SQUAMOUS CELL CARCINOMA OF THE LARYNX WITH SARCOMA-LIKE STROMA

A CLINICOPATHOLOGIC ASSESSMENT OF SPINDLE CELL CARCINOMA AND "PSEUDOSARCOMA"

HENRY D. APPELMAN, M.D., AND HAROLD A. OBERMAN, M.D.

Department of Pathology, The University of Michigan, Ann Arbor, Michigan 48104

Spindle cell neoplasms of the upper respiratory tract and oral cavity are unique lesions which pose not only therapeutic problems for the clinician but also difficult interpretive problems for the pathologist. Because of their bizarre microscopic appearance they have frequently been interpreted as sarcomas; however, recent studies suggest that most of these neoplasms are squamous cell carcinomas with a spindle cell growth pattern. Because of the dispute as to whether the spindle cell component is stromal or epithelial in origin, and inflammatory or neoplastic, such lesions have occasionally been termed "pseudosarcomas," "carcinosarcomas," or "spindle cell carcinomas."

Many reports of these lesions have noted the paradox of long survival in patients whose tumors manifested microscopic features of malignancy. There have also been sporadic reports of "true sarcomas," usually fibrosarcomas, of the upper respiratory tract, often associated with a favorable outcome. Although authentic malignant mesenchymal neoplasms surely must arise in this location, it is reasonable to speculate whether or not most of these sarcomas are actually carcinomas with prominent spindle cell patterns.

The larynx, typical of the upper respiratory tract, is often the site of such peculiar lesions. In the following study, the histologic spectrum of these neoplasms is presented, and the relation between their gross, microscopic, and clinical features is assessed.

REVIEW OF LITERATURE

Lane\(^2\) first used the term "pseudosarcoma" to refer to a presumably non-neoplastic connective tissue response, suggestive of sarcoma, adjacent to a squamous cell carcinoma. He reviewed 10 such neoplasms from the mouth and upper respiratory tract, including 4 from the larynx. All were polypoid and intimately associated with squamous cell carcinoma, often inconspicuous and frequently \textit{in situ}. In no instance did the stroma metastasize with the carcinoma. Nevertheless, he believed that the absence of mingling of stromal and epithelial elements militated against their being carcinosarcomas, and the favorable outcome of inadequately treated lesions precluded their being highly malignant carcinomas. He concluded that the sarcoma-like areas were non-epithelial, distinct from the associated carcinoma, and most suggestive of a reparative process.

Sherwin and associates\(^3\) reported 3 polypoid spindle cell carcinomas, 2 primary cases in the tongue and 1 in the larynx. They disliked the term "pseudosarcoma" because it had also been applied to fibromatoses not associated with carcinoma. They concluded that the sarcoma-like areas were neoplastic. In support of this deduction, they illustrated transition of infiltrative carcinoma to the spindled elements. Moreover, intracytoplasmic droplets, similar to those seen in cells of squamous cell carcinoma in tissue culture, were present in the spindle cells. They further concluded that the favorable outcome of these polypoid lesions was a result of their superficial situation which allowed more complete removal. In contrast, Lane\(^2\) doubted such a transition between carcinoma and stroma. Most of the patients reported by Lane\(^2\) and by Sherwin and co-workers\(^3\) were men whose average age was in the late fifties.

Ash and Raum,\(^1\) discussing mesenchymal neoplasms of the larynx, mentioned changes in the overlying epithelium, including squa-
## TABLE 1
### SUMMARY OF FINDINGS IN 11 PATIENTS WITH BIZARRE SQUAMOUS CELL CARCINOMAS OF LARYNX

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting Symptoms (Duration)</th>
<th>Location of Tumor</th>
<th>Gross Findings</th>
<th>Microscopic Findings</th>
<th>Initial Treatment</th>
<th>Subsequent Course*</th>
<th>Follow-Up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>Hoarseness, weight loss, 1 yr.; dyspnea, 1 wk.</td>
<td>Right ventricle; right true cord</td>
<td>Fungating filled glottis</td>
<td>Fusion of SCC† and spindle cells</td>
<td>8000 r</td>
<td>Local recurrence, 10 mo.</td>
<td>Died, 1.5 yr.</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>M</td>
<td>Hoarseness, 3 mo.; otalgia</td>
<td>Anterior half left true cord</td>
<td>Polypoid, 1 cm. diameter</td>
<td>SCC with demarcated sarcoma-like areas</td>
<td>Hemilaryngectomy 7600 r</td>
<td>Local recurrence, 5 mo.; radium implant</td>
<td>Alive and well, 15 yr.</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>Hoarseness, difficulty swallowing, 3 mo.</td>
<td>Base of epi-glottis to right arytenoid</td>
<td>Polypoid 2 cm. diameter</td>
<td>Fusion of SCC and spindle cells</td>
<td>Snare excision. 7200 r</td>
<td>? cervical node metastasis, 1 mo., 2500 r</td>
<td>Died, 2.5 yr.</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>None; found 33 mo. after x-ray treatment of tonsillar ca. (2000 r)</td>
<td>Right arytenoid</td>
<td>Sessile, &quot;large&quot;</td>
<td>SCC intermixed with spindle cells; osteoid and chondroid areas</td>
<td></td>
<td></td>
<td>Died, 5 mo.</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>M</td>
<td>Hoarseness, 3 mo.</td>
<td>Left true cord</td>
<td>Sessile</td>
<td>Predominant bizarre spindle cell neoplasm</td>
<td></td>
<td></td>
<td>Died, 8 mo.</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>M</td>
<td>Difficulty swallowing, 6 mo.</td>
<td>Hypopharynx, false cord</td>
<td>Sessile</td>
<td>SCC intermixed with spindle cells; osteoid and chondroid areas</td>
<td>X-ray (? dose)</td>
<td>Local recurrence, 3 mo.</td>
<td>Died, 5.5 yr., cervical node metastasis</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>M</td>
<td>Dysphagia, 7 mo.</td>
<td>Right true cord</td>
<td>Sessile, 2 x 3 cm.</td>
<td>SCC intermixed with spindle cells; osteoid metaplasia</td>
<td>5500 r</td>
<td>Local recurrence, 4 yr.; total laryngectomy</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>M</td>
<td>Hoarseness, 9 mo.; neck pain, 1 mo.</td>
<td>Right true cord</td>
<td>Polypoid</td>
<td>Fusion of SCC and spindle cells</td>
<td>Hemilaryngectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Sex</td>
<td>Presentation</td>
<td>Lesion Characteristics</td>
<td>Histology</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>M</td>
<td>Hoarseness, 2 yr.; dysphagia, 3 mo.</td>
<td>Both true cords and commissure</td>
<td>Fusion of SCC and spindle cells</td>
<td>Total laryngectomy</td>
<td>Died, 10 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>F</td>
<td>Hoarseness, dysphagia, weight loss, 6 wk.</td>
<td>Right ventricular fold</td>
<td>Fusion of SCC and spindle cells</td>
<td>Total laryngectomy</td>
<td>Died, 2.5 yr.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>M</td>
<td>Hoarseness, 10 mo.</td>
<td>Right true cord</td>
<td>SCG with demarcated sarcoma-like areas</td>
<td>Total laryngectomy</td>
<td>Alive and well, 1.5 yr.</td>
<td></td>
<td></td>
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</tbody>
</table>

* Duration after initial treatment.
† Squamous cell carcinoma.
mous metaplasia and even squamous cell carcinoma. Saphir believed such tumors were either anaplastic carcinomas with severe pleomorphism of tumor cells, or marked stromal reactions to carcinomas. Clerf and later Diehl, in discussions of laryngeal sarcomas, noted that the peripheral portions had a relatively benign histologic appearance, in contrast to the more anaplastic central areas. Nevertheless, they believed that the former were more reliable for predicting the behavior of the entire neoplasm.

Frank and Lev examined 62 laryngeal carcinomas and found that almost one-half of them manifested a whorled configuration of spindle-shaped carcinoma cells. Some of these neoplasms seemed to penetrate dense fibrous tissue, thus producing sarcomatous patterns. They were unable to correlate either prior radiation therapy or chronic inflammation with the "sarcomatous" changes. They concluded that the spindle pattern implied a greater invasive tendency, but at the same time, the large amount of fibrous tissue represented increased host resistance.

In the past 40 years approximately 54 laryngeal sarcomas have been reported in the English language literature. Characteristically these have been polypoid lesions with little tendency to deep infiltration of adjacent soft tissue. Most arose in the true vocal cords and enlarged slowly. Surprisingly, the reports of almost half of the cases lacked any histologic description. Twenty-six of these neoplasms were diagnosed as fibrosarcomas, usually well differentiated, 7 as malignant lymphomas, 5 as chondrosarcomas, and the remainder as rhabdomyosarcoma, osteogenic sarcoma, angiosarcoma, leiomyosarcoma, or sarcoma of undetermined type. In none of these case reports was there any mention of an associated carcinoma. Therapy involved either excision or irradiation. The response to radiation, even exclusive of the "lymphomas," was better than would have been expected with sarcomas. Only 8 lesions recurred; 5 of these were treated successfully by more radical operations. Eighteen patients were followed for 5 years or more, and, of these, only 3 developed metastases and died. Several of the patients with "lymphomas" later developed generalized disease. Because of the polypoid configuration of these lesions, their unusually good response to therapy, and the paucity of adequate histologic description, one wonders whether many of these lesions might have been either "pseudosarcomatous" stromal responses to carcinoma or else polypoid spindle cell carcinomas.

**MATERIALS AND METHODS**

A review of laryngeal neoplasms accessioned in the Department of Pathology of The University of Michigan Medical Center revealed 36 lesions coded as "pseudosarcoma," "carcinosarcoma," "sarcoma," or "spindle cell sarcoma." Six of these lacked sufficient tissue for adequate evaluation; 13 were miscellaneous benign mesenchymal lesions or manifestations of reticuloendothelial neoplasia, and 6 were not primary in the larynx. The remaining 11 laryngeal neoplasms, in all of which there was a bizarre spindle cell histologic pattern, constitute the subject of our report.

The case histories were reviewed, with special attention to the ages of the patients, duration of symptoms, physical findings, treatment, and outcome. All cases were followed either to the death of the patient or to the present time, except for 1 patient who, 14 years after treatment, was lost to follow-up. Multiple microscopic sections were examined in each case, using hematoxylin and eosin as the routine stain. Masson's trichrome stain was employed in each case, and the phosphotungstic acid-hematoxylin technic was used in selected lesions.

**CLINICAL FINDINGS**

These 11 patients ranged in age from 42 to 77 years when initially treated, and, remarkably, there were 10 males and only 1 female (Table 1). All but 1 complained of hoarseness; furthermore, 4 had dysphagia; 2 had cervical or aural pain; and 2 had dyspnea. Nearly all of these patients had had symptoms for at least 3 months before seeking medical assistance. Moreover, 3 patients had had symptoms for 9 to 12 months before receiving treatment. One patient (Case 7) was seen in this hospital for recurrent laryn-
FIG. 1 (upper left). Case 11. Extreme nuclear pleomorphism and atypical mitotic figures in polypoid laryngeal neoplasm. Occasional multinucleated cells are present. Hematoxylin and eosin. X 300.


geal neoplasm, having had an area of leuko­
plakia excised from the larynx 7 years previ­
ously and having received radiation therapy
for laryngeal carcinoma 2 years later. An­
other patient (Case 4) had received radiation
therapy to the left tonsillar pillar 33 months
before diagnosis of his laryngeal neoplasm.

All of the neoplasms were confined to the
larynx except 2 (Cases 3 and 6), which also
involved the epiglottis and hypopharynx. The
lesions varied from discrete polypoid
masses to diffusely infiltrating, constricting
tumors, up to 5 cm. in diameter. Four of
the masses were partially or totally polypoid
(Cases 2, 4, 8, and 11). Seven were sessile
and infiltrated underlying tissue.

The treatment varied. Five patients were
treated surgically, either by total laryn­
gectomy or by hemilaryngectomy. Four pa­
tients were treated only with radiation, and
2 had local excision of the neoplasm or
laryngectomy with supplemental radiation
therapy. In 1 patient radium needles were
used, whereas the remainder received deep
x-ray treatment.

Unfortunately, necropsies were not per­
formed on any of the fatal cases, so that
death certificates and information from at­
tending physicians have been relied upon for
follow-up. Six of the patients died with
locally recurrent neoplasms, 5 months to 2
years after initial therapy (Table 1). A
seventh (Case 7) died 5.5 years after radi­
ation therapy for laryngeal carcinoma and
1.5 years after total laryngectomy for recur­
rence. One patient (Case 4) developed an
enlarged cervical lymph node 1 month after
removal of the laryngeal neoplasm. This
mass was believed clinically to be a metastasis, and 2500 r were administered. The
patient was clinically free of neoplasm 9
months later; however, he died 18 months
thereafter, and the cause of death was not
known. Three patients are alive and well, 18
months, 14 years, and 15 years, respectively,
after initial treatment.

**PATHOLOGIC FINDINGS**

After multiple sections were examined, ob­
vious squamous cell carcinoma was detected
in 10 of these neoplasms, although the sar­
coma-like pattern predominated in each.

The 11th (Case 5) contained chiefly the
spindle cell and giant cell mixture, but small
nests of malignant cells, apparently carci­
noma, were present. The squamous cell car­
cinomas varied from the well-differentiated,
keratin-producing type to the poorly dif­
ferentiated one. All carcinomas invaded
stroma, although several of the carcinomas
were principally intramucosal. Necrosis of
stroma was unusual, although some necrosis
of the carcinomatous elements was common.
The degree of vascularity and inflammatory
reaction varied.

Two of the neoplasms (Cases 2 and 11)
were composed of atypical giant and spindle
cells arranged haphazardly in a fine fibrillar
or mucoid stroma (Figs. 1 and 2). These cells
had abundant, granular, or finely vacuolated
cyttoplasm ranging from amphophilic to
lightly eosinophilic. The cell nuclei were con­
spicuously pleomorphic and a few cells were
multinucleated. Nuclear hyperchromatism
and prominent nucleoli were common. Ab­
normal mitotic figures were few, and cross
striations were absent. Both of these tumors
were polypoid with widespread surface ul­
eration (Figs. 3 and 4). Rare small foci of
well-differentiated squamous cell carcinoma
superficially invaded the spindle cell com­
ponent. Most distinctive in these 2 neo­
plasms was the abrupt transition between
the invasive carcinoma and the sarcoma-like
component (Fig. 5). Both lesions were re­
moved by biopsy, and residual neoplasm was
not present in the subsequent laryngectomy
specimen.

Six neoplasms (Cases 1, 3, 5, 8, 9, and 10)
had a predominantly spindle cell stroma
with focal intercellular collagen. The spindle
cells were arranged in bundles and whorls,
or occasionally haphazardly (Fig. 6). Mitotic
figures were usually numerous. Foci of defi­
nite squamous cell carcinoma were present
in each case, although often only in isolated
areas. In contrast to Cases 2 and 11, there
was blending of the overt carcinoma with
the sarcoma-like elements so that a definite
demarcation could not be perceived (Figs.
7 and 8). Cross striations were absent in
the cytoplasm of the spindle cells; however,
in several neoplasms, dense cytoplasmic
eosinophilia in the spindle cells suggested

FIG. 6 (upper right). Case 3. Multinucleated and spindled cells simulating sarcoma. Well-differentiated squamous cell carcinoma was present in other areas. Hematoxylin and eosin. X 300.


keratinization. In Case 10, a cervical lymph node removed at laryngectomy contained only metastatic, well-differentiated carcinoma without any atypical stroma, whereas the original laryngeal lesion simulated a sarcoma. Case 8 was a pedunculated neoplasm removed by local excision, whereas the other lesions were broad-based.

Three neoplasms manifested osteoid, chondroid, or osseous metaplasia. In 2 instances (Cases 6 and 7) these elements were seen in recurrent neoplasm after prior radiation therapy for the primary lesion. Unfortunately, neither primary carcinoma was available for review. The third such neoplasm (Case 4) was not preceded by radiation to the larynx; however, a well-differentiated keratinizing squamous cell carcinoma of the tonsillar pillar had been irradiated 33 months previously. In other respects these lesions were similar to the preceding 6 tumors, in which foci of squamous cell carcinoma merged imperceptibly with the sarcoma-like component. In Case 7 carcinoma was seen only after examination of multiple sections. Intercellular collagen was present in various amounts in these neoplasms, and focally the neoplastic cells surrounded partially calcined osteoid seams. Neoplastic cells enveloped by the osteoid and cartilage simulated osteocytes and chondrocytes (Figs. 9 to 11). In Case 7 there was no calcification of the osteoid and no cartilage was formed. One of these 3 neoplasms was polypoid (Case 4), whereas the remainder were sessile or infiltrative.

DISCUSSION

All of these neoplasms manifested a sarcoma-like growth pattern associated with small, often inconspicuous, foci of obvious squamous cell carcinoma. Most surprising was the favorable clinical course of several of these patients, despite the severe cellular atypism in their tumors. In an attempt to explain this clinicopathologic inconsistency, the cases were grouped as to histologic and gross variations.

Nine neoplasms presented an intermixture of invasive epithelial and sarcoma-like elements. This blending often consisted of a “dropping off” of individual carcinoma cells into the stroma, similar to the “junctional change” described by Sherwin and associates.30 Dense cytoplasmic eosinophilia, suggestive of intracellular keratinization, was occasionally evident in the spindle cells. Neither cross striations nor intracellular lipids were seen in these neoplasms. Although we cannot definitely exclude the possibility that some of these neoplasms may represent carcinosarcomas, in which the stroma of the epithelial tumor has become malignant, or “collision tumors,” representing separate primary epithelial and mesenchymal neoplasms, it is most likely that the sarcoma-like areas are of epithelial origin. Only one of these patients is still alive. In the others, the disease pursued a comparatively rapid fatal course.

Three of these neoplasms (Cases 4, 6, and 7) had areas of osteoid, cartilage, or bony metaplasia. These 3 patients had in common a prior history of radiation. The one patient who had such changes in his original biopsy had radiation administered to the tonsillar area for a primary well-differentiated squamous cell carcinoma in that location approximately 2 years prior to presentation of the laryngeal neoplasm. The other 2 patients had such changes in recurrent neoplasm. They had received laryngeal radiation at the time of diagnosis of their original laryngeal carcinoma. Unfortunately, the initial biopsy material in these 2 cases was not available for examination. It seems likely that the bone and cartilage formation, although appearing neoplastic, was a nonmalignant, bizarre, reactive change in stroma.

Two of the neoplasms (Cases 2 and 11) had distinct carcinomatous and bizarre spindle cell elements with no blending of the 2 components. In both instances the carcinomas were small and moderately well differentiated, whereas the sarcoma-like areas were anaplastic. This was not a reparative or reactive process, because there was no capillary proliferation in the apparently sarcomatous areas. Similar areas were present in some of the 9 lesions in which there was blending of carcinoma and stroma. We share the opinion of Sherwin and associates that the sarcoma-like areas are, at least in part, neoplastic, and represent a pleomorphic
Fig. 9 (upper left). Case 6. Recurrent invasive squamous cell carcinoma. Note blending of neoplastic and stromal cells. Hematoxylin and eosin. X 145.

Fig. 10 (upper right). Case 6. Chondroid metaplasia simulating chondrosarcoma. Hematoxylin and eosin. X 180.

Fig. 11 (lower). Case 6. Partially calcified osteoid in anaplastic laryngeal carcinoma. Hematoxylin and eosin. X 120.
stromal response to invasive carcinoma. These 2 neoplasms are equivalent to the "pseudosarcomas" documented by Lane, and both of our patients are still alive. Certainly the outcome of the disease in these 2 patients has been more favorable than was suggested by the microscopic appearance of the neoplasms. It should be noted that grossly both of these neoplasms were polyloid, as was true of Lane's and Sherwin's cases.

In all of our cases, we found only 1 feature of the neoplasms which allowed us to correlate the pathologic findings with the clinical course: the gross configuration. If the lesions were polyloid or pedunculated, regardless of histologic composition, the outcome was apt to be favorable. If, however, the neoplasm had any other configuration, the outlook was poor, just as was that of invasive laryngeal carcinoma. Furthermore, after excisional biopsy of a polyloid tumor, the subsequent laryngectomy specimen generally lacked any residual neoplasm.

Four of the 11 cases (Cases 2, 4, 8, and 11) were grossly polyloid. Two of these (Cases 2 and 11) manifested the aforementioned pattern of sharply demarcated carcinomatous and bizarre sarcoma-like areas, 1 contained chondro-osseous tissue, and the fourth was a pure spindle cell lesion with blending of stroma and carcinoma. Two of these patients with polyloid neoplasms have survived for more than 14 years after treatment, and a third is clinically free of tumor more than 1 year after therapy. The fourth died 2 1/2 years after laryngectomy. No necropsy was performed in this case; however, the patient was clinically free of neoplasm 10 months after treatment. In contrast, all of the remaining 7 patients died as a result of clinically manifest neoplasm, surviving for an average of 13 months after definitive treatment. All of their neoplasms were deeply infiltrating or constricting lesions.

Although the treatment of the 11 neoplasms varied, it seems that the most successful form was complete excision. Consequently the polyloid tumors were more amenable to total removal. Grigg and co-workers concluded that all of these lesions should be treated as carcinomas and that the apparent sarcomatous changes should be disregarded. From our experience, we concur.

In conclusion, the long-term survival of some of these patients with histologically bizarre neoplasms seems to be more closely related to the gross configuration, and consequent ease of total excision, than to the histologic composition. Therefore, the difficult and often arbitrary decision as to whether a given lesion is a squamous cell carcinoma with spindle cell pattern, a carcinoma with a pseudosarcomatous benign stroma, a "collision tumor," or a carcinosarcoma assumes secondary importance.

SUMMARY

Eleven laryngeal neoplasms microscopically manifesting sarcoma-like areas with squamous cell carcinoma are described. In most, the sarcoma-like component apparently was infiltrative spindled squamous cell carcinoma, although in some tumors this component might have been, in part, an atypical stromal response to invasive carcinoma.

The most important factor in assessing prognosis was the configuration of the neoplasm. The exophytic or polyloid tumors had a favorable clinical course, whereas the sessile, infiltrative neoplasms had a prognosis similar to that of invasive, poorly differentiated, squamous cell carcinoma.

The histopathologic composition of these neoplasms varied. It could not be correlated with prognosis as well as could the gross configuration. These sarcoma-like lesions, which often manifest severe microscopic pleomorphism, may pursue either a favorable or a rapidly fatal course. This course depends upon their situation, configuration, and amenability to total excision.

REFERENCES