Original Research

Diagnosing Hypocellular Collagenized Spindle Cell Squamous Carcinoma of the Head and Neck: A Rare Subtype with Misleading Histologic Features

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Spindle cell squamous carcinoma of the head and neck (SCSCHN) is a high-grade variant of squamous cell carcinoma (SCC) that is histologically characterized by the presence of a conventional SCC and an associated malignant spindle cell stromal component. Typically, the spindle cell infiltrate expresses epithelial markers such as cytokeratin and is hypercellular and pleomorphic and readily identifiable as malignant. However, the stromal component in the hypocellular collagenized variant of SCSC is very hypocellular with prominent collagenization. In addition, cytokeratin immunoreactivity can be absent in up to 40% of cases of SCSC, and the conventional SCC component may be absent. These features create diagnostic challenges, and literatures addressing these issues are lacking. We describe the clinical, pathologic and immunohistochemical features of three cases of hypocellular collagenized SCSCHN and discuss major differential diagnoses that will allow for its proper identification.
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Key Words: *spindle cell squamous carcinoma, head and neck, hypocellular collagenized, clinicopathologic*

INTRODUCTION

The most commonly encountered neoplasm of the head and neck is squamous cell carcinoma (SCC), which comprises more than 90% of all head and neck malignancies. Squamous cell carcinoma can present as multiple histopathologic variants, particularly verrucous carcinoma, basaloid SCC and spindle cell squamous carcinoma (SCSC). Spindle cell squamous carcinoma of the head and neck (SCSCHN) is the rarest subtype, and most commonly presents as a biphasic high-grade variant, consisting of a spindle cell component in intimate association with a conventional SCC.[1] The spindle cell component usually manifests as undifferentiated pleomorphic spindle-shaped cells, whereas the squamoid component can range from invasive carcinoma to in-situ carcinoma or even dysplastic epithelium. In addition, the epithelioid component can demonstrate varying degrees of keratinization. However, not infrequently, a clear-cut differentiated SCC component may not be present at all, and immunohistochemical stain for cytokeratin may be negative in up to 40% of the cases. To complicate its identification even more, a subset of SCSC lesions have a prominent collagenized stroma and are very paucicellular, the so-called hypocellular collagenized SCSC, which may create diagnostic challenges in recognizing these lesions as malignant neoplasms. To our best knowledge, there are no clear diagnostic criteria and guidelines for evaluating these lesions in the literature. We hereby describe three cases of hypocellular collagenized SCSCHN, with an emphasis on the clinical, pathologic and immunohistochemical features that will allow for an accurate diagnosis.

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METHODS

Case Selection

We retrospectively searched the database of the Department of Pathology at Beth Israel Medical Center for cases of hypocellular collagenized SCSCHN that had immunohistochemical studies performed as part of the routine clinical work-ups between January 1990 and August 2007. Cases with hypercellular stroma or entirely necrotic and fragmented tissue samples were excluded. The clinical data were obtained by review of the medical records. The study was conducted according to an institutional review board-approved protocol.

Histologic Evaluation and Immunohistochemical Analysis

We reviewed archived hematoxylin and eosin (H&E)-stained biopsy sections for each case. We also performed immunohistochemical stains using formalin-fixed, paraffin-embedded tissue sections and antibodies against AE1/AE3 (Signet/Covance, Princeton, NJ; 1:200), CAM5.2 (Becton-Dickinson, Franklin Lakes, NJ; 1:10), CK907 (34bE12; DAKO, Carpinteria, CA; 1:50), p63 (Lab Vision/NeoMarkers, Fremont, CA; 1:200), and p16

(Novocastra/Leica Microsystems, Bannockburn, IL; 1:20). All studies were performed using the Bond Polymer High Contrast with Counterstain detection kit (Novocastra/Leica Microsystems), an automated system for staining sections of formalin-fixed, paraffin-embedded tissues. This kit is a biotin-free, polymeric horseradish peroxidase-linked antibody conjugate system for the detection of tissue-bound mouse and rabbit immunoglobulin G as well as some mouse immunoglobulin M primary antibodies. This detection system avoids the use of streptavidin and biotin, and therefore eliminates the nonspecific staining that could occur as a result of endogenous biotin in the sample.

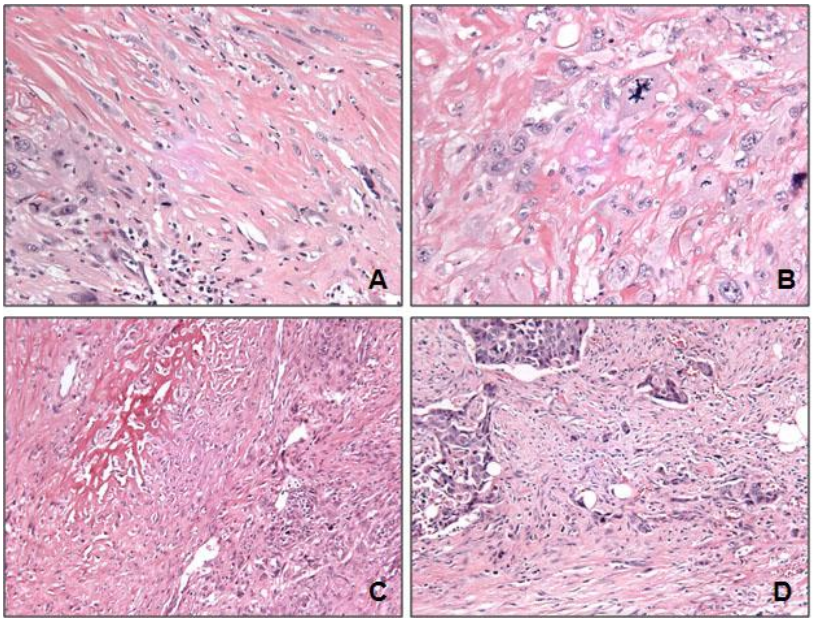

Figure 1. A case of hypocellular collagnenzied spindle cell squamous carcinoma. **(A)** Lower power magnification shows markedly paucicellular and collagnenized stroma with nuclear pleomorphism (case 2, H&E, 200x). **(B)** Higher power magnification reveals spindle-shaped cells with pleomorphic nuclear contours, prominent nucleoli and atypical mitotic figures (case 3, H&E, 400x). **(C)** Focal osseous metaplasia (case 1, H&E, 100x). **(D)** Conventional squamous cell carcinoma component (case 1, H&E, 100x).

RESULTS

Clinical Findings

We identified three cases of hypocellular collagenized SCSCHN out of 60 cases of SCSCHN (5%) between 1990 and 2007. All three patients were men, two were 62 years old and one was 65 years old at the time of initial diagnosis. None of the patients had a history of prior head and neck malignancies or treatment. The status of human papillomavirus was not available for all three patients. Symptoms at presentation varied according to the location and size of the lesions and included hoarseness, odynophagia, dysphagia and retropharyngeal obstruction. All tumors presented with a polypoid growth pattern. In two cases, the lesions were localized to the laryngeal true vocal cord. In the other case, it arose at the base of the tongue. Both laryngeal lesions protruded into the laryngeal space causing a partial obstruction of the laryngeal lumen and an ulcerated surface that was apparent on gross examination.

Morphologic Findings

At low power magnifications, all three lesions appeared polypoid in configuration and were characterized by a prominent collagenized stroma (**Figure 1A**). At higher magnifications, a variably cellular spindle-shaped component and an epithelioid cell proliferation were noted within the collagenized matrix. Despite the relatively paucicellular nature of the infiltrate, the individual cells showed marked nuclear pleomorphism with hyperchromasia and increased nuclear-to-cytoplasmic ratios. Increased mitotic figures including multiple atypical forms were identified (**Figure 1B**). The cytoplasm appeared fibrillary and showed basophilic to eosinophilic staining. A heterologous focus was identified in one case, consisting of benign-appearing bone (osseous metaplasia) without osteoblastic rimming (**Figure 1C**). Foci of differentiated SCCs were identified in two cases, including keratinizing dysplasia and an invasive SCC component (**Figure 1D**).

Immunohistochemical Analyses

The immunohistochemical profile of hypocellular collagenous variant of SCSCHN was comparable to that of the conventional cellular type (**Table 1**). There was variable reactivity to cytokeratins (Figure 2A-2C) ranging from areas with faint or no staining to rare foci with prominent staining. All three cases expressed AE1/AE3 and CK907/34bE12, two high molecular weight cytokeratins. One case additionally expressed CAM 5.2, a low molecular weight cytokeratin. Interestingly, all three cases were positive for p63 (**Figure 2D**), a homologue of the tumor suppressor p53 that is highly expressed in the basal layers of many epithelial tissues, and all three cases were negative for the tumor suppressor p16.

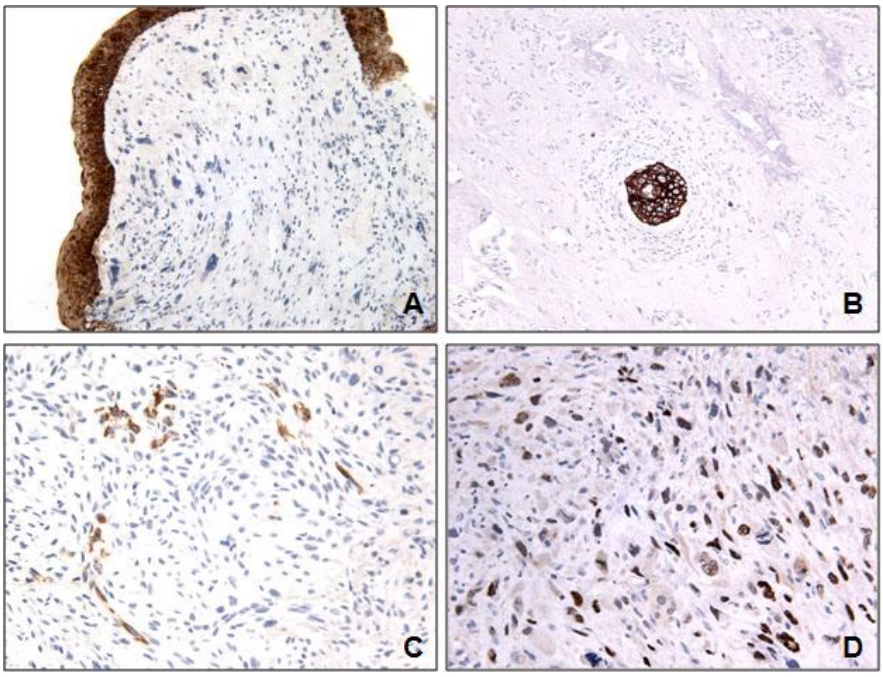

Figure 2. A case of hypocellular collagnenzied spindle cell squamous carcinoma. Immunohistochemical stain for AE1/AE3 shows that both the epitheliod component (**A**, case 2 and **B**, case 1) and spindle cell component (**C**, case 2) are positive (100x). (**D**) p63 stain shows positive nuclear staining in the pleomorphic spindle cells (case 3, 100x).

Table 1. Immunophenotypic profile of three cases of hypocellular collagenized spindle cell squamous carcinoma.

Case	Cell Type	AE1/AE3	CAM 5.2	CK 907	p63	p16
1	Spindle	+	±	+	+	-
	Epithelial	+	+	+	+	-
2	Spindle	+	-	+	+	-
	Epithelial	+	-	+	+	-
3	Spindle	+	-	+	+	-
	Epithelial	+	-	+	+	-

DISCUSSION

The majority of patients with SCSCHN are men (85%) in the sixth to eighth decade of life. These tumors can occur anywhere in the upper aerodigestive tract with a predilection for the laryngeal glottis and are characterized by polypoid or exophytic growth patterns.[2] The name "spindle cell squamous carcinoma" may be an oxymoron, manifested by the innumerable names and synonyms given to this entity; the most common being sarcomatoid carcinoma, carcinosarcoma, pleomorphic carcinoma, metaplastic carcinoma, pseudosarcoma and collision tumor. Nevertheless, the histopathologic features of SCSC are well-established and include: (1) the presence of a conventional SCC component, and (2) an associated malignant spindle-shaped and pleomorphic cell proliferation. Typically, the spindle-shaped and pleomorphic cell infiltrate is hypercellular and characterized by marked nuclear pleomorphism, increased mitotic activity, and atypical mitotic figures. The SCC component can present in the form of dysplasia, carcinoma in-situ and/or invasive carcinoma. Both components are Immunoreactive to cytokeratins in over half of the cases, which supports its epithelial origin and serves as a useful marker for the diagnosis of SCSC.[3]

The so-called hypocellular collagenzied variant of SCSC, as illustrated in our study, is characterized by a relative paucity of cellularity combined with a prominent collagenized stroma, but nuclear pleomorphism and mitotic figures are usually present.[4] This may create some diagnostic difficulties, especially when a clear-cut differentiated SCC is less apparent or entirely devoid, as occurs in tumors with surface ulcerations and associated fibrinoid necrosis, granulation tissue and mixed acute and chronic inflammation which may preclude the identification of any otherwise identifiable epithelial component. At this point, immunohistochemical stains may not be useful. Moreover, the absence of cytokeratin immunoreactivity has been reported in approximately 40% of the cases of SCSC.[5] This may be further complicated by the presence of immunoreactivity to certain mesenchymal markers (e.g., vimentin, desmin) that has been reported in some cases.[2,6,7]

The major differential diagnoses include various reactive (myo)fibroblastic lesions and sarcomas. The pathologists should be aware of this entity, especially the lesion's ability to mimic other disease processes. Multiple biopsy samplings, serial deeper sections, as well as immunohistochemical stains using multiple epithelial markers may be helpful to identify scant epithelial component. In cases with no apparent squamous cell differentiation by light microscopy or by immunohistochemistry, electron microscopy might reveal tonofilaments and/or desmosome-like structures to prove the epithelial component and distinguish it from sarcomas. Multiple sampling and sectioning may also be helpful to identify areas with nuclear pleomorphism and/or mitotic figures in the hypocellular stroma in order to rule out a reactive process. Therefore, it is crucial for pathologists to thoroughly examine these biopsy samples and work closely with clinicians to identify any other lesions in order to appropriately classify this disease process.

Immunoreactivity to p63 in both the epithelial and stromal components of this tumor may serve as another clue in rendering the correct diagnosis. Transcription factor p63 is a homolog of the tumor suppressor p53, and is critical for the development of stratified epithelial tissues.[8-10] Its expression therefore supports the theory of an epithelial origin of this tumor, and argues against a diagnosis of sarcoma. It is also implicated in tumor formation and progression in stratified epithelia.[8-10] Ansari-Lari et al showed that the epithelial and spindled components of SCSC demonstrated identical patterns of p53 protein expression, suggesting that both components share a common pathway of tumorigenesis despite their conspicuous divergence at the phenotypic level.[11] Therefore, p63 and p53 could be a useful addition to the standard immunohistochemical panel for SCSC.

In addition to the aforementioned difficulties in distinguishing these lesions from a reactive condition or a sarcoma, these neoplasms can present with multiple heterologous components as well. In one of our cases, an osseous component was identified. Another unique finding is that the morphologically mesenchymal spindle cell component may express a dual antigen profile characteristic of both epithelial and mesenchymal cells. This could be explained by a possible sarcomatous metaplasia of the squamous component and/or an epithelial-mesenchymal transition that could lead to the different morphologic appearance of the spindle cell component.[12,13] This anaplastic-like progression has also been supported by a mouse model demonstrating the up- and downregulation of different growth factors and chemokine receptors in spindle cell squamous carcinoma.[14] These changes have been considered a stromal activation associated with the reaction between the malignant process and the patient's host response and bear no prognostic significance.[15]

In conclusion, it should be recognized of the existence of a hypocellular collagenized variant of SCSC, and its capability to mimic a variety of reactive processes and sarcomas. Multiple sampling and sectioning, identification of nuclear pleomorphism and mitotic figures in the stromal component, immunostains using a panel of cytokeratins, electron microscopy to identify residual epithelial component, as well as working closely with clinicians to obtain information on its clinical behavior will facilitate an accurate diagnosis.

CONFLICT OF INTEREST
None.

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