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An Interesting Entity Mimicking Malignancy: Laryngeal Candidiasis

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Primary candidiasis in the laryngeal mucosa is rare but has many predisposing factors, in particular immune insufficiency and long-term antibiotic use. This study involved a reassessment of 530 laryngeal biopsy specimens originally examined between 2004 and 2009, from which 11 cases of hyperplastic laryngeal candidiasis were identified according to their clinical and histopathological features. Among possible predisposing factors, immune insufficiency was identified in three patients, there was long-term antibiotic use in two cases, use of inhaled corticosteroids in four cases, smoking in eight cases and reflux symptoms in four cases. Dysplasia as well as hyperplasia was seen in two cases. Endolaryngeal lesion excision was performed in eight cases and biopsy leading to radical surgery was done in three. In clinical follow-up no lesions were observed in nine cases while two had new leukoplakic lesions.

KEY WORDS: Laryngeal candidiasis; Hyperplasia; Carcinogenesis

Introduction

Primary candidiasis in the laryngeal mucosa is a rare entity[1] that mostly follows pulmonary, pharyngeal or oesophageal candidiasis, or emerges as a result of a disseminated disease. Laryngeal involvement has many important predisposing factors,[2] led by immune insufficiency and long-term antibiotic use.[3–5] The clinical and pathological presentations of laryngeal candidiasis might be confused with those for benign or malignant lesions. The classic presentation is white plaques with a pseudomembranous or vegetative mass appearance.[6,7] Lesions may resemble carcinoma, both clinically and histopathologically.[3,8] Candidal infections have been claimed to lead to malignant transformation and there is strong evidence in large series that oral candidal lesions can lead to the development of dysplasia or cancer. This study emphasizes that laryngeal candidiasis should be considered in the differential diagnosis of carcinoma, and that there is a relationship between candidiasis and carcinogenesis.

Patients and methods

SELECTION OF CASES

Laryngeal biopsy specimens that had been sent for examination to the Department of Pathology, Uludag University Medical School, Bursa, Turkey, between 2004 and 2009 were reassessed. Cases with a diagnosis of hyperplastic laryngeal candidiasis based on the clinical features and

histopathological characteristics of the specimens were identified from the original paraffin blocks with haematoxylin and eosin and periodic acid–Schiff staining.

Approval for the study was provided by the Ethics Board of Uludag University.

TREATMENT AND OTHER DATA COLLECTED

All patients' demographic data, clinical history and pathology reports were examined, including gender, age, smoking status, therapeutic drug use, concomitant diseases and disorders, immune status, and the results of endoscopy, pathology and microscopy. Patients underwent endolaryngeal excision of lesions or pre-operative biopsy. Decisions about whether or not to perform radical surgery were based on clinical features and histopathological findings in frozen-section and biopsy samples. Patients were not offered antifungal therapy.

Results

A total of 11 cases of hyperplastic laryngeal candidiasis were identified from the 530 cases that were reassessed, based on the clinical features and histopathological characteristics of the specimens. Their mean age was 53 years, nine (81.8%) patients were male, two (18.2%) were female and eight (72.7%) had a history of smoking. Patients' characteristics and predisposing factors for hyperplastic candidiasis are summarized in Table 1.

Immune insufficiency was seen in three (27.3%) patients for various reasons. In two of these patients this was due to diabetes mellitus. In the other patient, immune insufficiency was due to multiple myeloma and this patient was in intensive care owing to sepsis and was receiving intensive

TABLE 1:
Summary of patients' characeristics and predisposing factors for hyperplastic candidiasis

Case No.	Age (years)	Sex	Smoker	Immune insufficiency	Medication use	Reflux
1	42	Male	Positive	Negative	Positive (antibiotics)	Positive
2	59	Female	Negative	Positive (multiple myeloma and sepsis)	Positive (antibiotics)	Negative
3	78	Male	Positive	Negative	Negative	Negative
4	54	Male	Negative	Negative	Positive (inhaled corticosteroids)	Negative
5	52	Female	Negative	Positive (diabetes mellitus)	Positive (inhaled corticosteroids)	Positive
6	43	Male	Positive	Negative	Negative	Negative
7	68	Male	Positive	Negative	Positive (inhaled corticosteroids)	Negative
8	42	Male	Positive	Negative	Negative	Negative
9	39	Male	Positive	Negative	Negative	Positive
10	54	Male	Positive	Positive (diabetes mellitus)	Negative	Positive
11	49	Male	Positive	Negative	Positive (inhaled corticosteroids)	Negative

antibiotic therapy; this patient also had glucose intolerance. One other patient from the 11 studied was taking long-term antibiotic treatment which was for hoarseness. Four other patients were on long-term medication, which comprised inhaled steroids for chronic obstructive lung disease.

The most frequent symptom related to laryngeal candidiasis, seen in seven (63.6%) patients, was hoarseness. Other than this, two (18.2%) patients had shortness of breath, one in which this was accompanied by difficulty in swallowing, and another patient (9.1%) had a sore throat also accompanied by difficulty in swallowing. Reflux was endoscopically indicated in four (36.4%) patients, with evidence of arytenoid oedema and interarytenoid plica.

Endoscopy was performed in all 11 patients. This was not undertaken specifically to assess candidiasis, however, in six (54.5%) patients it was reported that the endoscopic appearance of candidiasis lesions was that of a vegetative mass. In one of these patients, the mass was incidentally detected during endoscopy performed for decannulation of a tracheotomy after long-term intubation in intensive care. One of the two patients who had shortness of breath also had a leukoplakic lesion on the front surface of the right arytenoid, detected during endoscopy to investigate obstructive sleep apnoea. One (9.1%) patient had multifocal leukoplakic lesions. In four (36.4%) patients candidiasis plaques had the classic thick, white, pseudomembranous appearance.

Eight patients underwent endolaryngeal lesion excision and the other three underwent pre-operative biopsy of lesions. Microscopy examination revealed epithelial hyperplasia, hyperkeratosis and parakeratosis in the vocal cord mucosa of all patients. Yeast formation was seen only in five patients but occasional leucocytes with polymorphic nuclei on the keratin layer, hyperplastic epithelium and thin fungal hyphae vertical to the mixed epithelia were seen in all patients (Fig. 1). Mycological verification by culture was not carried out in any of the patients. In one patient the epithelial hyperplasia was papillary hyperplasia mimicking squamous papilloma. Two patients exhibited dysplasia on surface epithelia (Fig. 2): slight dysplasia was seen in addition to candidal hyperplasia in the biopsy sample of one patient and, in the other patient, multiple biopsy investigations showed initial slight dysplasia that developed into severe dysplasia.

Even though the pre-operative biopsy of three of the patients did not indicate malignancy, radical surgical treatment was used because the findings of frozen-section assessment were suggestive of squamous cell carcinoma in two patients and verrucous carcinoma in one. Pathological examination of radical specimens confirmed these diagnoses.

In clinical follow-up over a period of 12 – 72 months, no lesions were found in nine of the patients, whereas leukoplakic lesions were observed in two patients.

Discussion

Mycotic infections of the larynx are frequently seen in patients with immune insufficiency,[1,3] although they have also been reported in individuals with normal immune status.[9] Changes in immune status or mucosal barriers have notable roles in the development of laryngeal candidiasis. Candidiasis is frequently seen in patients with immune insufficiency syndromes or diabetes mellitus, those receiving immunosuppressive treatment,[3,4] and in individuals whose mucosal barriers are affected by antibiotic use, use of inhaled

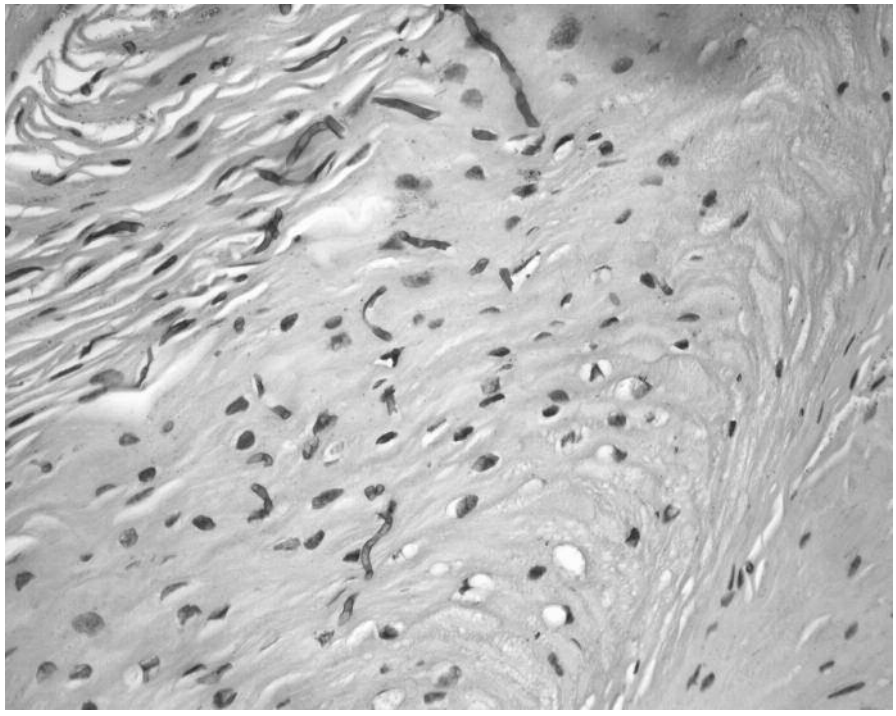

FIGURE 1: Fungal hyphae visible in a hyperplastic endolaryngeal epithelium sample (periodic acid–Schiff stain; original magnification ×400)

corticosteroids,[6,10] radiation treatment, smoking, trauma, gastroesophageal reflux or chemical–thermal damage.[4] History of smoking, inhaled steroid use, long-term antibiotic use and reflux were reported among the 11 patients studied in the present report. In addition, some patients had diabetes, multiple myeloma or sepsis.

Laryngeal candidiasis can present with various symptoms, such as odynophagia, dysphagia, hoarseness, respiratory distress and stridor.[11,12]

Among patients in the present study, the most frequent symptom was hoarseness, but other symptoms, such as shortness of breath and difficulty in swallowing, were also seen.

The laryngoscopic appearance of candidiasis generally includes oedema, erythema, ulceration, white plaque and pseudomembranous formations.[6] In some cases, exophytic lesions clinically mimicking laryngeal papilloma or squamous cell carcinoma develop.[1,7] Pseudomembranous formation and a vegetative mass appearance were seen in patients in the present study. Candidiasis with the appearance of a vegetative mass was clinically considered as indicating malignancy.

The hyperplastic epithelial changes and non-specific inflammation seen in laryngeal candidiasis are similar to those seen in oral candidiasis.[3,4,11,13,14] For diagnosis, the presence of *Candida* spp should be histopathologically and mycologically confirmed. Yeast or hyphae forms belonging to *Candida* spp can sometimes be seen in sections stained with haematoxylin and

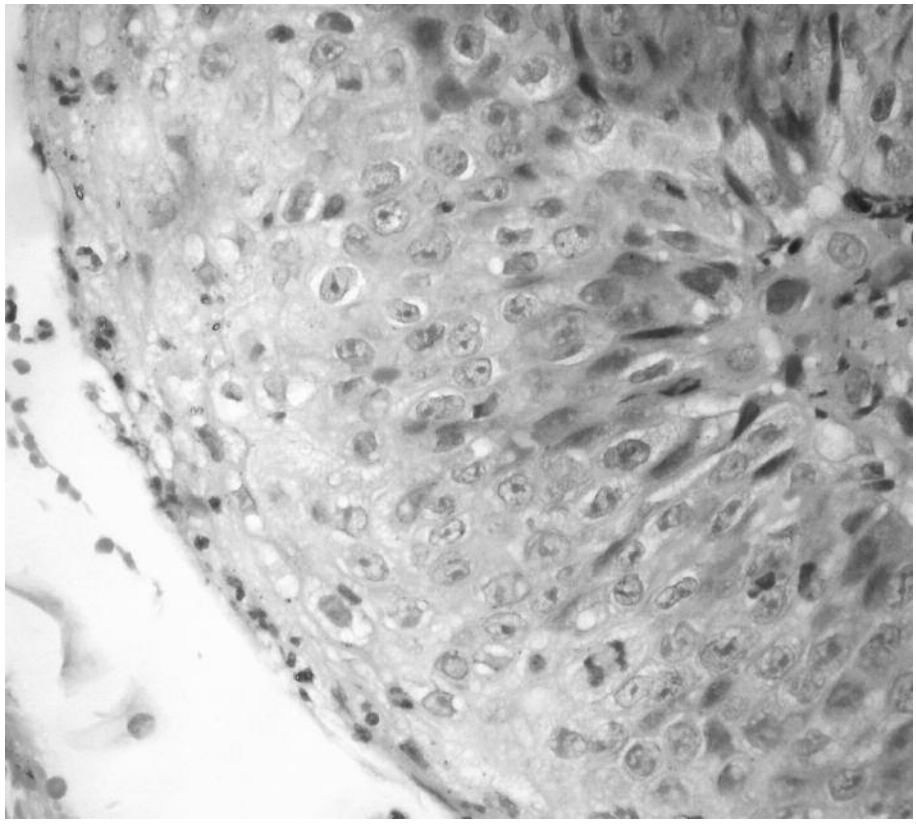

FIGURE 2: Dysplastic changes characterized by nucleomegaly, hyperchromasia, disorganization and mitotic figures in a surface hyperplastic endolaryngeal epithelium sample (haematoxylin and eosin stain; original magnification ×400)

eosin, but they are easily spotted with periodic acid–Schiff or Gömöri methenamine silver staining.[3,4] In patients in the present study, hyphal forms were detected in some samples stained with haematoxylin and eosin, and periodic acid–Schiff staining made visualization of these more distinct. Mycological confirmation by culture was not carried out in any patient; diagnoses were confirmed by histopathological examination.

According to some authors, candidal infection leads to epithelial hyperplasia and, possibly, to the development of epithelial atypia with observable malignant changes. Most studies concerning this issue, however, have been conducted in patients with oral hyperplastic candidiasis.[15 – 17]

Even though the role of fungi in carcinogenesis is not yet clear, their contribution has long been recognized. For example, in a rat study, Russell and Jones[16] mentioned that long-term oral candidiasis affecting the tongue resulted in hyperplasia and dysplasia. Krogh *et al.*[17] showed that *Candida albicans* produces carcinogenic nitrosamines. The nitrosamine complexes produced by some *Candida* spp have been

purported to activate proto-oncogenes directly or in combination with other chemical carcinogens and to lead to development of oral epithelial neoplasia.[18]

Mild hyperplasia that advanced to severe dysplasia was seen in one patient in the present study and resembled the relationship between oral candidiasis and epithelial dysplasia or carcinoma.[16 – 18] This may be interpreted as indicating an effect of laryngeal candidal infection on neoplastic transformation.

In the three patients who underwent pre-operative biopsy in the present study, although no evidence of malignant disease was observed in the biopsy specimens, diagnoses of carcinoma were made after radical surgery. *Candida albicans* was present in the biopsy specimens of these patients and long-term candidal infection might have started the malignancy process.

Laryngeal candidiasis is a little known entity. Laryngoscopic and microscopic appearances might mimic benign and malignant lesions, such as squamous papilloma, verrucous carcinoma and squamous cell carcinoma.[1,3,8,19,20] Biopsy is, therefore, an essential part of the differential diagnosis of candidiasis. As laryngeal candidiasis can be treated with antifungal agents, a clear diagnosis could prevent unnecessary surgical interventions. Information on laryngeal candidiasis is currently limited and many issues are awaiting clarification. Studies in large case series are, therefore, necessary.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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