

## Atypical Carcinoid Tumor of the Larynx: A Challenging Diagnostic Case

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### Abstract

**Background:** Atypical carcinoids are rare neuroendocrine tumors, but they are the most common type of non-squamous cell laryngeal neoplasms. Recent literature addresses the importance of adequate diagnosis, but lacks consensus in treatment strategy.

**Case report:** A 69-year-old man presented with dysphagia. Diagnosis of supraglottic hemangioma was based on fiberoptic examination. After treatment with CO<sub>2</sub> laser excision histopathological diagnosis stated paraganglioma. Dysphagia recurred after 6 months. (18)F-FDG PET/CT-scan revealed high FDG-uptake at the right aryepiglottic fold. After CO<sub>2</sub> laser excision histopathology showed atypical carcinoid. Total laryngectomy and neck dissection was performed to secure tumor-free margins, followed by adjuvant radiotherapy due to lymph node metastases. A month after termination of radiotherapy no lesions were determined by somatostatin receptor scintigraphy.

**Conclusion:** Personalized management should be based mainly on mitotic rate and locoregional extension. Surgical treatment and lifelong multidisciplinary follow-up is mandatory, while the role of adjuvant therapy remains debatable.

**Keywords:** Hemangioma; Paraganglioma; Neuroendocrine tumors; Larynx

### Introduction

Neuroendocrine tumors occur in all organs, but most often in the gastrointestinal or bronchial tract. They account for 0.5-2% of all malignancies and approximately 1% of laryngeal cancers [1]. Various classification systems and terms have been used to indicate neuroendocrine neoplasms of the larynx, without universal agreement. Precise diagnosis and definitive tumor subtyping is based on histomorphological features supported by immunohistochemistry. This can be challenging but crucial for prognosis, as neuroendocrine tumors vary from benign to very aggressive. A common classification in four groups: paraganglioma, typical carcinoid, atypical carcinoid and small cell carcinoma [2,3]. Atypical carcinoid tumors are also referred to as moderately differentiated neuroendocrine carcinoma, grade II or large cell neuroendocrine carcinoma [4].

Goldman et al. describe an atypical carcinoid tumor of the larynx for the first time in 1969. Atypical carcinoid tumors of the larynx are usually malignant, have an aggressive clinical prognosis and have been confused with other tumors frequently [5]. Paragangliomas of the larynx are first described by Blanchard and Saunders in 1955, less than 90 cases of paraganglioma of the larynx have been described since and are considered benign with an excellent prognosis [6]. Almost all reported cases of malignant paraganglioma and many cases of typical

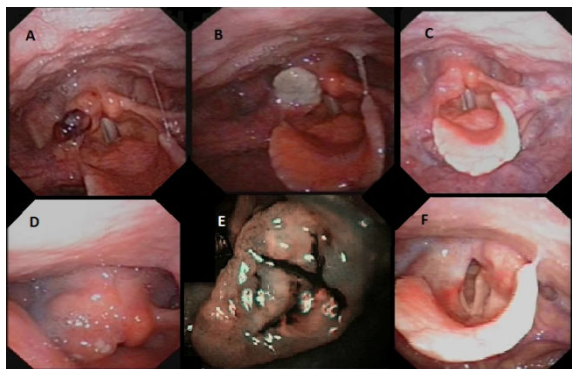
carcinoid are reclassified as atypical carcinoid on review [7]. Therefore, it is difficult to determine the exact number of atypical carcinoid cases.

In this paper, we present a challenging case of an atypical carcinoid tumor at the level of the right aryepiglottic fold.

### Case Report

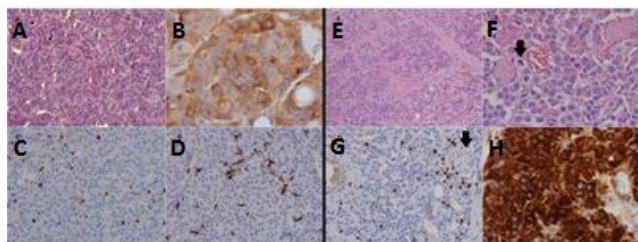
A 69-year-old man was referred to our tertiary center with the tentative endoscopic diagnosis of a laryngeal hemangioma. The patient reported dysphagia and globus sensation without accompanying symptoms. The patient had a 13 pack-year history of cigarette smoking and two units of alcohol were consumed daily.

Endoscopic evaluation revealed a pedunculated red-brown submucosal mass (7 × 7 × 9 mm) at the level of the right aryepiglottic fold. No other relevant findings were present at clinical examination. Complete excision of the lesion at the level of the right arytenoid was performed using CO<sub>2</sub> laser during direct laryngoscopy. The histopathology report suggested paraganglioma. The tumor was described as organoid and consisted of rounded nests of atypical cells without necrotic change. Four mitoses per 10 high-power fields (HPF) were found (Figure 1).



**Figure 1:** Fiberoptic laryngoscopy of the larynx with atypical carcinoid at the right aryepiglottic fold. (A) Before excision; (B) 11 days after CO<sub>2</sub> laser excision; (C) 1 month after CO<sub>2</sub> laser excision; (D) 6 months after CO<sub>2</sub> laser excision; (E) Narrow Band Imaging close-up, 7 months after CO<sub>2</sub> laser resection; (F) After repeated CO<sub>2</sub> laser excision.

Immunohistochemical examination showed cytoplasm positive for synaptophysin and chromogranin and negative for cytokeratin (CK). Scattered S100 positive sustentacular cells were seen. The Ki67 index was up to 6% (Figure 2). Based on these results, clinical endoscopic follow-up was recommended.

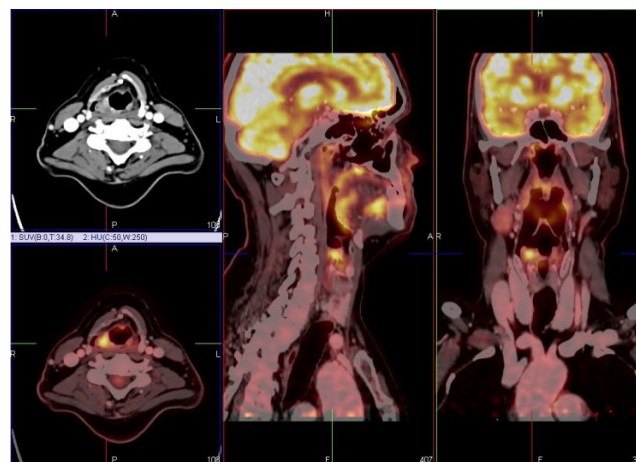


**Figure 2:** Histopathology and immunohistochemistry. After the first CO<sub>2</sub> laser excision: (A) tumor composed of somewhat rounded structures (HE, 200X); (B) the cytoplasm of the tumor cells is positive with synaptophysin (synaptophysin, 400X); (C) Proliferation index Ki67 of 6% (Ki67, 200X); (D) Scattered S100 positive cells mimicking sustentacular cells (S100-) After CO<sub>2</sub> laser re-excision: (E) Overview of tumor with more infiltrative growth with fine tumoral nests and strands (HE-100X); (F) Detail with mitotic figure (arrow) (HE-200X); (G) Proliferation index with Ki67 14%, perineural invasion (arrow=nerve, Ki67, 200X); (H) Cells are CK7 positive (CK7, 400X).

Symptoms of dysphagia recurred within 6 months, accompanied by a tingling sensation in the laryngeal region that worsened during ingestion of food. A pink-whitish lesion occurred on the right aryepiglottic fold (Figure 1). Narrow band imaging during fiberoptic laryngoscopy showed neovascularization suspect for malignancy (Figure 1). An (18) F-FDG PET/CT-scan revealed high FDG-uptake from a lesion at the right aryepiglottic fold with a diameter of 8 mm. No suspicious lesions were determined elsewhere in the body (Figure 3). Blood examination showed elevated levels of neuron-specific

enolase (NSE, 17.3 µg/L, n<16.3 µg/L) and chromogranin A (CgA, 229 µg/L, n=40-170 µg/L).

CO<sub>2</sub> laser excision of the lesion was repeated and histopathology revealed atypical carcinoid (Figure 2), surgical margins were not free of tumor cells. The lesion contained regions with infiltrative growth of fine tumoral strands and nests in addition to solid areas. Necrosis and perineural invasion were present. The mitotic index was 5 per 10 HPF. The cells were CK7 and synaptophysin positive; CK20 negative. The Ki-67 index was 14% (Figure 3).



**Figure 3:** (18) F-FDG PET/CT scan with whole body images and dedicated high-resolution head and neck images showing a lesion 8 mm in diameter with high FDG uptake at the right aryepiglottic fold. No other suspicious lesions were determined in the neck or elsewhere in the body.

Total laryngectomy and unilateral supraomohyoid elective neck dissection of region II-III-IV at the right side was performed. Postoperative CgA blood levels remained elevated (219 µg/L) and NSE levels remained within normal limits. Final diagnosis was an atypical carcinoid tumor of the larynx, pT1N2bMx R0 (TNM 7th edition, UICC 2009). As metastatic lymph nodes were identified in the neck dissection specimen adjuvant postoperative radiotherapy (30 sessions of 2 Gy bilateral) was proposed.

Somatostatin receptor scintigraphy (SRS, OctreoScan) an (18) F-FDG PET/CT-scan were performed a month and three months after termination of radiotherapy respectively. No lesions were determined. Every therapeutic decision was discussed with the local multidisciplinary head and neck tumor board.

## Discussion

Atypical carcinoids have a 5-year disease-specific survival of about 50% and 30% after 10 years [4,7]. More than 60% of the patients have recurrence despite aggressive treatment. Delays can occur even after the conventional 5-year follow-up period. Despite adequate treatment, almost 70% of these patients develop distant metastasis [7]. Negative prognostic factors are a Ki67 index higher than 5% or the presence of regional lymphatic metastasis [8].

Overlap in histopathological features of atypical carcinoids and paragangliomas is presented (Table 1) [4,5,9].

Atypical carcinoid tumor	Paraganglioma
Subepithelial lesion with or without ulceration of the mucosa	Subepithelial lesion without ulceration of the mucosa
Trabecular and/or organoid pattern	Organoid pattern with aggregation of chief cells in the Zellballen pattern characteristic but not pathognomonic of this tumor
Glandular and/or squamous differentiation	Sustentacular cells
Oncocytic and oncocytoid changes may be present	Prominent vascular lesion
Mucinous changes may be present	Mitoses and necrosis are infrequent
Squamous nest may be present	
Rosettes may be present	
2 to 10 mitoses per 2 mm <sup>2</sup> (10 high-power fields)	
Mild to moderate nuclear pleomorphism	
Sustentacular cells may be present	
Necrosis (often punctuate)	
Tendency to grow in nests and cords of cells, often with peripheral palisading of nuclei	
Focally Zellballen pattern may be present	
Cysts with intracystic papillary like projections of tumor cells may be seen	
Large cells with abundant eosinophilic, finely granular cytoplasm with vesicular nuclei and prominent nucleoli	

**Table 1:** Histopathological criteria for diagnosis of atypical carcinoid tumor and paraganglioma.

Atypical carcinoids can have a distinct paraganglioma-like appearance, with cell nests resembling a Zellballen pattern [5]. Atypical carcinoids of the larynx show immunoreactivity for both epithelial and neuroendocrine markers.

In the reported case, findings on the first biopsy correlated with a tentative diagnosis of paraganglioma based on the cytokeratin (CK) negativity and presence of sustentacular cells with some positivity for S100. Detection of mitosis, however, is not common in cases of paraganglioma and might be more compatible with a diagnosis of atypical carcinoid (Table 1). Both paragangliomas and atypical carcinoids are immunohistochemically positive for chromogranin and synaptophysin [10,11]. In general atypical carcinoids are positive for low molecular weight CK as well as other epithelial markers, and CK is negative in cases of paraganglioma [4]. This makes CK is the most useful immunomarker for differential diagnosis. S-100 protein stains are strongly positive in the sustentacular cells of paragangliomas but they can also be positive in atypical carcinoids (Table 2) [4,5,9-11].

Staining agent	Atypical carcinoid tumor	Paraganglioma
Cytokeratin (CK)	+ (low molecular weight)	-
Epithelial membrane antigen	+	-
Carcinoembryonic antigen (CEA)	+	-
Chromogranin	+	+
Synaptophysin	+	+
CD56	+	+
Neuron-specific enolase (NSE)	+	+
S-100 protein	+/- (negative in most cases)	+ (in sustentacular cells)

**Table 2:** Immunocytochemical findings in atypical carcinoid tumor and paraganglioma.

Mitosis (per 2 mm<sup>2</sup>, 10 HPF)<2 indicates typical carcinoid, 2-10 indicates atypical carcinoid and >11 indicates small cell neuroendocrine carcinoma; mitoses are rare in paraganglioma [4,12]. Mitotic rate may be the easiest way to differentiate between neuroendocrine tumors and their aggressiveness. In our case the mitotic rate of 4 in the first histopathological report may have pointed out the diagnosis of atypical carcinoid rather than paraganglioma.

X-ray computed tomography (CT) and magnetic resonance imaging are useful to demonstrate local extension of neuroendocrine tumors [13]. Small tumors may be visualized only by endoscopic assessment and not by conventional imaging. Multiple cases describe that somatostatin receptor scintigraphy (SRS, OctreoScan) can reveal lymph node metastases that are not clinically present [14]. SRS image fusion with low-dose CT is important for better anatomical localization of scintigraphic findings. The overall sensitivity of SRS is 89%. This is high compared to (123) I-MIBG scintigraphy (52%) and (18)F-FDG PET (58%) [15]. However, in tumors with a high proliferation rate (Ki67>15%), (18)F-FDG PET has the highest sensitivity (92%) compared to SRS (69%) and (123) I-MIBG scintigraphy (46%). SRS and (18) F-FDG PET provide complimentary diagnostic information and are both of value for neuroendocrine tumor patients [15]. In our case the histopathologic report states Ki67 14% and high uptake on (18)F-FDG PET before surgery. Follow-up by endoscopy and (18) F-FDG PET is provided.

Radical surgical removal is recommended in both paragangliomas and atypical carcinomas of the larynx [4,5,9]. In atypical carcinomas, selective neck dissection is recommended in addition to radical surgery of the primary tumor, patients who did not have neck dissection developed regional recurrence without local recurrence in almost 30% of cases [7]. Chemotherapy or radiation therapy does not improve the cure rate of atypical carcinoid tumors and does not result in a better 5-year disease-specific survival rate [4,7,9]. These results are challenged by small series and cases that state that atypical carcinoids respond well to combined therapy and that postoperative radiotherapy is useful in the case of substantial local extension, multiple node metastases and/or extracapsular disease [14].

## Conclusion

The reported case indicates that differentiation between paraganglioma and atypical carcinoid is challenging. Expert analysis of histopathological and immunohistochemical findings is crucial to distinguish between neuroendocrine tumors. Personalized management should be based mainly on mitotic rate and locoregional extension. Surgical treatment and lifelong multidisciplinary follow-up is mandatory, while the role of adjuvant therapy remains debatable.

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