Chapter 31: Recurrent respiratory papillomatosis

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It is over 100 years since Mackenzie described what was thought to be an entity - juvenile laryngeal papillomata (Mackenzie, 1880). The implication was that papillomata were common only in children and that the only site of involvement was the larynx. This notion prevailed until the 1960s when it became apparent that the disease is not confined to the laryngeal mucosa and does occur in other areas of the respiratory tract. Furthermore, it became obvious that the disease was notoriously recurrent and that it persisted into adult life and, on other occasions, presented initially in adult life. This being the case, it appeared that a more descriptive term would be recurrent respiratory papillomatosis.

Background

The purpose of this chapter is to describe the characteristics of the disease, its behaviour and its management in children. The author's experience is based on 258 patients who were followed at University Hospital, Boston, USA, between 1971 and 1985. Of these patients, 150 were followed for one year or more and 81 patients were under the age of 15 years. Patients who could not be followed for more than one year are not included in the quoted statistics.

Presenting symptoms

The majority of children with recurrent respiratory papillomatosis present before the age of 4 years, although a not insignificant number may present during the first 6 months of life.

The initial symptom is hoarseness of voice or an abnormal cry. Increasing stridor and acute respiratory obstruction may occur but are usually late manifestations of the disease process. Papillomata form initially on the vocal cords themselves so interference with laryngeal function occurs early in the disease and hoarseness in a child should not be dismissed as being the result of vocal abuse: an endoscopy must be performed to establish the diagnosis.

There is a tendency for papillomata to occur at the anterior aspect of the glottis and the anterior commissure itself is frequently involved. It is uncommon for the interarytenoid mucosa to be involved in early cases; perhaps the thickness of the mucus blanket and the more rapid rate of its movement exerts a protective role in this situation. When the larynx is extensively involved the normal flow of the mucus blanket is disrupted and the papillomata then invade the whole of the larynx with equal facility. The disruption of the tracheal mucus blanket that occurs after tracheostomy may also be a factor in the often explosive increase in tracheal papillomata that is seen after a tracheostomy has been performed. It is for this reason that a tracheostomy should be avoided if it is possible to establish a normal airway by endoscopic removal of the papilloma.
Characteristics of the disease

The papillomata of recurrent respiratory papillomatosis are benign squamous papillomata that occur in clusters on the involved mucosa; the fronds of papilloma may be sessile and spread over a wide area of mucosa or they may be pedunculated and localized. The lesions are characteristically non-keratinizing.

It is characteristic that the lesions are multiple; occasionally at the onset of the disease or if the disease is about to become quiescent, only a single lesion may be manifest.

The lesions are notoriously recurrent even after the most radical extirpation. Recurrence may become an airway problem within 2 weeks or nothing may be visible for perhaps 5 or 20 years. The reason for this is that the lesions do not recur from the depth of the wound, but rather from the apparently normal mucosa adjacent to the original lesion. On some occasions it appears that removal of the papillomata has an enhancing effect on the growth rate of the lesions, so that the recurrence may be larger than the original lesion.

Recurrent respiratory papillomatosis is a diffuse diathesis of the mucous membrane of the upper air and food passages; the papillomata may be encountered in the nostrils at the mucocutaneous junction, on the gingiva and lips, on both surfaces of the soft palate and the adjacent tonsillar pillars, in the larynx, in the tracheobronchial tree and occasionally in the pulmonary parenchyma and at the oesophageal inlet. The lesions have a predilection for points of airway constriction, where there is increased air flow, drying, crusting, and irritation; this is particularly evident around the tracheostomy site and at the tip of the tracheostomy tube. Most commonly the larynx is the site of greatest involvement and is often the only site (Strong et al, 1976).

Aetiology

The aetiology or recurrent respiratory papillomatosis is now known to be infection of the epithelial cells with human papilloma virus. Although electron microscopy has only rarely demonstrated viral particles in papilloma specimens (Incze et al, 1977), immunofluorescent techniques have shown incontrovertible evidence of the footprints of human papilloma virus DNA having been incorporated into the cellular DNA (Steinberg et al, 1983). Furthermore, it has been shown by electron microscopy and immunofluorescence that apparently normal mucosa adjacent to the papillomata contains intracellular viral DNA of human papilloma virus. After removal of the lesions, these infected cells may become activated, leading to the formation of another lesion - a recurrence. This of course explains the difficulty in affecting 'a cure' of the disease by using mechanical means of removal alone. This phenomenon has been duplicated in the finding of latent human papilloma virus in the normal skin surrounding genital warts (Ferenczy et al, 1985). So far it has not been possible to isolate and propagate the virus.

Epidemiology

Recurrent respiratory papillomatosis has a world-wide distribution, although in some countries and areas it is more prevalent than in others. The incidence in the USA was 7/100,000 per year in 1976 (Strong et al, 1976); this suggests an incidence of approximately
1500 or more new cases per year. These cases were distributed between children and adults; slightly more cases being diagnosed before the age of 16 years than after. Furthermore, recurrent respiratory papillomatosis is found in all socio-economic segments of society and is not confined to disadvantaged patients as was previously thought. At the present time there is a suspicion that the incidence of the disease starting in early adult life is increasing.

The natural history of recurrent respiratory papillomatosis

Transmission

The transmissibility of recurrent respiratory papillomatosis must be very low because, as yet, it has not been recorded in siblings. There is considerable circumstantial evidence that, in some patients, the disease is transmitted at the time of delivery from a mother infected with genital warts. If a child contracts a disease before 5 years of age, there is a 60% probability that the mother had genital warts at the time of delivery (Strong et al, 1976). Because of this worrisome association, some thought was given to advising the mother of a child with recurrent respiratory papillomatosis who is infected with genital warts, to consider having the delivery of her next child by caesarean section. However, since the disease has not been demonstrated in siblings, this precautions seems to be unnecessary.

Remission

Remission of recurrent respiratory papillomatosis can take place at any age and at any time; whether remission occurs or not appears to be unrelated to the thoroughness of the removal or to the method of removal of the disease. The use of the CO₂ laser allows removal of all visible disease while causing minimal damage to the laryngeal musculature and function. Table 31.1 shows that the chance of remission is greatest if the disease presents between the ages of 6 and 10 years (P = 0.01). The overall chance of achieving remission in patients less than 16 years of age at the time of presentation is 46% if they are followed for one year and treated by appropriate endoscopy and laser destruction; this can be compared with a 26% chance of remission if the disease becomes manifest at 16 year of age or later. Furthermore, the disease is more likely to undergo remission in the larynx (48%), than in the tracheobronchial tree (27%) or in the lungs (0%).

Duration of remission

The duration of remission varies from 2 years to life long; relapses may occur at any time and for no apparent reason. Since a relapse may occur in any patient at any time, the best we can hope for at present is prolonged remission rather than cure.

Recurrence respiratory papillomatosis does have the potential to spread. In 34 patients who had disease confined to the larynx and required tracheostomy for airway control prior to being seen by the author's team, 29 patients had developed tracheobronchial lesions that frequently were more difficult to keep under control than the original laryngeal lesions; in seven patients the disease progressed to involve the pulmonary parenchyma. In the lungs, the squamous epithelium of recurrent respiratory papillomatosis produces cystic spaces that are clearly visible on X-ray; the cysts are lined with squamous epithelium and are filled with fluid.
and sometimes air. Because the pulmonary spread is usually multicentric, it is relentlessly progressive and eventually fatal.

**Malignant degeneration**

The risk of malignant degeneration is extremely low unless radiotherapy had been used in an attempt to control the disease; thus radiotherapy is contraindicated in recurrent respiratory papillomatosis. In adults who smoke, malignant degeneration is not unusual; in this series two cases of squamous cell carcinoma and three of verrucous carcinoma were encountered. A few cases have been documented in the literature (Matsula et al, 1985).

**Management**

**Surgery**

The only satisfactory treatment of this condition is surgical, and this is usually carried out endoscopically. Endoscopy is carried out after the airway has been secured by the passage of an endotracheal tube. On occasions, the tube is withdrawn and ventilation continued with the Venturi apparatus to allow complete removal of papillomata on the arytenoids and elsewhere. The patient is then reintubated prior to the termination of anaesthesia.

Biopsy and total destruction of the papillomata with the CO$_2$ laser are carried out with complete removal of all visible papillomata on at least one occasion. If disease is found to involve the anterior commissure, two operations, 4 weeks apart, are required to avoid web formation, first treating one cord and then the other. In the event of recurrence, laryngoscopy and CO$_2$ laser destruction are repeated as often as necessary to preserve the airway and the voice; a purposeful attempt is made during these repeated operations to avoid exposing muscle.

**Current adjuvant therapy trials**

Because surgical removal with or without the laser does not eradicate the disease but merely preserves the airway and voice until such a time as a spontaneous remission occurs, the need for an effective adjuvant therapy is self evident.

Topical 5-fluorouracil was used after surgical removal in 11 patients; there was not question that the drug had a therapeutic effect on the residual lesions, but unfortunately after 8-10 months the disease would 'break through' the treatment. Topical 5-fluorouracil was therefore abandoned.

Systemic cisretinoic acid has been used in a controlled series of patients. The recurrence rate appeared to be slowed in some patients while in others there was no effect. One patient went into remission for 3 years - it is of interest that she had received the placebo! The side-effects of cisretinoic acid were significant. Elevation of liver enzymes and skin excoriation were most troublesome. Systemic cisretinoic acid is of no value in the treatment of recurrent respiratory papilloma.
Initially interferon held promise as an adjuvant therapy; the early reports from Scandinavia, Houston and Iowa were encouraging (Haglund et al, 1981; Goepfert et al, 1982; McCabe and Clark, 1983). However, in the cold light of day, it was apparent that in using currently available varieties of interferon, the most that can be anticipated is a slowing of the rate of recurrence or a temporary remission of the disease; the incidence of prolonged remission appears to be no greater than that accounted for by chance and spontaneous remission. Because frequent and prolonged remissions are not to be expected, the cost and morbidity of interferon are not warranted at this time.

**Conclusions**

Recurrent respiratory papillomatosis is a diffuse diathesis that affects the mucosa of the upper air and food passages in children. Spontaneous remissions of one year's duration occur in about 50% of patients, followed-up for one year. Dependable adjuvant therapy is not yet available. Treatment should be directed towards maintaining the airway and voice, and avoiding tracheostomy. Thus far, adjuvant therapy has not been shown to be of value. We must await the outcome of future clinical trials.