody (C52, Cell Signaling Technologies, Inc.; Figure 7),[75,77] or by other methodologies (FISH, reverse-transcriptase PCR, targeted next-generation sequencing).

Outcome and management. Conventional treatments are ineffective, which yields a poor overall prognosis of about 10 months (median survival).[73] Molecular targeted therapies with pharmacogenomic agents may yield growth arrest and prolonged survival, but blood–brain barrier limitations are a consideration for sinonasal tract tumors.[71,78]

Sinonasal Neuroendocrine Carcinoma

Sinonasal neuroendocrine carcinomas are rare, high-grade tumors that must show morphologic and immunophenotypic features of neuroendocrine differentiation, separated into large and small cell types, the latter included in the differential diagnosis herein.

Clinical. Patients present in middle age (40–55 years), with men more commonly affected than women.[52,79–81] A smoking[53] and high-risk HPV[82] association are rare. Symptoms are non-specific, with tumors involving the ethmoid sinus, followed by nasal cavity and maxillary sinus, with advanced local disease

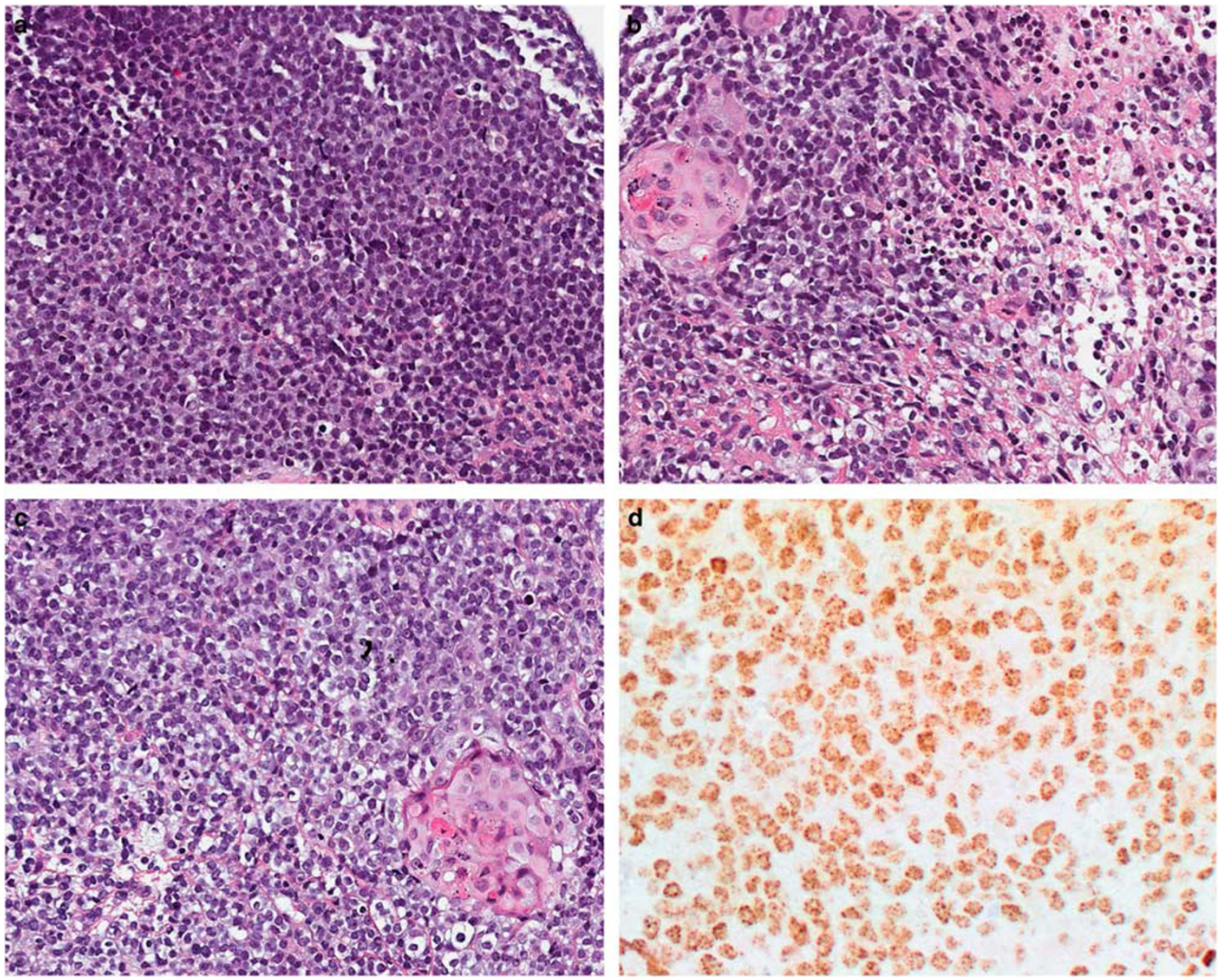

Figure 7 NUT carcinoma. Undifferentiated, small round blue cells (a), often associated with necrosis and areas of abrupt squamous differentiation (pearl formation; b,c). There is a strong nuclear punctate reaction with NUT immunohistochemistry (d).

(pT3 or T4) and regional or distant metastases at presentation common.[52,53,80,83,84]

Histopathology. In general, the tumors are clinically large and destructive, frequently accompanied by tumor necrosis (Figure 8), showing bone destruction, perineural invasion, and lymphovascular invasion.[52,80,85] The tumors grow in multiple patterns, including sheets, nests, lobules (Figure 8), ribbons, festoons, and trabeculae, occasionally showing rosettes or palisading. The cells are small to medium, with nuclear molding, apoptosis, prominent crush artifact, and cannibalism, with a high mitotic index (>10/10 high power fields) including atypical forms. The cells may be round, polygonal to spindled, with cytoplasm that is generally scant, but ranges from granular, eosinophilic to amphophilic. Nuclear neuroendocrine features must be present, and include salt-and-pepper clumped nuclear chromatin without prominent nucleoli (Figures 8 and 9). Rarely, small cell carcinoma may be combined with a squamous cell carcinoma or adenocarcinoma,[86,87] but neuroendocrine histologic features must be present rather than just detected by immunohistochemistry.

Special studies. Small cell neuroendocrine carcinomas are usually strongly and diffusely reactive with cytokeratins (AE1/AE3, CAM5.2) and EMA, often in a perinuclear dot-like reaction (Figure 9). At least one neuroendocrine marker (synaptophysin [Figure 9c], chromogranin, NSE, CD56) must be positive.[64,80,84,88,89] Rarely, S100 protein may be positive, but it is diffuse rather than sustentacular.[52] p16 is strongly expressed, TTF-1 may be seen (Figure 9d), whereas p63 and calretinin may show rare, focal reactivity.[57,88]

Outcome and management. Tumors are managed by multimodality combination of surgery and chemoradiation, yielding an overall 5-year disease-free

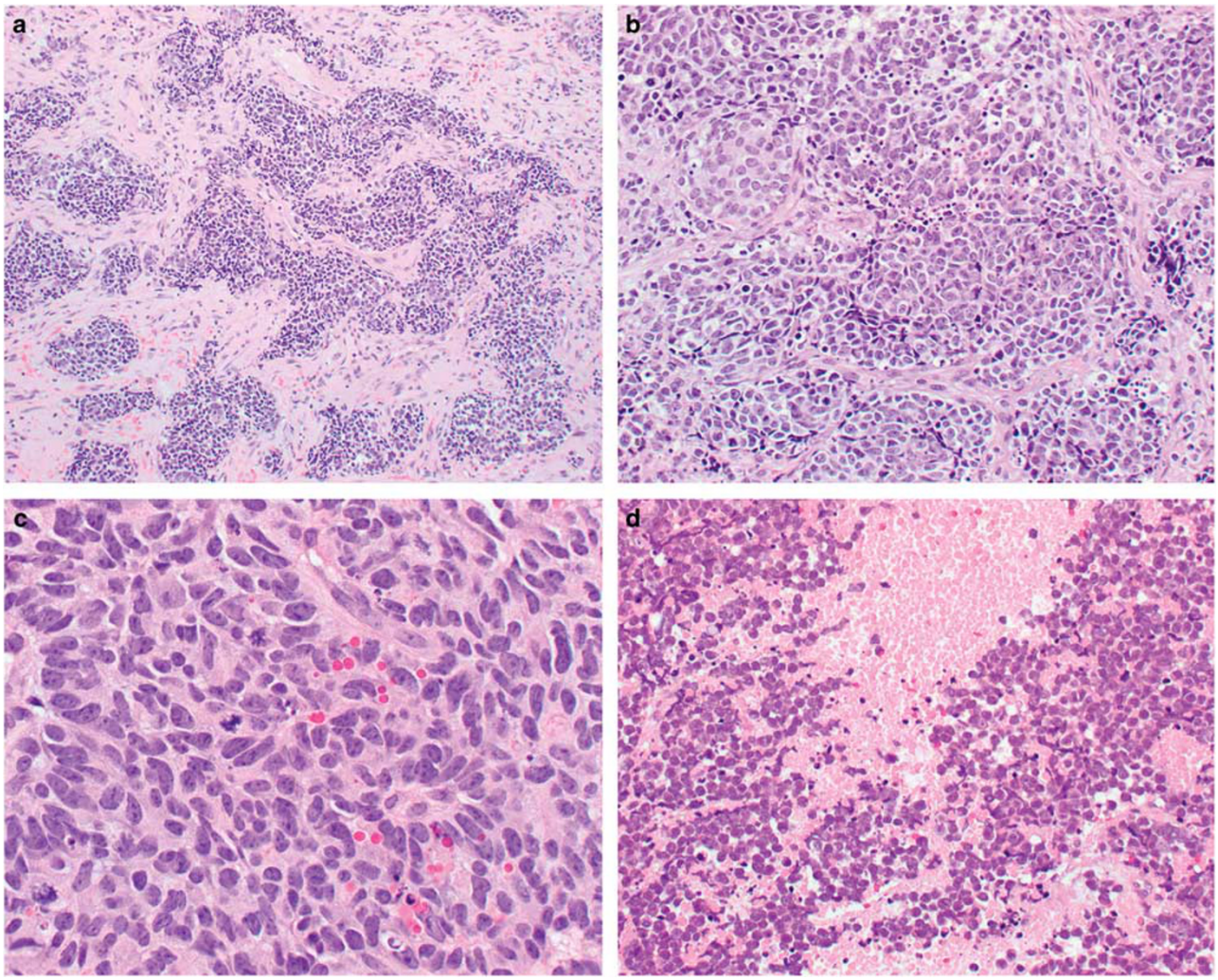

Figure 8 Sinonasal neuroendocrine carcinoma. A sheet-like to nested appearance (a) is composed of small cells that are molded to one another, with apoptosis (b). There is a delicate, salt-and-pepper nuclear chromatin (c) even when the tumor cells show slight elongation. Mitoses are easily identified. Tumor necrosis is frequent (d).

survival of about 50–65%, often better for sphenoid sinus (~80%) rather than maxillary or ethmoid sinus (~33%) tumors.[64,79,80,84,90]

Small Cell Osteosarcoma

Osteosarcomas are defined as malignant tumors whose cells produce bone, but are very rare in the sinonasal tract.

Clinical. Sinonasal tract osteosarcomas affect the sexes equally, but develop about 10–20 years later than appendicular counterparts.[91,92] The majority are spontaneous, but post-radiation and Paget disease of bone are etiologic agents.[93,94] Bone destruction by a mixed radiolucent–radio-opaque mass helps define the extent of disease radiographically.[91,94]

Histopathology. Neoplastic osteoid produced by highly atypical osteocytes is required for the diagnosis. Bone remodeling and destruction at the periphery of the tumor is not bone production. The bone matrix varies from focal to diffuse, showing immature lace-like osteoid to more sclerotic and mineralized bone. In the context of a small round blue cell tumor, the neoplastic cells are anaplastic and pleomorphic polygonal to epithelioid cells set within the bony matrix. Mitoses and necrosis may be seen. Associated cartilage, fibroblastic cells, and irregular bony trabeculae may be seen in other variants of osteosarcoma. Importantly, when cartilage is found, a chondroblastic osteosarcoma is more common in the sinonasal tract than primary chondrosarcoma, thus a diligent search for malignant bone is recommended.

Special studies. Osteosarcoma generally lack reactivity with other markers in the differential diagnostic considerations of a small round blue cell tumor,

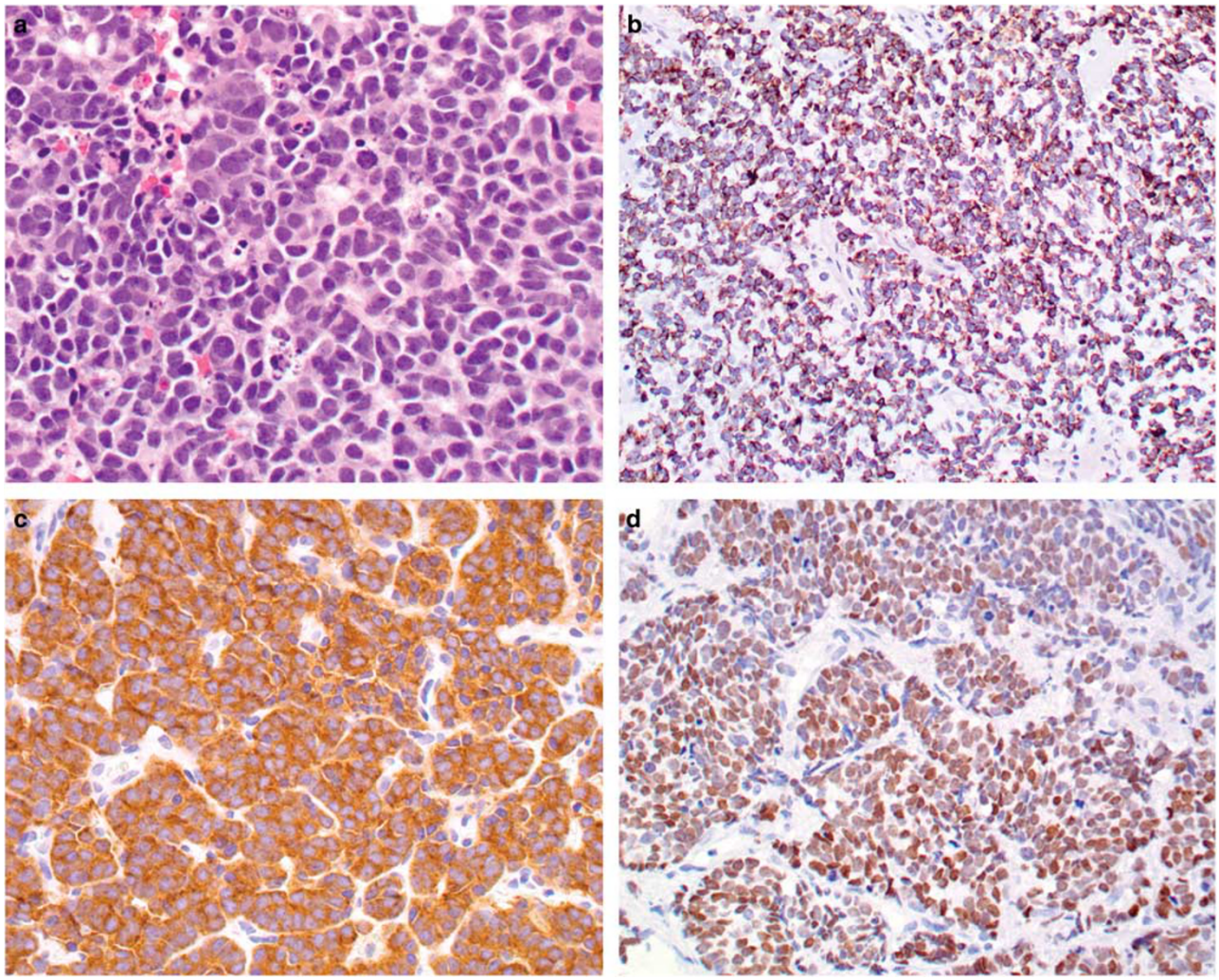

Figure 9 Sinonasal neuroendocrine carcinoma. Neoplastic cells with a high nuclear to cytoplasmic ratio, scant cytoplasm, molding and delicate nuclear chromatin (a) are characteristic. A dot-like cytoplasmic pancytokeratin (b) reaction, whereas synaptophysin (c) shows a strong cytoplasmic reaction. TTF-1 (d) may be expressed in primary sinonasal tract neuroendocrine carcinomas.

but MDM2, CDK4, and osteonectin may help in difficult cases.[95,96]

Outcome and management. Osteosarcomas of the sinonasal tract must be resected with clear margins if a good outcome is to be expected, but difficult to achieve in this site, with chemotherapy frequently employed.[97,98]

Lymphoma or Plasmacytoma

Extranodal natural killer (NK)/T-cell lymphoma, nasal type is a lymphoma with a cytotoxic phenotype, universally associated with Epstein–Barr virus (EBV), whereas extra osseous plasmacytoma is a mass-forming proliferation of monoclonal plasma cells without underlying multiple myeloma. A complete discussion of hematolymphoid diseases is discussed elsewhere in this issue,[99] with only a few pertinent points presented here.

Clinical. Extranodal NK/T-cell lymphoma, nasal type, is pathogenetically related to EBV, showing a complex geographic and racial increased prevalence in East Asians and indigenous peoples of Mexico, Central and South America.[100–103] Tumors most commonly present with obstruction and central destruction or perforation of the nasal cavity and paranasal sinuses,[104–106] most patients presenting with low stage I or II disease.

Histopathology. NK/T-cell lymphoma, nasal type shows an arc of development clinically, with a similar arc histologically. In the beginning there is a mixed B- and T-cell population, including eosinophils, histiocytes, and mast cells. However, with time, there is a diffuse infiltrate, showing an angiocentric and angiodestructive growth with geographic-type tumor necrosis (Figure 10). The neoplastic cells are dyscohesive, of variable size and shape, often showing nuclear folds and grooves, with coarse

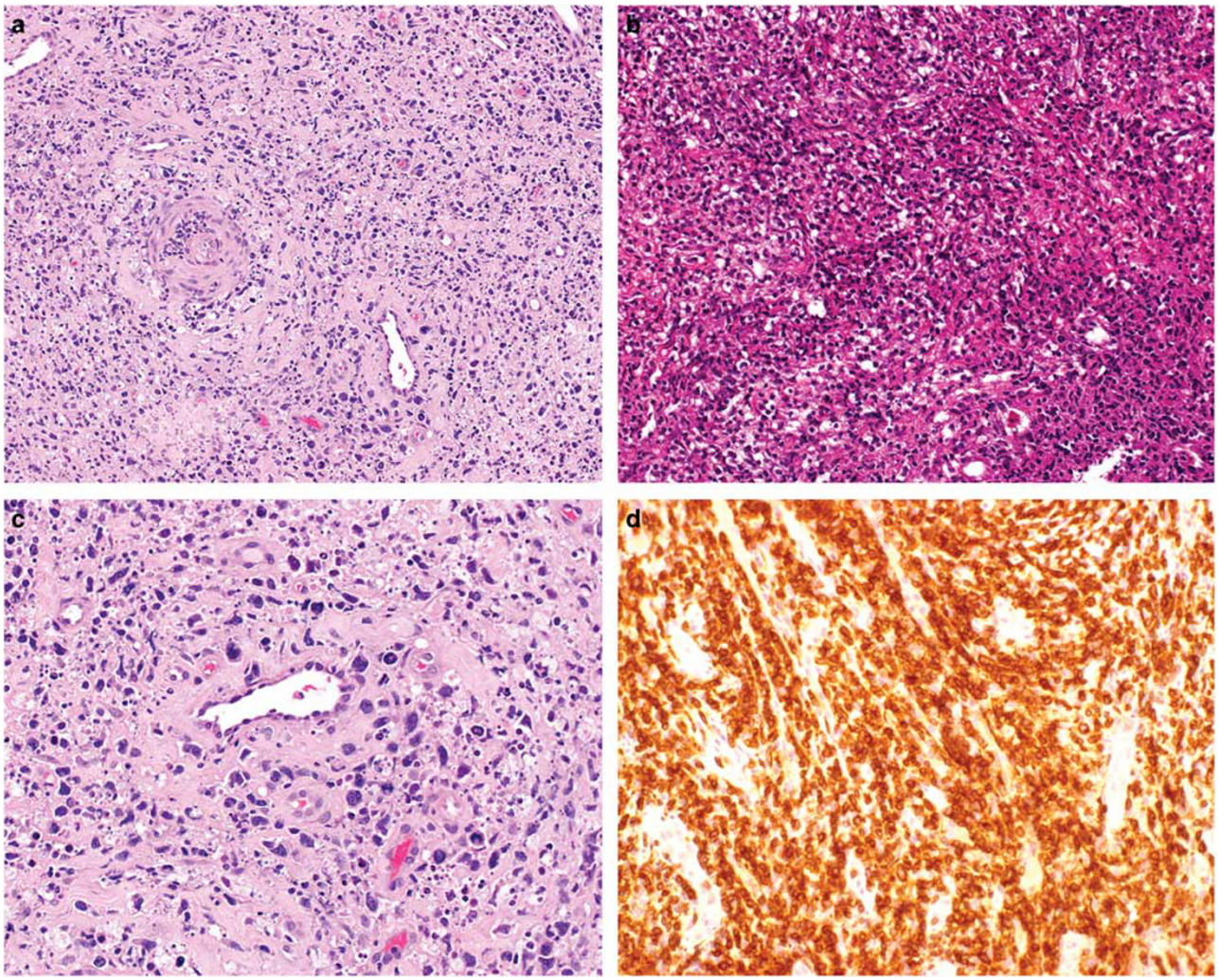

Figure 10 NK/T-cell lymphoma, nasal type. An angiocentric and angioinvasive pattern is characteristic (a). A sheet-like distribution of atypical dyscohesive cells may be seen (b). The vessel wall is infiltrated by highly atypical lymphocytes (c). The neoplastic cells are strongly reactive with CD3e (d).

irregular nuclear chromatin distribution. A surface pseudoepitheliomatous hyperplasia may obscure the true nature of the neoplastic proliferation.

By contrast, plasmacytoma shows a diffuse, sheet-like infiltration of well to poorly differentiated plasma cells,[107,108] showing the characteristic clock-face chromatin distribution and eccentric cytoplasm. Cytoplasmic immunoglobulins, Mott cells, and nuclear Dutcher bodies may help with diagnosis, while extracellular amyloid is occasionally present.[109] MALT-type lymphomas with extensive plasmacytic differentiation may be seen.

Special studies. The neoplastic cells are reactive with CD45RB, cytoplasmic CD3, cytotoxic markers, (TIA-1, granzyme B, perforin), and quite commonly CD56.[104,105,110,111] Although most are NK-cells, T-cell lineage tumors may also be seen with CD5 reactivity. The neoplastic cells are uniformly positive with EBER by *in situ* hybridization (EBV LMP1 should not be tested);[112,113] negative cases are considered peripheral T-cell lymphoma.[114,115] CD57, muscle markers and epithelial markers are non-reactive.

Plasmacytic markers including CD138, CD38[116] and CD79a are usually seen, with rare CD20 co-expression. EMA may be positive. PAX5 is negative. Monotypic immunoglobulin light chains are usually demonstrated by immunohistochemistry or *in situ* hybridization.

Outcome and management. Stage, surrogately detected by circulating EBV DNA plasma levels is of prognostic significance,[117–119] with chemoradiation regimens achieving 70–80% 5-year survival rates.[118,120] The outcome for plasmacytoma is better than multiple myeloma, with patients managed by localized radiation.[108,121]

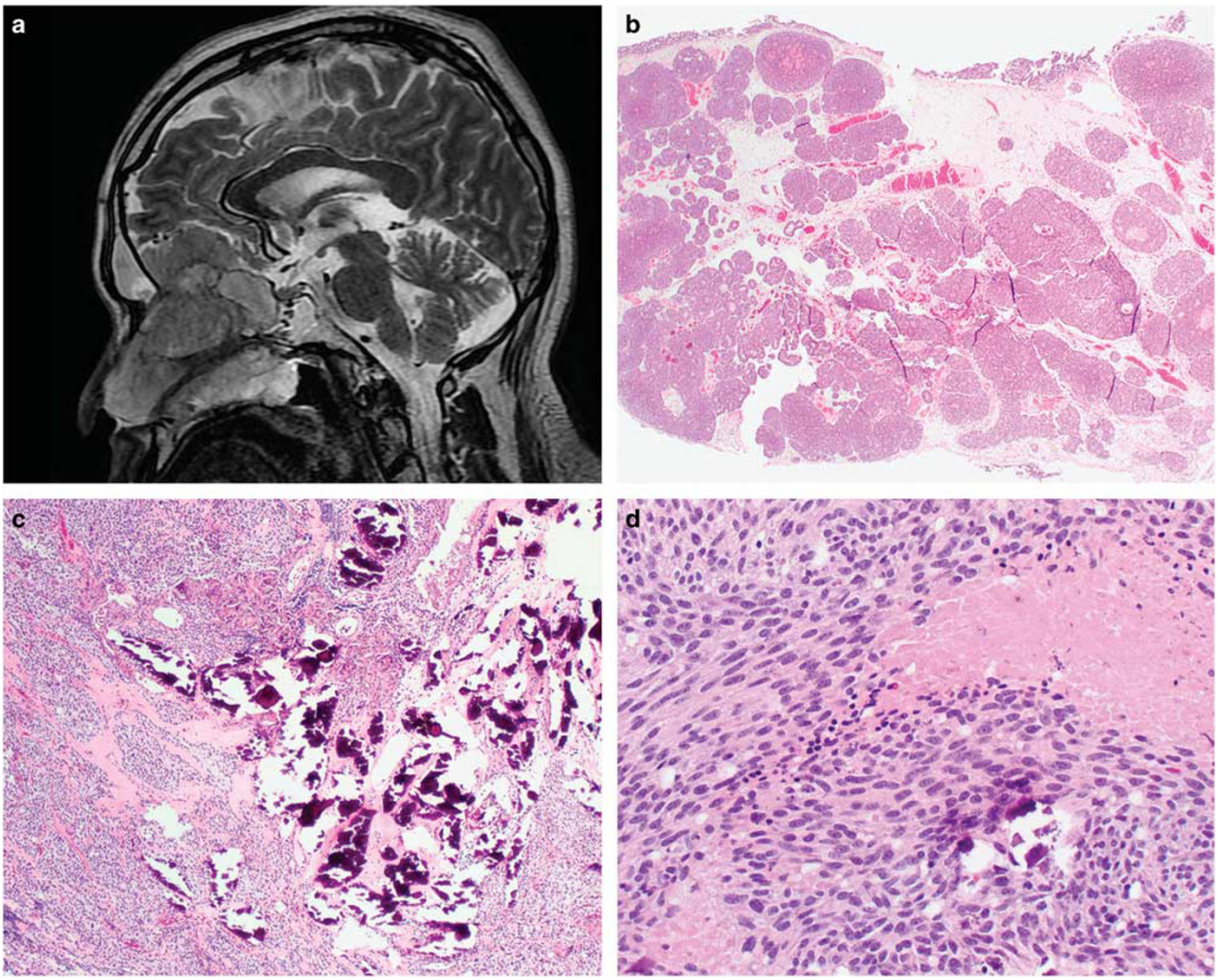

Figure 11 Olfactory neuroblastoma. Enhancement is noted within a large nasal cavity and intracranial mass on T2-weighted MRI (a). A lobular architecture is nearly always present (b). Calcifications may be seen (c). Tumor necrosis (d) and increased mitoses are generally seen in higher grade tumors.

Olfactory Neuroblastoma (Esthesioneuroblastoma)

Olfactory neuroblastoma is a malignant neuroectodermal tumor with neuroblastic differentiation, most often localized to the superior nasal cavity and ethmoid sinus, accounting for about 3% of all sinonasal tract tumors.[122–125]

Clinical. Patients of all ages are affected, with a peak in the 5th–6th decades, with males slightly more often affected than females (1.2:1).[126,127] Symptoms are non-specific; anosmia and paraneoplastic syndromes are rare.[128] Biopsy is discouraged due to high vascularity. MRI preferentially highlights intraorbital or base of skull extension showing avid enhancement with contrast of a dumbbell-shaped mass, the waist at the cribriform plate (Figure 11). Tumor cysts and speckled calcifications are commonly seen on computed tomography (but may be seen histologically also; Figure 11). The ethmoid sinus, superior turbinate, and upper half of the nasal septum are the sites of predilection, with ectopic locations diagnoses of exclusion only.[124,129] Expansion into adjacent sinuses or

Table 3 Olfactory neuroblastoma grading

Feature	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Architecture	L	L	L	L
Mitoses	–	+	++	+++
Anaplasia	–	+	++	+++
Matrix	++	+	+/–	–
Rosettes	HW	HW	FW	FW
Necrosis	–	–	±	+

Abbreviations: L, lobular; FW, Flexner–Wintersteiner rosettes; HW, Homer Wright rosettes.

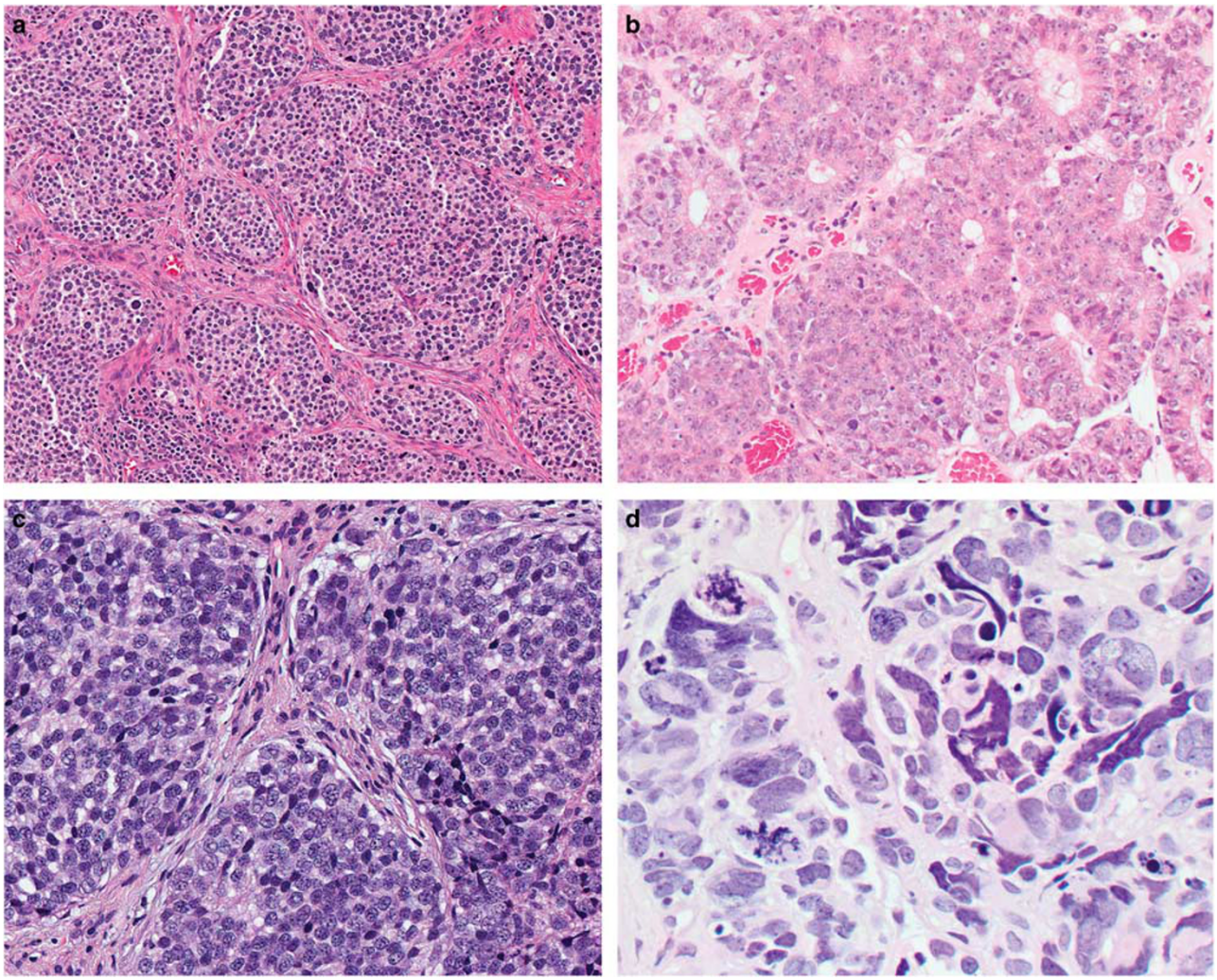

Figure 12 Olfactory neuroblastoma. The lobules of tumor are separated by a rich fibrovascular stroma (a). There are true rosettes noted in this tumor with prominent nucleoli (b). The nuclei are slightly larger than lymphocytes and show a slightly increased nuclear to cytoplasmic ratio in this grade 2 tumor (c). Profound pleomorphism and atypical mitoses (d) are characteristic of a grade 4 tumor.

base of the skull and brain help define tumor stage, with the Kadish system most commonly employed.[130–132]

Histopathology. Often polypoid, there is usually an intact surface mucosa; rarely, an *in situ* component will be identified in the olfactory epithelium. No matter the tumor grade, the tumor cells are arranged in variably sized lobules to sharply demarcated nests, separated by a vascularized to fibrous connective tissue stroma (Figures 11 and 12). The tumor grade determines the histologic appearance, with low-grade tumors being the classical finding (Table 3). The tumor cells are small and uniform (about the size of lymphocytes), with scant cytoplasm surrounding round and regular nuclei with slightly hyperchromatic, delicate, punctate, salt-and-pepper nuclear chromatin (Figure 12). Nucleoli are inconspicuous. The cells appear syncytial, often showing neuropil or neural tangles, which occasionally create Homer Wright pseudorosettes (Figure 11) when the nuclei cuff or palisade around the fibrillar matrix. As the tumor grade increases, tumor necrosis (Figure 11), increased mitoses (Figure 12), pleomorphism (Figure 12), and true Flexner–Wintersteiner rosettes may be seen (tight annular structures with lumen and possible secretions; Figure 12). The grade (Table 3) is related to the degree of maturation, amount of neuropil, mitoses, necrosis, and pleomorphism,[133] and is strongly correlated to outcome.[130,132,134–138] Although rare, melanin pigment, ganglion cells, rhabdomyoblasts, and even squamous or glandular differentiation may be seen.[124,139–141]

Special studies. The neoplastic cells will be reactive with neuroendocrine markers (synaptophysin, chromogranin-A, neuron specific enolase, CD56),

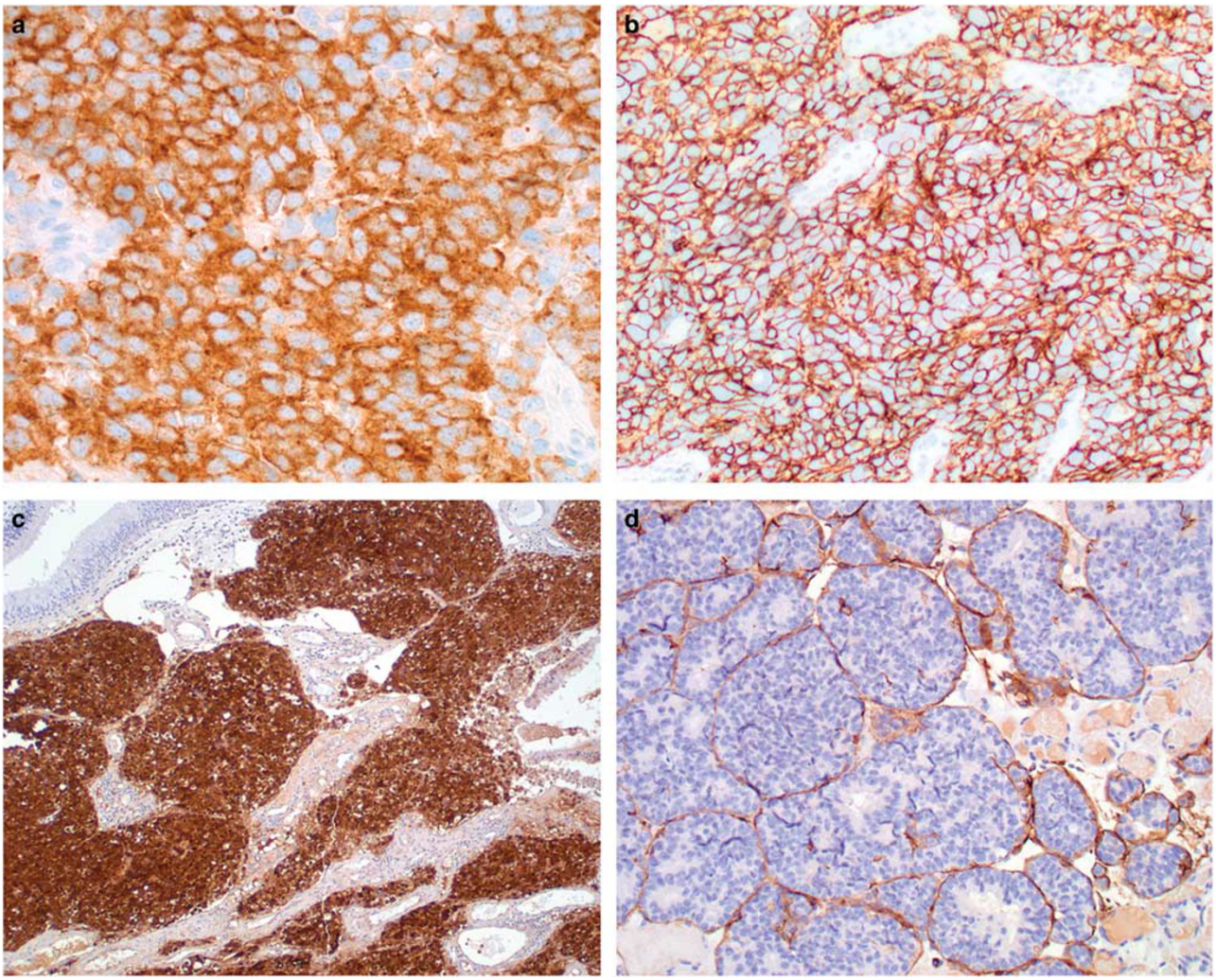

Figure 13 Olfactory neuroblastoma. The neoplastic cells show a strong and diffuse reaction with synaptophysin (a), CD56 (membrane b), and calretinin (c). There is a delicate, supporting sustentacular reaction with S100 protein at the periphery of the lobules (d).

along with calretinin (nuclear and cytoplasmic); S100 protein and/or GFAP highlights the sustentacular supporting cells at the periphery of the tumor lobules (Figure 13). CAM5.2, CK18 or pancytokeratin may be focally expressed in some olfactory neuroblastoma; desmin or myogenin may be seen in tumors with rhabdomyoblastic differentiation. Negative markers include CD45RB, CD99, p63, and FLI-1.[4,57,80,140,142–146]

Outcome and management. Using a predominantly surgical approach, combined with radiation and chemotherapy in certain settings, the tumor grade and stage are the most significant prognostic factors,[130,132,134–138] with metastatic tumors showing a worse disease-free survival. Recurrences usually develop within 2 years, seen in up to 30% of patients, whereas distant metastases are uncommon (about 10%).

Ewing Sarcoma/Primitive Neuroectodermal Tumor

Ewing sarcoma/primitive neuroectodermal tumor is a high-grade primitive small round cell sarcoma with neuroectodermal differentiation defined by the presence of an *EWSR1* gene translocation. Up to 10% develop in the head and neck.[147]

Clinical. Tumors develop slightly more often in males, most commonly in young patients, but older patients may be affected.[148–150] The skull and jaws are much more commonly affected than the sinonasal tract.[150] Symptoms are non-specific, but tend to develop rapidly, with imaging studies showing orbital or intracranial extension.

Histopathology. Polypoid tumors frequently display ulceration, with bone invasion noted. The tumors show high cellularity arranged in a diffuse,

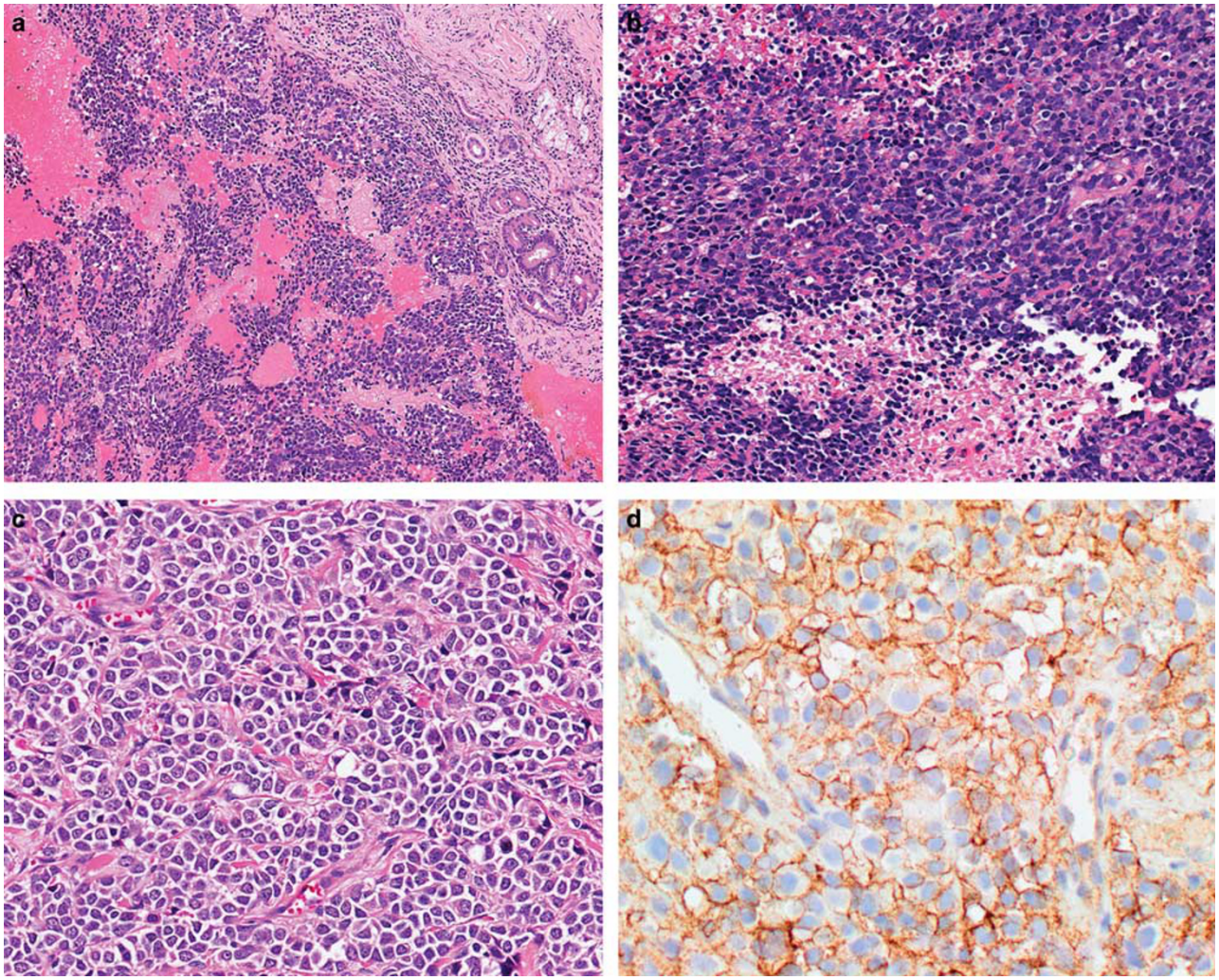

Figure 14 Ewing sarcoma. There is tumor necrosis and a sheet-like distribution (a) of the neoplastic cells. Comedonecrosis (b) is seen; the cells have scant cytoplasm. There cells may have a more coarse nuclear chromatin (c) and high nuclear to cytoplasmic ratio. The neoplastic cells show a strong, membranous, and cytoplasm reaction with CD99 (d).

sheet-like to lobular appearance. Necrosis is usually easily identified with limited vascular stroma (Figure 14). Mitoses are usually easily identified. The neoplastic cells are small and uniform, with scant pale to cleared cytoplasm surrounding round to oval nuclei with powdery to finely clumped chromatin, and small, inconspicuous nucleoli. Pseudorosettes may be present, but true neural rosettes are rare. In the sinonasal tract, the adamantinoma-like variant may be seen.[151,152]

Special studies. Glycogen may be demonstrated by diastase-sensitive, PAS-positive material. A strong and diffusive membranous CD99 reactivity (Figure 14) is the most sensitive marker for this tumor; nuclear FLI1 and ERG are also commonly identified, but are not specific.[6,50,81,153,154] Importantly, pancytokeratin may be expressed in a dot-like pattern (up to 30% of cases), but more often in adamantinoma-like tumors;[150,152,155] p63 is infrequently identified;[57] neural markers may be seen (NSE, S100 protein, synaptophysin, chromogranin); CD117 is uncommon, and desmin is rarely coexpressed. A FISH *EWSR1* break-apart probe helps to identify the class of tumor, although it does not confirm the translocation partner (which is usually FLL1). *CIC-DUX4* fusions may be seen in *EWSR1*-negative cases,[156] although controversial.[157]

Outcome and management. The 50–75% 5-year survival for sinonasal Ewing sarcoma is much better than other sites, but local recurrence and metastases, when they develop are usually soon (2 years) after initial presentation.[147,150] Tumors are managed with multimodality therapy, but there is a risk of post-treatment sarcoma development. Poor prognosis may be related to p53 aberrations.[158]

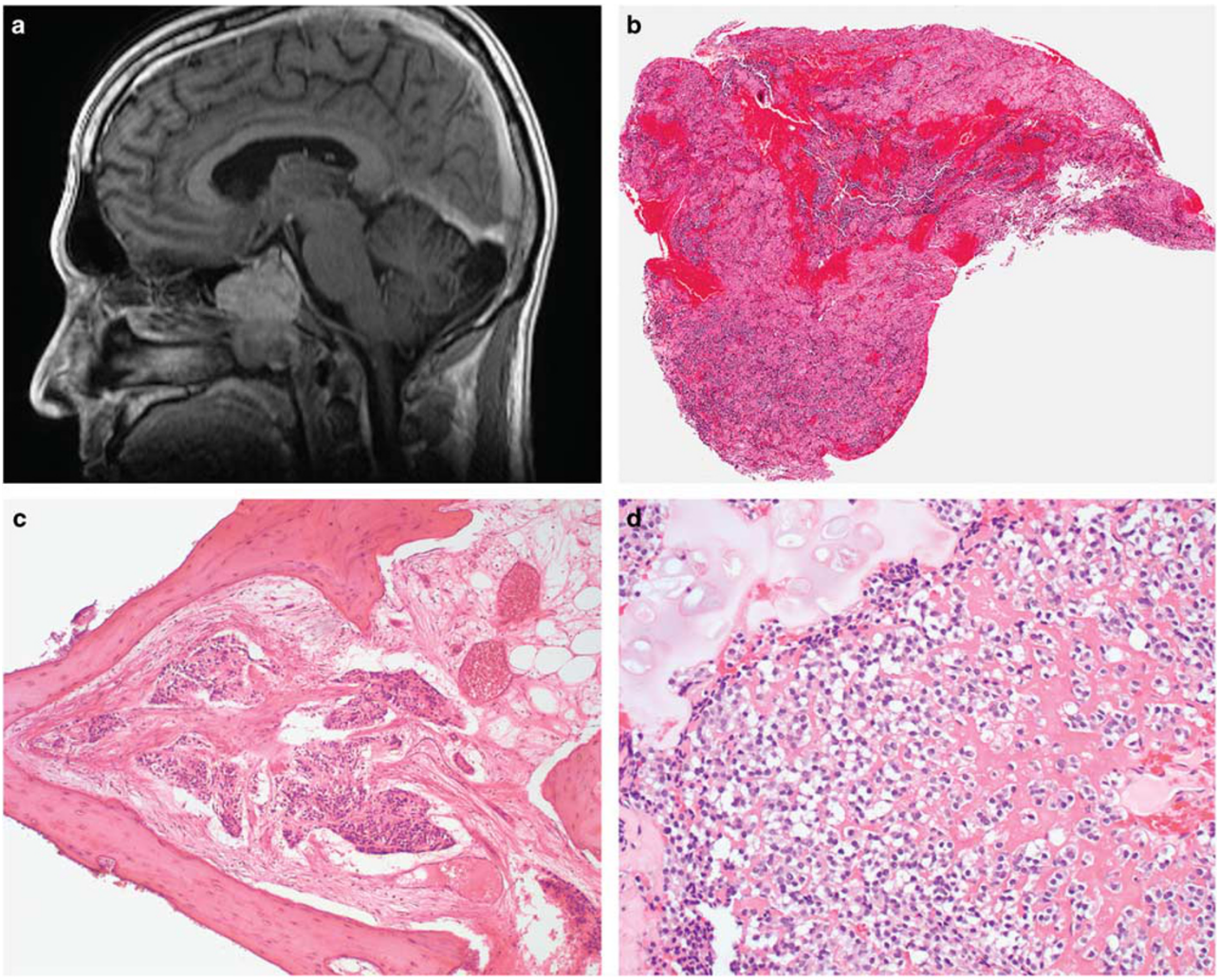

Figure 15 Pituitary adenoma. This sagittal MRI shows a large mass within the pituitary sella and expanding into the sphenoid sinus (a). The tumors often appear polypoid (b). Bone invasion (c) may be seen, while cartilage invasion (d) may also be present. This is not neoplastic cartilage or bone, but destruction of the native structures.

Pituitary Adenoma

Whether ectopic (remnants of Rathke pouch) or by direct extension from the sella, pituitary adenoma may involve the sphenoid sinus and sinonasal tract. Direct extension is more common than ectopic tumors, comprising $< 3\%$ of all tumors in this site.[159–161]

Clinical. Patients present over a wide age range, but show a mean presentation in the mid-50s, females affected slightly more often than males (1.3:1). Sphenoid sinus and nasopharynx are the most commonly affected sites.[159] Symptoms are non-specific, although visual disturbances are more common with sella involvement, whereas endocrinopathies are infrequent,[162] and about 10% of patients are asymptomatic. Imaging studies are generally encouraged to exclude direct extension (Figure 15), where bone destruction is present.[159,163]

Histopathology. The frequently polypoid tumors can be quite sizeable (8 cm), often associated with bone invasion and necrosis (Figure 15).[159,164] The submucosal tumors show a variety of growth patterns, with a solid, organoid, and trabecular growth patterns most common, but hypocellular, heavily collagenized tumors may be seen (Figure 16). Rosettes and pseudorosettes may be present. The cells range from polygonal, epithelioid to plasmacytoid, generally with round nuclei and salt-and-pepper nuclear chromatin, often with intranuclear cytoplasmic inclusions. Glandular spaces may be seen with secretions (Figures 16 and 17). Profound pleomorphism in isolation is part of an endocrine organ neoplasm. Squamous differentiation is not appreciated. Mitoses can be found, but atypical forms are not present. Lymphovascular and perineural invasion are not seen.[159,165]

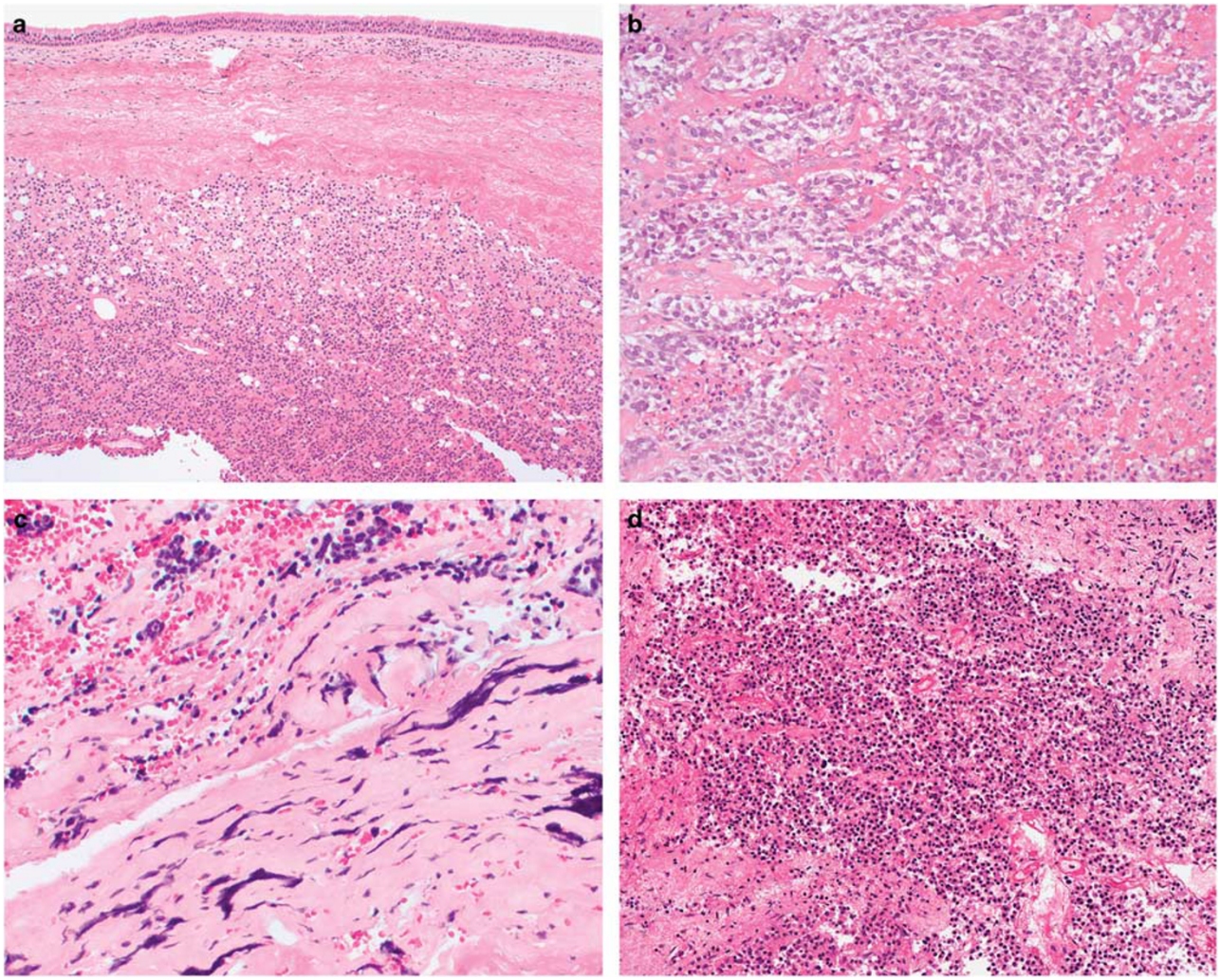

Figure 16 Pituitary adenoma. There is separation from the intact surface epithelium (a). Tumor necrosis may be seen. This tumor has a lobular or trabecular growth (b). Dense fibrous stroma may obscure the neoplastic cells and compress them (c). There is usually a rich fibrovascular stroma in neuroendocrine tumors (d).

Special studies. The neoplastic cells show neuroendocrine and epithelial markers (Figure 17b), with synaptophysin (Figure 17c) more commonly expressed than chromogranin or NSE. CK-pan is seen in about 80% (Figure 17b), often with a perinuclear dot-like pattern. Prolactin (~60%) is one of the most common pituitary hormones expressed (Figure 17d), but any pituitary hormone or transcription factor (Pit-1, T-pit, SF-1) may be expressed (single or multiple hormones/factors).[159,164]

Outcome and management. Medical management (such as bromocriptine), surgery or radiation (unresectable tumors) may be employed with pituitary adenomas, with recurrences noted in incompletely removed tumors.

Conclusion

It is important to think broadly about epithelial, mesenchymal, neuroendocrine, and lymphoid tumors within the sinonasal tract small round blue cell tumor group. The mnemonic of MR SLEEP can help to focus the differential diagnostic considerations, keeping in mind the exact and specific anatomic site, imaging findings, and combining the histologic features with pertinent positive and negative immunohistochemistry findings, using additional molecular results as necessary to confirm the diagnosis. There will be significant histological and immunohistochemistry overlapping, but when combined with the site of origin, imaging findings, and other clinical findings, the correct result can be achieved.

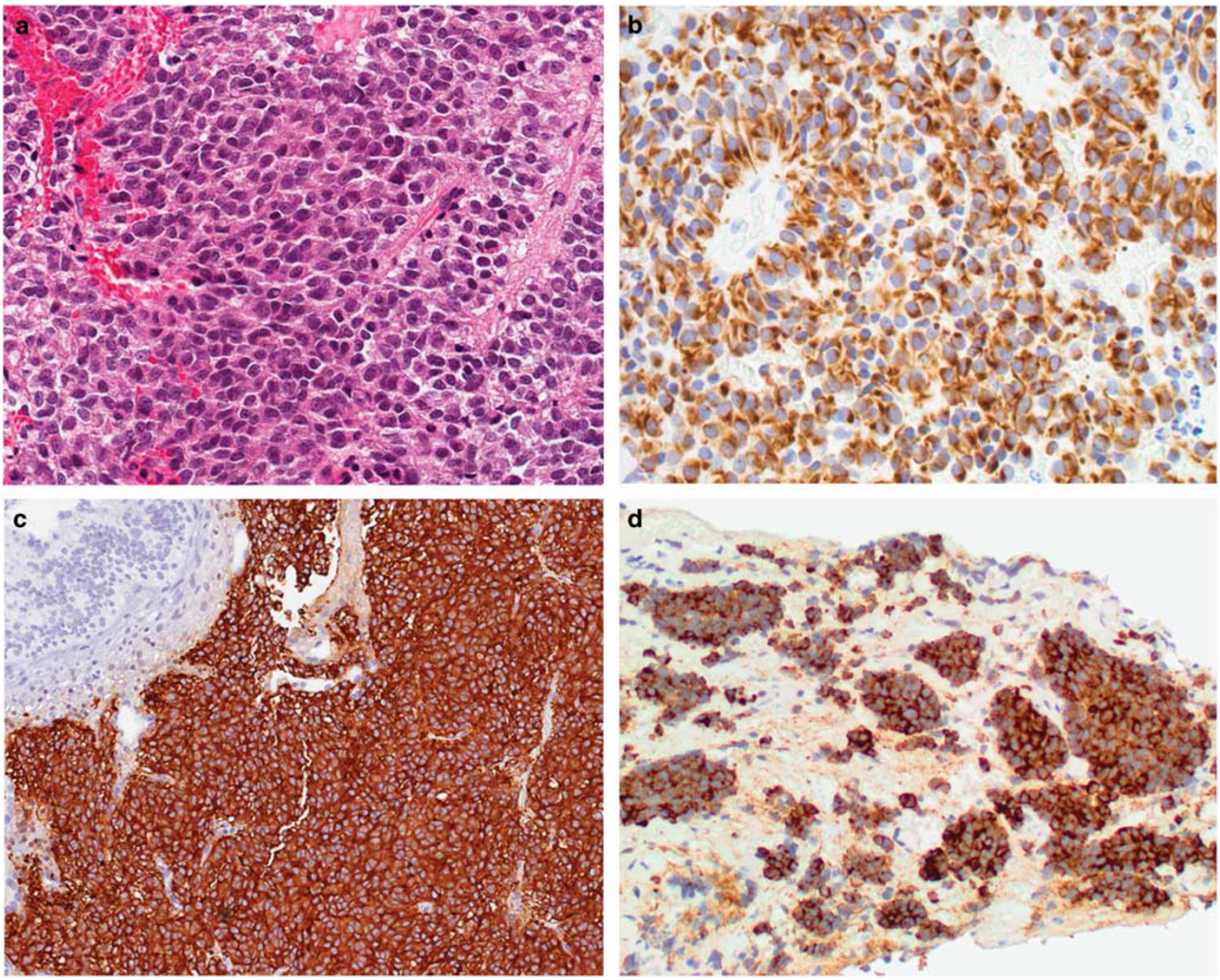

Figure 17 Pituitary adenoma. The neoplastic cells are small, showing delicate-fine to coarse nuclear chromatin (a). The neoplastic cells show a characteristic paranuclear dot-like reaction with pancytokeratin (b), strong cytoplasmic reaction with synaptophysin (c), and a diffuse reaction with prolactin (d).

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Disclosure/conflict of interest

The author declares no conflict of interest.

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