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Case Report

Sinonasal Teratocarcinosarcoma: A Case Report in a 13-Year-Old Male

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Abstract

Teratocarcinosarcoma is rare malignant sinonasal neoplasm with immature and malignant endodermal, mesodermal, and neuroepithelial elements resembling immature teratoma, commonly with *SMARCA4* loss or activating *CTNNB1* mutation. The carcinoma component may be either squamous or adenocarcinoma and the mesenchymal component may be composed of spindle cells, cartilage, bone, smooth muscle, or skeletal muscle. Due to the uncommon nature of this malignancy, there are frequently diagnostic difficulties that result in management problems. Herein we report a teratocarcinosarcoma arising in the nasal cavity of a 13-year-old boy with *CTNNB1* activating mutation and copy number variations by next-generation sequencing along with an abnormal karyotype. This tumor must be included in the differential of neoplasms with immature elements, more likely seen in pediatric patients.

Keywords

nasal cavity, paranasal sinus neoplasm, teratocarcinosarcoma, *CTNNB1* mutation, adolescent, differential diagnosis, high-throughput nucleotide sequencing, teratoma, mutation

Introduction

Teratocarcinosarcoma is a rare malignant sinonasal track neoplasm with immature and malignant endodermal, mesodermal, and neuroepithelial elements resembling immature teratoma, commonly with *SMARCA4* loss or activating *CTNNB1* mutation.[1,2] The carcinoma component may be either squamous cell carcinoma or adenocarcinoma while the mesenchymal component may be composed of spindle cells, cartilage, bone, smooth muscle, or skeletal muscle. Primitive neuroepithelial tissue, blastemal elements, neurofibrillary matrix, and rosettes comprise the neural-type elements. This tumor probably originates from stem cells in the olfactory membrane that produces the neuroectodermal features but may also differentiate into somatic cells.[3] Almost all cases are reported in adults with a significant male predominance.[4] There are 6 previously reported cases in pediatric patients.[5-10] Teratocarcinosarcoma is an aggressive tumor with frequent local recurrences within the first couple years.[7] Herein is a description of a primary sinonasal teratocarcinosarcoma in a 13-year-old male.

Case report

A 13-year-old male presented with 3-week history of chronic nasal discharge from his left nostril. CT scan revealed a large, lobulated 6.0 cm mass in the left nasopharynx and sinonasal tract, extending into the left sphenopalatine foramen, posterior choana, nasal cavity, sphenoid and ethmoid sinuses, with destruction of the cribriform plate giving intracranial extension. There was outward bowing of the left lamina papyracea.

A debulking sample showed a composite of various elements that included carcinoma, a primitive neuroepithelial component with immature teratoma-like pattern, and a low-grade fibrosarcoma-like proliferation. The surface epithelium was uninvolved, with the tumor identified in the deep subepithelial stroma. There were several areas that show an epithelial appearance, seeming to be primitive squamous epithelium (Figure 1(a)), but also showing glandular differentiation with mucin formation (Figure 1(b)). The cells had a remarkably high nuclear to cytoplasmic ratio and coarse to

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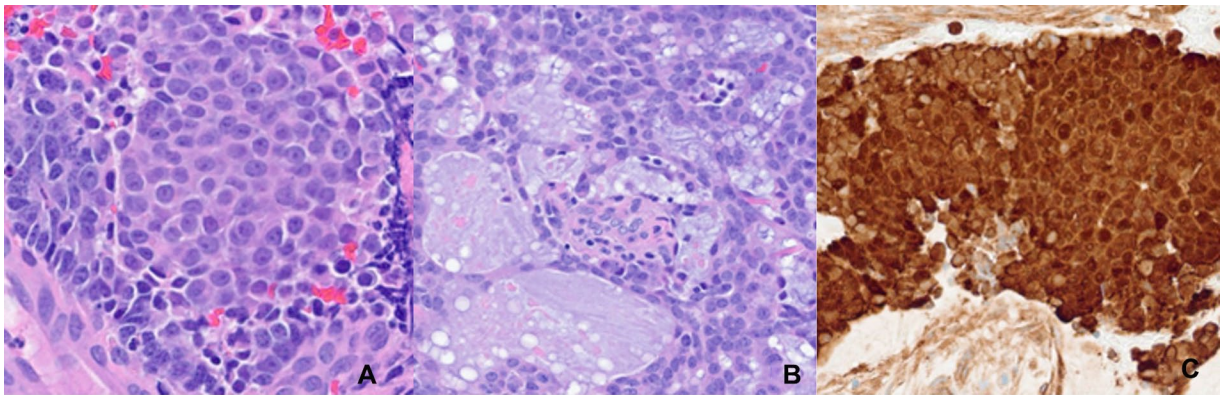

Figure 1. (A) Epithelial component shows primitive squamous differentiation (40X). (B) Epithelial component shows showing glandular differentiation with mucin formation (40X). (C) The epithelial component shows scattered positivity for nuclear β-catenin (40X).

even chromatin distribution. There was brisk mitotic activity including atypical forms. There was no pigmentation, no rhabdoid or plasmacytoid differentiation, and no mature teratoma-like elements. Yolk-sac differentiation was absent.

Immunohistochemical studies demonstrated a wide diversity of immunoreactivity, each element highlighted by its own markers: epithelial cells were positive with pan-cytokeratin, focal CK7, vimentin, and TLE1, along with scattered nuclear β-catenin (Figure 1(c)); the primitive spindled component filled in the spaces between the epithelial and primitive blastemal elements (Figure 2), showing pleomorphism, increased mitoses, and a variably amount of myxoid stroma, immunoreactivity with calretinin, desmin (dot-like), and vimentin. The primitive neuroepithelial component (Figure 3(a)) was immunoreactive with synaptophysin, chromogranin A (Figure 3(b)), NSE, calretinin, vimentin, and TLE1. All the cells showed an intact INI1 and BRG1. The Ki-67 proliferation index was more than >80%. Primitive, epithelial (glandular), and sarcomatous components of teratocarcinosarcoma were included in Figure 4. Further work-up excluding other neoplasms, demonstrated negative or noncontributory immunohistochemistry: NUT, p40, p63, p16, GFAP, CD45, CD3, CD20, cyclin-D1, SOX10, S100 protein, SATB2, SMA, myogenin, MYOD1, CD56, CD99, NKX2.2, CD31, ERG, FLI1, PHOX2B, androgen receptor, EBER, DUX4, and BCOR. Frozen tissue was submitted for our in-house next-generation sequencing Comprehensive Solid Tumor panel, which can detect variants and fusion events in 720 genes. Nucleic acid was isolated and target enrichment of the regions of interest was performed by a hybridization-based methodology using long biotinylated oligonucleotide probes followed by polymerase chain reaction (PCR) and sequencing on an Illumina NovaSeq 6000. An in-house bioinformatics pipeline was applied for read alignment variant filtering, and variant/fusion calling. Next-generation sequencing identified a *CTNNB1* c.98C>T (p.Ser33Phe) gain of function point mutation. Copy number variation detected by next-generation sequencing included chr5q35.1-35.3 deletion, whole arm deletion of chr8p, and deletion of chr7p22.3-p14.3. There was no *EWSR1* rearrangement or *SS18* rearrangement. Karyotype showed 50~53, XY, add (2) (q37), +1~2r, inc [cp5]/46, XY [23]. Chromosomal microarray was performed on the DNA extracted from the patient's specimen and processed on the Illumina® Infinium

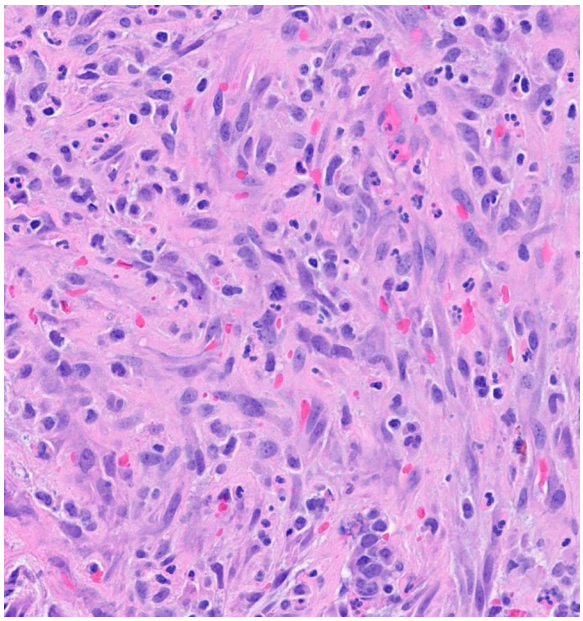

Figure 2. The sarcoma component is a low grade, but still atypical spindled cell, fibrosarcoma-like proliferation (40X). There is a mitosis in the center.

Global Diversity bead array. Using SNP (single nucleotide polymorphism) probes, the array detects copy number losses and gains with a resolution of approximately 5 kb across the genome. Oncology microarray demonstrated 8q gain. The significance of these abnormalities in sinonasal teratocarcinosarcoma are unknown and not previously reported. The patient received multimodal therapy with surgical debulking, chemotherapy, and coned field radiation. He is doing well 3 months following therapy completion.

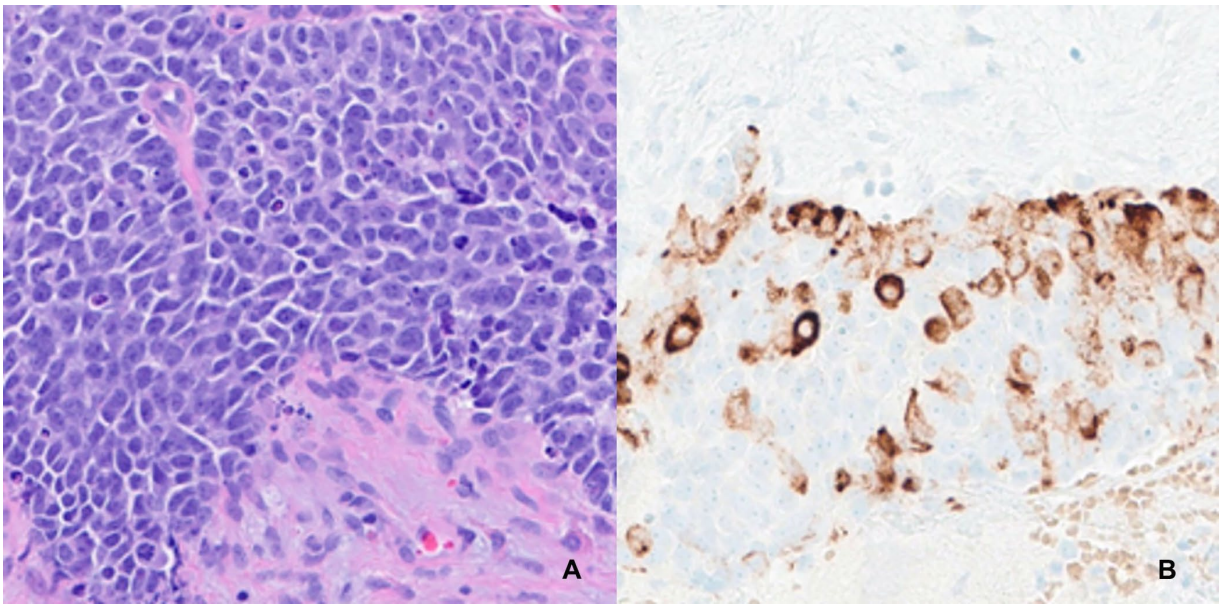

Figure 3. (A) The blastemal- to primitive neuroepithelial component is the dominant histologic pattern. The cells have a remarkably high nuclear to cytoplasmic ratio, coarse to even chromatin distribution (40X). (B) The blastemal component is positive for chromogranin A (40X).

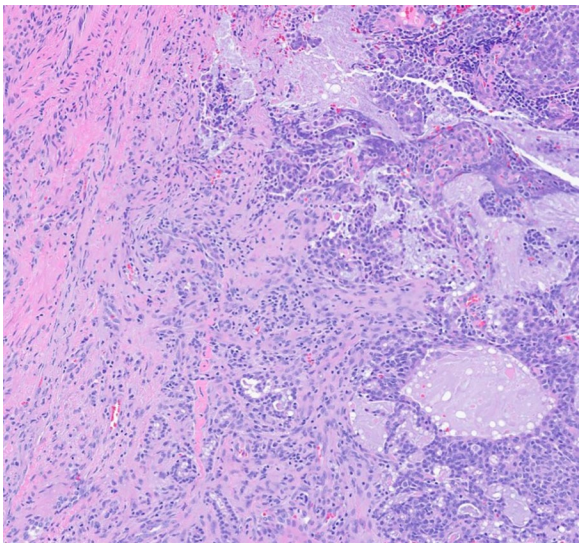

Figure 4. Primitive, epithelial, and sarcomatous components of teratocarcinosarcoma were included in the same picture (10X).

Discussion

Teratocarcinosarcoma is a malignant sinonasal tract neoplasm with mixed epithelial, mesenchymal, and primitive neuroepithelial elements. Recurrent molecular driver alterations are documented, particularly biallelic inactivation of *SMARCA4* and activating *CTNNB1* point mutation.[1,2] Importantly, the negative immunohistochemistry findings are especially useful in excluding selected tumors considered in this setting, such as NUT carcinoma, adamantinoma-like Ewing sarcoma, neuroendocrine carcinoma, and rhabdomyosarcoma. NUT carcinoma and adamantinoma-like Ewing sarcoma may both show significant squamous differentiation, but they do not generally develop heterologous elements and would not show such a diverse immunophenotype. The SWI/SNF complex-deficient sinonasal carcinomas must lack INI1 or BRG1 immunohistochemically, both of which were intact in this tumor, even though it is known that *SMARCA4* loss is seen in teratocarcinosarcoma, and these tumors lack the multilineage elements presented in teratocarcinosarcoma. A mesenchymal chondrosarcoma has a spindled malignancy with focal areas of chondrosarcoma but usually lacks overt squamous differentiation. An ameloblastic carcinoma can develop malignant spindle-cell transformation with heterologous elements (sarcomatoid ameloblastic carcinoma) but must demonstrate unequivocal centering in the jaws along with a demonstrable ameloblastic component, even if only focal. An olfactory carcinoma does not show a spindled component, nor the β-catenin expression seen in the current tumor, recognizing that olfactory carcinoma can have *CTNNB1* alterations in a subset of tumors.[11] Neuroendocrine carcinoma must demonstrate neuroendocrine morphologic features along with immunohistochemical evidence of neuroendocrine differentiation (i.e., chromogranin A and INSM1), features not seen in this tumor even though neuroendocrine immunoreactivity was present in the primitive elements. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are defined as neoplasms where a neuroendocrine neoplasm is morphologically recognizable, distinct and separate from the non-neoendocrine neoplasm, usually a squamous cell carcinoma or adenocarcinoma, but not usually with a primitive, blastemal or teratoid

concurrent component.[12,13] Malignant teratoma shows the features of malignant components of germ cells, most likely yolk sac tumor, or less commonly malignant transformation of squamous epithelium, with the absence of molecular alterations of *CTNNB1* or *SMACA4*. Please see Table 1 for the summarized differential diagnosis of teratocarcinosarcoma.

Teratocarcinosarcoma is an exceedingly rare tumor, with males affected much more commonly than females, usually in adults. The tumors develop most commonly high in the nasal cavity and ethmoid sinus, as in this case. The tumors are generally large, bulky, polypoid friable masses, often >4 cm with associated necrosis and hemorrhage. Teratocarcinosarcoma contains both carcinomatous and sarcomatous tissues, along with teratoma-like elements represented by primitive neuroepithelium or blastemal tissues. Immunohistochemistry is remarkably variable, depending on which cellular component is present, as delineated above. Differential diagnosis is quite broad, especially when only limited sampling may include only one of the elements while the remaining components are unsampled. Careful evaluation of the tissue, possibly including performing larger biopsies may be required to document all the tumor constituents. Teratocarcinosarcoma is a highly aggressive neoplasm with a poor prognosis, although a group of patients will sometimes achieve a long-term disease-free survival; unfortunately, no histologic features seem to predict this accurately. Rapid recurrences are common (about 40%), often with intracranial extension, developing within 2 years of diagnosis.[14] Lymph node metastasis occurs in about 20% of patients. Multimodality therapy yields a survival advantage over surgery alone, but does not seem to affect recurrence.[14] Overall, about 50% of patients are alive without evidence of disease (mean 40 months) age independent.[6,14] The patient received multimodal therapy with surgical debulking, chemotherapy, and coned field radiation. He is doing well 3 months following therapy completion. There is no definite distal metastasis.

Table 1. Common Sinonasal Tumors as Differential Diagnosis of Teratocarcinosarcoma.

Diagnosis	Age distribution	Presentation	Histopathological key features	Immunohistochemical stains	Molecular alterations
Teratocarcinosarcoma	Wide range of 0.1-85 years	Nasal obstruction, epistaxis, and headaches	Heterogeneous neoplasm with intermingled features of carcinoma, sarcoma, and immature teratoma	Epithelial components positive for cytokeratins, CK5/6, EMA, p63, and p40. Sarcoma components positive for vimentin, GFAP, calponin, desmin, myoglobin, myogenin, and actins. Neuroepithelial/blastema elements positive for chromogranin, synaptophysin, INSM1, CD99, and S100 protein; rarely AFP. Positive for β-catenin (nuclear staining). Loss of SMARCA4, detected by BRG1 loss	Biallelic inactivation of *SMARCA4* and activating *CTNNB1* mutation
NUT carcinoma	Peak in young adults (median 24 years)	Mass lesion, locally destructive and infiltrative	Sheets of primitive-appearing undifferentiated cells with focal and abrupt squamous differentiation	Strong and diffuse nuclear positivity with speckled pattern on NUT stain	*BRD4::NUTM1* fusion
Adamantinoma-like Ewing sarcoma	Usually seen in adults especially salivary or thyroid glands	Rapidly developed symptoms of pain, mass, teeth mobility, and obstruction	Well-developed rosettes usually present, at least focally, and overt squamous differentiation (compact keratin pearls)	Strong, membranous CD99 expression and nuclear NKX2.2 positivity, and positivity for cytokeratin, p63, and p40 at epithelial differentiation	*EWSR1::FLI1* translocation
Neuroendocrine carcinoma	Adult presentation, usually sixth decade	Rapid clinical presentation of destructive mass	Stippled (salt and pepper) nuclear chromatin arranged in solid nests, sheets, or ribbons to trabeculae	Positive for neuroendocrine markers such as synaptophysin, INSM1, chromogranin A, and NSE and positive for epithelial markers cytokeratins (AE1/AE3, CAM5.2, OSCAR, and CK7) and EMA	Not clinically relevant
MiNENs	Adult presentation	Rare mass lesion with aggressive biological behavior	A rare biphasic tumor, composed by neuroendocrine neoplasm and non-neoendocrine neoplasm, usually a squamous cell carcinoma or adenocarcinoma	Positive for neuroendocrine markers such as synaptophysin, INSM1, chromogranin A, and NSE and positive for epithelial markers such as cytokeratin with diffuse cytoplasmic and membranous staining in tumor cells	Not clinically relevant
Rhabdomyosarcoma	Vast majority less than 20 years	Mass lesion	Primitive mesenchymal cells with rhabdomyoblasts	Positive for desmin, myogenin, and MyoD1	Alveolar rhabdomyosarcoma with *FOXO1* gene fusions with *PAX3* or *PAX7*, spindle cell rhabdomyosarcoma *with NCOA2* rearrangements
SWI/SNF complex-deficient sinonasal carcinoma	Wide range of 11-89 years	Rapid clinical onset of large mass lesion resulting in obstructive symptoms	Compact, cohesive nests, sheets, cords, and lobules of tumor lacking specific line of differentiation, basaloid cells and rhabdoid to plasmacytoid cells common	Negative stains for INI1 and BRG1	*SMARCB1* gene deletion most common, biallelic inactivation of *SMARCA4* results from loss of function (usually truncating) mutations
Mesenchymal chondrosarcoma	Broad age range, but peak incidence in second-third decades	Nonspecific symptoms of pain or swelling	Small to spindled malignancy with focal areas of chondrosarcoma but usually lacks overt squamous differentiation	Small cells positive for CD99, S100 protein, and SOX9	*HEY1::NCOA2* fusion
Ameloblastic carcinoma	Wide age range	Painful swelling or mass, often rapidly growing, majority in mandible and uncommon in maxilla	Features of ameloblastoma (peripheral palisading, reverse polarization, and central stellate reticulum) with epithelial pleomorphism	High Ki-67 score may help differentiate from ameloblastoma	CGH has shown amplification of 5q13
Olfactory carcinoma	Broad age range from 12 to 82 years	Mass effect including nasal obstruction, epistaxis, nasal or orbital pain, and altered mental status.	Neuroendocrine features and epithelial differentiation in the form of nonfocal keratin expression or gland formation	Positive for at least 1 specific neuroendocrine marker and positive for some degree of keratin expression, nonfocal in majority of cases	Most common alterations are Wnt pathway mutations, including *CTNNB1* and *PPP2R1A*
Malignant teratoma	Most are present at birth	Significant respiratory distress	Yolk sac tumor is the most common head and neck malignant extragonadal germ cell tumor. Choriocarcinoma, embryonal carcinoma, and seminoma are extremely rare.	Yolk sac tumors are positive for AFP, SALL4, and glypican-3	Not clinically relevant

Author Contributions

All authors confirm they have meaningfully contributed to the research and read and approved the final manuscript.

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Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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