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Invasive laryngeal candidiasis: a cause of stridor in the previously irradiated patient

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Abstract

Upper airway obstruction is always a serious condition. In patients who have previously been irradiated for a laryngeal malignancy, it normally implies either residual or recurrent disease. We report a case of stridor due to invasive laryngeal candidiasis in a patient who had undergone radiotherapy for a T_{1a} N_0 squamous cell carcinoma of the glottis eight months earlier. Extensive investigation failed to identify recurrence of disease and the patient responded to prolonged topical antifungal therapy. Infection with *Candida* species is most frequently found in debilitated or immunocompromised patients. Although cases of upper airway obstruction in children secondary to idiopathic laryngeal candidiasis have been reported, to our knowledge no such presentation has been described in adults. This report highlights the difficulty of diagnosis and treatment. Familiarity with candidal infection is important for early diagnosis and appropriate treatment.

Key words: Laryngeal neoplasms; Carcinoma, squamous cell; Radiotherapy; Candidiasis

Introduction

Laryngeal mycosis is well documented in the literature and can be confused with the diagnosis of malignancy or tuberculosis (Lyons, 1966; Fisher *et al.*, 1992). *Candida albicans* is normally a commensal organism in the upper aerodigestive tract. It behaves pathologically when the host defence mechanism is altered by the use of antibiotics, steroids, chemotherapy or radiotherapy (Boggs *et al.*, 1961; Yonkers, 1973; Fisher *et al.*, 1992; Hollis *et al.*, 1996). Laryngeal candidiasis is usually secondary to pulmonary or pharyngeal infection and is classified as superficial or invasive on the basis of the degree of epithelial infiltration (Fisher *et al.*, 1992). The common symptoms are hoarseness, pharyngeal discomfort and dysphagia (Tashjian and Peacock, 1984). We describe the management of a patient who developed stridor having previously undergone radiotherapy for carcinoma of the larynx. Repeated biopsies failed to demonstrate the recurrent malignancy which was strongly suspected but rather, revealed epithelial invasion by Candida. The patient required a tracheostomy and a combination of various antifungal therapies. Awareness of invasive candidiasis of the larynx is important because prompt therapy minimizes morbidity and prevents systemic dissemination of disease.

Case report

In February 1995, a 76-year-old man presented with dysphonia due a right-sided T_{1a} squamous cell carcinoma of the glottis with no evidence of local or distant metastatic disease. He had stopped smoking two years earlier. Previous medical history included chronic bronchitis which was treated with a salbutamol inhaler. He was otherwise healthy without diabetes or any immunosuppressive condition. He was treated with primary radical radiotherapy (65 Gray) and he responded well to treatment.

In November 1995, a symptomless oedema over the right arytenoid cartilage was noted in the head and neck clinic. No other abnormality of the larynx was noted. He was prescribed a two-week course of antibiotics and steroids. He failed to respond to medical treatment thus it was decided that an examination under general anaesthetic was required.

Two days before the operation the patient was admitted under the care of the physicians as an emergency with dyspnoea. A chest radiograph did not show any focal lung disease. Blood count showed a neutrophil leukocytosis and a sputum culture grew *E. coli.* He was diagnosed as having an acute chest infection and treated accordingly. After two days he was referred to the ENT surgeons because he developed stridor. Fibre-optic examination now showed a friable yellowish-white mass in the supraglottic region which obscured the vocal folds (Figure 1). It did not extend into the pharynx and a provisional diagnosis of tumour recurrence was made.

An anaesthetic opinion deemed him not suitable for a general anaesthetic because of this chest infection. However, despite aggressive medical therapy the stridor worsened and so a tracheostomy was performed under local anaesthetic. Examination showed the larynx to be generally oedematous. The supraglottis was filled with a friable yellowish-white mass but the vocal folds did not appear to be involved. Histopathological examination of multiple biopsies taken from the larynx did not reveal any malignant cells but the tissue was extensively infiltrated with fungal spores and hyphae suggestive of candidiasis (Figure 2). The patient was treated with oral fluconazole 100 mg once daily and nystatin suspension 200,000 units,

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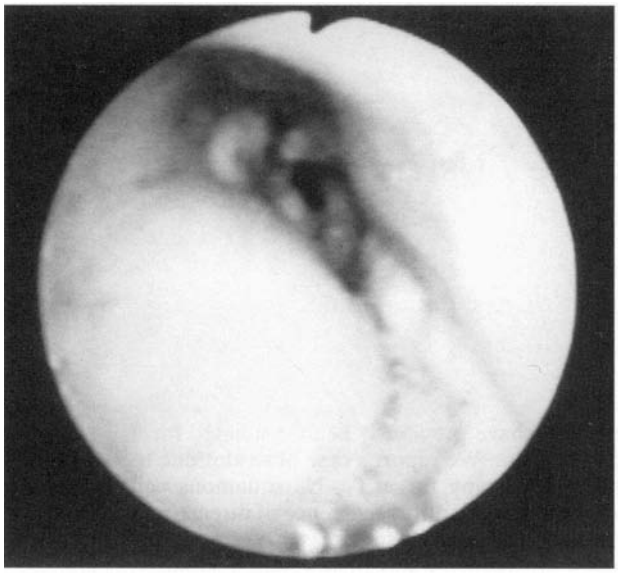

FIG. 1
Fibre-optic view of the larynx showing a right-sided yellow mass in the supraglottis partly obscuring the glottis.

four times daily by mouth. The chest infection resolved and repeat sputum culture did not grow any *E. coli*, but did grow a methicillin-resistant *Staphylococcus aureus*.

Repeat laryngeal examination following two weeks of antifungal treatment still showed marked tissue abnormality (Figure 3). Deep biopsies from the supraglottis showed areas of fibrosis induced by the radiotherapy and numerous spores and a few hyphae. No evidence of malignancy was noted. After further discussion with the microbiologists he was treated systemically with low dose intravenous amphotericin (50 mg once daily), oral fluconazole (100 mg once daily), and twice-daily topical nystatin using a McIntosh laryngoscope and Rogers crystal spray (Figure 4). During the course of the amphotericin, the patient's renal function was monitored and he did not develop any systemic side-effects. Following this treatment repeat fibre-optic examination showed complete resolution of the supraglottic fungal growth and resolution of the swelling. The right vocal fold was found to have reduced mobility but no evidence of recurrence of the primary neoplasm. This was probably because the invasive

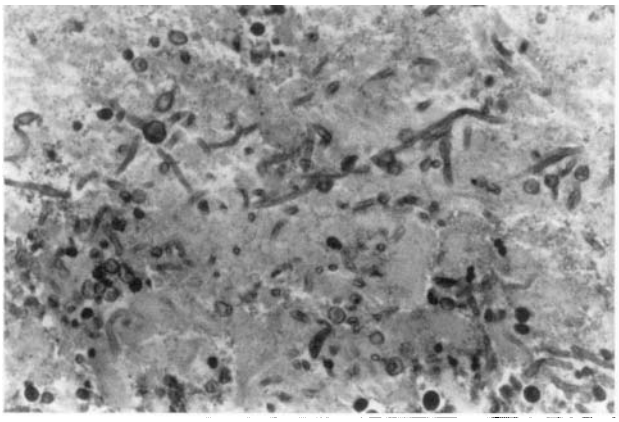

FIG. 2
Photomicrograph of a laryngeal biopsy demonstrating infiltration by fungal spores and hyphae but no evidence of malignancy. (PAS, stain, × 400).

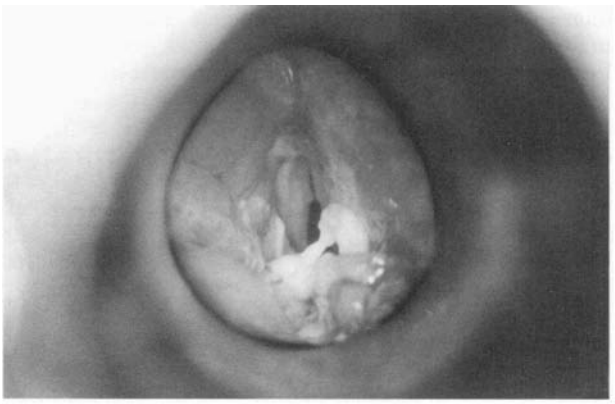

FIG. 3
Microlaryngoscopy following two weeks of antifungal treatment still showing a distorted and diseased larynx.

candidiasis had further increased the degree of fibrosis in an area which had already sustained an irradiation-induced fibrosis.

The patient was discharged with his speaking-valve tracheostomy tube *in situ* on a three-month course of oral fluconazole. Following this, his larynx was again examined under general anaesthetic. It merely showed atrophic laryngeal mucosa and no evidence of any fungal lesion or carcinoma. Swabs for fungal cultures were negative. He remains well one year after this episode.

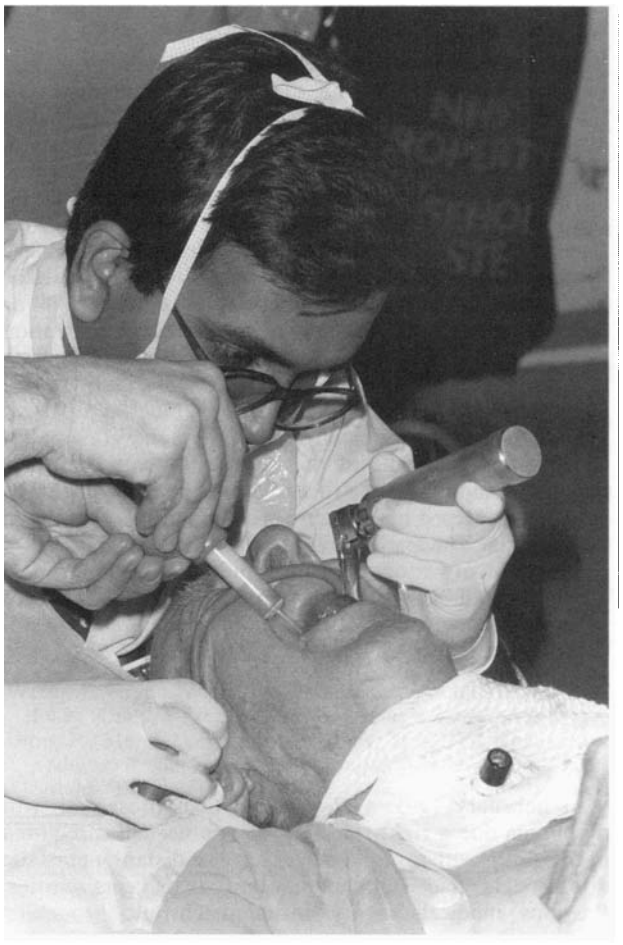

FIG. 4
Topical application of nystatin suspension directly onto the laryngeal mucosa using a McIntosh laryngoscope and Rogers crystal spray.

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Discussion

Primary radical radiotherapy is the usual treatment in the UK for a non-metastatic T_1 squamous cell carcinoma of the glottis because of the morbidity, efficacy and voice preservation compared to surgery. Subsequent stridor or progressive dysphonia following radiotherapy implies either residual or recurrent disease.

Laryngeal candidiasis is a well documented condition that can present as an isolated finding or as part of a systemic involvement (Boggs *et al.*, 1961; Yonkers *et al.*, 1973). The most common presenting symptom is dysphonia due to laryngeal oedema. Laryngeal fibrosis and permanent hoarseness can occur if the infection is not treated fully (Tashjian and Peacock, 1984).

Candida usually involves the glottis but can also involve the supra- or subglottis. The diagnosis is obvious when the candida involves the oral cavity, but the absence of oral or oropharyngeal involvement does not exclude laryngeal involvement. The diagnosis depends on the demonstration of candidal yeasts, hyphae and pseudohyphae, either by culture or tissue biopsy (Fisher *et al.*, 1992). Invasive forms can only be diagnosed by biopsy and subsequent histological examination, a technique regarded as sensitive and specific, giving an accurate diagnosis in the majority of cases (Tedeschi and Cheren, 1968; Sheft and Shrago, 1970).

Various predisposing factors have been described for candidal infection to occur. The most common of these is concurrent antibiotic administration. Other factors include prolonged treatment with steroids, myeloproliferative disorders and immunosuppressive therapy, hypoparathyroidism, radiotherapy and acquired immunodeficiency syndrome (AIDS) (Perrone, 1970; Yonkers, 1973; Tashjian and Peacock, 1984; Walsh and Gray, 1987). A history of diabetes mellitus is frequently present and diabetes may even be heralded by development of the infection.

The usual treatment for candidiasis is with antifungal agents. Fluconazole is a synthetic bistriazole which is absorbed well after oral administration. Unlike other azole anti-fungals it is weakly (12 per cent) protein-bound in serum giving it excellent penetration into most body sites. Azoles block the 14 α-demethylation step in the biosynthesis of ergosterol, altering fungal cell membrane composition. Thus an alteration in the cell membrane-associated functions develops and cell membrane leakage and cellular death can occur. Fluconazole has a wide spectrum of action although, notably, it is ineffective in aspergillosis. It is effective for most forms of mucocutaneous candidasis although some strains of *Candida albicans* exhibit resistance (Brammer and Tarbit, 1987).

The polyene antifungals (Sugar, 1986) are a large group of drugs which bind to the sterols in eukaryotic cell membranes affecting barrier function with resultant cellular leakage and cell death. Most of this group are equally toxic to fungal and mammalian cells. Nystatin is the product of *Streptomyces albulus* or *Streptomyces noursei.* It is generally used topically for mucocutaneous candidiasis.

Amphotericin B (Gallis *et al.*, 1990) is an insoluble fermentation product of *Streptomyces nodosus.* It is the drug of choice in most systemic mycoses such as disseminated candidosis, cryptococcosis and aspergillosis and is the only hope of success (in combination with radical debridement) in mucormycosis. It is poorly absorbed following oral administration and is given intravenously as a micellar suspension with sodium desoxycholate and because it precipitates in a pH of less than 4.2, it should not be mixed with any other drugs during infusion. It is quite toxic causing fevers, headache, vomiting, hypokalaemia, anaemia and renal damage (which may be irreversible). For this reason analgesics, antihistamines or steroids may be needed during infusions and renal function must be closely monitored.

A variety of treatment modalities have been described for candidiasis in ENT practice. These include oral nystatin (Tedeschi and Cheren, 1968), oral ketoconazole (Hughes *et al.*, 1983) and oral fluconazole (Hollis *et al.*, 1996), parental low dose amphotericin B (Drutz *et al.*, 1968) or direct laryngoscopy with topical application of nystatin (Medoff *et al.*, 1972) or aerosolized amphotericin B (Jacobs *et al.*, 1982). The diagnosis of epithelial invasion of *Candida* is important because the superficial form responds well to topical therapy whilst resistant cases may need intravenous treatment (Drutz *et al.*, 1968; Tedeschi and Cheren, 1968).

Our patient was unusual in that he developed an invasive supraglottic candidiasis in the absence of spread to the glottis, subglottis or into extralaryngeal tissues and no oral or oropharyngeal involvement. However, his larynx had been previously irradiated and he had been treated with steroids and antibiotics for his laryngeal oedema. This combination probably resulted in candidal infection. The antifungal therapy was guided by the microbiologists. The logic for treatment was based on the fact that the excellent usual effect of topical nystatin on *Candida* may not occur in this case because it would not come into contact with the laryngeal mucosa in any great concentration. Thus oral (systemic) fluconazole was added because of its good tissue penetration and low morbidity. However, following the second biopsy where deep involvement of *Candida* was shown it was decided that the greater efficacy of intravenous amphotericin B outweighed the considerably greater morbidity associated with it. Direct application of nystatin solution to the laryngeal mucosa using a spray was added to the therapy to further enhance treatment response, and oral (systemic) fluconazole was given for three months to ensure all spores were eradicated from the deep fibrotic tissues by systemic action. The duration of amphotericin B therapy was based on the clinical improvement and regular fibre-optic examination of the larynx.

The message of this case is that the typical appearances of recurrent malignancy may be caused by fungal infection and therefore recurrence should not be assumed. A prompt biopsy is essential to ensure that appropriate treatment is instituted and morbidity is kept to a minimum.

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