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Primary non-Hodgkin's lymphoma of the larynx in an AIDS patient

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Abstract

A case of primary non-Hodgkin's lymphoma of the larynx in an AIDS patient is presented with a review of the literature. Non-Hodgkin's lymphomas in AIDS patients are common but the primary laryngeal presentation is very rare. The symptoms usually include dysphonia and progressive airway obstruction requiring tracheostomy. As with laryngeal non-Hodgkin's laryngeal lymphomas in non-HIV positive patients the majority are of B cell lineage and respond well to radiotherapy. Our patient had a high grade lymphoma of B cell lineage which showed a good response to radiotherapy. The role of chemotherapy and surgery is not yet established. We suggest that the diagnosis of AIDS should not influence the management of these patients unless the individual is in the terminal disease stage.

Key words: Laryngeal neoplasms; Lymphoma, non-Hodgkin's; Acquired Immunodeficiency Syndrome (AIDS)

Introduction

Lymphomas account for less than one per cent of all laryngeal neoplasms (Friedmann and Piris, 1986). Reported cases include non-Hodgkin's lymphoma (NHL) (including the lethal midline granuloma type), mycosis fungoides and plasmocytoma (Horny and Kaiserling, 1995).

The first malignant primary lymphoma of the larynx was described by Mackenty in 1934 (Mackenty, 1934). Diebold in 1990 documents 83 previously reported primary NHLs of the larynx (Diebold *et al.*, 1990). Many of the documented cases lacked precise histopathological classification, but it was clear that both small cell and large cell lymphomas have been described. There have been occasional reports of lymphoma of MALT type (Diebold *et al.*, 1990; Issacson and Norton, 1994). Age at diagnosis in the non-immunocompromised individual ranges from 4.5 to 81 years and the condition is more frequent in the male population. Symptoms at presentation include dysphonia, dysphagia stridor and cervical lymphadenopathy (Swerdlow *et al.*, 1984; Kleinsasser, 1988). Eighty per cent of these lymphomas arise from the vestibule and aryepiglottic folds and the swelling is usually diffuse and often spherical, occasionally extending to the epiglottis and hypopharynx (Kleinsasser, 1988).

Radiotherapy is the principal form of treatment at times combined with surgical excision and/or chemotherapy. Where lymphoma is localized to the larynx, response to treatment is often good and in many cases may be curative (Swerdlow *et al.*, 1984; Kleinsasser, 1988; Morgan *et al.*, 1989).

NHL occurs approximately 20 times more frequently in patients with human immunodeficiency virus (HIV) infection compared with the general population (Sparano, 1995) and is an AIDS-defining illness. Up to 75 per cent of tumours arise in extranodal sites and the most common sites in order of frequency are the central nervous system, bone marrow, ileum, Waldeyer's ring and oral cavity, anorectum, stomach and colon (Isaacson and Norton, 1994). Lymphomas outside the central nervous system are seldom localized and the histology is usually of a high grade diffuse large cell, immunoblastic or poorly differentiated type. The vast majority possess a B cell phenotype (Sparano, 1995).

Primary NHL of the larynx has to date been previously documented in four HIV-positive patients (Leess *et al.*, 1987; Bullingam and Mackenzie, 1989; Siegel *et al.*, 1992; Laing *et al.*, 1995). We present a further case of primary NHL of the larynx in a patient with a four-year history of AIDS. Despite only single doses of radiotherapy being used on two separate occasions, the patient survived for two years, being disease-free at the time of his death from fulminant AIDS.

Case report

A 41-year-old homosexual male who had been diagnosed as HIV-positive with AIDS four years previously (CDC of 26 at diagnosis) was referred to the Department of Otolaryngology with a two-week history of progressive dyspnoea, dysphonia and sore throat. He was a teetotal non-smoker, with no family history of malignancy. He had survived two episodes of *Pneumocystis carinii* prior to this episode and had generalized molluscum contagiosum. A mild biphasic stridor was evident at rest. Indirect laryngoscopy revealed oedematous vocal and vestibular folds, and a provisional diagnosis of acute laryngotracheobronchitis of candidal or viral origin was made. There was no

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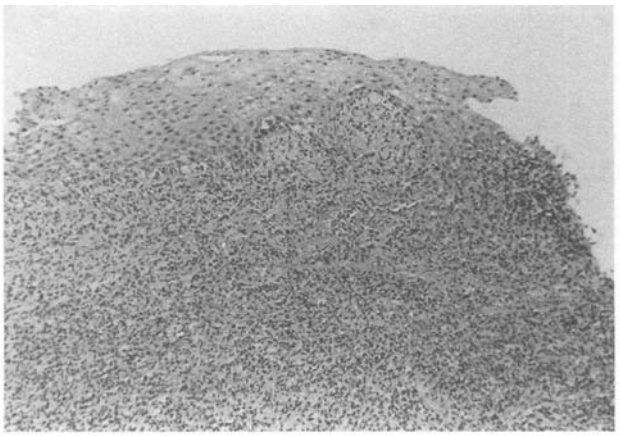

FIG. 1
Ulcerated laryngeal mucosa infiltrated by lymphoma (H & E; × 50).

palpable cervical or peripheral lymphadenopathy, nor hepatosplenomegaly.

His serum electrolytes and liver function test were within normal limits except for an increased total protein of 95 g/l. Haematological investigations showed a diminished white cell count of 2.2 × 10^9/l, Haemoglobin 12.7 g/dl, and plasma viscosity of 277. Chest X-ray was normal.

Examination of the larynx was performed under anaesthetic with a fibreoptic endoscope via a laryngeal mask and also by direct rigid examination. This showed oedematous vocal true and false vocal folds. In view of the narrow slit-like airway a tracheostomy was performed and a size 8 Portex cuffed tracheostomy tube inserted. Biopsies of both vocal folds were reported as demonstrating 'oedematous laryngeal mucosa associated with increased vascularity and patchy non-specific chronic inflammatory cell infiltrate. There were no granulomata and a Ziehl-Nielsen stain for acid fast bacilli was negative. Occasional hyphal elements were seen within the tissue consistent with *Candida* sp. There was no evidence of neoplasia.

A month later in view of a general deterioration of the patient's condition repeat direct laryngoscopy was performed. This showed a friable mass above the right vocal fold extending into the ventricle with no other abnormality on laryngopharyngoscopy. A biopsy of the lesion revealed a high grade NHL of B-cell lineage (CD20 positive, L26 positive, CD3 negative, UCHL 1 negative) (Figures 1 and 2). The lymphoma was of diffuse infiltrative appearance and the tumour cells were of variable morphology. There was an admixture of medium to large atypical lymphoid cells. The latter included some of centroblastic morphology and occasional cells of immunoblastic appearance. There was no evidence of head and neck lymphatic involvement either within the cervical chain nor in Waldeyer's ring. Computed tomography and bone marrow biopsy did not reveal any evidence of disease outside the larynx. He was referred for primary radiotherapy and received a single fraction of 800 cGy to the left neck two weeks later.

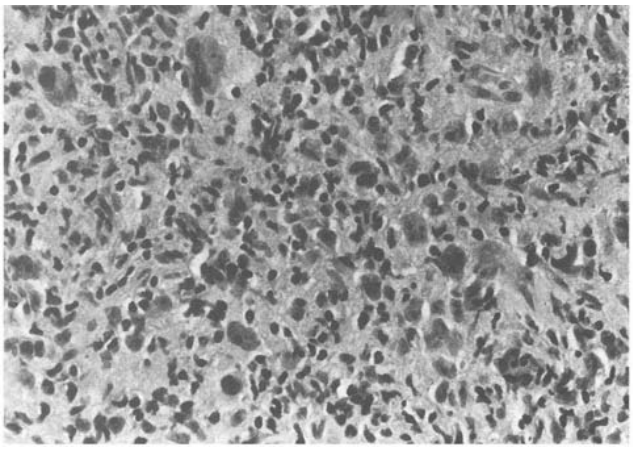

FIG. 2
Diffusely infiltrative high grade lymphoma with admixture of medium and large atypical lymphoid cells (H & E; × 400).

The patient remained asymptomatic with the tracheostomy in place and subsequently underwent examinations under anaesthetic at seven and nine months to consider decannulation. However these procedures revealed a stenotic subglottis of 3 mm of diameter with fixed rigid vocal folds. On both occasions the stricture was dilated to size 32 FG with bougies, and the biopsied oedematous vocal folds had histological features consistent with radionecrosis with no evidence of recurrence. He was then treated with 30 sessions of hyperbaric oxygen which produced a reduction in the observed laryngeal oedema.

Five months later, he became virtually aphonic and his tracheostome was found to be oedematous and with some areas of granulation tissue. A further examination under anaesthetic showed again a very oedematous supraglottic area especially on the right side. Biopsies taken from this site and the tracheostome revealed recurrence of the primary tumour in both sites. A further dose of 600 cGy of radiotherapy was given in this occasion via an anterior neck field. He remained asymptomatic and repeated fibreoptic nasendoscopic examination of the larynx did not reveal any signs of tumour recurrence. Eight months later the patient died of generalized debility, recurrent pneumonia and dementia.

Discussion

A significant minority of patients with AIDS have their first medical contact through Otolaryngology clinics with upper aero-digestive pathology, these include NHL, Kaposi's sarcomas, squamous cell carcinomas, candidiasis, chronic cough due to *Pneumocystis carinii* and atypical mycobacteria pneumonias, herpes simplex and oral hairy leukoplakia (Marcusen and Sooy, 1985; Stafford *et al.*, 1989; Corey and Seligman, 1991).

Primary lymphoreticular malignancies of the larynx include NHL, mycosis fungoides, plasmacytomas and malignant histiocytomas (Mackenty, 1934; Horny and Kaiserling, 1995). Such opportunistic malignancies in patients who are HIV-positive are considered AIDS-defining illnesses (Sparano, 1995). Other malignant manifestations of the larynx reported in association with AIDS are Kaposi's sarcoma (Stafford *et al.*, 1995) and squamous cell carcinoma (Munoz *et al.*, 1994). Kaposi's sarcoma of the larynx is found exclusively in AIDS patients. These sarcomas tend to be multifocal and affect other parts of the head and neck region at the same time (Stafford *et al.*, 1989). Squamous cell carcinoma of the larynx in the AIDS population is again extremely rare with just two cases described. These affected relatively young patients, and had a generally more aggressive clinical course than in non-AIDS patients (Munoz *et al.*, 1994).

When considering cases of NHL in the non-HIV infected population, 10 to 35 per cent originate in extranodal sites, particularly those of the gastrointestinal tract and the head and neck region (Swerdlow *et al.*, 1984). Their natural history often differs from primary nodal disease (Swerdlow *et al.*, 1984). NHL limited to the larynx is rare. Symptoms at onset generally include hoarseness

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TABLE I

JOURNAL SOURCE, CLINICAL FEATURES, MANAGEMENT AND OUTCOME OF AIDS PATIENTS WITH PRIMARY NON-HODGKIN'S LYMPHOMA OF THE LARYNX

Patient no.	Source/date	Age : Sex	Presenting symptoms	Site	Histological type	Management	Outcome
1	Lees *et al.* (1987)	52 : Male	Sore throat Stridor	Supraglottis Hypopharynx	Intermediate grade Diffuse mixed cell	Laryngoscopy Tracheostomy	Rapid death Haemorrhage
2	Bullingham and Mackenzie (1989)	30 : Male	Stridor Dysphonia Cough	Subglottis	Non-Hodgkins (not specified)	Laryngoscopy Tracheostomy	Not specified
3	Siegel *et al.* (1992)	48 : Male	Dysphagia Odynophagia	Supraglottis	CMV laryngitis probable lymphoma	Laryngoscopy Radiotherapy Gancyclovir	Not specified
4	Laing *et al.* (1995)	31 : Male	Sore throat Stridor Dysphagia	Larynx	High Grade B cell Lymphoma	Laryngoscopy Tracheostomy Radiotherapy	Temporary significant improvement
5	Simo *et al.* (present case)	41 : Male	Stridor Sore throat	Glottic Supraglottic	High Grade B cell Lymphoma	Laryngoscopy Tracheostomy Palliative radiotherapy × 2	Significant improvement Died disease-free 2 years

which may be observed a few years prior to diagnosis. The majority are of diffuse histology when classified by the Rappaport system (Swerdlow *et al.*, 1984). Swerdlow in 1984 reported 16 cases of laryngeal NH lymphoma treated primarily by deep radiotherapy who were disease-free after a mean follow-up of 6.5 years. The tumoral dose ranged from 400 to 6100 cGy and was supplemented by chemotherapy in one patient and laryngeal surgery in a further two patients (Swerdlow *et al.*, 1984).

External beam deep radiotherapy would appear to be the curative treatment of choice in these lymphomas. Further deep radiotherapy may be used for recurrence with the expectation of prolonged survival (Swerdlow *et al.*, 1984; Kleinsasser, 1988; Morgan *et al.*, 1989). Chemotherapy may be used on an adjuvant basis (Kleinsasser, 1988). The role of surgery is primarily for diagnostic purposes and for debulking the tumour but the role of surgical excision has not been fully defined in the literature (Swerdlow *et al.*, 1984; Kleinsasser, 1988).

Within the English literature we have identified four previous reports of NH lymphomas of the larynx in HIV positive patients. In 1987, Leess *et al.* reported four AIDS patients with NHL of the head and neck, one of them from a laryngeal site, but the patient died of a laryngeal haemorrhage before any curative therapy could be instituted (Leess *et al.*, 1987). Bullingam and Mackenzie in 1989 reported an AIDS patient with a subglottic NHL but details of therapy or outcome were not stated in the report (Bullingam and Mackenzie, 1989). Siegel *et al.* in 1992 described a probable case of NHL of the larynx. This author suggested that cytomegalovirus may have indirectly oncogenic by reactivating Epstein-Barr virus and so producing neoplastic change (Siegel *et al.*, 1992). Recently, in 1995, Laing *et al.* reported four AIDS patients who had been treated for stridor, one of them was found to have a high grade B cell lymphoma of the larynx, details of the specific laryngeal site or the current status were not given (Laing *et al.*, 1995) (Table I). To our knowledge this case therefore, represents the only fully documented account of the diagnosis, treatment and outcome of an AIDS patient with high Grade B cell NHL of the larynx.

Histologically, two cases are of high grade, one of intermediate grade, one not specified and one not confirmed. The clinical presentation in these patients in the context of AIDS is much more aggressive with progressive acute stridor and upper respiratory distress, usually requiring tracheostomy to secure the airway (Leess *et al.*, 1987; Bullingam and Mackenzie, 1989; Siegel *et al.*, 1992; Laing *et al.*, 1995). One patient was treated with radiotherapy. Initially the patient had a rapid significant improvement however, the long-term outcome was not recorded (Laing *et al.*, 1995). Our patient after a single dose of 800 cGy also had a good clinical response. Although he required a second treatment for recurrence, again the clinical response was excellent, his larynx being clinically disease-free at the time of his death.

The effect of deep radiotherapy in the treatment of AIDS patients with NHL of the larynx therefore appears to be analogous to its role in non-AIDS infected individuals.

Taking into account that recent advances in the treatment of AIDS may provide the means of maintaining immunological function and substantially postponing disease progression and death (Cohn, 1997) we would suggest that AIDS patients affected by NH laryngeal lymphoma should be treated in an equivalent manner to their non-AIDS counterparts. This would in most cases take the form of external beam deep radiotherapy, although the optimum dose is yet to be determined. The role of chemotherapy, as with non-AIDS individuals has not been established (Swerdlow *et al.*, 1984). Surgery in AIDS patients with primary laryngeal NH lymphomas has been restricted to obtaining tissue for histological diagnosis and tracheostomy for airway management, both in the acute phase and in relation to radiotherapy. Long-term decannulation has not been possible in these cases (Leess *et al.*, 1987; Bullingham and Mackenzie, 1989; Laing *et al.*, 1995). As in non-AIDS patients with laryngeal lymphoma, the role of laryngeal resection surgery in AIDS patients has not been established.

This case report highlights the importance of careful laryngoscopic assessment with adequate biopsy for HIV positive/AIDS patient with laryngeal symptoms. Although the number of AIDS patients with NH laryngeal lymphoma is extremely small, this case report indicates that some patients may have a relatively good response to treatment. The treatment chosen should carefully take account of the overall disease state. Unless the patient is in the terminal stage of AIDS, radiotherapy with curative intent should be used as the primary treatment modality.

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