CASE REPORT
Russell B. Smith, MD, Section Editor

LEIOMYOSARCOMA OF THE LARYNX AS A LOCAL RELAPSE OF SQUAMOUS CELL CARCINOMA—REPORT OF AN UNUSUAL CASE

Hans-Ullrich Völker, MD,1 Andreas Zettl, MD,1 Eugenia Haralambieva, MD,1 Bernd Blume, MD,2 Rudolf Hagen, MD,3 Hans-Konrad Müller-Hermelink, MD,1 Matthias Scheich, MD3

1 Institute of Pathology, University Würzburg, Germany. E-mail: ullrich.voelker@mail.uni-wuerzburg.de
2 Institute of Pathology, Schweinfurt, Germany
3 Department of Otorhinolaryngology, University Würzburg, Germany

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Abstract: Background. The authors report on leiomyosarcoma after previously treated squamous cell carcinoma (SCC) at the glottis.
Methods. Primary tumor and relapses were investigated morphologically, immunohistochemically, and with molecular methods.
Results. The SCC was typical, but few cells showed a spindle-shaped pattern. The relapse tumor was a spindle-shaped and epitheloid tumor with the morphological and immunohistochemical appearance of leiomyosarcoma (sm-actin+, desmin+, caldesmon+, vimentin+, keratin–).
The comparative genomic hybridization (CGH) revealed some gains and losses in the leiomyosarcoma. Because of altered material, the investigation failed in the primary. A fluorescence in situ hybridization (5p) focally detected 3 chromosomal copies, corresponding to gains on 5p in CGH of leiomyosarcoma.
Conclusion. Leiomyosarcoma after SCC is very uncommon. A connection between both seems likely in this case. Transdifferentiation, also seen in other tumors or carcinosarcomas, could be based on aberrant differentiation of a pluripotent stem cell.

The most common malignant tumors in the upper aerodigestive tract, including the larynx, are the squamous cell carcinomas (SCCs), whereas malignant mesenchymal tumors such as leiomyosarcomas are very rare.1–4 All reported cases are primary leiomyosarcoma.2 Additionally, the benign counterpart, leiomyoma, is rarely reported.4 The reason for the paucity could be the low amount of smooth muscles in this region. The development of leiomyosarcoma after previously treated SCC is an unreported event at this anatomic site. We report on a patient with this uncommon constellation.

Keywords: leiomyosarcoma; squamous cell carcinoma; larynx; transdifferentiation

CASE REPORT

Clinical History. An 85-year-old man (non-smoker for 30 years) was referred to our ENT department because of acute dyspnea. He
showed an inspiratory stridor, which had been progressive during the previous 4 weeks. Ten months before, he had received microlaryngoscopic laser resection of an SCC of the right vocal fold. The initial TNM stage was T1a, N0, M0, G2, and RX.

Magnified laryngoscopy showed a big prolapsing exophytic tumor. The glottis was not visible. An emergency tracheostomy was performed immediately with local anesthesia, which was directly followed by a microlaryngoscopy and tumor debulking in general anesthesia.

We proposed a complete laser resection followed by postoperative radiation, but the patient refused any further therapy.

Sixteen months after tumor debulking, he was free from relapses and metastases. Laryngoscopy showed a stable small tumor. Tracheostomy was no longer used and was already closed by a button. So the permanent closure of the tracheostomy was performed with local anesthesia.

**Histological and Immunohistochemical Investigations.** The primary tumor was diagnosed at 2 biopsies each with a size of 0.4 cm. Histologically, in routinely formalin-fixed (4% buffered), paraffin-embedded, and stained material (hematoxylin–eosin [H&E] stain), a moderately differentiated SCC with keratinization was detectable without diagnostic problems (Figure 1A). A very small focus showed an area with some spindle-shaped cells (Figure 1B), which obviously had a typical squamous cell differentiation.

The specimen of local relapse showed grossly around 10 ccm fragmented, tan-white, rough tissue with filamentous structure on cross sections. The H&E stain of formalin fixed (4% buffered) and paraffin-embedded material showed a prevailing spindle cell neoplasm with moderate pleomorphism of tumor cells (Figure 1C), weak mitotic activity, and focal necrosis. Other areas showed an epitheloid pattern with marked pleomorphism (Figure 2A), but without signs of residual SCC and without keratinization. Epitheloid pattern was found in approximately 40% of the relapsed tumor. The morphology was suggestive of leiomyosarcoma and an immunohistochemical investigation was done (KIT: Advance; DAKO). The spindle-shaped and epitheloid tumor cells expressed vimentin (Clone V9, 1:8000; DAKO) and smooth-muscle actin (1A4, 1:80; Immunotech), but no epithelial markers like PanKeratin (AE1/AE3, 1:800; DAKO; KL1, 1:75,
DAKO; CAM5.2, prediluted, Becton Dickinson; MNF116, 1:100; DAKO), CK5/6 (D5/16B4, 1:800; DAKO), or p63 (4A4+Y4A3, 1:4000; Neo-markers), examples are shown in Figures 2B–2D. Additionally, expression of desmin (D33, 1:400; DAKO) and caldesmon (H-CD, 1:200; DAKO) was examined. Desmin was expressed in all tumor cells (Figure 2E), and caldesmon showed a weak expression in single cells (Figure 2F). The proliferation index Ki67 (MIB1, 1:200; DAKO) was up to 60%. In conclusion, a leiomyosarcoma with partially epithelioid pattern was diagnosed. The diagnosis was confirmed by 3 experienced pathologists.

After this second diagnosis, we reevaluated the primary tumor and performed immunohistochemical investigations. Thereby, keratin and CK5/6 were expressed in all areas. Vimentin and actin were completely negative as well as desmin and caldesmon (not shown).

**Molecular Investigations.** A comparative genomic hybridization (CGH) was performed for both, primary tumor and relapse tumor. The DNA
was extracted from paraffin-embedded material fixed with buffered formalin in accord with previously published protocols. Unfortunately, the investigation failed in the primary tumor because of insufficient amount of material and artificial changes in the course of laser resection. The chromosomal gains and losses of leiomyosarcoma are shown in Table 1.

After that, we tried fluorescence in situ hybridization (FISH) of changes of some peculiar chromosomes of CGH. FISH on metaphase preparations and cell suspensions was performed in accord with a standard protocol. The probe used investigated the 5p region (LSI D5S721, D5S23; Abbott). The SCC showed 3 copies of the 5p region in a small part of tissue (5% to 10%), corresponding to the area with spindle-shaped tumor cells. However, the areas with clear identifiable SCC did not show this chromosomal change.

**DISCUSSION**

We presented a very uncommon case of a leiomyosarcoma after primary SCC of the larynx (glottis). To our knowledge, this constellation has not been reported in this anatomic site.

The primary SCC showed microfocally a spindle-shaped differentiation; however, in all sections the tumor was easily recognizable as SCC, whereas the relapse tumor did not show characteristics of SCC (morphologically and immunohistochemically). Some areas showed an epitheloid pattern, but without signs of keratinization and without immunohistochemical expression of epithelial markers. Thereby, the relapse tumor was localized at the identical anatomic site in the larynx like the primary. Unfortunately, a direct comparison of chromosomal gains and losses via CGH was not possible, because this investigation failed technically in the primary stage due to pre-existing thermoalteration of tissue after laser resection and only small samples of tumor. However, we found 3 copies of the 5p region via FISH in the area of primary tumor with spindle-shaped cells. This finding may suggest a connection between both tumors, because of the corresponding gains on chromosome 5p in the CHG of leiomyosarcoma.

Transdifferentiation of malignant tumors in relapses or metastases is a rare, but possible event and should be considered in the differential diagnosis. Another example of transdifferentiation from a common pluripotential stem cell is the development of carcinomasomas in some locations or, for example, the possible rhabdomyosarcomatoid dedifferentiation in malignant melanomas. In cases like the one presented here, the connection is more clear than in metastatic tumors; hence, the tumors are located identically. In metastases, the distinction may fail in a number of cases, especially without molecular investigations.

The recent literature contains only few cases of synchronous or metachronous occurrence of leiomyosarcoma and SCC. Interestingly, most cases are reported in the esophagus but not at the vocal cord. We think that most of these tumors could follow the same principle.

Sarcomatoid dedifferentiation of SCC can occur after irradiation. However, the patient received surgical therapy. A lot of changes found here are more compatible with results on SCC than leiomyosarcoma. So common changes in laryngeal SCC frequently affect chromosomes 1, 3, 5, 8, and 16 (gains) and 1 and 13 (losses). Thus, losses on chromosome 13q are frequently associated with recurrence or poorer prognosis, respectively. We found some of these alterations in leiomyosarcoma, especially gains on chromosome 3 and 5 (5p) and losses on chromosome 13. Corresponding to this result we could detect 3 copies of the 5p region in a small area of SCC, which has shown a more spindle-shaped differentiation with vague similarities to the epithelial areas in the leiomyosarcoma. The better differentiated parts of SCC remain inconspicuous in this investigation. Chromosomal changes in leiomyosarcoma have mostly been investigated for uterine tumors. The changes in primary leiomyosarcoma of the upper aerodigestive tract are not reported, hence we cannot compare the data in this setting. Some leiomyosarcoma coincided with SCC should be investigated for better detection of similarities or discrepancies.
CONCLUSION
Development of leiomyosarcoma after primary SCC has not been reported in the larynx. However, similar to other anatomic sites, this event is rarely possible and may be based on differentiation/transdifferentiation of pluripotent tumor stem cells. However, we do not interpret the relapse tumor as spindle cell carcinoma (due to the complete absence of epithelial markers) but as a true mesenchymal tumor (leiomyosarcoma). The prognosis of this constellation remains unclear, but seems surprisingly not worse than in conventional SCC, because the patient is well alive 16 months after last surgery without any aggressive/extended therapy apart from tumor debulking.

REFERENCES