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

Lane22 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 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 associates30 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, Lane22 doubted such a transition between carcinoma and stroma. Most of the patients reported by Lane22 and by Sherwin and co-workers30 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</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 epiglottis to right arytenoid</td>
<td>sessile, &quot;large&quot;</td>
<td>Fusion of SCC and spindle cells</td>
<td>7600 r</td>
<td>Local recurrence, 3 mo.</td>
<td>Died, 14 mo.</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>Polypoid 2 cm. diameter</td>
<td>SCC intermixed with spindle cells; osteoid and chondroid areas</td>
<td>Snare excision. 7200 r</td>
<td>Local recurrence, 4 yr.; total laryngectomy</td>
<td>Died, 2.5 yr.</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>X-ray (? dose)</td>
<td>Local recurrence, 3 mo.</td>
<td>Died, 5 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>5500 r</td>
<td>Local recurrence, 4 yr.; total laryngectomy</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>Alive and well, 13.5 yr.</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>Alive and well, 13.5 yr.</td>
<td>Alive and well, 13.5 yr.</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Lesion Characteristics</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Metastasis</td>
<td>Outcome</td>
<td></td>
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<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>Sessile 5 x 3 cm.</td>
<td>Fusion of SCC and spindle cells</td>
<td>Total laryngectomy</td>
<td>Metastasis in cervical lymph nodes, 3 mo., 6675 r</td>
<td>Died, 10 mo.</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>Sessile 5 x 3 x 3.5 cm.</td>
<td>Fusion of SCC and spindle cells</td>
<td>Total laryngectomy</td>
<td>Regional recurrence, cervical lymph node metastasis, 10 mo., 7700 r</td>
<td>Died, 2.5 yr.</td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>M</td>
<td>Hoarseness, 10 mo.</td>
<td>Right true cord</td>
<td>Polypoid</td>
<td>SCC with demarcated sarcoma-like areas</td>
<td>Total laryngectomy</td>
<td></td>
<td>Alive and well, 1.5 yr.</td>
</tr>
</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 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 "pseudo-sarcomatous" 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 lesions coded as "pseudosarcoma," "carcinosarcoma," "sarcoma," or "spindle cell sarcoma." Six of these lacked sufficient tissue for adequate evaluation; 3 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.

Fig. 2 (upper right). Case 2. Haphazardly arranged neoplastic cells separated by mucoid and edematous matrix in polypoid laryngeal neoplasm. Hematoxylin and eosin. X 300.

Fig. 3 (lower left). Case 2. Polypoid configuration of neoplasm. Overt squamous cell carcinoma is present at the base. Hematoxylin and eosin. X 30.

Fig. 4 (lower right). Case 2. Ulceration of surface of neoplasm (at top). Hematoxylin and eosin. X 200.
geal neoplasm, having had an area of leukoplakia excised from the larynx 7 years previously and having received radiation therapy for laryngeal carcinoma 2 years later. Another 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 laryngectomy or by hemilaryngectomy. Four patients 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 performed on any of the fatal cases, so that death certificates and information from attending 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 radiation therapy for laryngeal carcinoma and 1.5 years after total laryngectomy for recurrence. 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, obvious squamous cell carcinoma was detected in 10 of these neoplasms, although the sarcoma-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 carcinoma, were present. The squamous cell carcinomas varied from the well-differentiated, keratin-producing type to the poorly differentiated 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 cytoplasm ranging from amphophilic to lightly eosinophilic. The cell nuclei were conspicuously pleomorphic and a few cells were multinucleated. Nuclear hyperchromatism and prominent nucleoli were common. Abnormal mitotic figures were few, and cross striations were absent. Both of these tumors were polypoid with widespread surface ulceration (Figs. 3 and 4). Rare small foci of well-differentiated squamous cell carcinoma superficially invaded the spindle cell component. Most distinctive in these 2 neoplasms was the abrupt transition between the invasive carcinoma and the sarcoma-like component (Fig. 5). Both lesions were removed 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 definite 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. 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 150.

Fig. 11 (lower). Case 6. Partially calcified osteoid in anaplastic laryngeal carcinoma. Hematoxylin and eosin. X 120.
The 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 polypoid, 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 polypoid 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 polypoid tumor, the subsequent laryngectomy specimen generally lacked any residual neoplasm.

Four of the 11 cases (Cases 2, 4, 8, and 11) were grossly polypoid. 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 polypoid 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 2½ 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 polypoid 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 polypoid 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**

5. Coakley, L. P., and Sale, G. G.: Fibrosarcoma...