Original Article

A histologic approach to spindle cell lesions of salivary glands

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ABSTRACT

Spindle cell lesions of the salivary glands (SGSCLs) include a broad range of conditions, from high-grade malignancies to benign reactive alterations. Some epithelial and myoepithelial lesions in the salivary glands may take on spindle forms, although spindle cell proliferations are often associated with mesenchymal origin. Diagnostic challenges may result from a wide range of potential differential diagnoses and the substantial clinicopathological feature overlap of SGSCLs. However, it is crucial to establish precise diagnoses to provide the proper clinical care for any specific SGSCLs. Evaluation of growth patterns, cytologic atypia, and component cell border traits are crucial. Immunohistochemistry (IHC) and other ancillary tests are beneficial in situations with complex morphology. This study focuses on the histological characteristics and alternative diagnosis of typical SGSCLs that can broadly be categorized into three major groups: 1. non-neoplastic lesions; 2. benign lesions; 3. malignant lesions. Each category includes a distinct table of differential diagnosis and a panel of IHC markers and molecular tests.

Keywords: Histopathology, Salivary glands, Spindle cell lesions

Introduction

Spindle cell lesions of the salivary gland (SGSCLs) include a broad range of conditions, from high-grade malignancies to benign reactive alterations. Some epithelial and myoepithelial lesions in the salivary gland may take on a spindle form; however, spindle cell proliferations often have a mesenchymal origin. Diagnostic challenges may result from a broad range of potential differential diagnoses and the substantial clinicopathological feature overlap of SGSCLs. However, it is crucial to establish precise diagnoses to provide appropriate clinical care for SGSCLs. Evaluation of growth patterns, cytologic atypia, and component cell border traits are crucial. In cases with complex morphology, immunohistochemistry (IHC) and other supplementary tests are beneficial. This study focuses on the histological characteristics and alternative diagnoses of typical SGSCLs. The medical literature has been thoroughly searched, including Google Scholar, PubMed, and various textbooks on the pathology, surgery, and oncology of the salivary glands from 2000 to 3 July 2022.

We found 11 types of SGSCLs categorized into three main titles: 1. non-neoplastic lesions, 2. benign lesions, and 3. malignant lesions.(Table 1)

Non-neoplastic lesions (Table2)

Nodular fasciitis (NF)

NF is a benign fibroblastic/myofibroblastic proliferation that may resemble malignancy due to its tendency for fast development. Historically, it has been categorized as reactive [1]. There are just a few instances of NF affecting the parotid in any patient in the English literature [2,3]. These lesions may form at any age without a distinct sex predisposition, although they are more prevalent in the third or fourth decade of life. Most patients see a doctor for an assessment within a few months after their symptoms appear, typically starting over a few weeks [4]. IHC may provide proof to support the NF diagnosis. Smooth muscle actin IHC staining revealed cytoplasmic reactivity in spindle cells. However, due to the cells' fibrohistiocytic and myofibroblastic characteristics, IHC staining for CD68 may also be helpful when smooth muscle actin is negative. As a result, if the tumor has a history of fast growth, pathologists may search for mitotic, multinucleated, ganglion-like, or inflammatory cells like neutrophils or lymphocytes after suggesting NF in the differential diagnosis. If cytologic characteristics point to NF, IHC testing for alpha-smooth muscle actin and CD68 may be

helpful. B-catenin nuclear positive staining is the distinctive feature in fibromatosis; however, it is missing in NF [5]; hence IHC analysis of B-catenin may be helpful in the differential diagnosis between fibromatosis and NF.

Inflammatory pseudotumor (IP)

Brunn introduced IP in 1939 [6]. Only 15% of IP cases are found in the non-orbital head and neck area, with the lung and orbit being the most common sites [7, 8]. Three fundamental patterns of IPs were identified in a review of the literature that included 84 cases: (a) myxoid, vascular, and inflammatory; (b) spindle cells with lymphocytes and plasma cells; and (c) dense collagenous type resembling scar tissue. In contrast to hematologic malignancy, necrosis and mitotic features are often absent. IgG4 disease must meet the following criteria according to the Centers for Disease Control (CDC): a clinical examination demonstrating localized edema; blood tests demonstrating high serum IgG4; and histology demonstrating lymphocytic infiltration with $IgG^+/IgG4^+$ cells >40% [10]. Spindle cells, plasma cells, lymphocytes, fibroblasts, myofibroblasts, histiocytes, and an inflammatory infiltration are the most important characteristics of IP on a pathologic examination. When IP is examined using immunohistochemistry, it often exhibits positive cytokeratin, smooth muscle actin, ALK, CD20 stains, and an increased number of $IgG4^+$ plasma cells [11].

Benign lesions(table3)

Schwannoma

Fascial nerve schwannomas are uncommon, with 83.6% occurring in the temporal bone [12]. They constitute a negligible proportion of intraparotid neoplasms [13]. Schwannoma accounts for 0.5–1.5% of all parotid gland tumors [14]. In close proximity to the facial nerve, schwannoma often manifests as a spherical, encapsulated, pink-to-dark mass with defined boundaries and a diameter <5 cm [15]. Histologically, the tumor is a well-encapsulated lesion with pushing borders, without the invasion of the surrounding tissue within the mass, the presence of a biphasic tissue architecture made up of areas of relative hypocellularity with abundant acellular material punctuated by bland, cigar-shaped nuclei and ill-defined cytoplasm with occasional nuclear palisading and Verocay body formation (Antoni A architecture) [16]. In addition to perivascular hemosiderin and hyaline alteration of vessels, perivascular hemosiderin may indicate schwannoma. Larger lesions may exhibit significant cystic degeneration and lipid-laden macrophages or xanthoma cells [15].

If histology cannot provide a precise diagnosis, IHC may assist in reducing uncertainty and narrowing the differential diagnosis. S100, smooth muscle actin, CD68, and pan-cytokeratin IHC may be performed to exclude alternative diagnoses. While the other pan-cytokeratin has negative findings, with the possible exception of areas where they may focally stain for their intended target, S100 staining is predicted to be significantly positive . A ki67 proliferative index is expected to be less than 1%. Leiomyoma is meant to be ruled out using a smooth muscle antigen stain. Due to the abundance of xanthomatous alteration within the schwannoma, CD68 may be utilized to exclude the likelihood of a histiocytic lesion. A pan-cytokeratin stain may be used to rule out a spindle cell carcinoma or another tumor with epithelial origin. Calretinin, another stain, may be useful because it has been demonstrated to be useful in separating schwannoma from neurofibroma since schwannoma exhibits widespread staining whereas neurofibroma may stain weakly or not at all [17].

Neurofibromas

Neurofibromas generally are non-encapsulated, poorly defined masses with hypocellular architecture on a myxoid background, bland spindled cells with low mitotic activity, and thick, rope-like collagen strands. In contrast to schwannoma, which tends to push axons aside with development, neurofibroma is intimately linked with the nerve, and one may often see axons on histology. In addition, mast cells may be found inside the stroma. On IHC, a neurofilament protein stain will assist in identifying axons inside the lesion, and variable, moderate S100 staining will be seen [18]. Furthermore, as indicated in schwannoma, schwannoma stains diffusely, but neurofibroma stains weakly and focally [17].

Myoepithelioma

The description of a salivary neoplasm resembling a myoepithelioma was first attempted in 1943 [18].

Less than 1.5% of all tumors of the salivary glands are myoepitheliomas [19]. The parotid gland (4%) and the palate [20, 21] are the sites of most myoepitheliomas of the head and neck region [20, 21]. Myoepitheliomas have a similar age and sex distribution as mixed tumors. Myoepitheliomas are asymptomatic, slowly expanding masses. Parotid lesions seldom cause the palate to ulcerate, nor do they result in facial nerve dysfunction or cervical lymphadenopathy [21]. At first glance, they seem to have a solid, tanned, or yellow-tanned, shining cut surface. Several morphologic forms have been reported, including spindle-cell, hyaline (plasmacytoid), epithelioid, and clear-cell [22].

Spindle cell-type tumors may be confused for lesions of fibroblasts, Schwann cells, or smooth muscle cells due to their stroma-like appearance [23]. Actin and keratin microfilaments may be seen ultrastructurally and immunohistochemically [24]. Additionally, most myoepitheliomas exhibit p63 and p40 reactivity, whereas S100 may be positive or negative [25](figure 1). The neoplastic myoepithelial cells often have immunohistochemical reactivity for keratin, both forms of the S100 protein, p63, p40, actin, and, in certain instances, vimentin, calponin, and myosin [26-33]. Notably, many myoepitheliomas do not respond to smooth muscle actin in this way [34].

Solitary fibrous tumor (SFT)

SFT is one of the uncommon soft tissue tumors of the parotid gland. SFT is a typically encapsulated, non-metastasizing lesion that is believed to be a subtype of hemangiopericytoma. Few instances of SFT of the parotid gland have been described in the English literature, making it uncommon [36,37]. SFT affects both men and women equally often [35,38-40]. The ages of the parotid gland SFT patients varied from 11 to 79 [36, 37]. Clinically, individuals with parotid gland SFT often have a well-defined, palpable, slowly-growing, painless mass that has frequently been present for a sizable amount of time [36, 37, 41]. The tumors were encapsulated in varying degrees. Grossly speaking, the tumors were defined as hard, white-tanned, or gray masses [38, 42]. Numerous histologic characteristics, such as alternating hypercellular and hypocellular to fibrous regions, are recognized as diagnostic indicators. With multiple medium-sized ramifying vessels, the tumor cells are organized in fascicular, storiform, or fibrosarcoma-like patterns. The walls of the vessels might exhibit thickening or hyalinization. The tumor cells have a fusiform appearance and range in shape from round to spindle [43]. Collagen that was deposited between the neoplastic cells was keloid-like to wavy. There was no necrosis; however, mitosis was evident [40]. The immunophenotype of SFT seems consistent, independent of its location in the body. The neoplastic cells exhibit near-uniform reactivity with vimentin and CD34, although most cases also exhibit reactivity with bc12 and CD99. CD34 is the most essential and sensitive diagnostic marker for SFT but is not always positive [36, 45, 46]. A lot of the tested indicators were negative. Specifically, the absence of S100 protein, cytokeratin, EMA, CAM5.2, p63, desmin, smooth muscle actin, smooth muscle myosin chain, and CD117 will aid in the differential diagnosis of the parotid gland [36, 37, 39, 46].

Malignant lesions(Table 4)

Malignant myoepithelioma

Numerous malignant instances of myoepithelioma with spindle cells have been identified [47-51]. Malignant tumors are also known as malignant myoepithelial carcinoma. They are generally distinguished by their infiltrative growth, enhanced cellularity, mitotic activity, necrosis, and cytologic atypia [52]. A common growth pattern consists of massive invasive lobules with necrosis in the center. These malignant myoepitheliomas are rare, making up only around 2% of salivary gland malignancies. They may develop as the malignant transformation of a myoepithelioma, benign mixed tumor, basal cell adenoma, or de novo [53,54].
Despite being present in all salivary gland locations, they are more often seen in the parotid gland. Tumors with high mitotic activity, necrosis, and pleomorphism tend to behave as high-grade carcinomas, with no official grading system [51]. Immunohistochemical findings are the same as myoepithelioma.

Malignant peripheral nerve sheath tumor (MPNST)

Over 95% of mesenchymal tumors affecting the main salivary glands [55–57] comprise 2–5% of all salivary gland tumors. MPNST prevalence in parotids is very low, with a 1–58% range. If the tumor comes from a pre-existing benign nerve sheath tumor or neurofibroma, or the tumor shows a constellation of histological signs of Schwann cell differentiation and is satisfied, a sarcoma is presumed to be MPNST. MPNST is often diagnosed using immunohistochemistry in conjunction with histology, highlighting the differentiation of Schwann cells in this tumor. Approximately 50–90% of MPNST cases have S100 protein positivity [60, 61]. Schwannoma [62] is the main diagnosis to rule out. Although MPNST often has infiltrating boundaries and is not encapsulated, it might superficially seem well-circumscribed. Histologically, a range of patterns may be seen, such as relatively monomorphic spindled nuclei grouped in a herringbone or storiform pattern, more differentiated epithelioid tissue, or a schwannian look with nuclear palisading. Geographic necrosis and frequent mitoses are common. According to reports, MPNSTs may develop from cranial nerves, often after previous radiation treatment [63]. Furthermore, although MPNSTs will have localized S100 staining, this is often only seen in regions with a more epithelioid appearance [64].

Inflammatory myofibroblastic tumor (IMT)

An IMT is made up of myofibroblasts that are proliferating against a backdrop of lymphocytes, eosinophils, and chronic inflammatory cells. Initially, it was believed that IMT was a reactive process brought on by infectious agents such as the Epstein-Barr virus, *Actinomyces*, and human herpesvirus 8 [67–69]

Desmoplastic malignant melanoma in the parotid

Despite making up 15% of all malignant neoplasms and 25% of malignant melanomas occurring in the head and neck area, malignant melanoma affecting the parotid gland is quite uncommon (70]. The majority of melanomas that affect the parotid gland are believed to spread from cutaneous sites in the head and neck region, according to a literature review [71]. Nevertheless, occasional instances of primary malignant melanoma believed to originate in the parotid gland have been described. If neuromelanin pigmentation is absent, tumors with a prominent spindle cell phenotype may be difficult to distinguish from spindle cell carcinomas or even pleomorphic sarcoma. Immunohistochemistry might be helpful in certain situations to identify the origin of the tumor. Most melanomas do not show cytokeratin markers and, instead, stain favorably with an antibody to the S100 protein. In certain circumstances, staining with an anti-HMB-45 antibody may be a helpful adjustment [72–74].

Spindle cell squamous cell carcinoma (SCSCC)

The parotid gland is most often affected and accounts for 0.4% of all malignant salivary gland tumors that are squamous cell carcinomas (SCC) [75–77]. Spindle and/or pleomorphic cells are characteristics of SCSCC, a rare type of SCC [78].

Due to its mesenchymal appearance, SCC without an underlying squamous component is challenging to diagnose since it might be mistaken for a sarcoma [79–81]. The epithelial origin of this tumor may be confirmed by immunohistochemical testing. These tumor cells express keratin or other epithelial markers, such as CEA and EMA [82, 83]. Vimentin may be the sole identifiable sign when cytokeratin expression has completely disappeared. However, the absence of an epithelial marker does not eliminate the likelihood of an SCC. A conversion process in which the tumor gradually loses its epithelial phenotype and gains some mesenchymal matrix, such as fibronectin and type I collagen, and expresses mesenchymal-type integrins, such as fibronectin receptor 5-B, results in the focal co-expression of cytokeratin and vimentin, which has been seen in 20–50% of cases [84].

Additionally, non-epithelial malignancies such as malignant melanoma, myoepithelial carcinoma, and leiomyosarcoma may exhibit this co-expression [85].

Monophasic synovial sarcoma (MSS)

The fourth most frequent kind of salivary gland sarcoma is synovial sarcoma (SS) [89]. The literature describes the monophasic and biphasic SS subtypes. The co-expression of markers in MSS and the presence of spindle cells make diagnosis difficult. It is challenging to diagnose MSS only based on morphology. Therefore, further research employing cytogenetics and immunohistochemistry is required. In addition to cytokeratin and vimentin co-expression, this form of tumor exhibits a variable expression of CD99 (60–70%) [86–87]. According to a cytogenetic investigation, the chromosomal translocation t(X, 18) is present (p11.2,q11.2). This translocation is considered a distinctive genetic defect for synovial cell sarcoma as it is present in >90% of these tumors [88].

Finding a translocation between chromosomes allows for a differential diagnosis with other spindle cell cancers, such as fibrosarcoma, leiomyosarcoma, and neurogenic sarcoma. This is especially true for the monophasic variety of SS [90].

Conclusion

Salivary gland spindle lesions (SGSCLs) are heterogeneous lesions with mesenchymal, melanocytic, epithelial, or myoepithelial origins and range from benign reactive processes to aggressive malignant tumors. There are many potential differential diagnoses, ranging from primary lesions of the salivary glands to metastases. Clinical history, radiographic findings, immunohistochemical patterns, and molecular abnormalities are helpful. However, because of overlapping features, care should be exercised when interpreting the results of ancillary examinations.

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