JUVENILE PAPILLOMA OF THE LARYNX TREATED BY LOCAL INJECTION OF BLEOMYCIN

SAKA SAKURAI, MASAHIRO TAKAHASHI, YASUO NAKAJIMA and TOSHIO ISHIZAKA

(Department of Otorhinolaryngology, Keiyu Hospital, Yokohama, Japan)

(Received for publication Sept. 30, 1974)

ABSTRACT

The case of a 3 year 2 month-old girl with a history of multiple papilloma and unsuccessful surgical treatments is reported in this paper. Microsurgery of the larynx and local injection of Bleomycin produced an effective result, however, and phonation was close to normal after 3 local injections. There has been no recurrence for one year after this last procedure, and the patient is considered to have been cured.

INTRODUCTION

There are many opinions regarding to the etiology of laryngeal papilloma. To date, however, the subject has not been fully explored and there is no decisive method of treatment.

Recently, a case of juvenile laryngeal papilloma was presented to our hospital in which repeated surgical treatment produced no improvement but which was cured by local injection of Bleomycin.

CASE REPORT

A 3-year-old girl visited our out-patient clinic on November 30, 1970 for investigation of a two-year history of marked hoarseness. At the time of examination, she was suffering from stridor and her home pediatrician made a diagnosis of bronchial asthma. The stridor had recently worsened and dyspnea developed after she caught a cold. There was nothing abnormal in her family

Reported by:
The 25th Annual Meeting of the Japan Broncho-esophagological Society (October 13-14, 1973)
history. She was born in [underline]. Physical examinations was within normal limit. She was well developed and nourished. No abnormality in the chest or abdomen was observed.

Otorhinolaryngeal examinations showed no abnormality of the ears, nose or throat. Indirect laryngoscopic examination revealed the reddish, melberry-like tumor tissue on both sides of the vocal cord. The glottis was almost closed except for a slight opening at the posterior part.

Based on the clinical findings, the girl was hospitalized for surgery in November 1970. Blood pictures, ECG, and pediatric examination showed no abnormalities. Duration of phonation was 2 seconds.

Trachotomy was carried out under general anesthesia followed by microsurgery of the larynx, on November 30, 1970. Numerous papillomatous tumors melberry-like in shape were observed bilaterally on the vocal cords, and the glottis was opened only at the posterior part. As much as possible tumorous tissue was removed. Histopathological examination revealed the presence of papillary proliferation (Fig. 1A). The epithelium consisted of hyperthrophied and multilayered squamous cells, irregular in arrangement. Slight irregularity of the nuclei but no mitotic figure was observed. As shown in Fig. 1B, basement membrane was maintained and basal cells were regularly arranged. Dilated capillary vessels were aggregated in the submucosal tissue and the stroma was slightly edematous. On the basis of these findings a diagnosis of laryngeal

Fig. 1A Histopathological examination revealed the presence of papillary proliferation.
Papilloma of the Larynx Treated Bleomycin

Fig. 1B Basement membrane was maintained and basal cells were regularly arranged. Dilated capillary vessels were aggregated in the submucosal tissue.

Papilloma was made. Postoperatively, her condition improved and she was discharged from hospital on December 12, 1970.

Regular follow up examinations were made after the first operation. A second operation was performed on March 23, 1971, due to recurrence of symptoms. Surgery was carried out 5 additional times until August 31, 1971, or at intervals of 1–2 months. When additional microsurgery of the larynx was performed on November 5, 1971, local injection of Bleomycin was administered. A solution of 15 mg of Bleomycin dissolved in 3 ml of distilled water was injected bilaterally into 4 sites in the subepithelial layer of the vocal cords, using a Keio type silicone injection needle, with a 0.5 mm tip. Although there was slight seepage, about one-half of the solution was successfully injected. After surgery, 2 mg of Decadron (Dexamethasone), 1 ampoule of Kimopsin (α-Chymotrypsin), and 500 mg of Keflodin (Cephaloridine) were injected intramuscularly for 3 days. The patient's condition was improved following the injection of Bleomycin but recurrence was observed, and microsurgery of the larynx was carried out again on February 3, 1972. The area of papilloma on both vocal cords appeared to be healed. Recurrence was observed in the area of the arytenoid cartilage. After removal of these papilloma Bleomycin ointment was applied to the site. Microsurgery of the larynx with local injection of Bleomycin was carried out 3 times until October 27, 1972. No recurrence has been observed for about 1 year since
the last local injection, and the lesion seems cured. A phonation test on August 17, 1973, showed duration of phonation to be 13 seconds, duration of expiration 16 seconds, and expenditure Index (Expiration time/phonations time) coefficient 1.2. Sonagraphic pattern, as shown in Fig. 2, indicated only a slight noise component. A distinct formant, and high sound were well appeared. Since there was no preoperative sonagram, it was not possible to make a comparison but this sonagram appeared to be normal. Improvement of phonation was also observed. At present, phonation is a little difficult but the girl can now sing and considerable improvement is evident.

COMMENT

There are various theories on the formation of laryngeal papilloma, such as viral origin, endocrine dysfunction, chronic irritation, and predisposition; however there is as yet no one definitive explanation. There are many interesting clinical manifestations. Although there is no great histological difference in the papilloma between children and adults, there is considerable clinical difference. In children, such papillomas are multiple and scattered, and are liable to recur. In adults, the papilloma is single and isolated, less liable to recur, and tends to become malignant. There have been many reports on its treatment but there is no decisive method since its etiology is still not fully explained. Surgically, the disease requires repeated operations, and it is necessary to consider measures against difficulty in removal of the cannula after trachectomy, treatment after recurrence, and measures against untoward postoperative effects upon phonation.

General treatment may be summarized as follows:

1) Surgical treatment: This is the most frequently employed therapy. Rarely is this disease cured by single surgery, and there is a possibility that
surgery may promote recurrence or diffusion to the larynx and bronchus. It has become possible in recent years to lessen injuries to healthy mucosa by microsurgery of this larynx, but this is very difficult when there are multiple lesions that have spread over a wide region. Surgery of the anterior commissure must be made with caution as there is a possibility of producing postoperative diaphragma of vocal cord.

2) Physical treatment: Electric cauterization and diathermy are said to produce contraction and are not currently used. Irradiation with x-rays, radium, and radon is said to be effective, but is not recommended due to the possibility of obstruction and contraction or of malignant change. In recent years, cryosurgery has been employed. Marres and others\(^1\) reported a cure after cryosurgery on a 20 month-old girl and Pearson\(^2\) also reported a cured case. Supersonic wave has also been recommended as effective therapy for this disease. Palva and Meurman\(^3\) and Birk and Manhart\(^4\) reported effective utilization of supersonic wave and inhibition of the growth of a virus. Preibisch-Effenberger\(^5\) reported 27 of 33 cases of supersonic wave therapy were effective and recommended its use in early stages of juvenile papilloma.

3) Immunological treatment: Moffitt\(^6\) employed a vaccine obtained from bovine wart and reported effective results in 4 cases. Holinger and others\(^7\) used autogenous vaccine in 8 cases and reported effective results in 3 of 4 juvenile cases and in all 4 adult cases, though there was some difference in the degree of effectiveness. A report by Holinger on cases treated in 1968\(^8\) described the autogenous vaccine as effective in 28 (55%) of 51 cases and ineffective in 13 cases (25%). Strome\(^9\) reported autogenous vaccine was effective in 3 cases, ineffective in 2 cases, and produced worsened effects in 2 of 7 cases. Thus vaccinotherapy yields negative as well as positive or indeterminate effects.

4) Drug therapy: Arsenic and magnesium have been used but are not being used at present. (a) Podophyllin treatment: Hollingsworth and others\(^10\) used podophyllin, a cell poison, with 5 children and reported cures without side-effects. Schilovtseva\(^11\) divided 110 cases into three groups of surgery alone, surgery with podophyllin and celandine, and surgery with celandine or podophyllin, combined with the use of magnesium, calcium, and (or) bromine, and reported the best results were obtained in the last group of 42 cases. Schilovtseva noted the very low content of magnesium and calcium in patients' serum before the treatment. (b) Hormone therapy: Follicle hormone is used principally; male hormone is ineffective. Broyles\(^12\) treated 5 children by directly spraying the larynx with oily follicle hormone and reported all cases cured after 6 months, with no side-effects. Szpunar,\(^13\) using a modified Broyles' method, injected follicle hormone locally into the submucosa and obtained a cure in 54 of 107
cases. The action of the follicle hormone is its local effect on connective tissue rather than specific endocrine action. In addition, the hormone is said to protect against bacterial infection. (c) Antibiotic treatment: Holinger and others used Aureomycin for 2–3 weeks and obtained good results in 5 of 7 cases. Bradburn used Teramycin in 4 cases and reported a cure in 2 cases and effective results in 2 other cases after 2 months.

In 1969, Utsumi and others injected 5–10 mg of Bleomycin intravenously twice weekly for prevention of recurrence of tumor after microsurgery of the larynx and reported complete remission, without side-effects.

In the present case, repeated surgery had to be performed. But with local injection of Bleomycin after the microsurgery of the larynx markedly effective results were obtained. Complete cure was not obtained with a single local injection but the intervals between surgery became longer. During the second microsurgery, some of the previous tumor lesions were heated and another local injection was given. A total of 3 local injection were given without an evidence of recurrence observed during a postoperative follow-up of more than a year.

The action mechanism of Bleomycin against cancer is said to be its inhibition of metabolism of cancer cells, but no definitive explanation is available. Consequently, it is still unknown why Bleomycin is effective against papilloma; however the antibiotic may inhibit the growth of tumor cells since papilloma like carcinoma is an epithelial tumor. Comparison between systemic administration and local injection indicates the latter method is more trenchant with local injection as in papilloma the tumor cells are said to be non-existent histopathologically in regions deeper than the basement membrane. In addition, systemic administration is known to produce stronger side-effects than local injection. In local injection, the necessity for surgical treatment increases but the amount of the drug administered is small. In the present case, four local injections were administered and the total dosage of Bleomycin was 30 mg, including that which seeped out. Consideration should be given with local injection, to the administration of steroids for dilatation of the glottis. Recently, Tanaka and others reported successful cure of 4 cases with local injection of 5-fluorouracil. Anticancer agents seem to be effective against papilloma.

Despite numerous reports on the treatment of laryngeal papilloma there is still no decisive method. However local treatment with an anticancer agent is one method to be tried at least once.

REFERENCES