Molecular Basis of Synovial Sarcoma and the Rare Case of its Localization in Palatine Tonsil: A Review of the Literature

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ABSTRACT

Synovial sarcomas (SS) are rare soft tissue malignant tumors that mainly arise from the lower extremities, especially the lower thigh-knee region. The literature has shown that this tumor may be observed in uncommon regions such as the abdominal wall and the head and neck region which are non-synovium-lined spaces. SS rarely occurs in the head and neck region, as only 3-10% of these neoplasms appear in this region. The parapharyngeal space is the most common location, whereas primary SS of the palatine tonsil is extremely rare as only a few cases of primary tonsillar SS have been described. It is considered as a high grade malignant tumor, however current investigation regarding its clinical and histopathological features revealed in all these cases a biphasic morphology. Molecular analyses detected a typical *SYT* gene t(X;18) (p11; q11) translocation and a representative *SYT*/*SSX1*fusion type. Immunohistochemical analysis recorded cytokeratin OSCAR, Bcl-2, EMA, vimentin, TLE1 and PGP 9.5, were diffusely positive. The aim of the current review was to present the molecular basis of SS and SS rare location in palatine tonsil.

Keywords: *Synovial Sarcoma, Translocation, Molecular Biology, Tonsil*

Introduction

Synovial Sarcoma (SS) is a mesenchymal tumor characterized of spindle cells that show changeable differentiation of the epithelial component, including gland formation, and a specific chromosomal translocation t(X;18) (p11; q11). It is thought to arise from pluripotent mesenchymal cells with both epitheloid and spindle differentiation (Fisher *et al*., 2002). SS is the fourth most frequent soft tissue sarcoma after liposarcoma, malignant fibrous histiocytoma, and rhabdomyosarcoma (Enzinger and Weiss, 2001). Despite the term, SS has no association with synovium and may occur at any site of the human body, mostly in the deep soft tissue of body limbs (80%) (Eilber and Dry, 2008). SS rarely appears in the head and neck location, as only 3-10% of these neoplasms have been found in this region

(Fisher *et al*., 2002; Vogel *et al*., 2007; Vogel *et al*., 2010), especially in the cervical and parapharyngeal region (Dei Tos *et al*., 1998), whereas it has been revealed in the trunk (8%) and retroperitoneal/abdominal region (7%), which are the most frequent non-extremity primary sites of the tumor (Clair JM *et al*., 2016). The most common locations in the head and neck region are hypopharynx, parapharyngeal space and posterior pharyngeal wall. Primary palatine tonsillar SS is extremely rare and only a few adult cases have been described up to now, whereas it is responsible for 5-10% of soft tissue sarcomas (Khademi *et al*., 2010; Vogel *et al*., 2010; Soria-Cespedes *et al*., 2013). SS can develop at any age, is typically observed in adolescents, however is most commonly observed in young adults, and the annual incidence rate is 0.5-7/million in children and adolescents younger than 20 years of age (Okcu *et al*., 2003). The origin of SS is uncertain, since the normal cellular transcript for this tumor is unknown. Some reports suggest that SS arises from a mesenchymal stem cell with ability for epithelial differentiation (Noguchi *et al*., 1997; Yakushiji *et al*., 2000). SS is characterized by four histologically subtypes, monophasic fibrous tumor, biphasic tumors, monophasic epithelial tumors, and poorly differentiated tumors (Tsuji *et al*., 1998).

Synovial Sarcoma Molecular Basis

SS monophasic variant mainly composed of mesenchymal spindle cells with or without solid epithelial regions (Clark *et al*., 1994; Meis-Kindblom *et al*., 1996), and the biphasic variant contains various rates of epithelial cells arranged in a glandular configuration in a background of mesenchymal spindle cells (Clark *et al*., 1994; Gaertner *et al*., 1996).

Molecular analyses disclosed a typical t(X;18) (p11.2; q11.2) translocation (Turc-Carel *et al*., 1987). The presence of the mentioned chromosomal translocation has been observed at a rate higher than 90% of SS cases (Turc-Carel *et al*., 1987; Sreekantiah *et al*., 1994), and is proposed to be the primary causal element in SS cases (Ladanyi *et al*., 2002).

Cloning of the breakpoints of this translocation revealed the fusion of two genes, *SYT* that is located on chromosome band 18q11 and *SSX* that is located on Xp11 chromosome region (Clark *et al*., 1994). The *SYT* gene is fused with one of three closely associated genes, *SSX1*, *SSX2*, and in rare cases *SSX4* (de Leeuw *et al*., 1995), located on chromosome X in the vicinity of ornithine amino- transferase like (OATL) pseudogene 1 and 2 (Xp11) (de Leeuw *et al*., 1995; Crew *et al*., 1995). The frequency of *SYT-SSX4* fusion still remains unknown.

Whether the accurate location of the X chromosome breakpoint links with the histological morpho- logy of SS has been discussed for some time. It has been hypothesized (Kawai *et al*., 1998) that

a significant association between histological subtype, monophasic and biphasic, and the type of *SYT-SSX* fusion transcript exists. The *SYT*/*SSX1* translocation is correlated with the biphasic and monophasic histological subtypes, whereas the *SYT*/*SSX2* translocation is commonly correlated with only the sarcomatous (monomorphic) pattern (Thaete *et al*., 1999; Ladanyi *et al*., 2002; Kato *et al*., 2002). However, other researchers (Willeke *et al*., 1998) failed to confirm such findings.

Consequently, it has been recommended that precise functional differences between *SYT-SSX1* and *SYT-SSX2* may influence the epithelial differentiation in these sarcomas. Supposedly, the differences in 13 amino acids of the carboxy-terminal end of *SYT-SSX1* and *SYT-SSX2* proteins may influence specific protein-protein interactions that may lead to differentiation of SS (Kawai *et al*., 1998; Willeke *et al*., 1998; Antonescu *et al*., 2000; Ladanyi *et al*., 2001; Ladanyi *et al*., 2002). The biological basis of those observations is still unclear, and this model requires experimental confirmation. Fluorescence in situ hybridization (FISH) laboratory technique is used for detecting and locating a specific DNA sequence on a chromosome. After performing that technique an association was proposed from three independent groups between the two histologic subtypes of SS and breakpoints in the OATL1 or OATL2 region, now known to comprise the *SSX1* and *SSX2* genes, respectively (de Leeuw *et al*., 1994; Renwick *et al*., 1995). However, similar reports failed to confirm those findings (Crew *et al*., 1995; Shipley *et al*., 1994; Shipley *et al*., 1996).

Moreover, recent microarray-based expression profiling reports of SS have recognized genes that show different expression between SS and other Synovial Cell Sarcomas or biphasic and monophasic histological subtypes (Allander *et al*., 2002; Nagayama *et al*., 2002; Nielsen *et al*., 2002). The fused genes are responsible for a chimeric protein in which 8 amino acids of the carboxy- terminal end of *SYT* are substituted by 78 amino acids from the carboxy-terminal end of either of the *SSX* proteins. Five highly homologous *SSX* genes (*SSX1–5*) have been detected, and are localized on chromosome region Xp11.2 (Crew *et al*., 1995; de Leeuw *et al*., 1996; Gure *et al*., 1997).

There is limited information regarding the operating role of the mentioned proteins in cancer pathogenesis. Similar to other chromosomal translocations in sarcomas the mentioned translocation leads to the formation of a chimeric protein that possibly deregulates the transcriptional factors such as CRB/p3006 and hBRM/hSNF2a, a component of the SWI/SNF complex that regulates chromatin remodeling (Ladanyi, 1995; Thaete *et al*., 1999; Nagai *et al*., 2001; Kato *et al*., 2002). In the *SYT-SSX* fusion transcript, the amino-terminal repressor domain of *SSX* is substituted by the carboxy-terminal domain of *SYT*, which has been found to act as a transcriptional activator (Brett *et al*.,1997). The chimeric protein, *SYT-SSX*, which has been localized in the nucleus, possibly deregulates the

transcription of other genes, whose identity has not yet been clarified, especially through protein-protein interaction, as they seem to lack DNA-binding domains (dos Santos *et al*., 1997). In agreement with the intracellular location of transcriptional regulators, *SYT*, *SSX*, and *SYT–SSX* are nuclear proteins (dos Santos *et al*., 1997). Moreover, the *SSX1* and *SSX2* amino-terminal regions comprise a repressor domain that acts as inhibitor of transcription (Brett *et al*., 1997).

In the chimeric transcript of SS this repressor domain, encoded by the 5 part of *SSX1* and *SSX2*, is replaced by all but the 3-end of *SYT*, an extensively expressed gene encoding a region that can act as a transcriptional activation domain (Brett *et al*., 1997).

The amino-terminal regions of *SSX1* and *SSX2* proteins, that are not maintained in the fusion proteins, contain two well-maintained domains. The first one is similar to Krüppel-associated box-A (KRAB) domain (Crew *et al*., 1995), and the other is located in the carboxy-terminal, and both of which show suppression activity. Moreover, KRAB domain is not maintained at the fusion with *SYT* (Lim *et al*., 1998).

It is possible that *SSX1* and *SSX2* genes come from a relatively current duplication process and encode proteins with remarkable homology, 81%. Recently, additional related *SSX* genes, obviously not involved by the mentioned translocation, have been recognized in Xp11 location (de Leeuw *et al*., 1996; Chand *et al*., 1995).

The biological functions of normal *SYT* and *SSX* proteins are to a great degree unknown. However, it has been demonstrated that the wild-type *SYT* and *SSX* proteins have an active role in the process of transcription through interactions between proteins, despite the fact that they do not have direct DNA-binding domains, as already mentioned (Brett *et al*., 1997; dos Santos *et al*., 1997). The normal *SYT* gene is extensively expressed in a wide diversity of cell types during early embryogenesis (Bruijn *et al*., 1996), however the function of the proteins is unknown. The *SYT* gene is widely expressed in human tissues, whereas the *SSX* genes seem to be expressed only in testis and thyroid (Crew *et al*., 1995; Türeci *et al*., 1996).

Within the carboxy-terminal part are three supposed Src homology (SH) binding domains (Clark *et al*., 1994). The presence of these SH binding domains suggests that *SYT* is implicated in intracellular signaling pathways. Moreover, research on other translocations showed (Rabbitts, 1994) that the affected genes often encode transcription factors. Consequently, it has been suggested that the *SYT* gene may encode a transcription factor (Clark *et al*., 1994).

SSX2 gene expression has also been revealed in melanoma (dos Santos *et al*.,2000), whereas

recently, other related *SSX* genes have been revealed, but they are not implicated in the mentioned trans- location in SS cases (Smith and McNeel, 2010).

E74 Like ETS Transcription Factor 3 (ELF3) is a protein that in humans is encoded by the ELF3 gene that belongs to ETS transcription factors family, and is implicated in epithelial differentiation control. A great amount of genes that their expression occurs in the epithelium contain consensus binding locations for ETS transcription factors in their enhancer or promoter regions (Gambarotta *et al*., 1996; Rodrigo *et al*., 1999). ELF3 (Oettgen *et al*.,1997) is one of the differentially expressed genes between monophasic and biphasic tumors (Allander *et al*., 2002), increasing the possibility that ELF3 gene might have a dominant role in SS epithelial differentiation, specifically its overexpression might be associated with glandular epithelial differentiation in SS cases. Moreover, ELF3 gene shows differentially over-expression in biphasic tumors, compared with the monophasic ones (Allander *et al*., 2002).

Oncogenic progression in sarcomas can be distinguished into two separate groups, cytogenetically. The first concerns sarcomas that show a discrete, definite chromosomal translocation, such as SS (t18:X) (q11; q11), Ewing sarcoma (t11:22) (q24; q12), myxoid chondrosarcoma (t 9:22) (q22; q12), alveolar rhabdomyosarcoma (t 2:13) (q35; q14), clear cell sarcoma (t12: 22) (q13-q14; q12), dermatofibrosarcoma protuberans [ring 17 or t(17;22) (q24;q12)], and desmoplastic small round cell tumor (t 11:22) (p13; q25), whereas the second one contains sarcomas with complex karyotypes.

It is possible that multiple genetic alterations are responsible for the mentioned complex sarcomas, each of which leads to a biologic survival advantage for the malignant cell. Inversely, sarcomas such as SS depend on a discrete genetic alteration that is the dominant event and has an intense effect on the malignant cells phenotype (Dei Tos and Dal Cin, 1997).

The Effect of E-Cadherin Inactivation in Synovial Sarcoma Pathogenesis

E-cadherin, is a cell-cell adhesion molecule, it performs vital operations in the biological processes of embryogenesis and tissue architecture as it is responsible for intercellular junction complexes formation, and cell polarization (Takeichi, 1993; Overduin *et al*., 1995; Hirohashi *et al*., 1998). The extracellular domain of E-cadherin acts as a molecular barrier that mediates cell–cell adhesion, whereas the cytoplasmic tail is connected to cytoskeleton of actin across catenins (Ozawa *et al*., 1990). E-cadherin expression loss is involved in the invasive and metastatic properties of malignant cells (Kemler, 1993; Takeichi, 1993; Hirohashi *et al*., 1998).

E-cadherin downregulation is observed during epithelial-mesenchymal transitions (EMT), a

process of cellular morphological alterations in epithelial cells. Epithelial and mesenchymal cells differ in phenotype as well as function, though both share inherent plasticity. Epithelial cells express high levels of E-cadherin, whereas mesenchymal cells express N-cadherin, fibronectin and vimentin. Thus, EMT entails profound morphological and phenotypic changes to a cell and leads to a representative fibroblastic and flattened phenotype (Batlle *et al*.,2000; Cano *et al*., 2000; Locascio *et al*., 2002; Nieto, 2002; Thiery, 2002).

Several mechanisms are involved in the impairment of E-cadherin function. Mutations are responsible for E-cadherin inactivation, and have been revealed in diverse tumors and cancer cell lines (Berx *et al*., 1995; Machado *et al*., 1999; Saito *et al*., 2001; Endo *et al*., 2001). Reduced E-cadherin expression is responsible for cellular morphological alterations in epithelial cells, and leads to an altered phenotype, as mentioned above (Frixen *et al*., 1991; Vleminckx *et al*.,1991; Batlle *et al*.,2000; Cano *et al*., 2000; Locascio *et al*., 2002; Nieto, 2002; Thiery, 2002). Its expression in some sarcomas, especially in biphasic SS glandular structures has found to be to a large extent limited (Saito *et al*., 2000; Yoo *et al*., 2002; Laskin and Miettinen, 2002).

SS spindle cell element often indicates histological characteristics that closely are similar to those of other sarcomas spindle cell such as Malignant Fibrous Histiocytoma, Leiomyosarcoma, and Malignant Peripheral Nerve Sheath Tumors (MSNST), although sarcomas with spindle cell component other than SS rarely display morphological epithelial differentiation (Saito *et al*., 2004). Genetic and epigenetic alterations act as potential mechanisms for E-cadherin inactivation as are responsible for E-cadherin gene silencing. Such mechanisms have been examined in SS cases. Missense mutation of E-cadherin gene has been revealed in some SS cases resulting in E-cadherin gene inactivation and leading to the monophasic spindle cell histological subtype of SS (Saito *et al*., 2004).

E-cadherin missense mutation and gene promoter hypermethylation have been detected evenly in 12.5% of SS cases, and the first finding was found only in monophasic histological subtype that contains *SYT-SSX1* fusion gene, whereas in only one of which its expression was silenced. Moreover, the presence of unmethylated zones in samples that contained E-cadherin gene promoter methylation, increased the possibility that E-cadherin methylation status might be heterogeneous within distinct monophasic tumors. On the other hand, E-cadherin promoter methylation status could be different in different cell types, epithelial and spindle cells, in biphasic tumors (Saito *et al*., 2004). A supposed cause-effect relation between E-cadherin inactivation by missense mutation or promoter hypermethylation and SS histological morphology was proposed based on similar findings in gastric and breast cancer specific subtypes (Berx *et al*., 1995; Machado *et al*., 1999; Saito *et al*., 2001).

Saito, *et al*. (Saito *et al*., 2004) revealed *SYT-SSX1* fusion in all SS cases that comprised E-cadherin missense mutations, finding that might explain why that fusion could indicate either a monophasic or a biphasic phenotype. SS cells morphological transitions could be similar to EMTs in other biological systems. However, it remains unclear whether E-cadherin expression loss is a differentiation passive result or whether it might play a supplementary causal role in the spindle cell morphology differentiation in SS cases.

Another mechanism of downregulation of E-cadherin expression except genetic and epigenetic alterations is the process of transcriptional repression. E-cadherin downregulation is correlated with the glandular epithelial differentiation loss or absence in some SS cases. Moreover, E-cadherin expression loss is linked with histologic and molecular variety in SS cases (Saito *et al*., 2004).

Overexpression of Snail transcription Factor as a E-cadherin Inactivation Mechanism in Synovial Sarcoma

Snail is a family of transcription factors that promote the repression of the adhesion molecule E-cadherin to regulate EMT during embryonic development. It is responsible for blocking the E- cadherin gene expression by binding directly to the E-boxes that are present in the proximate promoter of E-cadherin. Fibroblasts and some epithelial tumor cells are responsible for its expression. (Batlle *et al*., 2000; Cano *et al*., 2000). An inverse relation between expression of endogenous E-cadherin and expression of endogenous Snail has been recorded (Nieto, 2002; Thiery, 2002), how- ever there are no published findings in the cases of sarcomas.

mRNA expression of E-cadherin in SS cases is correlated with reduced expression levels of Snail, finding that is consequent with the probability of E-cadherin transcriptional repression by Snail in those cases (Saito *et al*., 2004). The mentioned transcriptional repression of E-cadherin in SS cases can lead to downregulation of E-cadherin expression, however these mechanisms require confirmation regarding the functional level. E-cadherin expression might be arranged by molecular switching through Snail, leading the SS tumor cells differentiation to an epithelial phenotype. That inverse association between E-cadherin and Snail in SS cases is indirect as SS tumor cells with epithelial features will have the trend to express restricted levels of mesenchymal-associated proteins such as Snail (Saito *et al*., 2004).

Chromatin-mediated effects such as chromatin remodeling and chromatin modification are an additional possible level of E-cadherin expression control (Brown, 2003). The possible E-cadherin expression regulation by Snail and its silencing by missense mutation may play a crucial role in understanding the SS phenotypic heterogeneity (Saito *et al*., 2004).

Allander, *et al*. suggested that epithelial-related genes silencing, such as E-cadherin gene, might be

responsible for the acquirement or maintenance of the SS spindle cell morphology (Allander *et al*., 2002).

The inverse association between Snail and E-cadherin, (Nieto, 2002; Thiery, 2002), proposes the ability of E-cadherin transcriptional repression by Snail in SS cases, finding that has been observed in epithelial malignancies but not in sarcomas. In addition, the EMT process can actually be a reversible process, as it occurs several times during embryonic development process (Sefton *et al*., 1998; Auersperg *et al*., 1999). E-cadherin reexpression occurs in the metastatic process in which the migrant malignant cells must install connection to their destination tissue (Mareel *et al*., 1991; Bukholm *et al*., 2000; Graff *et al*., 2000). Those observations may indicate that loss of E-cadherin expression has a causal role in SS spindle cell morphology acquirement, and is in accordance with the previous finding of inactivation of E- cadherin gene through missense mutations in some monophasic SS cases (Saito *et al*., 2001).

A comparison was carried out regarding the expression of E-cadherin and ELF3 transcript levels with the type of *SYT-SSX* fusion, to assess them as possible epithelial-specific downstream target genes of the fusion examined. The outcomes showed no correlation between their expression at the RNA level and type of *SYT-SSX* fusion. The exact role of ELF3 expression in SS cases is presently unknown, however its increased level of expression in biphasic SS cases suggests a possible role in epithelial glandular differentiation process (Saito *et al*., 2004). Among biphasic SS may be required supplementary events for SS tumor cells with E-cadherin protein expression to indicate glandular differentiation, such as the remodeling of the extracellular matrix (Saito *et al*., 2002).

Possible Role of Epidermal Growth Factor Receptor and HER-2/neu Expression in Synovial Sarcoma Pathogenesis

The human Epidermal Growth Factor Receptor (EGFR, ERBB) family of Receptor Tyrosine Kinases (RTK) is a critical group of mediators that are involved in survival, cell proliferation, differentiation, migration, and adhesion (Yarden, 2001). The family contains four distinct receptors, EGFR (ErbB1, HER1), ErbB2 (HER2, neu in rodents), ErbB3 (HER3), and ErbB4 (HER4) that are stimulated by a diversity of ligands, whereas it has not been identified a known ligand for HER-2/neu. A variety of neoplasms in several organs is characterized by EGFR expression (Dorkin *et al*., 1997; Nemoto *et al*., 1997; Kersemaekers *et al*., 1999), and HER-2/neu expression is amplified in a diversity of primary human carcinomas (Natali *et al*., 1990; Bongiorno *et al*., 1994; Cirisano and Karlan, 1996) and lung carcinomas.

Little information is available regarding the ERBB family expression in SS cases. A robust EGFR membrane expression in two SS cases was detected (Gusterson, 1985). In a previous analysis of eight monophasic SS specimens using spotted cDNA expression profiling was found the clustering of EGFR with the *SSX* genes, proposing that this RTK may be associated with SS-specific expression (Nielsen *et al*., 2002). Previous researches (Nielsen *et al*., 2003; Barbashina *et al*., 2002) recorded the immunopositivity of SS cases compared to other soft tissue sarcomas. Similar studies investigated the HER-2/neu expression in SS cases. Allander, *et al*. (Allander *et al*., 2002) explored differences between SS and Malignant Fibrous Histiocytoma regarding gene profiling using array technology, and revealed increased HER-2/neu expression in the SS cohort.

However, the mentioned reports were not in agreement with a previous study that examined a large cohort of pediatric sarcomas in which was showed that HER-2/neu overexpression was a rare event in mesenchymal tumors including SS (George *et al*., 1992). It is obvious that EGFR and HER-2/neu expression in SS cases is controversial.

Dafydd, *et al*. analyzed 38 SS cases for assessing EGFR and HER-2/neu expression using immune-histochemical and molecular methods and detected expression of both genes, although at relatively low levels in the larger part of cases examined (Dafydd *et al*., 2005). Those outcomes confirm the findings of previous reports (Gusterson *et al*., 1985; Allander *et al*., 2002; Nielsen *et al*., 2002; Nuciforo *et al*., 2003), however were in contrast with an immuno-histochemical study of sarcomas and small round cell tumors of childhood (George *et al*., 1992) in which none of the SS cases studied showed immuno-histochemical staining for HER-2/neu.

Two previous researches focused on the *SYT/SSX* fusion type contribution to the EGFR and HER-2/neu expression. A precondition for understanding the contribution of the *SYT/SSX* fusion type to the regulation of translation of EGFR and HER-2/neu expression, is the two gene products normal function.

Native *SYT* links with p300/CBP in G1 arrested cells, and leads to the activation of 1 integrin (Eid *et al*., 2000). Activated 1 integrin regulates cell adhesion. The *SSX* genes group on X chromosome are responsible for encoding proteins that indicate strong expression in normal thyroid and testes (Crew *et al*., 1995), in addition to malignant tumors, such as melanomas (dos Santos *et al*., 2000). In those *SYT/SSX* fusion proteins, the binding of *SYT* to p300/ CBP is maintained whereas the adhesion function is lost (Eid *et al*., 2000).

It is possible that *SYT/SSX* mediates its action through configuration of other proteins responsible for transcription and translation. As mentioned the *SYT/SSX* fusion protein binds to the p300/CBP

complex, process that is implicated in the HER-2/neu gene transcriptional regulation (Chen and Hung, 1997).

It has also been demonstrated the wide-ranging transcription of EGFR and HER-2/neu gene but suggested the absence of translation regulation, mainly in SS specimens comprising the *SYT*/*SSX1* fusion gene. This was unexpected as *SSX1* and *SSX2* genes are almost similar in amino acid synthesis. Moreover, the *SYT/SSX* fusion protein was not directly responsible for the mentioned lack of translational regulation. The researchers also concluded that EGFR and HER-2/neu expression may constitute an important molecular event in SS pathogenesis (Dafydd *et al*., 2005).

Tonsillar Synovial Sarcoma

SS may appear in rare sites such as masticator space, tongue, sinonasal cavity, and trachea (Shmookler *et al*., 1982; Meer *et al*., 2003; Vogel *et al*., 2010; Villarroel-Salinas *et al*., 2012). However, primary tonsillar SS has been previously documented in only a few cases (Khademi *et al*., 2010; Vogel *et al*., 2010; Soria-Cespedes *et al*., 2013) mainly in young males with an age range of 19-35 years. In all of those cases the tumors were histologically biphasic, but only one showed poor differentiation areas. The tumor cells show strong, diffuse, positive nuclear staining for the TLE1antibody (transducin like enhancer of split1)/E (sp1), which is a highly susceptible marker of SS (Valente *et al*., 2013). This antibody homolog, Drosophila co-repressor groucho (Gro) is one of four members of the TLE gene family associated with embryogenesis, neuronal and epithelial differentiation, and hematopoiesis (Fraga *et al*., 2008; Kosemehmetoglu *et al*., 2009; Valente *et al*., 2013). TLE1 is a transcriptional corepressor that binds to a number of transcription factors and is implicated in the WNT/b-catenin signaling pathway, which is known to be associated with SS cases (Pretto *et al*., 2006). TLE1 positive nuclear expression has been detected at a rate higher than 90% of SS cases, formally in more than 50 % of the cells (Coindre *et al*., 2003; Kosemehmetoglu *et al*., 2009; Valente *et al*., 2013). Lower levels of positive staining for TLE1 can be observed in other mesenchymal tumors that can mistakenly be considered as SS, and are Ewing sarcomas, schwannomas, Malignant Peripheral Nerve Sheath Tumor (MPNST), and malignant fibrous histiocytomas (Terry *et al*., 2007). Consequently, TLE1 should be used in combination with antibodies and other biomarkers such as keratins, EMA, Bcl-2, and CD34 (Kosemehmetoglu *et al*., 2009; Valente *et al*., 2013).

The diagnosis requires additional immune-histochemical and in some cases cytogenetic examination. No immuno-reactivity has been described for actin (HHF-35), myoglobin, CD34, or desmin (Frisman, 2012).

In monophasic SS, the tumor is consisted of closely packed spindle cells with inadequate pale cytoplasm that form variably arranged bundles. Immuno-histochemically, the spindled cells were immune-reactive for cytokeratin OSCAR, EMA, Bcl-2, vimentin, CD99, and PGP 9.5, and showed a strong nuclear expression of TLE1. A small quantity of glandular-like formations can be identified focally that are able to react positively to cytokeratin OSCAR and EMA (Soria-Cespedes *et al*., 2013). The S-100 protein, another tumor marker may be focally expressed in up to 21 % of tumors (Coindre *et al*., 2003). Moreover, histopathologic examination of monophasic SS showed occasional glandlike structures against a sarcomatous background. Immuno-histochemical study for cytokeratin revealed positive staining in the scattered epithelial component and that for vimentin revealed positive staining in the sarcomatous cells of the tumor (Khademi *et al*., 2010).

FISH is positive for the *SYT* (SS18) rearrangement, confirming the diagnosis of monophasic SS (Vogel *et al*., 2007; Sharma *et al*., 2021).

Biphasic SS cases consisted of intersecting bundles of spindle cells with few foci of groups of cuboidal cells/tubules (epitheloid component). Mild pleomorphism with numerous mitosis have also been revealed. CD99, CK, EMA, CD55, CD57 and Bcl-2 were positive, and Ki-67 was positive in 50% of SS cases (Silambu V *et al*., 2020). Biphasic SS morphology may contain wide regions of spindle cells that are positive for vimentin, Bcl-2, CD99, and calponin intermixed with glandular structures positive for EMA cytokeratin (AEA1/3), bcl2, and CD99 (Vogel *et al*., 2010; Khademi *et al*., 2010).

Immuno-histochemical examination of biphasic SS for Pan CK, CK19, CK18, CK7 showed positive staining in the epithelial component and staining for vimentin showed positive staining in the mesenchymal component, whereas neural and muscle markers were negative (Vogel *et al*.,2010; Khademi *et al*., 2010).

Poorly differentiated tumors have rarely been described (De Silva *et al*., 2003), however in such cases was observed a mixture of epithelioid and spindle cells that were unreactive for cytokeratin, CD34, actin, and desmin. The mitotic index was increased and the proliferative activity based on ki67 staining was up to 50% (Vogel *et al*., 2010).

Conclusion

SS of palatine tonsil is a rare and extremely malignant tumor, thus the investigation of its molecular biology and development pathways could improve the patients' survival rate and prognosis.

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