Synovial Sarcoma- A Review

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ABSTRACT

Synovial sarcoma is an uncommon soft tissue neoplasm, whose origin is very controversial. Clinically, it shows a very aggressive behavior, histopathologically, it presents as a biphasic tumor displaying epithelial and spindle cells arranged in several patterns but not showing classical features of a high grade. Therefore the diagnosis of this neoplasm is very challenging. This article reviews the pathogenesis, clinical features, histopathology and ultrastructure of the tumor. Also it highlights the various differential diagnosis, treatment modalities and prognosis of the tumor.

Keywords: Synovial Sarcoma, Chromosomal Translocation, Micro RNAs, Biphasic, Epithelial Cells, Spindle Cells.

INTRODUCTION

Synovial sarcoma is a clinically, morphologically and genetically distinct neoplasm. This spindle-cell tumor shows inconstant epithelial differentiation, comprising of glandular formation and has a specific chromosomal translocation t(X; 18) (p11; q11). It represents about 5.6% to 10% of all soft-tissue sarcomas. Synovial sarcoma of the head and neck region was first described by Jernstrom in 1954, and Ambleetal, suggested approximately 9% of these tumors occur in head and neck region.[1]

PATHOGENESIS

The origin of synovial sarcoma remains debatable. Synovial sarcoma displays histologic resemblance to developing synovium, hence called synovial sarcoma, but there is no proof suggesting its origin from the synovial tissue.[1-4] No derivation from or continuity with, pre-existing epithelium has been known. Intercellular junctions, microvilli, external lamina, and epithelial differentiation are not frequently observed in normal synovium, but can be seen in synovial sarcoma.

It is now believed that synovial sarcomas "originates from undifferentiated or pluripotent mesenchymal cells with a dual differentiation capacity, both epithelial and mesenchymal".[2,3]

Recent studies suggest that microRNAs may play an extended role in the tumorogenesis of cancer. Precisely, the overexpression of a microRNA, miR-183, has been found to act as an oncogene through down regulation of EGR1 translation, a tumor suppressor that is associated strongly with tumor formation and transformation processes when its levels are exhausted. Another overexpressed miRNA, let-7e, has been shown to down regulate expression of HMGA2, a transcription factor which works in concert with the SS18-SSX fusion product to reduce the levels of SNAI1, a transcriptional repressor, eventually producing epithelial differentiation and transition in synovial sarcoma. Significantly, when let-7e was repressed by a miRNA inhibitor, the proliferation of the synovial sarcoma cells gets suppressed. These newer findings provides better understanding of the fundamental molecular basis for synovial sarcoma tumorigenesis.[4]

Subramaniam MM et al. (2011)[5] analyzed the immunohistochemical expression of E-cadherin, Snail, Slug, and dysadherin in synovial sarcoma, they witnessed the overexpression of Snail, Slug, and dysadherin and activation of Wnt and PI3K/Akt signaling was associated with inactivated E-cadherin in the spindle cells of monophasic fibrous synovial sarcomas, further emphasizing the hypothesis that this subtype has developed through neoplastic epithelial-mesenchymal transition.

CLINICAL FEATURES

Synovial sarcoma is frequently seen in 3rd and 5th decades of life. Most common site is the lower extremities, particularly around the knees. In the head and neck region, tumors are seen in the retropharyngeal or parapharyngeal region. In oral cavity, it involves tongue, soft palate, cheek or parotid. Usually a deep seated, slow growingand palpable mass that may or may not be associated with pain. The local symptoms like dysphagia, dyspnea, hoarseness and head ache are related to effects of the tumor mass. Radiographically, small irregular spotty calcifications (snow storms) can be identified; which will aid in diagnosis.[6,7]

HISTOPATHOLOGICAL FEATURES

Histologically, the tumor comprises of two morphologically different cell types: Epithelialcells, similar to those of carcinoma and fibrosarcoma-like spindlecells. Depending on the relative predominance of the two cellular elements and the degree of differentiation it can be broadly classified into:Biphasic (epitheloid and spindle cell), Monophasic fibrous cell, Monophasic epithelial type and Poorly differentiated (round cell) type.

Biphasic synovial sarcoma has epithelial and spindle cell components, in varying proportions. These cells are bounded by spindlecells that simulate subsynovial mesenchymal cells. There can give apseudoglandularappearance by forming glands with lumina (containing homogenous eosinophilic secretions) or papillary structures with one or (occasionally) more layers of uniform cells. The glandular component can predominate with large closely packed glands and a scanty spindle component that can be ignored, leading to misinterpretation as adenocarcinoma. The epithelial component can also form solid,cords, nests

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or roundedclusters. Squamous metaplasia, sometimes with keratinization, occurs in about 1% of cases.
The spindlecells are uniform and relatively small, with ovoid, dark - staining nuclei and inconspicuous nucleoli. Cytoplasm is sparse and cell borders are indistinct, so thenuclei appears overlapped. Mitoses can be infrequent, except in poorly differentiated synovial sarcoma. Generally the cells form solid, compact sheets. Frequently, the cellular portions of synovial sarcoma alternate with less celluar areas displaying hyalinization, myxoid change or calcification. The collagen in the hyalinized zones may be diffusely scattered or form narrow bands or plaque like masses which can sometimes be associated with markedly thickened basement membrane, separating the epithelial and spindle cell elements. The myxoid areas are generally less conspicuous and tend to conquer only a small ill-defined portion of the tumor. Mast cells show no particular arrangement but are more numerous than in the epithelial portions of the neoplasm. The degree of vascularity varies in some cases; it is a dominant feature with numerous dilated vascular spaces resembling hemangiopericytoma.

Monophasic fibrous synovial sarcoma - The spindle cell component of synovial sarcoma will be presented alone as monophasic synovial sarcoma. They present as densely packed cellular sheets and fascicles, and also exhibit nuclear palisading and haemangiopericytomatous pattern. Stroma is composed of scanty collagen. The stroma may also show focal areas of Hyalinization and Myxoid change. They may also present as alternating hyper and hypocellular zones.

Monophasic epithelial synovial sarcoma – this variant of synovial sarcoma is composed of plump epithelioid cells and is identical to adenocarcinoma.

Calcifying synovial sarcoma - Few tumors show focal calcification, areas of hyalinization may further get calcified and these areas are predominantly seen at the periphery of the tumor. This may also present with areas of ossification and chondroid change.
Poorly differentiated synovial sarcomas are high cellular. Cells appear as darkly stained ovoid or rounded cells which looks intermediate between epithelial and spindle cells. Abundant cellular mitoses and areas of necrosis are also seen.
They may be highly vascular and resemble hemangiopericytoma.[8-14]

ULTRASTRUCTURE

The epithelial cells of the tumor show cells comprising intermediate filaments including tonofilaments. Cells are attached to each other by terminal bar complex and the protrusion of surface microvilli is seen in the glandular lumen.[10] The prominent rough endoplasmic reticulum in spindle cells is indicative of fibroblasts with few intercellular gaps into which protruding cellular processes are seen. Transition between the spindle and the epithelial cellular components are not apparent. Areas of calcification indicate intra-mitochondrial needle - like calcifications.[8,10]

IMMUNOHISTOCHEMISTRY

The epithelial component of Synovial sarcomas expresses cytokeratins (CK). Several CK subtypes are expressed including cytokeratins 7 and 19.[10,11,14]

Epithelial membrane antigen (EMA) is expressed more often and more widely than CK, mostly in the poorly differentiated subtype. S100 protein may be noticeable (in nuclei and cytoplasm) in 30% of synovial sarcomas.
CD99 is positive in the cytoplasm of epithelial cells and membrane positivity is appreciated on the spindle cells. bcl2 protein is diffusely expressed in all synovial sarcomas, especially in spindle cells. Calponin is positive in most of the cases.[10,11,14]

DIFFERENTIAL DIAGNOSIS

Many tumors have a close resemblance to synovial sarcoma namely carcinosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, hemangiopericytoma thus will be considered in the differential diagnosis of synovial sarcoma.
Biphasic synovial sarcomas may demonstrate pseudo glandular appearance resembling carcinosarcomas, but the glandular element in carcinosarcoma shows a significant nuclear pleomorphism compared to the epithelial component seen in synovial sarcoma.
Fibrosarcoma is another tumor showing features similar to monophasic fibrous synovial sarcoma, but the multilobular growth pattern and prominent plump nuclei in the synovial sarcoma helps in the differentiation. Additional features such as occurrence of mast cells, calcification, hemangiopericytoma-like areas and expression of cytokeratin and EMA in neoplastic cells.
Leiomyosarcoma also displays close resemblance to monophasic fibrous synovial sarcoma. The cells of leiomyosarcoma show blunt ended nuclei, paranuclear vacuole and densely eosinophillic cytoplasm and are positive for smooth muscle actin and muscle specific actin or desmin.
Malignant peripheral nerve sheath tumor (MPNST) is also considered under the differential diagnosis of synovial carcinoma. MPSNT shows cells with wavy or buckled nuclei. CK7 and CK19 are negative in MPNST whereas HMGA2 is constantly positive in malignant peripheral nerve sheath tumor and rarely seen in synovial sarcoma.[8,9]

CYTOGENETICS

Regardless of the location, type or grade of differentiation, translocation t(X;18) (p11.2;q11.2) is specific for synovial sarcoma. This translocation is the result of fusion of the 5' part of the SS18 gene and the 3' part of SSX1, SSX2, SSX4 gene, or rarely the splice variant SSX4v.
Polymerase chain reaction has greatly aided in detecting the SYT-SSX fusion gene that results from the translocation of the SYT gene on chromosome 18 with the SSX gene on the X chromosome. Other methods useful in the detection translocation include cytogenetic analysis, reverse transcription polymerase chain reaction, and fluorescent in-situ hybridization.

TREATMENT AND PROGNOSIS

The treatment of Synovial sarcoma is complete excision of the lesion with negative margins. In the head and neck region, is not well described because of its rarity and varied occurrence. However, complete excision of the intraoral lesions cannot always be possible because the tumors may infiltrate fascial

and muscle planes beyond the palpable tumor margins, and extensive surgery to achieve adequate margins may lead to a loss of vital structures.[1]

Primary therapy is established on surgical resection with an adequate margin and maximal preservation of function. The minimal satisfactory margin has not been established; however, the susceptibility for microscopic infiltration of tumor cells into the pseudocapsule of the tumor is possible. Dissection through the pseudocapsule will facilitae easy removal as it has the least plane of resistance, creating a false sense that the tumor has been completely excised. With this method microscopic and probably gross residual tumor may be unnoticed.

Considering several positive or negative margins with local recurrence, distant metastasis, and subsequent modalities, it has been suggested that 1- to 2-cm margins will lead to adequate clearance of the tumor. Andrassy et al, based on their experience, have suggested "a tumor-free margin of 1- to 3-cm in adults". This huge margin cannot be achieved in most children and in deep-seated tumors next to to bone or important neurovascular structures.[16]

Subsequently, a multimodal therapeutic approach, comprising of excision with wide margins and postoperative radiation therapy, is often suggested. Adjuvant chemotherapy for soft tissue sarcoma is often controversial and is not an ideal option for adult soft tissue sarcoma. However, recent reports have suggested a benefit in disease-free state and overall increase survival rate in high-risk patients. Controversially, other investigators have not been able to appreciate a positive impact of chemotherapy on progression-free survival or overall survival.[1]

A literature review suggests that, postoperative radiotherapy in the range of 65 Gy is advocated for oral tumors, but adverse effects like radiation mucositis, ulceration, and osteoradionecrosis are expected.[1] even though postoperative radiotherapy decreases local recurrence, it has no effect on survival rate.[1]

Post-treatment recurrence rate for synovial sarcoma is about 50%. Most cases recur in the initial 2 years after treatment. Five-year survival rate is seen in almost 36% to 51%. Prognosis depends on tumor size, location, patient age, histological subtype, extent of involvement, mitotic activity, and margin of resection. Of these tumors size remains the most important prognostic factor. Patients with tumors greater than 5 cm in diameter will have a poorer prognosis than those with tumors less than 5 cm in diameter.[2]

In spite of advances in the treatment of local disease, distant metastasis remains the principal cause of death.[2]

CONCLUSION

Synovial sarcoma is a soft tissue tumor of ambiguous origin presenting a definitive cytogenetic arrangement. It is a challenging tumor to be diagnosed as the spindle cell component of tumor can mimic numerous soft tissue tumors A complete understanding and correlation of the clinical and the histopathological features along with the combined use of immunohistochemistry and cytogenetics will help in the accurate diagnosis. Best presented evidence advocates a multimodal therapy which involves aggressive surgical resection followed by radiation and chemotherapy.

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