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Teratocarcinosarcoma -Molecular Genetics & Histogenesis: A Review of Literature

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Abstract

Teratocarcinosarcoma (TCS) is a rare and aggressive tumour with intermixed teratomatous, carcinomatous, and sarcomatous elements, which remains poorly understood. Even though a few literature reviews about TCS were published, none of them focused on molecular genetics or histogenesis. Understanding the correct genetic alteration of a tumour not only helps in diagnosis of disease, but also can pave way for developing the targeted drug therapy which may cure the disease. A biomedical literature search was done in the Google Scholar & PubMed databases using the following key words: "sinonasal teratocarcinosarcoma" "teratocarcinosarcoma"& "molecular genetics." Out of 107 TCS cases that were tested for various molecular alterations, a major proportion of 49% (52 cases) demonstrated the SMARCA4 mutation, while 18% (19 cases) showed retained SMARCA4. β-catenin mutation was detected in 5% of cases. Meanwhile 6% (6 cases) had both SMARCA4 & β-catenin mutations. These findings suggest a role for the Wnt/β-catenin pathway & SWI/SNF deficiency as the primary and frequent genetic drivers in TCS tumorigenesis. SMARCA4 & β-catenin mutations can be used for diagnosing TCS in limited material. Furthermore, precision medicine trials can be employed to identify and apply targeted therapy options like specific inhibitors of β-catenin, Enhancer of Zeste Homolog 2 and Cyclin-Dependent Kinase 4/6 inhibitors for this difficult-to-treat tumour.

Keywords: Teratocarcinosarcoma, molecular genetics, histogenesis

Introduction

The term sinonasal teratocarcinosarcoma(SNTCS) was initially described by Heffner and Hyams in 1984 in their analysis of 20 cases.(1) Teratocarcinosarcoma (TCS) is a rare and aggressive tumour with intermixed teratomatous, carcinomatous, and sarcomatous elements, which remains poorly understood. The multiphenotypic differentiation of TCS has engendered persistent controversy about its histogenesis and leads to diagnostic overlap with several other malignancies.(2) A few studies were done to unravel the molecular genetics of this poorly understood tumour. Even though a few literature reviews about TCS were published, none of them focused on molecular genetics or histogenesis. Understanding the correct genetic alteration of a tumour not only helps in diagnosis of disease, but also can pave way for developing the targeted drug therapy which may cure the disease. So this article focuses on the molecular alterations and histogenesis described in the previously published articles about TCS.

Methods

A biomedical literature search was done in the Google Scholar & PubMed databases using the following key words: "sinonasal teratocarcinosarcoma" "teratocarcinosarcoma" & "molecular genetics." Bibliographic examinations of articles pertaining to TCS were also performed. Inclusion criteria included publications in the English language during the past 20 years that provided data on genomic alterations and chromosomal aberrations

of each TCS cases. Those studies with duplicated data were excluded.

Histogenesis

The histogenesis of SNTCS is unknown and very few are the available data on its pathogenesis and molecular features.(3) It is thought to arise from either totipotent olfactory epithelial cells or immature pluripotent cells sequestered in the sinonasal tract and capable of divergent differentiation into epithelial, mesenchymal and neuroectodermal lineages.(4) Birkeland et al. detected an activating mutation in the *CTNNB1* gene resulting in a constitutive overexpression and nuclear translocation of β-catenin in TCS. Based on this result, they suggested a potential involvement of Wnt/β-catenin pathway in the SNTCS tumorigenesis and a potential prospect for treatment of this tumour.(5) Later Belardinilli et al. proposed that PI3K/AKT/mTOR pathway may have a potential role in its tumorigenesis. (3) However, in most reported series, no germinoma, embryonal carcinoma, choriocarcinoma, or yolk sac elements have been demonstrated, hence, the assumption that SNTCS is a tumour that arises from multipotential somatic stem cells. Based on these findings and the lack of i12p, this tumour has been considered unlikely to be of germ cell origin (6) In 2021, Kakkar et al. suggested that, the loss of SMARCA4 expression in all components of TCS supports the hypothesis that it originates from a multipotential somatic stem cell with the ability to undergo divergent differentiation.(7) The explanation of their multiphenotypic growth remained an issue of controversy over decades. Although the term "malignant teratoma" was coined for them in the original description, it has been largely agreed upon that these tumors are distinct from genuine mixed germ cell neoplasms and are likely somatic in origin.(8)

Clinical & histopathologic characteristics

The average age of the patients was 54.5 years (range, 0.1 to 85 years), with a strong male predilection (7:1).(9) Most of them initially present with relatively benign complaints of recurrent epistaxis (53.52% of cases) and nasal obstruction. Other symptoms reported were progressive blurry vision, anosmia, rhinorrhea, headaches, nausea, emesis, and dysosmias.(6) Most common sites involved are the nasal cavity and paranasal sinuses. Bone erosion and intracranial extension were also found in 24.19% and 20.96% of the reported cases respectively.(10)

Histopathology is characterized by the presence of benign and malignant epithelial and mesenchymal tissue components, with areas of adenocarcinoma or squamous cell carcinoma.(10–12). Mesenchymal components may be composed of spindle cells, smooth muscle, skeletal muscle, cartilage, and bone.(10) The presence of “fetal appearing” clear cell squamous epithelium is a characteristic finding that supports the teratoid nature of this tumour. Neural tissue in the form of neural rosettes and neurofibrillary matrix is also commonly seen.(11,12)

Immunohistochemical staining is important for the identification of epithelial, neuroepithelial, and mesenchymal components. Epithelial components may stain positive for cytokeratin and epithelial membrane antigen, whereas neuroepithelial tissue may be positive for neuron-specific enolase, CD99, chromogranin, synaptophysin, glial fibrillary acidic protein, and S-100.(11,13) Mesenchymal components may demonstrate positive staining for vimentin, myogenic markers, or smooth-muscle actin.(11)

Cytological characteristics

Cytological features of only one TCS case have been reported till date. It was a case of SNTCS with metastasis to cervical node. Aspirate from the node showed predominantly discohesive tumour cells with moderate to abundant cytoplasm and enlarged vesicular nuclei with prominent nucleoli. Occasional cohesive fragments showed ovoid to spindled tumour cells attached to fibrovascular cores. Few loosely cohesive cells with scant cytoplasm and nuclei having stippled chromatin, and rhabdoid cells were also seen. Frequent mitoses, apoptosis and nuclear streaking were evident. Overt squamous or glandular differentiation was absent. Furthermore they cautioned that SMARCA4-deficient TCS should be considered in the differential diagnosis of metastatic poorly/undifferentiated malignancies in cervical lymph node aspirates, as all components of TCS as seen in the primary tumour may not be present in nodal metastases.(14)

Molecular Genetics of TCS in Literature

The study of molecular characteristics of TCS was traced back to 2008, when Salem et al. evaluated 3

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cases of SNTCS by fluorescence in situ hybridization (FISH) and demonstrated only 2 copies of chromosome 12 per case. They concluded that 12p amplification, if it occurs at all in this setting, is exceptional and that SNTCS is a somatic-type neoplasm exhibiting divergent differentiation rather than a germ cell tumour.(15)

However, in the same year, Vranic et al. published a paper that contrasted the above finding. It was a case of an 85-year-old lady with TCS which was analysed by conventional cytogenetic analysis of 20 metaphase cells. They identified a hyperdiploid clone characterized by trisomy 12, with an additional subclone characterized by a del(1 p). Karyotype of the tumour was described as: 47, XX, +12[18]/47, idem, del(1)(p31.1p36.3). Since Trisomy 12 is a well-known cytogenetic event occurring in majority of malignant germ cell tumours, they concluded that TCS can be of germ cell origin. Furthermore this case also demonstrated an additional finding of loss of 1p, which is a well characterized genetic feature of embryonal tumours & malignant GCT where it is associated with aggressive clinical course and a poor prognosis.(16)

In 2011, Thomas et al. reported SNTCS in a 51-year-old woman in which FISH analysis was done using a locus-specific probe for the short arm of chromosome 12 (12p13/ETV6). Even though the predominant population was normal for copy number of chromosome 12 and 12p13, a subpopulation in the tissue showed an extra copy of 12p13.(6)

McKean et al. published a paper in 2014 on a chemotherapeutic trial done in mice xenografts prepared from tissue obtained from a case of SNTCS in a 48-year-old patient. Here genome sequencing for 'targetable pathways' demonstrated a hotspot mutation in β-catenin.(17)

Birkeland et al. described 2 SNTCS cases in which IHC stains for β-catenin were performed. It demonstrated intense β-catenin overexpression and nuclear localization in both of them. A targeted exome sequencing of the specimen identified an activating p.S45F mutation in β-catenin.(5) Specifically, β-catenin staining was predominantly nuclear in the mesenchymal component and in a subset of the epithelial component. The majority of the epithelial component demonstrated membranous β-catenin staining.(18)

In contrast to the above finding, Minasi et al. reported a SNTCS case that failed to demonstrate β-catenin mutation by both IHC & Sanger's sequencing. Exon-3 β-catenin gene analysis by Sanger's sequencing detected no mutation at the c.134 (p.S45). In addition, the analysis failed to reveal mutations at the c.121 (p.D32), c.122 (p.S33), c.123 (p.G34), c.126 (p.S37), c.130 (p.T41), c.133 (p.P44), and c.134. They concluded that, the p.S45F mutation does not represent a common driver mutation in SNTCS & the key hot spots in exon 3 of CTNNB1 are not necessarily involved in its tumorigenesis.(19)

In 2020, Rooper et al. identified loss of SMARCA4 expression in 82% of TCS cases, including 68% with complete loss and 14% with partial loss. Cases with heterogeneous expression revealed SMARCA4 loss in the stromal elements but reduced or weak reactivity in the epithelial and the neuroepithelial components. Furthermore, they suggested that Enhancer of Zeste Homolog 2 (EZH2) and Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors may emerge as a potential tool for treating such tumours with SMARCA4 inactivation. Targeted next-generation sequencing(NGS) done on TCS cases confirmed biallelic somatic inactivation of SMARCA4, and they proposed the possibility that TCS may be a member of the spectrum of the newly described SMARCA4-deficient sinonasal carcinoma.(2) However, Agaimy et al. pointed out that convincing evidence is still lacking to conclude the same.(20)

In the next year, Belardinilli et al. performed a tumour mutational profile analysis on a SNTCS specimen from a 55-year-old man. It revealed a somatic activating mutation on the *PIK3CA* gene (p.His1047Leu). The authors also found a germline alteration in the DDR2 gene (p. Pro476Leu), whose oncogenic function is still considered unknown.(3)

Compton et al. in 2021 performed β-catenin and SALL-4 IHC on 7 SNTCS cases. Nuclear β-catenin expression was not identified in any of them, with all cases demonstrating membranous expression or cytoplasmic and membranous expression. SALL-4 IHC, however, was relatively sensitive (85.7%) and specific (89.5%) for SNTCS. They concluded that SALL-4 may have utility in distinguishing SNTCS from other high grade sinonasal tumours.(21)

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In the same year, Kakkar et al. conducted SMARCA4 IHC in 5 cases of TCS, & all of them demonstrated loss of SMARCA4. It was also found that SMARCA2 was retained in all the above cases. β-catenin was negative in 3 out of 4 cases.(7)

In 2022, Almarzooqi et al. reported a case of congenital TCS. It was a case of 3-week-old female with antenatally detected ocular mass with intracranial extension. The tumour consisted of malignant glands and mesenchymal elements of undifferentiated blastema-like cells and immature neuroepithelium. Molecular testing revealed a somatic CTNNB1 gene mutation.(22)

Mittal et al. evaluated 50 TCS cases for SMARCA4 IHC & found out that 68% had complete loss, 18% demonstrated partial loss, and 14% retained SMARCA4 expression. Cases with complete loss showed loss of staining in all three components (teratomatous, stromal, and epithelial). One case showed heterogeneity with complete loss in neuroectodermal areas and partial loss in sarcomatous areas.(23)

In 2022 Suarez et al. reported another TCS case in a 50-year-old male. Molecular analysis revealed DNMT3 deletion exon 4–15, KDM6A G5fs*15 & SMARCA4 mutation.(24)

Subsequently Hermsen et al. conducted whole exome sequencing(WES) in a TCS case & demonstrated SMARCA4 mutation. They also suggested that inhibitors of EZH2 may be useful for treatment of such cases.(25) They also performed a study in which, an in vitro model of TCS was made and studied by WES for genetic alterations. A cell line named TCS627 was established from a SNTCS specimen. The cell line had a predominant tetraploid karyotype with copy number loss at 1p and gains at 1q & 12p. WES revealed somatic frameshift mutations in ARID2 and CDKN2A, splicing mutations in SATB2 and SMARCA4, and missense mutations in NOTCH3, STAG2 and TET2, both in the primary tumour and the cell line. SMARCA4 expression was lost in the cell line but not in the primary tumour. CTNNB1 mutation was not observed. They concluded that TCS627 constitutes a useful tool for testing new therapeutic approaches for SNTCS.(26)

In the same year, Gopakumar et al. demonstrated loss of BRG1 immunostaining and β-catenin immunopositivity on a cell block prepared from cervical LN which had metastatic TCS.(14)

Rooper et al. evaluated SMARCA4 IHC in 30 TCS cases, in which loss of SMARCA4 was seen in 22 cases. NGS was done in 17 TCS cases. They showed inactivating SMARCA4 mutations in 65% and activating CTNNB1 mutations in 35%, including 5 cases with both. Of 5 cases that lacked SMARCA4 or CTNNB1 mutation, 1 harboured SMARCB1 inactivation and 1 had concomitant APC and ARID1A mutations, and 3 had other findings, including DICER1 hotspot mutation. They concluded that while SMARCA4 and β-catenin IHC may help confirm a challenging diagnosis, TCS should not be regarded as a molecularly defined entity.(27)

Rare sites of TCS

Even though this rare tumour is entitled sinonasal TCS, a lot of literature has described it in other sites like the ovary, cervix, thyroid, pharynx, and oral cavity.(4,28–31) Ito et al. in 2019 published a case of 45-year-old woman, who presented with a large polypoid mass on the cervix. Histology showed both epithelial and mesenchymal tissues consisting of immature glandular cells, neuroepithelial tissue, small blue cells with neuroendocrine differentiation, hyaline cartilage, and rhabdomyosarcoma. FISH analysis failed to show Human papillomavirus (HPV) infection or ESWR1 gene rearrangement. Furthermore, neither isochromosome 12p nor 12p amplification was observed. Based on these findings, the tumour was diagnosed as TCS of the uterine cervix.(28)

The World Health Organization recently published the 5th edition of Head and Neck Tumours, which mentions that TCS has been shown to have recurrent molecular alterations, specifically biallelic inactivation of SMARCA4 and activating CTNNB1 mutations.(32)

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Table 1: Summary of the molecular genetics of TCS in literature

Sl No	Year	Author	No of cases	Technique	Molecular alterations
1	2008	Salem et al.(15)	3	FISH	Absence of 12p amplification
2	2008	Vranic et al.(16)	1	Conventional cytogenetics	Hyperdiploid clone with trisomy 12 ; additional subclone with del(1p), Karyotype described as 47,XX,+12[18]/47,idem,del(1)(p31.1p36.3)
3	2011	Thomas et al.(6)	1	FISH	A subpopulation shows extracopy of 12p13 in 9% of cells
4	2014	McKean et al.(17)	1	Exomic targetable pathway sequencing done on mice xenografts	B catenin mutation
5	2016	Birkeland et al.(5)	2	IHC, Targeted Exome sequencing	Activating p.S45F mutation in β catenin
6	2019	Ito et al. (28)	1	FISH	No HPV infection, absent EWSR rearrangement, absent isochromosome 12p and 12 p amplification
7	2020	Rooper et al.(2)	22	IHC	SMARCA4 loss in 82%,complete loss seen in 68% & partial and heterogenous in 14 %.[same cases were included in another article by the same author(27)]
8	2021	Minasi et al.(19)	1	IHC	Absent β catenin staining; No mutation seen at p.S45
9	2021	Belardinilli et al.(3)	1	Multigene panel sequencing	Somatic activating mutation in PIK3CA Germline alteration in DDR2 gene
10	2021	Compton et al.(21)	7	IHC	All cases showed membraneous-cytoplasmic β-catenin staining, 6 cases showed SALL4 positivity.
11	2021	Kakkar et al.(7)	17	IHC	29.4% cases showed loss of SMARCA4 & retained INI. β catenin was negative in 3 out of 4 cases.
12	2022	Almarzooqi et al.(22)	1	-	CTNNB1 mutation.

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13	2022	Mittal et al(23)	50	IHC	34 cases showed complete SMARCA4 loss, 9 showed partial loss and 7 cases retained SMARCA4.
14	2022	Suarez et al.(24)	1	-	DNMT3 del exon 4-15, KDM6A G5fs*15, SMARCA4 mutation.
15	2023	Hermsen et al.(25)	1	Whole exome sequencing	SMARCA4 mutation.
16	2023	Hermsen et al.(26)	1	Invitro cell model studied by whole exome sequencing	Cell line showed frameshift mutations in ARID2 and CDKN2A, splicing mutations in SATB2 and SMARCA4, and missense mutations in NOTCH3, STAG2 and TET2, both in the primary tumour and the cell line. No CTNNB1 mutation seen.
17	2023	Gopakumar et al.(14)	1	IHC on cell block	Loss of BRG1 staining & β-catenin immunopositivity.
18	2023	Rooper et al.(27)	17	NGS	6 cases showed SMARCA4 only,1 showed CTNNB1 only,5 showed both the above mutations,1 showed SMARCB1,1 case showed APC& ARID1A,3 showed other findings, including DICER1 mutations.

Out of 107 TCS cases that were tested for various molecular alterations, a major proportion of 49% (52 cases) demonstrated the SMARCA4 mutation, while 18% (19 cases) retained SMARCA4. β-catenin mutation was detected in 5% of cases. Meanwhile 6% (6 cases) had both SMARCA4 & β-catenin mutations. It was also noticed that 3% of the cases demonstrated SMARCA4 mutation in the absence of β-catenin mutation. 6% of cases were detected to have both β-catenin & SALL4 mutations.

The results in this review can't be generalised to the TCS cases, as there are many limitations in analysing the previously published reports. One major drawback to be noted is that there is no homogeneity in methods used for molecular analysis by different authors. Additionally, each case was studied for a different set of mutations. Because of the rarity of the tumour, obtaining a good sample size for doing an elaborate molecular profiling is also challenging. Some case reports showed that even if mutation is demonstrated by IHC, further molecular tests may fail to demonstrate the same. A comprehensive multi-institutional study with a good sample size & a uniform molecular analytic technique is to be conducted before drawing a conclusion. Nevertheless, this article represents the largest and most complete review of literature regarding the molecular genetics of TCS to date.

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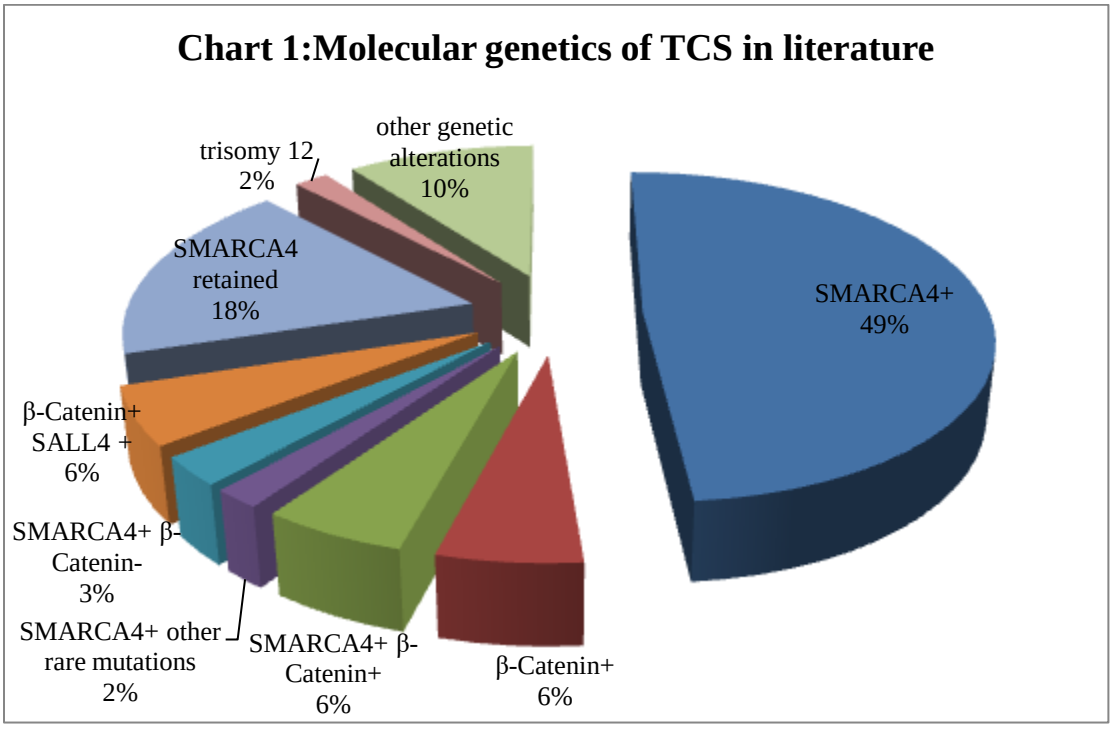

+: mutation present; - : mutation absent ; studies which had done IHC followed by other molecular techniques like NGS, only the results of latter is used.

Conclusion

TCS is a rare, aggressive & frequently misdiagnosed tumour. 49% of the published cases demonstrated SMARCA4 mutation. A considerable number of cases also showed β-catenin mutation. These findings suggest a role for the Wnt/β-catenin pathway & SWI/SNF deficiency as the primary and frequent genetic drivers in TCS tumorigenesis. SMARCA4 & β-catenin mutations can be used for diagnosing TCS in limited material. Furthermore, precision medicine trials can be employed to identify and apply targeted therapy options like specific inhibitors of β-catenin, Enhancer of Zeste Homolog 2 (EZH2) and Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors for this difficult-to-treat tumour. In depth molecular studies are necessary for better understanding of the tumorigenesis of TCS.

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