

## Bleomycin Treatment for Cystic Hygroma in Children

by

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Cystic Hygromas In Infants And Children are relatively common in the benign tumors of the neck and axillary regions. During the past 10 years 21 cases of cystic hygroma were treated in the 1st Department of Surgery, Nagoya City University Medical School.

The purpose of this paper is to review the incidence and clinical pictures of these tumors, and to discuss some therapeutic problems especially as to topical use of Bleomycin as a sclerosing agent in cases with postoperative recurrences and in nonresectable ones.

*Frequent Site of cystic hygromas and its etiological consideration*

Twenty-one cases were collected at our department in these 10 years, in 11 of them the lesion occurred predominantly in the neck and spread from there to face and shoulder, and in 5 cases it occurred in the axillary region and lateral chest wall, respectively (Fig. 1). It is generally accepted that cystic hygroma in children occurs in the neck and axillary area most frequently. As shown in Table 1, a similar tendency can be seen in reports from other

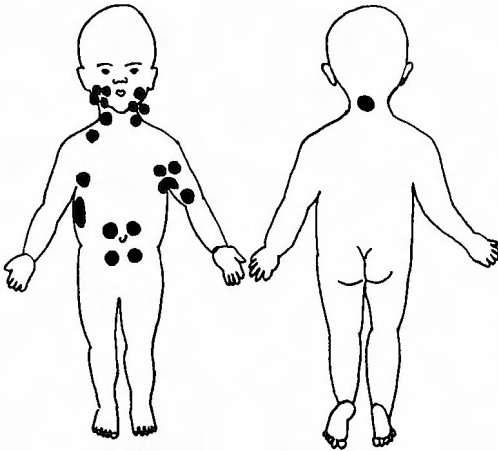


Fig. 1. Site of Cystic Hygromas in Children  
(a total 21 cases)

Table 1. Frequent Site of Cystic hygromas in Children

Author	Neck	Limbs		Trunk	Abdominal Cavity & Retroperitoneum
		Upper	Lower		
Ninh (1974)	79	23	10	17	0
Yagami (1974)	19		2	8	4
Ikeda (1969)	14		1	6	3
our Cases	11		1	5	4

Key Words : Cystic hygroma ; Bleomycin treatment ; etiology

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institutions<sup>1~3)</sup>. Incidences in the limbs and trunk vary to some extent according to investigators, which may be due to the fact that site of the cyst may be recorded differently depending upon its way of spreading.

The causes for frequent occurrence of cystic hygroma in the neck are considered as follows on the basis of the mode of development of lymphatic system in early fetal period. As described by SABIN<sup>4)</sup>, primitive lymph sacs developed in the cervical and iliac venous areas bilaterally, and also in the retroperitoneum from about 8th embryonal week and lymph vessels grow from these primitive sacs toward peripheral area. It has been shown that the cervical sac is the largest in size and grows earliest in fetal life than others. The concept of SABIN is that cystic hygroma originates from some abnormal development of remnant of primitive sac which has been left after sequestration occurred on the way of its development. Therefore, in the neck where primitive sac has developed most eminently, cystic hygroma appears more frequently. However, some objections have been proposed to the concept of sequestration of primitive sac, and several investigators such as GODART<sup>5)</sup> and BILL<sup>6)</sup> postulated that lymph vessels derived from mesenchymal system were cut off from communication to venous system on their way of development and changed into cystic hygroma. At any rate, the present status of the knowledge about cystic hygroma is that no definitive conclusion has been obtained regarding whether the lesion is true neoplasm or congenital abnormality in development, namely, malformation of tissue. In general, the intermediate attitude between the above two concepts are prevailing. Since 80 to 90% of this disease occurred in infants before 2 years of age and since there were only 2 cases which were older than 2 years in our series, the origin of the disease should be sought in embryonal period.

Usually, cystic hygroma appears as a superficial tumor with characteristic softness, by which it is possible to establish diagnosis definitively through palpation with ease. However, patients may be diagnosed only through the location of tumor and its characteristic appearance. Moreover, in case of tumor existing in peritoneal cavity or retroperitoneum, postulation is possible from the degree of hardness and scanty blood supply as evidenced by angiography.

#### *Clinical aspects of cervical cystic hygroma*

Cystic hygroma occurs frequently in the neck and most often in the posterior triangle of the neck. Although it is a superficial tumor, it often tends to spread by involving nervous and vascular systems in the neck and various muscle groups. Some cases have been encountered in which this benign tumor proceeded as if it were malignant one. Sometimes, it extends from depth of oral cavity to trachea or from infraclavicular area to mediastinum. Occasionally, infiltration of pharynx, larynx and peritracheal area causes severe respiratory distress syndrome.

Recently, YOSHIMURA<sup>7)</sup> et al reported a total of 20 cases undergone tracheotomy on account of severe dyspnea, 3 cases of which were their own cases and the rest were recruited from literature. According to the report, 7 of these 20 cases died, indicating

that in some cases prognosis is very poor in spite of its benign nature. We also experienced a one year old girl who came to our hospital with complaint of severe dyspnea and stridor developed secondarily to upper tracheal inflammation. She had received resection of large cysts of the neck soon after birth, although total excision was impossible due to small cyst infiltrating into esophagus, peritrachea and floor of the mouth. Therefore, it seems that proliferation of cyst which had already grown to some extent in the pharyngeal cavity was accelerated through infection. She was successfully treated by transoral aspiration of cyst and local injection of Bleomycin under trans-nasal endotracheal intubation.

Several papers have reported transient increase in cyst through complication of infection or hemorrhage in the cyst to aggravate disturbed respiration. NINH<sup>3)</sup> reported that infection developed in 16% of cases and bleeding in 12.6%. Once cyst is infected, it enlarges rapidly through lymphangitis and lymphedema.

A cystic hygroma which extends from the neck to mediastinum is called cervico-mediastinal hygroma. In such cases, not only dyspnea is caused by compression of the trachea but also dysphagia develops through compression of the esophagus, and at times even the superior vena cava is involved or obstructed. Therefore, it is required to examine the extent of the lesion by chest X-ray film, angiogram of the superior vena cava and esophagogram preoperatively, and occasionally to reduce operative risk, staged surgery should be considered.

#### *Therapeutic problem*

For the management of this disease, first of all excision should be carried out. The possibility of spontaneous regression cannot be excluded, and NINH<sup>3)</sup> reported two such cases. Other than the above described author, there are several investigators describing the correlation between the infection and spontaneous cure. However, in general, spontaneous healing lies beyond expectation, and if left untreated it proliferates progressively to infiltrate surrounding tissues intensively, resulting in making surgical treatment more difficult. In addition, there is a danger of infection of cyst and occurrence of disturbed respiration, so earlier excision should be recommended. However, since difficulty will be experienced in excision for newborns and immature infants, in particular, may be associated with damage to surrounding tissues and postoperative infection, surgical treatment should be delayed until 4th to 6th months after birth, if possible.

When the cystic hygroma is infected, it is proposed to postpone the operation for at least three months<sup>3)</sup>. Owing to the multilocular character of the cyst, inflammation is usually localized to a group of locules. But this area remains inflammation for a long time so operation should not be carried out when the risk of postoperative infection is considered.

As described before, this disease is not malignant. Therefore, care should be exerted not to leave ugly scar or disability due to nerve damage, and depending upon the affected site surgical treatment should be limited to partial excision. Widespread facial cyst is extremely difficult to resect. OHOMORI<sup>9)</sup> et al. reported cases in which facial cyst was successfully removed, and the author proposes that such operation should be carried out by

experienced, skilled plastic surgeon.

In the past unresectable cases were treated by puncture, incision or suction of the cyst, as well as radiotherapy or chemotherapy by means of infusion of Nitrogen mustard or other drugs with limited efficacy. Moreover, incision and suction were apt to be followed by unpleasant complications including infection of the cyst, leakage of body fluid and protein, and formation of fistula. Tincture of iodine has been applied locally to remaining cysts for many years. We have tried local injection of Bleomycin solution as a sclerosing agent, the results of which will be described below.

#### *Results of surgical treatment*

Data concerning 21 cases of our series are shown in Tabel 2, which indicates that

**Table 2.** Clinical Results of Cystic Hygromas

Operation	Treatment			Prognosis		
	No. of case	<sup>60</sup> Co Irradiation	Bleomycin injection	Cure	Suspected cure	Complication
Complete excision	9			9		Nerve paralysis 1
Incomplete resection	8	5	4	5	3	Nerve paralysis 2 Re-excision 2 Prolonged lymphorrhoea & wound sepsis 1
Not operated	4		4	3	1	
Total	21	5	8	17	4	

total excision was feasible in only 9 cases and that 8 cases received partial resection. These cases were found to have cyst showing diffuse infiltration into the parotid gland, pharynx, larynx, trachea, esophagus, mediastinum, intercostal space, and the area surrounding nerve and great vessels, and postoperatively partial paralysis of facial nerve developed in 3 cases. Recurrence occurred in 2 cases and severe lymphorrhoea and *Pseudomonas* infection were observed in one case.

Operation should be performed taking adequate time, and small fragil cyst should be carefully resected from surrounding nerve, blood vessels and organs, which cannot always be carried out easily. When small cysts are remained, they should be broken beforehand and application of tincture of iodine or injection of Bleomycin are considered to be useful.

After incomplete excision, recurrence cannot be avoided to some extent. YAGAMI<sup>2)</sup> and IKEDA<sup>1)</sup> described in their paper that no relapse occurred following incomplete excision. On the other hand, following total excision, newly developed cyst in the proximal side has been reported<sup>3)</sup>. In cases of incomplete excision, the more the remaining cyst is, the higher is the possibility of prolonged lymphorrhoea with greater loss of body fluid and protein. As the result, in the presence of reduced immunologic resistance there arises a severe local infection or sepsis. As described previously, one case of our series was suffered

from tenacious lymphorrhoea and wound sepsis due to *Pseudomonas* infection for 6 months.

*Local application of Bleomycin*

A total of 8 cases, consisting of 2 cases in which complete excision of cyst was impossible, 2 cases of postoperative relapse and one case having predominant lesion in the face, were treated locally with Bleomycin as a sclerosing agent (Table 3).

**Table 3.** Therapeutic Result of Local Administration of Bleomycin for Cystic Hygroma

Case	Age	Sex	Site of Cyst	Size	Bleomycin Doser & Times	Result	Remarks
1	1 Mo	M	r-face r-neck	4×6cm	0.5mg×7	Improved	.....
2	13 days	M	l-chest l-arm	Wide- spreaded	1.0mg×1	Improved	Injected at surgery
3	4 Mo	F	r-chest	8×8cm	3.0mg×7	Cure	Injected at surgery and postoperatively
4	1 Yr	F	r-neck	5×5cm	1.0mg×9 3.0mg×7	Cure	Injected for recurrence with dyspnea
5	13 days	M	r-face r-neck	8×7cm	1.0mg×7 4.0mg×2	Improved	No surgery
6	5 Mo	F	l-neck	3×3cm	1.0mg×4	Cure	No surgery
7	7 Mo	F	l-neck	3.5×3cm	1.5mg×3	Cure	No surgery
8	6 Mo	M	l-neck	6×5.5cm	1.0mg×6	Cure	No surgery

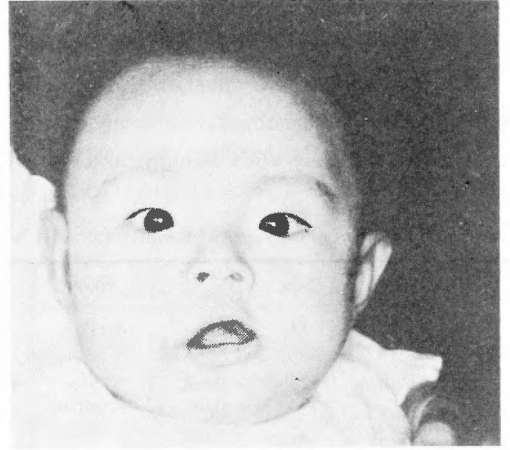
Bleomycin was administered as a local injection in a dosage of 1 to 3ml of the solution in physiologic saline with a concentration of 1mg/ml. Occasionally local anesthetic agent was given beforehand to relieve pain. In doing this treatment, it should be remembered that injection is not always applied into the cyst but into surrounding tissues as well and that intradermal injection should not be done. Since the amount injected was small, there was no need of hospitalisation. Usually, cysts are spread widely, injection was given once or twice a week at a predetermined site in several divided doses. Several injections were required to treat the whole cyst, total amount administered being 20 to 30 mg.

As side effects related to this treatment, transient fever developed following administration of large dose of Bleomycin, but leukopenia, rashes, dermal lesions, pulmonary fibrosis and growth retardation were not observed.

Case 5 had a lymphangioma of 8.5×7cm which developed soon after birth in the right facial area to cervix, and from objective findings existence of cavernous lymphangioma was indicated<sup>6)</sup>. Due to cosmetic reasons, resection was avoided, and local injection of 1mg (1.0ml) of Bleomycin twice a week was started from one month after birth at the outpatient clinic of our department. Findings before treatment are shown in Fig. 2. The site administered with Bleomycin developed induration of 2 to 3 cm in diameter, which gradually became soft in about two weeks. A clear-cut decrease in size of the lesion could be observed when the cyst was totally injected, and about one year later the patient was markedly improved as shown in Fig. 3. This child is now 3 years old without any growth inhibition, and the affected area is free from signs of relapse, though a slight swelling



**Fig. 2.** Thirteen days after birth. Before injection of Bleomycin. Lymphangioma is noted from the right cheek to the neck.



**Fig. 3.** One year after Bleomycin Treatment (the same patient as shown in Fig. 2). Swelling in the right cheek disappeared almost completely, and only mildly indurated area was palpable.

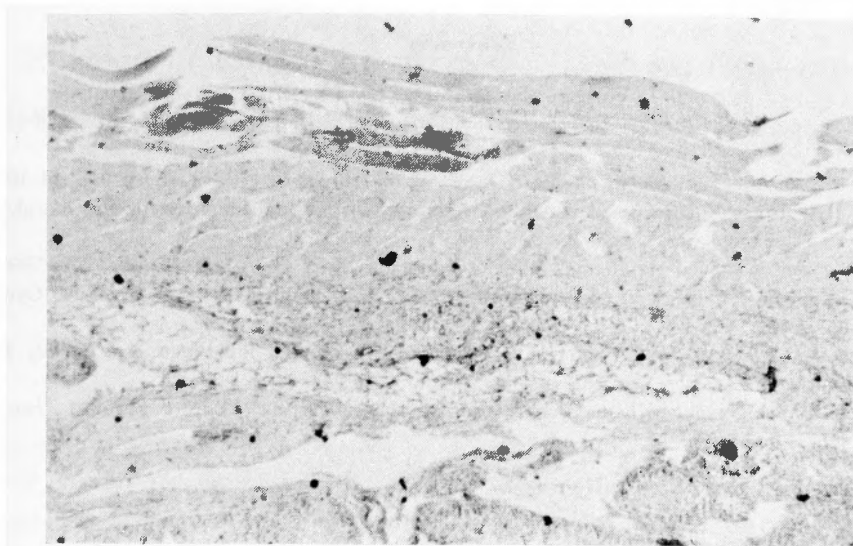
then the dosage was reduced to 1mg twice a week. By the time when total amount of 30 mg was given, the size of the tumor decreased to  $1.5 \times 1.5$  cm. Four years have passed since then, and no recurrence can be observed now. It should be noted that this patient sustained resection of Wilms' tumor when she was 2 years old. Since Wilms' tumor may sometimes be complicated with hemihypertrophy, the association with cystic hygroma in this case is interesting in that some casual relationship is conjectured.

Therapeutic results with Bleomycin were evaluated to be good in all of these 8 cases. In 4 unoperated cases and 2 cases of relapse, disappearance or clear reduction in size of tumor could be obtained, while in cases treated postoperatively early disappearance of lymphorrhea was noted in one (Case 3) and recurrence did not occur in any of these. As a whole 5 cases out of 8 cured completely.

Bleomycin has been used as a DNA inhibitor in the treatment of various malignant tumors including squamous cell tumor. However, it is still left unknown to what extent it inhibits growth of endothelial cell of cystic hygroma. Histological study on lymphoangioma resected three days after local injection of Bleomycin, showed marked appearance of fibroblasts. Similar findings were obtained in experiments in rabbits after infusion into testicular cavity. In these experiments, histological findings obtained 4 days after infusion of 0.3mg/kg of Bleomycin solution (dissolved in physiological saline to a concentration of 1mg/ml)

is still observed.

Case 4 is a patient with severe dyspnea, as described before. Administration of 3mg (0.3mg/kg) of Bleomycin on consecutive days was associated with fever of  $39^{\circ}\text{C}$ , and



**Fig. 4.** Histological picture of the Tunica vaginalis testis of rabbit biopsied 4 days after administration of 0.3mg/kg of Bleomycin dissolved in the concentration of 1mg/ml. Infiltration of fibroblast and adhesion are seen.

revealed marked infiltration of fibroblasts and adhesion in the Tunica vaginalis of testicular cavity, indicating efficacy of Bleomycin as a sclerosing agent (Fig. 4).

Effects of Bleomycin on tissues are chiefly evidenced by inflammatory processes developing as reactions to chemical irritation. Induration and fibrous change may be considered to reflect superiority of this effect of the drug. However, it seems worthwhile to make studies on the inherent effect of Bleomycin, namely inhibition of cellular proliferation and affection on activities of enzymes such as collagenase and elastase.

((Addendum))

In recent years we have tried local application of Bleomycin in the treatment of various cystic disease with really interesting results. For example, a remarkable effect could be observed in infants with hydrocele of the spermatic cord and thyroid cyst of adults. Thirteen cases with hydrocele have been treated with local Bleomycin, and in almost all of those cases cure could be obtained after injection into the cyst only once or twice. Bleomycin has not yet been tried in hydrocele testis, in which its effect on the testicle should be considered.

### Summary

The incidence, clinical characteristics, and etiology of cystic hygroma in children which develops most frequently in the neck were discussed. In the treatment total excision is most effective. However it should not leave severe nerve damage and ugly deformity. This paper showed 8 cases treated with local administration of Bleomycin for nonresectable and recurrent cystic hygroma in infants. The results were excellent and no side effects were seen.



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## 和文抄録

## 小児リンパ管嚢腫の治療, 特に Bleomycin の局所投与について

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教室における小児のリンパ管嚢腫21例について検討を加えた。その大部分は頸部および腋窩に発生していることから、その成因は、胎生早期の原始リンパ嚢がこの部により優位に発育し、これがその途上において中断、分離すると考えるのが妥当である。

管理上問題となるのは、頸部リンパ管嚢腫の周辺臓器への浸潤による呼吸障害ならびに循環障害であり、嚢腫に感染が加わるとこれが助長される。その本態は良性疾患でありながら、悪性腫瘍の如き臨床経過を示す症例があり、その管理にあたっては十分な配慮が必要である。

その手術成績を見ると、3例に不完全ではあるが顔面神経麻痺を残し、2例は再切除、1例には術後比較的長期に亘るリンパ瘻の形成および緑膿菌による創感染が認められた。

これらの手術合併症を予防し、治療成績の向上を計るべく、嚢腫の完全剔出の困難な症例ならびに顔面に発生して美容上手術的摘除に問題があるものおよび、呼吸障害のある症例など計8例に、Bleomycinの局所投与(1回1~3mgを1mg/mlの溶液として注入)を試み、5例の治療例および3例の治療期待例を得た。

制癌剤としてのBleomycinのリンパ管嚢腫に対する効果は、間葉系組織の化学的突症による硬化作用に帰すべきものと考えられる。実験的に家兎辜丸漿膜腔にBleomycinを注入して、組織学的変化を検討した結果では、著明な線維芽細胞の増成と癒着形成が認められる。なおBleomycinの内皮細胞に対する障害作用、破壊などについては今後検討すべき所である。