Sinonasal Small Round Blue Cell Tumors
An Immunohistochemical Approach

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KEYWORDS

• Sinonasal tumors • Small round blue cell tumors • Immunohistochemistry • Cytokeratin
• Squamous differentiation • Neuroendocrine differentiation

Key points

- The sinonasal small round blue cell tumor (SRBCT) differential diagnosis is extensive and fraught with pitfalls, necessitating a thoughtful immunohistochemical approach.
- A reasonable initial immunohistochemical panel for undifferentiated sinonasal SRBCT might include pancytokeratin, p63 (or p40), synaptophysin, chromogranin, S100, desmin, CD45, and CD99.
- Patchy pancytokeratin expression is frequently seen in nonepithelial SRBCTs and should not be interpreted as definitive evidence of epithelial differentiation.
- p63 or p40 positivity, although helpful, does not equate to squamous cell carcinoma; other SRBCTs may have similar staining but vastly different treatment and prognosis.
- Focal neuroendocrine marker reactivity is common in sinonasal SRBCTs and should not be mistaken for definitive evidence of a neuroendocrine neoplasm.

ABSTRACT

Although clinical history and morphologic appearance should be the initial considerations when evaluating small round blue cell tumors of the sinonasal tract, the final diagnosis often hinges on immunohistochemical findings. Unfortunately, interpretation of stains in these tumors is fraught with numerous pitfalls and limitations. This article presents an approach to sinonasal small round blue cell tumors based on four common immunohistochemical patterns: cytokeratin positivity, squamous marker positivity, neuroendocrine marker positivity, and cytokeratin negativity.

OVERVIEW

The so-called "small round blue cell tumors" (SRBCT) of the sinonasal tract encompass a wide range of epithelial, mesenchymal, neuroectodermal, and hematolymphoid neoplasms. Recently, the differential diagnosis of these challenging tumors has become even broader with description of several new entities.[1–6] In evaluating SRBCT, such clinical characteristics as age, location, and radiographic appearance can provide important diagnostic clues. Furthermore, the hematoxylin and eosin (H&E) appearance of architectural, cytoplasmic, chromatin, and stromal characteristics can significantly narrow the differential diagnosis.

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Despite this guidance, diagnosis of SRBCT almost always necessitates performance of immunohistochemistry (IHC). In the many cases with limited tissue, extensive crush artifact, nonspecific clinical presentation, or minimal differentiation, a broad panel of stains is often necessary. A reasonable initial work-up for such cases might include pancytokeratin, p63 (or p40), synaptophysin, chromogranin, S100, desmin, CD45, and CD99. Although several excellent thematic overviews of SRBTC have recently been published,[7–10] this article approaches this group of tumors as most practicing pathologists will: through the lens of IHC. Here, we discuss subclassification of cytokeratin-positive, squamous marker–positive, neuroendocrine marker–positive, and cytokeratin-negative sinonasal SRBCT, with particular focus on navigating pitfalls and limitations of each category.

CYTOKERATIN-POSITIVE SMALL ROUND BLUE CELL TUMORS

One of the most important distinctions in sinonasal SRBCTs is between tumors that demonstrate or lack epithelial differentiation. A strict definition of cytokeratin positivity is necessary to accurately separate these groups. Epithelial differentiation is best proven by diffuse, strong positivity for pancytokeratins, such as AE1/AE3; expression of low-molecular-weight cytokeratins (LMWCK), such as CAM 5.2, or high-molecular-weight cytokeratins (HMWCK), such as CK903 or CK5/6, is variable.[8] Although epithelial membrane antigen (EMA) reactivity may support individual diagnoses, EMA expression by itself is not specific for epithelial differentiation. Furthermore, it must be recognized that focal cytokeratin positivity is not sufficient evidence of definitive epithelial origin, because nonepithelial lesions, such as rhabdomyosarcoma (RMS), olfactory neuroblastoma (ONB), Ewing family tumors (EFT), and mucosal malignant melanomas (MMM), frequently display patchy reactivity.[11,12] This section presents the subset of cytokeratin-positive SRBCT that lack reliable squamous or neuroendocrine differentiation.

ΔΔ *Differential Diagnosis* — Cytokeratin-Positive Tumors

Consistent pancytokeratin positivity

- Adenoid cystic carcinoma (ACC)
- Adamantinoma-like EFT
- Human papilloma virus (HPV)-related ACC-like carcinoma
- Nonkeratinizing squamous cell carcinoma (SCC)
- Nasopharyngeal carcinomas (NPC)/lymphoepithelial-like carcinomas (LELC)
- NUT midline carcinoma
- SMARCB1-deficient carcinoma
- Sinonasal undifferentiated carcinoma (SNUC)

Focal nonspecific pancytokeratin staining

- EFT
- MMM
- ONB
- RMS

! *Pitfalls* — Cytokeratin-Positive Tumors

! Focal reactivity for cytokeratin does not prove epithelial differentiation and can be seen in EFT, MMM, ONB, and RMS

! Although EMA can help confirm certain diagnoses, true cytokeratin positivity is required to prove epithelial differentiation in the sinonasal tract

! SNUC is a diagnosis of exclusion and should not be made if there is more than focal squamous or neuroendocrine reactivity

SINONASAL UNDIFFERENTIATED CARCINOMA

SNUC is an aggressive sinonasal tumor that characteristically develops over weeks[13] and causes death within a year of diagnosis.[14,15] SNUC is morphologically and immunohistochemically a diagnosis of exclusion and has become less common with development of better immunohistochemical markers and description of more specific tumor types. SNUC demonstrates sheets of nondescript malignant cells with prominent nucleoli, abundant mitoses, and extensive necrosis (**Fig. 1**). No overt squamous, glandular, or neuroendocrine differentiation should be present.[14] SNUC expresses pancytokeratin and LMWCK but usually not HMWCK.[13,14,16] Although focal reactivity for p40, p63, chromogranin, and synaptophysin should not be taken as evidence of squamous or neuroendocrine lineage in SNUC, diffuse positivity for any such markers essentially negates this diagnosis.[17,18] Nonspecific staining for CD99 has been reported,[19] but SNUC lacks S100 or Epstein-Barr virus (EBV) positivity.[8,14,19]