Spindle Cell Lesions of the Head and Neck – Neoplastic or Non-Neoplastic?
Spindle Cell Carcinoma and Other Atypical Spindle Cell Lesions

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*Spindle cell lesions of head and neck mucosal sites are diverse and diagnostically challenging.

* Spindle cell carcinoma (SpCC) is the most common and should be strongly suspected in such cases. Most cases are clearly malignant – for these, the differential diagnosis includes spindle cell melanoma and true sarcomas such as angiosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, and others.

*Some non-neoplastic lesions such as sinonasal polyps and vocal cord nodules with stromal atypia, laryngeal contact ulcers, and granulation tissue polyps with stromal atypia after radiation are also in the differential diagnosis.

*Inflammatory myofibroblastic tumor (IMT) is a low grade neoplasm with a mixture of spindle cells and inflammation which should also be considered.

*A combination of the histologic findings, clinical information, examination of multiple tissue levels, and/or immunohistochemistry for cytokeratins, EMA, and p63 can distinguish SpCC from the myriad lesions that it can mimic microscopically.

Introduction

Spindle cell lesions of the head and neck are quite diverse and biologically and clinically highly variable. Some are highly malignant while many others are benign and/or simply reactive in nature. Spindle cell lesions can occur in head and neck skin, in the soft tissues of the scalp, orbit, submucosa, and neck, and along the upper aerodigestive tract (UADT) mucosa. The most common spindle cell lesion presenting along the UADT mucosa is spindle cell carcinoma (SpCC), which has many unique and challenging clinical and pathologic features. The spindle cell or sarcomatoid component of this tumor can mimic numerous other reactive, benign, and malignant lesions (Table
It is this feature that makes SpCC one of the most interesting and challenging of all head and neck tumors. While it is the most common malignant lesion to present here, this certainly does not mean that what is sitting on your microscope stage tomorrow morning is not a rare mucosal presentation of one of these other lesions. Keeping this in mind, this review will cover SpCC of the UADT, drawing particularly from five main clinicopathologic studies encompassing 326 cases(1-5), review several of the non-neoplastic and benign/low grade lesions that can mimic it, and finally discuss how to differentiate SpCC from them.

Table 1 Differential diagnosis for spindle cell lesions presenting at UADT mucosal sites.

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign or Low Grade</th>
<th>Non-Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spindle Cell Carcinoma</strong></td>
<td>Nodular Fasciitis</td>
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</tr>
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<td>Kaposi’s Sarcoma</td>
<td>Solitary Fibrous Tumor</td>
<td>*Contact Ulcer</td>
</tr>
<tr>
<td>Other sarcomas: Angiosarcoma, Synovial Sarcoma, MPNST</td>
<td>Ossifying and Non-Ossifying Fibroma</td>
<td>Giant Cell Fibroma</td>
</tr>
</tbody>
</table>

*Lesions covered in this review.

Discussion

Spindle Cell Carcinoma

SpCC is the preferred term for the head and neck mucosal form of sarcomatoid carcinoma. It is a variant of squamous cell carcinoma which has spindled or pleomorphic tumor cells which simulate a true sarcoma but are epithelial in origin.(6) For years, the true nature of this spindled component was debated, leading to numerous alternate terms, including carcinosarcoma (1, 7, 8), pseudosarcoma(9), pleomorphic carcinoma(1), and metaplastic carcinoma(1), among others. Many different theories for its pathogenesis were put forward in the past, including divergent differentiation of carcinoma cells, so-called “collision” tumors where there are two separate neoplastic
clones combined in the same lesion(7), and the concept that squamous carcinoma is "driving" the proliferation of a pseudosarcomatous stromal response(9). Over time, numerous studies analyzing the morphologic(2), immunohistochemical(1, 3, 5, 10-13), ultrastructural(13, 14), and molecular(15, 16) features of SpCC have shown epithelial characteristics in the spindle cell population as well as marked genetic similarity between the spindled and squamous portions of biphasic tumors, clearly indicating that the spindle cell component represents divergent differentiation by a what is a true carcinoma(17, 18). Most SpCC are biphasic tumors. In other words, they are composed of both a conventional squamous cell carcinoma and a spindle cell or pleomorphic component(1, 11, 13). However, as many as one-third are monophasic spindled or pleomorphic tumors making the diagnosis of carcinoma more difficult.

SpCC has the same demographics as conventional squamous cell carcinoma, occurring in the sixth decade, being strongly associated with smoking and drinking, and showing a strong male preponderance(1, 2, 4, 5, 10, 11). The larynx, particularly the glottis, is the most common primary site followed by the oral cavity, specifically the tongue, floor of mouth and gingival. Less common sites are the hypopharynx, oropharynx, sinuses, and nasal cavity(4, 10, 11, 19). A significant minority of patients have a history of previous radiation to the originating site. Combining five major SpCC clinicopathologic studies, 18% of the 326 cases occurred in a previously irradiated field at an average of 7 years and as late as 16 years later(1-5). This compares with a rate of only 1% or less for conventional squamous cell carcinoma(20). Tumors of the larynx present with rather typical symptoms such as hoarseness, voice change, dyspnea, stridor, and cough(1). Tumors of the oral cavity and oropharynx present with swelling, pain, a non-healing ulcer, dysphagia, or hemorrhage(2).

A unique clinical and pathologic feature of SpCC is its macroscopic growth pattern. Greater than 90% of laryngeal and pharyngeal tumors present as polypoid and exophytic masses projecting into the lumen(1, 3, 5). The average size of laryngeal tumors is approximately 2 cm, but lesions as small as 2 mm have been reported(1, 5). In the oral cavity, the growth pattern is somewhat more variable with 50-60% of tumors being exophytic(2). The average size of oral cavity and oropharyngeal tumors is 2 cm with lesions as small as 0.6 cm reported(2, 4). The exophytic masses are usually smooth, dark brown, and lobulated with extensive mucosal ulceration. Most SpCC are biphasic tumors with areas of conventional squamous cell carcinoma admixed with areas of spindled and/or pleomorphic tumor(1, 5, 11). In the Thompson et al. study of laryngeal SpCC from the AFIP, where they performed extensive H&E levels of cases sent to them in consultation looking keenly for a conventional squamous component, they identified it in 80% of cases(1). Other studies have ranged from 60 to 90%(1, 3, 5, 11-13, 21). The spindled component usually predominates. The squamous component can be either focal dysplasia, carcinoma in-situ, or frankly invasive squamous cell carcinoma. This latter component is usually present in the stalk of the polyp, at the deepest aspect or advancing front of the tumor. When dysplastic squamous epithelium remains on the surface, the spindle cells frequently can be seen “dropping off” from its basal layer(1, 2). Surface squamous neoplasia is probably lost in many cases due to the extensive surface ulceration which is typically present.

The spindled cells may be bland and regular or may be markedly pleomorphic with multinucleated giant tumor cells. There may be a wide variety of architectural patterns including fascicular, storiform, lace-like, or myxoid and on occasion, truly definable sarcomatous differentiation, such as osteosarcomatous, chondrosarcomatous, or rhabdomyosarcomatous, may be seen(1, 2, 4, 5, 8, 10, 13, 22). Typically, the spindle cell component is more haphazard than most true sarcomas, with any fascicle formation limited and irregular. Sometimes, “transition-type” cells with a morphology in-between
the carcinoma and spindled component are seen. These cells are epithelioid but not
nested. Finally, another pitfall is where the spindle cell component demonstrates loss of
cohesion of the tumor cells and consequently mimics an angiosarcoma. This has been
described in other body sites as pseudoangiosarcomatous carcinoma(23) and has also
been reported in oral cavity SpCC(24). Mitotic activity can vary, but averages
approximately 1 per high power field with a range from 0 to over 10. Atypical mitoses
are common (seen in ~75% of cases)(1).

Immunohistochemistry has been extensively analyzed in SpCC (Table 2).
Obviously key to the diagnosis is the confirmation of epithelial differentiation in the
spindle cells. Most, but unfortunately not all, cases of SpCC will show staining for one or
more epithelial markers. The most commonly used keratin stain, AE1/AE3 or
cytokeratin, is reported to be positive in between 26 and 62% of cases(1, 5, 11, 13).
Epithelial membrane antigen (EMA) staining is reported to be positive in between 4 and
47% of cases(1, 5, 10, 11). Finally, we examined p63 staining in 19 cases of SpCC with
positive staining in 63% of cases(5). When exhaustive keratin staining was combined
with EMA staining on laryngeal SpCC, Thompson et al. found that the spindle cell
component was positive for at least one epithelial marker in only 68% of cases(1). When
we combined pancytokeratin (AE1/AE3 + CAM 5.2), EMA, and p63, only 79% of cases
were positive for at least one of them(11). These numbers are not significantly different
for cases with a clearly-identifiable mixed component of squamous neoplasia and for
those without. This leaves a significant minority of cases where there is no definitive
light or immunohistochemical evidence of epithelial differentiation. SpCC has been
shown to be positive for mesenchymal-type markers as well. Virtually 100% of cases are
positive for vimentin(1, 5, 13), and a significant minority for smooth muscle actin (31 to
33%) and muscle specific actin (15 to 42%)(1, 21).

Given the unique growth pattern and the wide morphologic variation that is
possible in SpCC, the differential diagnosis is a long one. The features of several non-
neoplastic and benign or low grade lesions in this differential will be discussed, and then
the overall picture and the features and studies used to arrive at a diagnosis will be
included at the end.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Thompson et al. 2002 - larynx</th>
<th>Lewis et al. 1997 - larynx</th>
<th>Ellis et al. 1987 - all sites</th>
<th>Zarbo et al. 1986 - all sites</th>
<th>Nakhla 1993</th>
</tr>
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<tbody>
<tr>
<td><strong>Pancytokeratin</strong>&lt;br&gt;(AE1/AE3 ± CAM 5.2)</td>
<td>32/123 26%</td>
<td>12/26 46%</td>
<td>13/21 62%</td>
<td>7/16 44%</td>
<td>1/16 6%</td>
</tr>
<tr>
<td>EMA</td>
<td>21/117 18%</td>
<td>1/26 4%</td>
<td>4/21 19%</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>p63</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
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</table>
Granulation Tissue, Polyps, and Contact Ulcers

Inflamed granulation tissue can be clinically and histologically concerning for malignancy. This is particularly true in cancer patients after radiation therapy(25). The pathologist sees many such biopsies in daily practice. Because of the heterogeneity of the clinical scenarios here, these lesions can be seen anywhere along the UADT. There are also specific clinical lesions, such as the laryngeal contact ulcer or so-called “granuloma”(26), that consist of inflamed granulation tissue(27). These are frequently seen in patients after intubation, with ongoing, severe gastroesophageal reflux disease (GERD), or with a history of overuse of their voice(28). They are almost always on the posterior true cord or vocal process of the arytenoid(27-29), but rarely can be seen in other aspects of the true cord(27).

Clinically, the concerning tissue is at the edges of a heaped-up ulcer or sometimes can be exophytic and mass-forming with a smooth surface(26-30). It is usually granular and friable. Contact ulcers occur typically on the posterior true cords and are sometimes bilateral(30). They can be as large as 3cm(27) and usually are smooth surfaced and pink-tan. Histologically, all of these lesions have a similar appearance. There is an extensively ulcerated surface covered by fibrinopurulent material. The core of the tissue is made up of numerous small vessels with plump endothelial cells. The stroma around them is loose or edematous and occasionally quite myxoid. Within it are stellate and plump myofibroblasts and endothelial cells with tapered processes and round to oval nuclei, frequently with open chromatin and small nucleoli. The nuclei are not densely hyperchromatic. There may be multinucleation and mitotic figures are scattered but not overly prominent (rarely ever more than 1 per high power field). With extremely rare exception, there should be no atypical mitoses(25, 31). There are also intermixed inflammatory cells, frequently a rich collection of neutrophils, plasma cells, and lymphocytes. The neutrophils are particularly prominent in the superficial aspects under the ulcerated surface. In longstanding contact ulcers, a prominent and more cellular fibrosis may develop(28). After radiation, there may be extreme cytologic atypia, but this is uncommon(25). All of the fibroblasts and endothelial cells are negative by immunohistochemistry for cytokeratins(11, 25) and p63(11).

Granulation tissue will resolve with the associated lesion over time. Contact ulcers will resolve on their own as well, but one must consider the inciting cause. If GERD is responsible, this must be treated for the lesions to resolve. Surgical pathologists are good at recognizing the lesions as inflamed granulation tissue, but must be aware of contact ulcers as a specific entity to remind the clinician to treat any underlying cause(27, 29).

Vocal Cord Nodule with Stromal Atypia

This peculiar phenomenon is described in only a few reports in the literature. The vocal cord nodule (or polyp) is a specific and quite common(32-34) lesion seen on the true cord at the junction of the anterior one-third and posterior two-thirds. In the reverse of almost all other UADT mucosal lesions, vocal cord nodule (VCN) is much
more common in women(32) and is related to vocal abuse. Clinically, patients present with hoarseness and on laryngoscopy, the lesions are smooth, nodular, rounded, gray to yellow, and somewhat translucent (30). Most measure only a few millimeters.

Microscopically, VCN can be of four different types based on the stromal constituents: 1) myxoid 2) fibrinous 3) vascular 4) fibrous. There is often a mixture of different patterns(35). The stroma is loose and, for myxoid and fibrous types, has widely scattered, bland spindle cells. The vascular type has numerous small vessels in the stroma with some hemorrhage, and the fibrinous type has large lakes of extracellular, eosinophilic fibrin. The surface squamous epithelium is almost always intact (ulceration is quite uncommon) and may be completely normal or slightly hyperkeratotic.

Rare VCN may have atypical stromal cells that simulate malignancy(30, 36). These lesions have been described as clinically and macroscopically identical to typical VCN. Microscopically, there is a moderately cellular component of atypical fibroblasts which have relatively open chromatin and may have small nucleoli. In the reported cases, the background stroma has been myxoid and the surface mucosa intact, just as in typical VCN. There is no confluent cellularity, no collection of the cells beneath the epithelium to simulate a “cambium layer”, and no significant mitotic activity(30). The atypia is usually moderate in degree. Severe atypia has been reported in a single case report of a 1.5 cm myxoid mass on the true cord. It was excised endoscopically, and the patient was free of disease after two years of follow up. However, he was an 80 year old male smoker and nothing clearly distinguished this lesion from a small SpCC (36).

VCN with stromal atypia has not been noted to behave any different clinically than typical VCN. Excision is curative(30).

Sinonasal Polyp with Stromal Atypia

Sinonasal inflammatory polyps (IP) are a common and easily diagnosable part of head and neck pathology. However, rare cases may have stromal cells with marked cytologic atypia which may mimic true neoplasms such as a neurofibroma or a malignancy(37-39), particularly embryonal rhabdomyosarcoma. Other tumors such as SpCC, in theory, could be difficult given the polypoid growth, occasional ulceration, and marked inflammation. However, SpCC is usually relatively easily ruled out.

Typical IP are associated with long-standing rhinitis and allergy symptoms. They are non-neoplastic outpouchings of sinonasal mucosa with thickened, hyalinized basement membranes and a loose, edematous stroma with widely scattered fibroblasts and abundant mixed inflammatory cells, particularly eosinophils(40). Rare cases have marked cytologic atypia in the stromal fibroblasts(37-39). These patients have had the typical clinical history of chronic rhinosinusitis and have ranged in age from 4 to 47 years (average between 14 and 26 years)(38, 39) making them essentially no different than for typical IP.

Clinically and grossly, they have the usual appearance of IP with a glistening grey-yellow color and translucency and average size of 2 to 4 cm. Microscopically, they have a loose, edematous stroma with abundant mixed chronic inflammatory cells. There may be hemorrhage and thrombosed vessels (so called “angiomatous” features). There are areas with mildly increased cellularity. Scattered throughout, but particularly in these areas, are markedly atypical stromal cells with large, hyperchromatic nuclei, some with large, distinct nucleoli. They do not coalesce into cellular masses or collections, however, and there is no mitotic activity. Also, importantly, there is no subepithelial condensation that might mimic a “cambium layer” like that seen in a botryoid rhabdomyosarcoma(38, 39). The surface epithelium is typically respiratory and completely intact(39). However, it may be ulcerated or show squamous metaplasia.
One study has examined immunohistochemistry in IP with stromal atypia(38). In all 29 cases, the atypical cells were positive for vimentin. 62% of cases were positive for smooth muscle actin, 48% for muscle specific actin, and, surprisingly, 76% for pancytokeratin (AE1/AE3 + CK1). The cells are negative for desmin, myoglobin, GFAP, and S-100. In this thorough analysis which also included electron microscopy, the authors concluded that these cells are reactive myofibroblasts (38).

On long-term clinical follow-up, no patient has had clinically malignant disease. Polyps have recurred in a subset, but these are again removed, and the patients are otherwise fine(38, 39).

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a curious low grade tumor consisting of a proliferation of myofibroblastic cells with a variable admixture of inflammatory cells(41). It was previously thought to be reactive in nature, but recent studies have conclusively proven most cases to be neoplastic(42-45). Alternative terms include plasma cell granuloma and inflammatory pseudotumor(41). They have been reported in myriad sites but are most common in the soft tissue and viscera (particularly the lung) over a very broad age range but predominantly in children and young adults. The head and neck is a relatively uncommon site(46), particularly if one considers mucosal-based lesions. There are 15 reported cases in the larynx(41, 47-53), making it the most common of these. Other reported sites include the oral cavity(54), nasal cavity and paranasal sinuses(55-57), tonsil(58), salivary glands(59), and trachea(60-62). IMT has not been reported in the nasopharynx. In head and neck IMT, patients are usually adults, particularly for laryngeal cases(41), and although many patients present with constitutional symptoms, this is also uncommon in head and neck cases.

Clinically, IMT presents similarly to other lesions at the given sites, with hoarseness and stridor in the laryngeal cases(41). It is typically exophytic or nodular with smooth masses projecting into the lumen. Histologically, the mucosal surface may be intact, hyperplastic, or ulcerated but without dysplasia. Laryngeal lesions, in particular, are usually polypoid(41, 52, 53). IMT consists of a submucosal proliferation of spindled to stellate cells arranged in poorly formed fascicles or in a storeiform pattern. The cells can have very long cytoplasmic extensions which has been termed "spider-like"(41). The cellularity is moderately high, but overall loosely organized. The cells are typically plump but not markedly atypical. There is modest mitotic activity (rarely ever more than 3-4 per hpf) but atypical mitoses are never seen(41). The stroma is highly vascular and ranges from edematous to myxoid to hyalinized. There is abundant associated inflammation, consisting predominantly of plasma cells but also with lymphocytes and eosinophils (41, 53, 57). Immunohistochemistry is positive for vimentin, smooth muscle actin, and muscle specific actin in the spindle cells in all cases, with the actin staining ranging from diffuse to focal(41, 63, 64). Immunohistochemistry for cytokeratin is usually negative but has been reported to be focally positive in up to 60% of cases with AE1/AE3(63). Although approximately 60% of IMT are positive for the ALK-1 kinase(65, 66), most adult patient’s tumors are negative regardless of site. As would be predicted, virtually all head and neck IMT are negative(41, 46).

Most IMT pursue a benign clinical course. Patients undergo conservative resection or can also be treated with corticosteroid or non-steroidal anti-inflammatory drugs. Approximately 25% will recur locally and, although rare, IMT has metastasized(46). However, this has never been demonstrated in head and neck cases.

Differential Diagnosis of Mucosal Spindle Cell Lesions
The majority of spindle cell lesions presenting at UADT mucosal sites are straightforward to diagnose. However, there are some lesions that are quite difficult to classify. With a keen eye to the H&E morphology, attention to the clinical scenario, and judicious use of immunostains (Table 3), one can work through these difficult cases.

There are not many “absolutes” among these lesions, but there are several important points that strongly favor malignancy. Finding true squamous neoplasia, squamous carcinoma in-situ or invasive squamous cell carcinoma, blending with the lesion confirms SpCC. Obtaining deeper levels on small biopsies may be helpful to identify this. If the spindle cell lesion shows invasive growth at the periphery, has areas of dense cellularity, well-formed fascicles, or a dense collagenous background, this argues very strongly for malignancy. Lastly, individual cell features such as marked atypia in more than just scattered cells or marked nuclear hyperchromasia are very concerning. Finally, atypical mitoses, with only the rarest of exceptions(25) are not seen in benign lesions.

Features that are almost always indicative of a non-neoplastic or benign lesion include zonation or true organization, particularly of vessels in the lesion, only widely scattered nuclear atypia, lesional cells consistently having only vesicular chromatin with small nucleoli, and lack of mitotic activity. Only very rare SpCC will lack mitotic activity(1).

SpCC can be distinguished from benign, reactive granulation tissue and/or contact ulcers based on several features. The clinical scenario for granulation tissue will usually be short term (days to weeks), after treatment of some kind, such as surgery, radiation therapy, or associated with mucosal trauma. Although granulation tissue can be mass-like or polypoid, it should never be more than a 2-3 cm. SpCC usually has a longer clinical history (weeks to months), is larger than a few centimeters, and common in patients with a history of radiation for other malignancies, but only several years later, not just a few months(1, 2). On histology, the nuclei of reactive granulation tissue tend to have more open chromatin and sometimes small nucleoli. Although there is some degree of pleomorphism, it is rarely profound. SpCC nuclei, on the other hand, has hyperchromatic nuclei with much more pleomorphism. Although SpCC can be quite hypocellular, one can usually find at least focal areas of more confluent cellularity. Most SpCC will have some foci of squamous differentiation and doing additional tissue levels may be helpful to reveal it. Granulation tissue will have modest mitotic activity, but will almost never have more than 1 per high power field and will not have atypical mitoses. By contrast, SpCC usually has brisk mitotic activity and has atypical mitoses in ~75% of cases. The one glaring exception to the histologic distinction is a report of two cases of radiation-induced bizarre granulation tissue by Weidner et al.(25) where they describe ulcerated, tumefactive lesions of the postcricoid hypopharynx and right maxillary sinus. Both perfectly mimicked SpCC morphologically including very brisk mitotic activity, atypical mitoses, and no squamous neoplastic component. These lesions were negative for cytokeratin immunohistochemistry. However, since not all cases of SpCC have a squamous component or pancytokeratin reactivity, the true nature of these two lesions is not entirely clear. Immunohistochemistry for epithelial markers is negative in consistently negative in granulation tissue(11) and will be positive in approximately 70 to 80% of SpCC, specifically pancytokeratin and/or p63.

Vocal cord nodules with stromal atypia can be concerning histologically, but they will be myxoid, moderately cellular without inflammation, almost always have an intact surface epithelium, and have no mitotic activity. SpCC is typically highly mitotically active with atypical forms. Immunohistochemistry for epithelial markers is always negative in VCN, as well. Sinonasal polyps (IP) with stromal atypia also can be
concerning histologically, but they never reach a significantly dense cellularity and have no mitotic activity. Surface ulceration is uncommon in IP and virtually always present in SpCC. Interestingly, keratin immunohistochemistry is not discriminatory, being positive in the spindle cells of both lesions. The distinction lies squarely on histology, macroscopy, and clinical features.

IMT can be very difficult to distinguish from SpCC, occurring as exophytic, ulcerated, atypical spindle cell lesions projecting into the lumen of the UADT. Both lesions can be positive for cytokeratins as well (Table 3). The distinction lies in the absence of invasive growth, absence of markedly atypical cytologic features, and lack of atypical mitotic figures in IMT(41). In addition, although SpCC can have an associated chronic inflammatory infiltrate, it is rarely rich in plasma cells while this is a characteristic feature of IMT. Lastly, nodular fasciitis only rarely presents as a mucosal lesion and when it does, it is only around the oral cavity with an intact surface epithelium. The spindle cells of nodular fasciitis are plump but not atypical and although mitotic activity is brisk, there are no atypical forms. Immunohistochemistry for cytokeratins is negative (Table 3). All of these latter features are what distinguishes it from SpCC.

Table 3 – Immunohistochemistry in UADT spindle cell lesions.

<table>
<thead>
<tr>
<th></th>
<th>Cytokeratins</th>
<th>EMA</th>
<th>p63</th>
<th>SMA</th>
<th>M</th>
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<tbody>
<tr>
<td>SpCC</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
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<tr>
<td>VCN with atypia</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>IP with atypia</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
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<tr>
<td>Atypical GT &amp; Contact Ulcer</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>IMT</td>
<td>-/+</td>
<td>-/+</td>
<td>ND</td>
<td>++</td>
<td></td>
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<tr>
<td>NF</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>++</td>
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</table>

- ND = no data available.
Conclusion

There are numerous atypical spindle cell lesions which can present along the UADT mucosa. Because it is so common, spindle cell carcinoma should be strongly considered and ruled out before diagnosing one of the less common lesions. With attention to the clinical scenario, careful evaluation the H&E morphologic features, and judicious use of immunostains (Table 3), one can work through these difficult cases.

Reference List


(66) Cook JR, Dehner LP, Collins MH, Ma Z, Morris SW, Coffin CM, et al. Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor:
Spindle Cell Lesions – Neoplastic or Non-Neoplastic?

Spindle Cell Carcinoma and Other Atypical Spindle Cell Lesions of the Head and Neck

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3/08

Washington University in St. Louis
Head and Neck Spindle Cell Lesions

- **Etymology**
  - *spindle*
  - *spinel*, prop. "an instrument for spinning,"
  - from stem of *spinnan*
  - Fusiform, elongated, pencil-shaped

- **Sites**
  - Soft tissue
  - Bone
  - Mucosal
# Differential Diagnosis

<table>
<thead>
<tr>
<th><em>Spindle Cell Carcinoma</em></th>
<th>Synovial Sarcoma</th>
<th>Nodular Fasciitis</th>
<th><em>Sinonasal Polyp with Stromal Atypia</em></th>
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<td>Spindle Cell Myoepithelioma or Carcinoma</td>
<td>Glomangiopericytoma</td>
<td><em>Ulcer with Radiation-Induced Atypia</em></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Malignant Peripheral Nerve Sheath Tumor</td>
<td><em>Inflammatory Myofibroblastic Tumor</em></td>
<td><em>Vocal Cord Nodule with Stromal Atypia</em></td>
</tr>
<tr>
<td>Kaposi’s Sarcoma</td>
<td>Solitary Fibrous Tumor</td>
<td>Ossifying and Non-Ossifying Fibroma</td>
<td><em>Granulation Tissue</em></td>
</tr>
</tbody>
</table>

* To be covered in this talk
Spindle Cell Carcinoma

- Variant of squamous cell carcinoma
  - ~1% of HNSCC

- Terminology
  - Sarcomatoid carcinoma
  - Myriad others

- Pathogenesis
  - Divergent differentiation of carcinoma
Spindle Cell Carcinoma


= 326 cases
Spindle Cell Carcinoma

- Clinical features
  - M>>F; smoking; drinking
  - Previous radiation (18%)
  - Location

- Gross pathology
  - Polypoid growth
    - Larynx (95%)
    - Oral cavity (55%)
    - Hypopharynx (90%)
Spindle Cell Carcinoma
Spindle Cell Carcinoma

- Histologic features
  - Ulceration (82%)
Mucosal Ulceration
Non-ulcerated SpCC
Spindle Cell Carcinoma

- Histologic features
  - Ulceration (82%)
  - Squamous neoplastic component (81%*)
Squamous Dysplasia
Invasive Squamous Carcinoma
Spindle Cell Carcinoma

- **Histologic features**
  - Ulceration (82%)
  - Squamous component (81%*)
  - Sarcomatoid component
    - Patterns: haphazard, fascicles, storeiform, solid, myxoid, microcystic, pericytoma-like
    - Cellularity (low in 39%)
    - Malignant cartilage or bone (7%)
    - Mitotic activity (avg. 1.2 per HPF)
      - Range 0 to 10 per HPF
    - Atypical mitoses (74%)
Varying Cellularity
Spindle Cell Carcinoma

- **Histologic features**
  - Ulceration (82%)
  - Squamous component (81%*)
  - Sarcomatoid component
    - Patterns: fascicles, storeiform, solid, myxoid, microcystic, pericytoma-like
    - Cellularity (low in 39%)
  - Necrosis (14%)
  - Inflammation
Chronic Inflammation
Acute Inflammation
Other Exophytic Atypical Spindle Cell Lesions
Laryngeal Contact Ulcer

- Specific form of exuberant granulation tissue
- True vocal cord lesion
  - Posterior/arytenoid/~5% bilateral
- Etiology
  - Post-intubation
  - GERD
  - Voice overuse
Contact Ulcer
Granulation Tissue ± Radiation Atypia
Clinical photo –– exuberant GT

exuberant GT
Vocal Cord Nodule with Stromal Atypia
Vocal Cord Nodules
Vocal Cord Nodule
– Myxoid Type
Vocal Cord Nodule w/ Stromal Atypia
Vocal Cord Nodule w/ Stromal Atypia
Sinonasal Inflammatory Polyp with Stromal Atypia
Inflammatory Polyp
IP w/ Stromal Atypia
IP w/ Stromal Atypia
Inflammatory Myofibroblastic Tumor (IMT)

- **Location** - rare along UADT mucosa
  - Larynx
  - Others

- **Demographics**
  - Wide age range – average 55-60

- **ALK-1**
- **Clonality**
- **Behavior**
Inflammatory Myofibroblastic Tumor

Inflammatory Myofibroblastic Tumor
Inflammatory Myofibroblastic Tumor
Diagnostic Approach – How to Decide on Neoplasia

- **H&E histology**
  - **Features always (or almost) malignant:**
    - True squamous neoplasia in lesion *(deeper levels)*
    - Dense cellularity
    - Well-formed fascicles
    - Dense collagenous background
    - Invasive growth
    - Atypia in more than just scattered spindle/stellate cells
    - Nuclear hyperchromasia*
    - Atypical mitoses*
  - **Features always (or almost) non-neoplastic/benign:**
    - Zonation/organization
    - Only scattered nuclear atypia
    - Vesicular chromatin with small nucleoli
    - Lack of mitotic activity*

- **Gross characteristics**
  - Size
Diagnostic Approach – How to Decide on Neoplasia

- Look at everything in context of overall lesion
- Clinical features (talk to clinician)
  - Age
  - Location
    - Bilateral?
  - Rapidity of growth
  - Previous tumor
  - Prior treatment
Immunohistochemistry
- **AFIP larynx (123 cases)**
  - **Epithelial markers**
    - Keratins
      - Pancytokeratin (AE1/AE3)
      - CK 5/6
      - 34βE12
    - EMA
    - Any marker (68%)
  - **4 other major studies – 80 cases**
    - AE1/AE3 = 46% (range 29% to 62%)
    - EMA = 21%
    - Any epithelial marker = ~60-70%
  - **Mesenchymal**
    - Vimentin
    - SMA
    - MSA

<table>
<thead>
<tr>
<th>Antigen/antibody</th>
<th>No. (percentage) of positive immunoreactions in spindle cell component (n = 123)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>43/104 (41.0)</td>
</tr>
<tr>
<td>K4</td>
<td>0/104 (0)</td>
</tr>
<tr>
<td>K5/6</td>
<td>8/117 (6.8)</td>
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<tr>
<td>K6</td>
<td>9/104 (8.7)</td>
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<tr>
<td>K7</td>
<td>5/117 (4.3)</td>
</tr>
<tr>
<td>K8</td>
<td>0/104 (0)</td>
</tr>
<tr>
<td>K10</td>
<td>0/104 (0)</td>
</tr>
<tr>
<td>K13</td>
<td>7/104 (6.7)</td>
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<tr>
<td>K14</td>
<td>16/104 (15.4)</td>
</tr>
<tr>
<td>K15</td>
<td>2/104 (1.9)</td>
</tr>
<tr>
<td>K16</td>
<td>0/104 (0)</td>
</tr>
<tr>
<td>K17</td>
<td>14/104 (13.5)</td>
</tr>
<tr>
<td>K18</td>
<td>25/104 (24.0)</td>
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<tr>
<td>K19</td>
<td>5/104 (4.8)</td>
</tr>
<tr>
<td>K20</td>
<td>0/117 (0)</td>
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<tr>
<td>Epithelial membrane antigen</td>
<td>21/117 (17.9)</td>
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<tr>
<td>34βE12</td>
<td>10/117 (8.5)</td>
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<tr>
<td>Keratin cocktail</td>
<td>32/123 (26.0)</td>
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<tr>
<td>(AE1/AE3 and CK1)</td>
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<tr>
<td>CAM 5.2</td>
<td>0/122 (0)</td>
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<tr>
<td>Vimentin</td>
<td>108/108 (100)</td>
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<tr>
<td>S-100 protein</td>
<td>6/123 (4.9)</td>
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<tr>
<td>Smooth muscle actin</td>
<td>40/123 (32.5)</td>
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<td>Muscle specific actin</td>
<td>19/123 (15.4)</td>
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<td>Desmin (D33)</td>
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<tr>
<td>Desmin (DR11)</td>
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<td>CD34</td>
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<td>HMB-45</td>
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<td>Chromogranin</td>
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<tr>
<td>Glial fibrillar acidic protein</td>
<td>0/123 (0)</td>
</tr>
</tbody>
</table>

* The maximum number of tumors tested. Variable for each antibody.

Thompson, LDR, et al. *AJSP 2002*
p63 Immunohistochemistry

- Non-structural
- Multiple functions
  - Transcription factor
  - Cell signaling
- Nuclear staining
- Strong staining of squamous epithelium and all other squamous carcinomas
p63 Immunohistochemistry

- 6 of 19 cases negative for CK and EMA
  - 3/6 (50%) + for p63
- p63 staining more extensive
  - Nuclear

Table 2

<table>
<thead>
<tr>
<th>Head and Neck</th>
<th>Spindle Cell Component</th>
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<tbody>
<tr>
<td>Pan-cytokeratin (AE1/AE3 &amp; CAM 5.2)</td>
<td>5/17 29% (1.4+)</td>
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<tr>
<td>EMA</td>
<td>9/19 47% (1.8+)</td>
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<tr>
<td>MOC-31</td>
<td>3/19 16% (1.0+)</td>
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<tr>
<td>p63</td>
<td>12/19 63% (2.5+)</td>
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</table>

## Immunohistochemistry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Keratins</th>
<th>EMA</th>
<th>p63</th>
<th>SMA</th>
<th>MSA</th>
<th>Vimentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindle Cell Carcinoma</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Vocal Cord Nodule with Stromal Atypia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Inflammatory Polyp with Stromal Atypia</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Atypical Granulation Tissue &amp; Contact Ulcer</td>
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<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>++</td>
</tr>
<tr>
<td>Inflammatory Myofibroblastic Tumor</td>
<td>-/+</td>
<td>-/+</td>
<td>ND</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*ND = No Data
Summary

- Spindle cell lesions of H&N common
  - At mucosal sites, SpCC must be strongly considered
- Other atypical spindle cell lesions
  - Clinical context
  - Lack of dense cellularity or atypical mitoses
- Immunohistochemistry
References


- **Wenig BM, Heffner DK.** Contact ulcers of the larynx. A reacquaintance with the pathology of an often underdiagnosed entity. Arch Pathol Lab Med 1990 Aug;114(8):825-8.


