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Clinical features of malignant transformation in benign laryngeal papillomata

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Abstract

Laryngeal papillomata can undergo spontaneous malignant transformation without being detected histologically and, in some instances, the disease may become so advanced, before the diagnosis is confirmed, that it is beyond any form of curative treatment.

Because of this limitation imposed by histopathological investigation, a study was undertaken in 17 adults with benign laryngeal papillomata, (three of whom underwent malignant transformation) to determine whether malignant transformation can be predicted from the clinical behaviour of the tumour. The following features were analysed: age, sex, patient's symptoms, frequency of excision of the papillomata, site of lesion, presence or absence of laryngeal oedema, the need for tracheostomy, vocal fold mobility and presence or absence of cervical lymph nodes.

It was found that decreased vocal fold mobility, the presence of cervical lymph nodes, exuberant and rapid growth requiring very frequent excisions, oedema of the larynx with airway obstruction requiring a tracheostomy are clinical features suggestive of malignant transformation.

Key words: Laryngeal neoplasms; Papilloma

Introduction

Laryngeal papillomata can undergo malignant transformation without being detected histologically and, in some instances, the diagnosis only becomes apparent when there is either direct invasion of the soft tissue of the neck (Walsh and Beamer, 1950; Zehnder and Lyons, 1975; Kashima *et al.*, 1988) or metastases (Siegel *et al.*, 1979; Bewtra *et al.*, 1982).

Secondly, malignant transformation occurs both in irradiated (Le Jeune, 1941; Walsh and Beamer, 1950; McCart, 1954; Galloway *et al.*, 1960; Rabbett, 1965) and nonirradiated patients (Toso, 1971; Zehnder and Lyons, 1975; Keim, 1980; Olofsson *et al.*, 1980; Yoder and Batsakis, 1980; Lim and Chang, 1987).

If the management of a patient with laryngeal papillomata is dependent solely on histological diagnostic criteria, then malignant transformation will go unnoticed and the disease will progress to such an extent before the diagnosis can be established histologically that it will be beyond any form of curative treatment.

Materials and methods

Over a 10-year period, from 1981 to 1990, laryngeal papillomata were diagnosed histologically in 57 patients at King Edward VIII Hospital. Forty were of juvenile and 17 adult onset. Three adults were later found to have squamous cell carcinoma. A retrospective study was performed on these 17 adult patients, analysing age, sex, symptoms, the site of the lesion, frequency of excision, presence or absence of laryngeal oedema, the need for tracheostomy, vocal fold mobility, presence or absence of cervical lymph nodes and histological features to determine which of these correlated best with malignant transformation.

There were 11 males and 6 females. Their ages ranged from 23 to 70 years, as shown in Table I. All those with carcinoma were males and their ages were 50, 58 and 70 years. Besides hoarseness of voice and stridor, two patients presented with dysphagia, and both had carcinoma. The papillomata were supraglottic in one, glottic in nine, supraglottic and glottic in four, glottic and subglottic in one (patient with malignant transformation), supraglottic, glottic and subglottic in two (both with malignant transformation). Of the 14 patients with multiple excisions, in eight (57 per cent), the papillomata were confined to the same region (glottis). The interval between excision varied from one week to 40 months. In the non-carcinoma group (14 patients) the interval was never less than two months. Two patients who presented with dysphagia had oedema and inflammation of the epiglottis, false fold and arytenoids. The oedema was so gross that even after excision of the 'papillomata' no laryngeal airway could be secured, and a tracheostomy had to be performed. Limitation of vocal fold mobility was noted in three patients (all had malignant transformation).

Cervical lymph nodes were only present in those patients with carinoma. In the first patient, a 1 × 1 cm lymph node was present, at the initial visit. In the second

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TABLE I
NUMBER OF PATIENTS IN THE DIFFERENT AGE GROUPS

Age groups (years)	20–30	31–40	41–50	51–60	61–70
No. of patients	2	3	3	7	2

patient, a 1.5 × 2 cm lymph node was found after nine months and, in the third a 7 × 10 cm fixed lymph node was noted ten months later.

The histological features of three patients with carcinoma were as follows: in the first patient, of the two tissue samples taken at a one week interval, the first one displayed typical features of squamous papillomata but there were a few areas with increased mitotic activity, hyperchromatic nuclei and mild pleomorphism. In the second patient, of the seven tissue samples taken over a period of nine months, only the second one displayed occasional mitoses and few pleomorphic cells. In the third patient, of the five tissue samples taken over 10 months, the third displayed minimal atypia. None of these patients had had radiotherapy previously. These three patients are discussed in greater detail.

Case reports

Case 1

A 70-year-old African male, presented with a six-month history of hoarse voice and stridor. He had been smoking 100 g of tobacco per week for 50 years. Examination revealed a verrucous lesion, involving the right false fold, with slight limitation of movement of the arytenoid on that side. He had a 1 × 1 cm, soft, mobile, upper cervical lymph node on the right. The lesion was removed with a microcup forceps. The histology showed features of squamous papillomata but there were a few areas with increased mitotic activity, hyperchromatic nuclei and mild pleomorphism. Because of the cervical lymphadenopathy and restriction of vocal fold mobility, it was decided to rebiopsy the lesion. Three superficial biopsies were taken with a microcup forceps and one large piece of tissue (1 × 1.5 cm) was excised with a microscissors.

The histology of the three specimens was in keeping with benign squamous papillomata and that of the large specimen moderately differentiated squamous carcinoma. He refused surgery and was therefore treated with radiotherapy.

Case 2

A 50-year-old African male, presented in August, 1988, with a five-year history of hoarse voice. He had been treated for asthma for the preceding three years. He had smoked between 12 and 15 cigarettes per day for 25 years. Examination revealed a papillomatous growth involving the right and left true folds and the anterior commissure. The left fold was more involved than the right. The histology was consistent with benign squamous papillomata (Figures 1a and b).

Following this over a four-month period from October 1988 to February 1989, he was admitted four times to the hospital with symptoms ranging from difficulty in breathing out to progressive stridor and dysphagia. On all four occasions, he was taken to theatre for excision of the papillomata and the histology was always in keeping with squamous papillomata.

The fourth time a tracheostomy had to be performed because the supraglottic oedema which was noted previously had increased to such an extent that it prevented an adequate laryngeal airway. Direct laryngoscopy performed five weeks later revealed extensive transglottic papillomata on the left and persistence of supraglottic oedema. The papillomata, together with part of the oedematous supraglottic tissue was excised with the carbon dioxide laser to give him an adequate airway. The tracheostomy tube was removed, but had to be reinserted three weeks later because of severe stridor. Examination of the neck at that time revealed a 1.5 × 2 cm mobile, upper cervical, lymph node. On direct laryngoscopy a transglottic tumour, with a 2 cm subglottic extension was noted on the left.

Five pieces of tumour tissue were removed with a large microcup forceps and sent for histological examination. Three pieces showed papillary acanthosis and varying degrees of dysplasia, whilst two fragments showed evidence of squamous carcinoma (Figure 2). Laryngectomy and a left radical neck dissection was performed. The laryngeal specimen had a 3 cm transglottic ulcerating tumour. The histology showed features of an infiltrating, well differentiated, squamous carcinoma.

Histological analysis of the four cervical lymph nodes (one upper and three lower), showed reactive hyperplasia and sinus histocytosis, without any evidence of tumour.

Case 3

A 58-year-old African male presented in December 1989, with a two-year history of hoarseness and a two-week history of progressive stridor. He had smoked 10 cigarettes per day for 30 years. On examination, he had severe stridor and a tracheostomy was performed. Direct laryngoscopy revealed a verrucous lesion involving the right true fold, the ventricle and the posterior commissure. This was excised. The histology of the fragments showed features typical of benign squamous papillomata (Figures 3a and b).

Five months later in April 1990, he was readmitted with stridor. The tracheostomy tube was found to be partially blocked. The tube was changed. Direct laryngoscopy revealed extensive papillomatous growth, involving the right true and false folds and the posterior commissure, also oedema of the supraglottic region. A laryngeal airway could not be secured, even after complete excision of the papillomata, and therefore he could not be decannulated. One week later, examination of the larynx was performed under general anaesthesia; there was extensive papillomatous growth involving the true and false folds bilaterally.

Histology showed features of squamous papillomata but there were some areas with minimal mitotic activity and dysplasia. He did not keep his hospital appointment, and was lost to follow-up. Six months later he presented with severe dysphagia and a mass in the neck of three weeks' duration. On examination, a 10 × 7 cm fixed cervical lymph node was found in the left anterior triangle of the neck. Indirect laryngoscopy revealed the tumour mass to involve the base of the tongue. The histology of this mass and the one in the neck was in keeping with

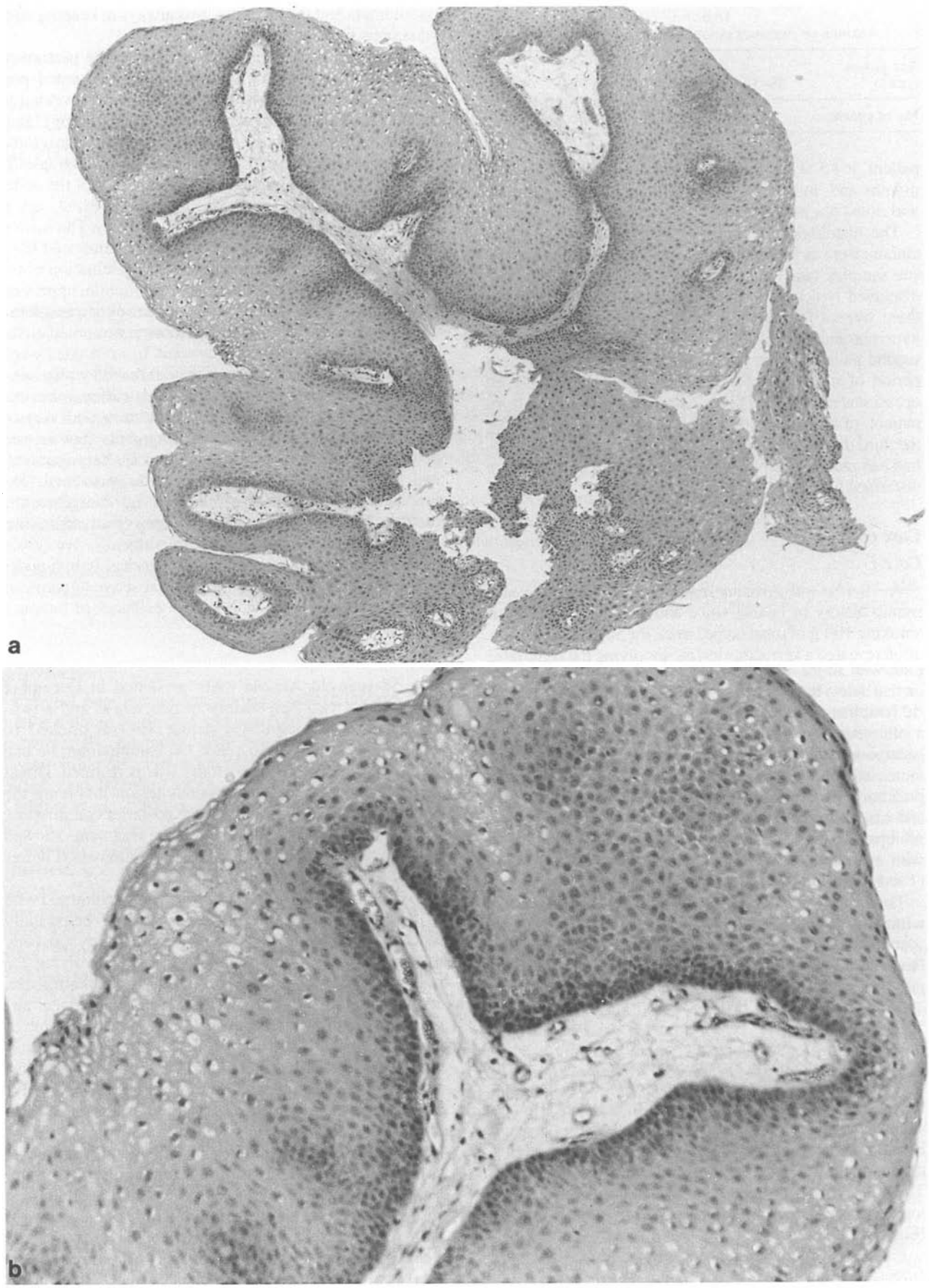

FIG. 1

(a) Low power photomicrograph showing papillary structure lined by acanthotic benign squamous epithelium. (b) High power photomicrograph showing acanthotic hyperplastic squamous epithelium with fibrovascular core and numerous vacuolated cells. (H & E).

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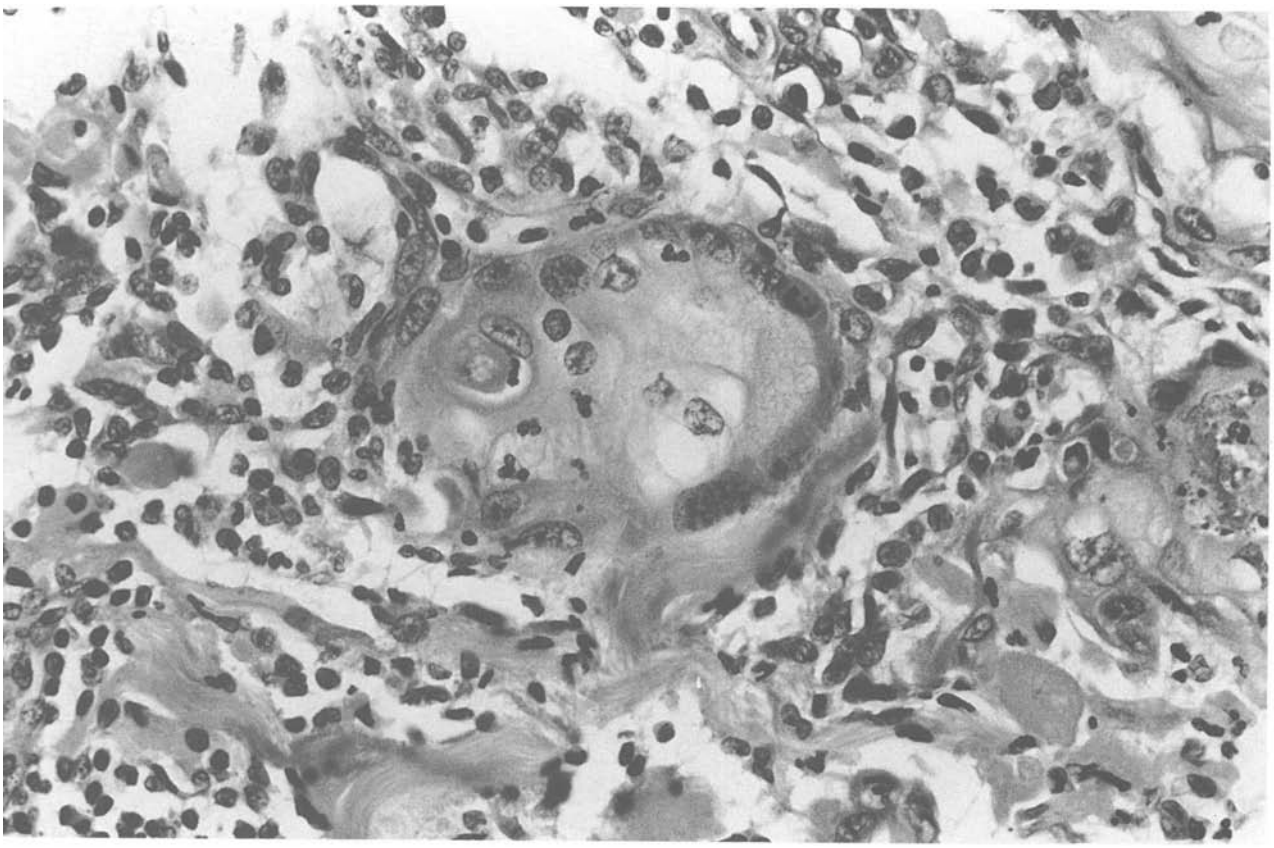

Fig. 2
High power photomicrograph showing infiltrating moderately differentiated squamous cell carcinoma. (H & E).

squamous carcinoma (Figure 4). He was given palliative radiotherapy.

Results

Of the 17 patients with benign laryngeal papillomata, malignant transformation occurred in three. All three were male patients and smoked heavily. Furthermore, all those with squamous carcinoma were 50 years of age and older.

The clinical features which correlated well with malignant transformation are listed in Table II.

Dysphagia

Of the 17 adult patients with laryngeal papillomata, two presented with dysphagia; in both it was indicative of malignant transformation. The dysphagia was due to gross oedema and inflammation of the supraglottis, especially the arytenoids.

This feature was also noted (Walsh and Beamer, 1950; Zehnder and Lyons, 1975; Matsuba *et al.*, 1985) in patients with malignant transformation.

Subglottic extension

This seems to be a strong clinical feature indicative of malignant transformation. In the present series, there were only three patients with subglottic extension and all three were later diagnosed as having squamous cell carcinoma. Similarly, those patients with malignant transformation have been reported by other authors (Shapiro *et al.*, 1976; Siegel *et al.*, 1979; Matsuba *et al.*, 1985) and all had subglottic extension.

The interval between excision

Excision of the papillomata to keep the laryngeal airway patent in a patient with benign laryngeal papillomata is usually greater than two months, but when the papillomata undergoes malignant transformation, the interval decreases to less than two months as observed in two patients, both with malignant transformation. Similarly, Siegel *et al.* (1979) reported that their patient with tracheobronchial papillomata, which underwent malignant transformation, required increasingly frequent removal of the papillomata to maintain the airway.

Tracheostomy

Patients with benign laryngeal papillomata generally do not require a tracheostomy unless they have severe stridor. This is a rare event if the patients are followed-up closely and the papillomata excised electively. If a tracheostomy is performed, the patients are usually easily decannulated after removal of the papillomata. In the present series, there were three patients who had tracheostomies performed at a peripheral hospital on their first presentation. All of them were decannulated after excision of the papillomata.

In two patients the laryngeal airway could not be secured even after complete excision of the papillomata and they required tracheostomies. In these patients the obstruction was due to the laryngeal oedema and not the papillomata as many attempts at decannulating them, by almost complete removal of the papillomata, failed. Both these patients were later found to have squamous cell car-

FIG. 3
(a) Low power photomicrograph showing papillary structure with central fibrovascular core covered by benign squamous epithelium. (b) High power photomicrograph showing acanthotic hyperplastic squamous epithelium with fibrovascular core and numerous vacuolated cells. (H & E).

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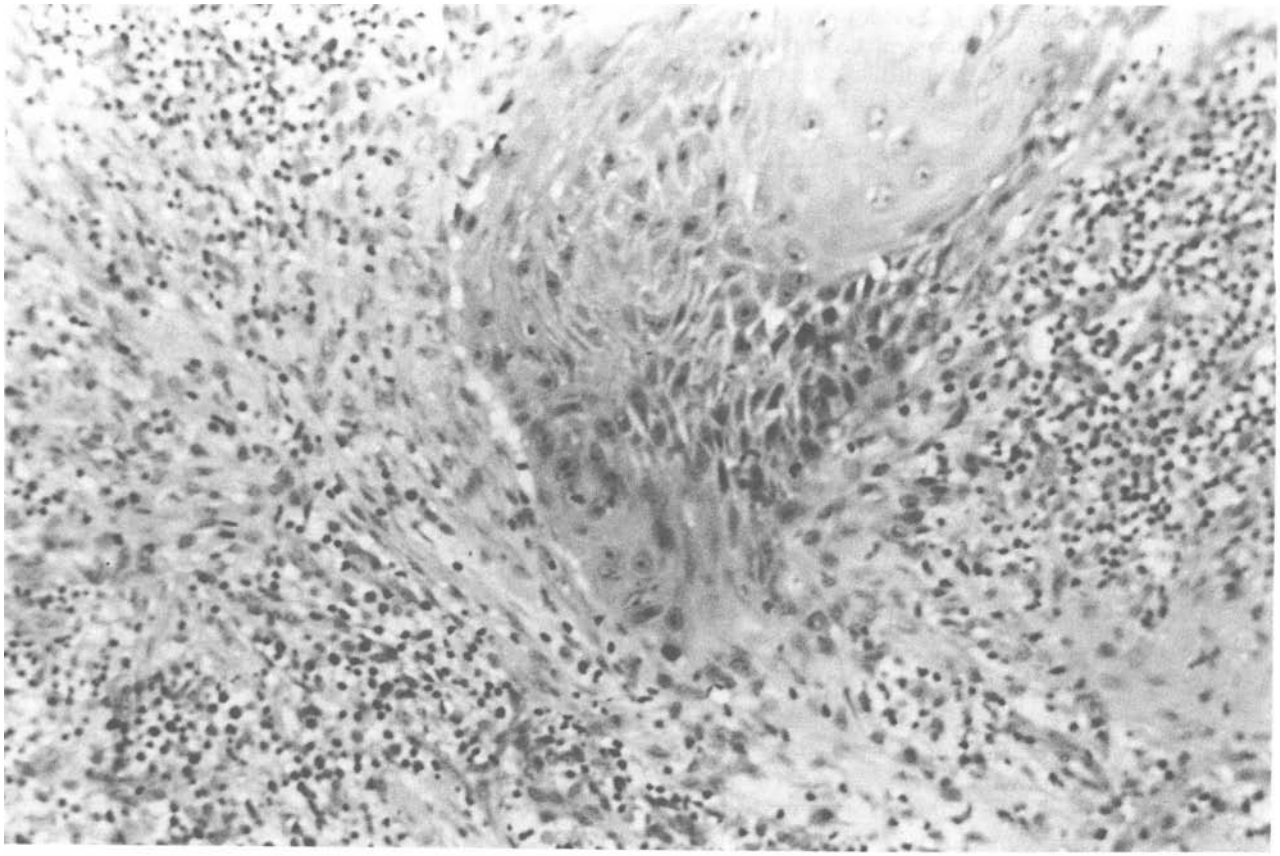

Fig. 4
Low power photomicrograph showing infiltrating metastatic squamous cell carcinoma involving a cervical lymph node. (H & E).

cinoma. Similar findings were reported (Seigel *et al.*, 1979; Bewtra *et al.*, 1982; Kashima *et al.*, 1988).

Limitation of vocal fold movement

Limitation of vocal fold movement is indicative of deep infiltration with muscle involvement and does not occur with benign squamous papillomata, which is basically a mucosal disease. If present then it is suggestive of malignant transformation. In the present series, limitation of vocal fold movement was noted in three patients. All three were later found to have squamous cell carcinoma. Walsh and Beamer (1950) also observed and reported limitation of vocal fold movement in one patient in whom the laryngeal papillomata underwent malignant transformation.

TABLE II
CLINICAL AND HISTOLOGICAL FEATURES ASSOCIATED WITH MALIGNANT TRANSFORMATION

Clinical and histological features	Benign squamous papilloma (14 patients)	Malignant transformation (3 patients)	Total
Dysphagia	–	2	2
Subglottic involvement	–	3	3
Interval between excisions <2 months duration	–	2	2
Tracheostomy	–	2	2
Limitation of vocal fold mobility	–	3	3
Cervical lymphadenopathy	–	3	3
Oedema of supraglottis	–	2	2
Atypia	2	3	5

Cervical lymphadenopathy

This does not occur with benign laryngeal papillomata, as no report of this has been found in the literature. Therefore any patient who is previously known to have benign laryngeal papillomata who presents with cervical lymphadenopathy has malignant transformation of the papillomata until proven otherwise. In the present series, there were three patients with cervical lymphadenopathy and all three had squamous cell carcinoma of the larynx.

Lymphadenopathy does not necessarily signify metastases as the histology of the four cervical lymph nodes removed by radical neck dissection in one of the patients showed reactive hyperplasia without any evidence of malignancy. Similarly Siegel *et al.* (1979) reported that the histology of paratracheal lymph node in a patient with malignant transformation of the tracheobronchial papillomata showed hyperplasia without tumour invasion. Thus lymphadenopathy, whether it contains metastatic tumour or not, signifies malignant transformation.

Gross oedema of the larynx

Oedema necessitating a tracheostomy to maintain an airway, even after excision of the papillomata has not been reported in the literature in patients with laryngeal papillomata, and neither has it been noted in any one of the 14 patients with benign laryngeal papillomata.

In the present series, three patients developed gross oedema of the larynx, resulting in airway obstruction and requiring tracheostomy. Malignant transformation occurred in all. Numerous attempts at decannulating them failed.

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Thus, if any patient who is known to have laryngeal papillomata presents with laryngeal oedema to such a degree that a tracheostomy is indicated, then malignant transformation must be suspected in such a patient.

Atypia

This is a histopathological feature which is not very helpful in either predicting or diagnosing malignancy as atypia of varying degree can occur in juvenile laryngeal papillomata at any one time (Quick *et al.*, 1979; Cohen *et al.*, 1980; Bjelkenkrantz *et al.*, 1983; Robbins and Howard, 1983). Secondly there is no progressive stepwise transformation of laryngeal papillomata to invasive squamous cell carcinoma, from mild to moderate, to severe atypia, and then obvious invasive carcinoma.

In the present series, six patients displayed atypia but only three were found to have squamous cell carcinoma. In the one patient, atypia was noted in the first (out of two) biopsy specimens and in another in the second (of seven biopsy specimens).

Discussion

Because of the limitation imposed by histopathological investigation in detecting malignant transformation, one has to rely very heavily on the clinical behaviour of the tumour in deciding on the definite management so as to prevent the tumour progressing to such an extent that it is beyond the bounds of any form of curative treatment. The decision in some instances may entail laryngectomy. Justification for performing a laryngectomy, without histological proof of malignancy, in this type of patient is that the patient virtually has a useless larynx and will need a permanent tracheostomy anyway. Attempts at decannulating often fails (Cases 2 and 3).

Laryngectomy has been performed previously on three patients with laryngeal papillomata, just on clinical evidence of invasion but without histological proof of malignancy (Fechner *et al.*, 1974; Robbins and Howard, 1983).

Conclusions

Benign laryngeal papillomata can undergo malignant transformation without showing any specific histological features suggestive of this change. In some instances, the tumour might progress to such an extent before the diagnosis of malignancy can be confirmed histologically, that it is beyond the realms of any form of curative treatment. Therefore, in order to avoid such an outcome, the definite management of this type of patient, should be decided by the clinical behaviour of the tumour rather than on the histological diagnosis.

From the present study the following clinical features have been found to correlate well with malignant transformation, dysphagia, sudden rapid and exhuberant growth requiring excision at an interval of less than two months to keep the airway patent, subglottic extension, oedema of the larynx, especially of the supraglottic region, causing obstruction to the laryngeal airway even after complete excision of the papillomata, the sudden need for a tracheostomy to maintain the airway, limitation of vocal fold mobility and cervical lymphadenopathy.

Since none of these features was present in the other 14 patients with laryngeal papillomata, it can be assumed that these clinical features are suggestive of malignant transformation.

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