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EOSINOPHILIC LYMPHOFOLLICULAR GRANULOMA IN PAROTID GRAND (KIMURA'S DISEASE):

A Report of Two Cases.

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Abstract

Two cases of eosinophilic lymphofollicular granuloma are reported, one developing in a 48 year old female and the other in a 19 year old male. The granuloma had recurred after previous surgery in both cases.

This entity is seen mainly in young males and is accompanied by such findings as eosinophilia and enlargement of lymph nodes or presence of subcutaneous masses. There are such histological findings as hyperplasia of lymph follicles and marked eosinophilic infiltration, but the true nature of this disease is yet unknown.

In the two cases reported, there was a mass in the region of the parotid gland and enlargement of the cervical lymph nodes on the same side which made the authors suspect malignant tumor of the parotid gland at first.

This lesion proliferates by infiltration, and if the tumor is enlarged, it is difficult to make total extirpation. As there is a strong tendency of recurrence even after surgery and although temporarily it responds to corticosteroids and radiation therapy, it is considered this disease falls in the realm of internal medicine rather than surgery. In Japan, this entity is known as Kimura's disease. The general physical condition is good and there have been no reports of death attributable to it to date.

INTRODUCTION

This entity is noted primarily in young males and is accompanied by eosinophilia and enlargement of lymph nodes or presence of subcutaneous masses. Histologically proliferation of lymph follicles is characteristic, but the true nature of this disease is yet unknown.

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It is understood there are hardly any reports of a similar disease in western countries, but it has recently to be considered an independent disease entity in Japan. Takeuchi[1] and Iizuka[2] state that it should be handled as an independent entity in view of its characteristic clinical symptoms and histological picture, and advocate that it should be named Kimura's disease as he was the first to provide a description of the entity in Japan.

As we experienced two cases considered to be afflicted with this disease, the findings will be reported and a review of literature will be presented on its nature, symptoms and therapeutic measures.

CASE REPORT

Case 1: A 48 year old female (teacher, junior high school) visited our clinic in August 1971 with the chief complaint of a horse-shoe shaped mass around her left ear.

In 1967, she noticed masses in the anterior and posterior regions of her left ear, which were removed surgically in April 1969. Facial paralysis developed immediately after surgery. All was uneventful for one year after surgery, but from the early part of 1970, masses became palpable again in the same site as before.

Review of past medical history revealed that a tumor, later diagnosed as Tietze's dystrophia, was also extirpated from the left sternoclavicular joint at the time of operation in 1969.

The patient's general physical condition was good. There was an elastic horse-shoe shaped mass around the left ear (Fig. 1). A firm mass was palpable within the soft tumor. Palpation revealed the tumor to be comparatively well-defined and firmly fixed to the surrounding tissue restricting mobility. Pea-sized lymph nodes could be palpated, 3 in the left submandibular region and several in the left cervical region.

Laboratory tests revealed mild anemia and eosinophilia (Table 1).

Sialogram showed a defect in the parotid gland. The pre-surgical diagnosis was recurrence of parotid tumor, and as lymph nodes became palpable recently, the possibility of malignant tumor was also considered. The operation was performed in August 1972.

Marked fibrosis was noticed at the time of operation. The facial nerve was firmly surrounded by the fibrous tissue as well as by the tumor tissue. We sent the specimen to the pathologist for the histological examination by a frozen section. As the diagnosis of malignant lymphoma was reported, the lesion was removed extensively with the

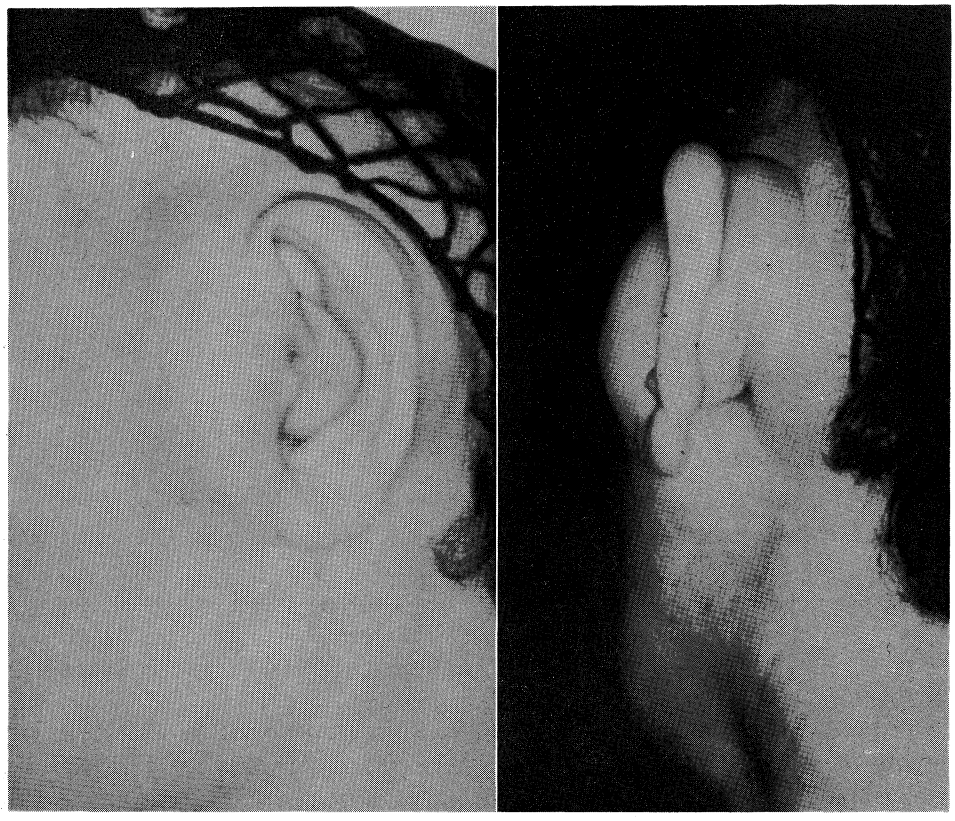

Fig. 1. Pre-surgical state of Case 1

sacrifice of the facial nerve. However, a part of the tumor in the temporal fossa was not removed completely and left to later radiation therapy.

Post-surgical histological examination showed lymph follicle formation in the connective tissue and lymphocytic and eosinophilic infiltration. Sporadic necrotic foci could be observed. These findings led to the diagnosis of lymphofollicular granuloma (Fig 2).

Post-surgical irradiation of ^{60}Co was administered to which the tumors in the cervical region were highly sensitive resulting in their disappearance. A total of 3000 rad administered.

Case 2: A 19 year old male with the chief complaint of left preauricular tumor visited our clinic in March 1973. He had undergone surgery at age 7 for removal of a mass located anterior to his left ear. Subsequently, he suffered from successive recurrences and received sur-

TABLE 1. Laboratory Data in Case 1.

Serum total protein	g/dl	6.9
A/G ratio		1.25
Cholesterol	mg/dl	178
Icterus index		3
GOT	unit	13
GPT	unit	10
Alkaline phosphatase	unit	2.0
Urinalysis		normal
RBC	$\times 10^4/mm^3$	387
Ht	%	36
Hb	g/dl	11.8
Reticulocyte	%	0.6
Platelet	/10HPF	23.1
WBC	$/mm^3$	8200
Differential	%	
Neutrophile		44
Lymphocyte		40
Monocyte		4
Eosinophile		12
Basophile		0

gery at ages 13 and 15. Facial paralysis resulted from his third operation.

About 1 year and a half ago, a mass developed in the anterior region on the opposite side, his right ear, and gradually increased in size. The patient complained of a strong localized prurits and on increase in size of the tumor after drinking alcoholic beverage.

There are no other remarkable findings in the past medical history.

His general physical condition was good. A relatively well circumscribed elastic tumor 2.5 cm in diameter was palpated anterior to the right ear. It was movable (Fig. 3), and several pea-sized lymph nodes were palpated in the right cervical, axillary and inguinal regions.

There were no abnormal findings in the laboratory tests (Table 2).

Sialogram showed a defect in the upper portion of the superficial lobe of the parotid gland, which corresponded well with site of the tumor. Leakage of contrast media into this defect could be observed (Fig. 4).

Partial superficial lobectomy of the right parotid was conduced under the diagnosis of parotid gland tumor. The tumor consisted of parotid gland tissue and fibrous tissue, and was firmly fixed to the over lying facial fascia. The outer surface of the tumor consisted of thick grayish white fibrous tissue and in the center was whitish yellow tissue material which appeared to be lymph nodes.

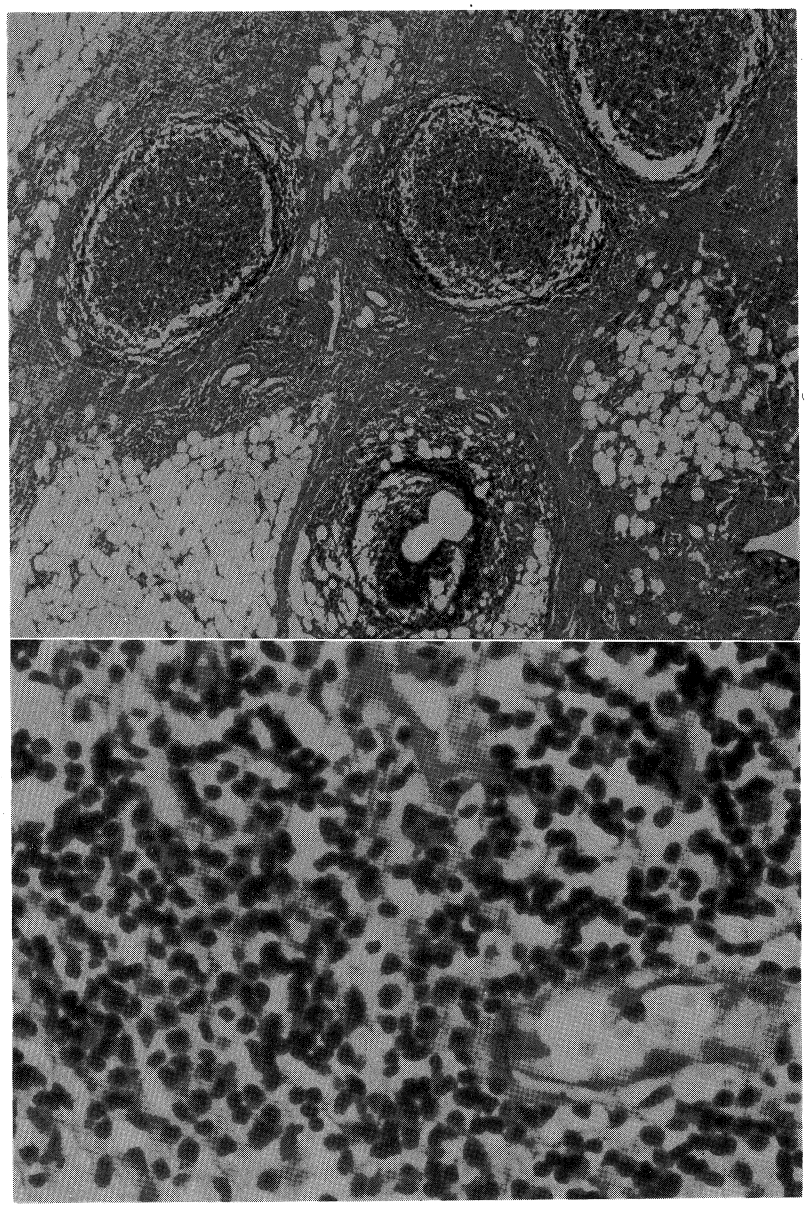

Fig. 2. H-E stain, upper: ×10, lower: ×134

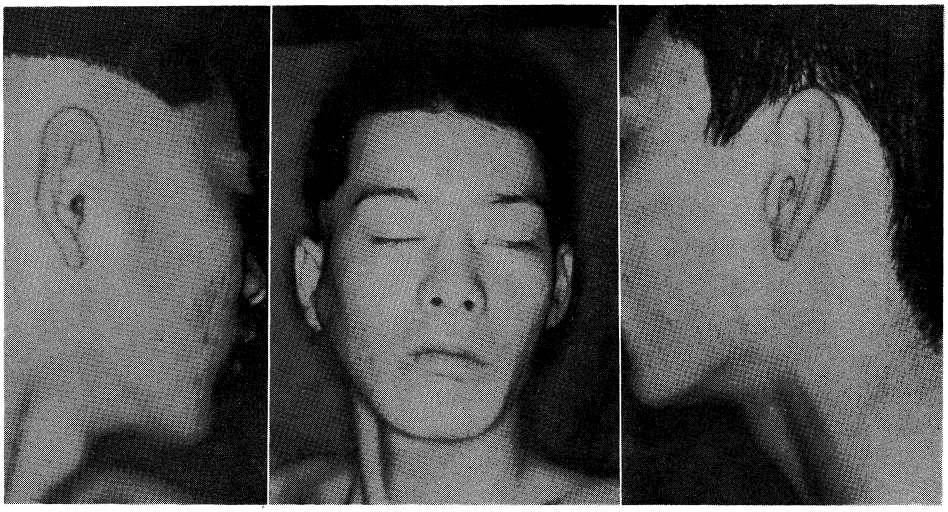

Fig. 3. Case 2-Pre-surgical state
A tumor 2.5 cm in diameter is located in the anterior region of the right ear. There are two operation scars in the anterior region of the left ear.

TABLE 2. Laboratory Data in Case 2.

Serum total protein	g/dl	6.4
A/G ratio		1.55
Cholesterol	mg/dl	133
Erythrocyte sedimentation	mm/1 hr.	3
	mm/2 hr.	9
ZnTT		3.7
Icterus index		4
CCFT		(+)
GOT	unit	11
GPT	unit	7
Alkaline phosphatase	unit	3.7
Choline esterase	pH/hr	0.55
WaR		negative
Examination of urine		normal
Examination of feces (parasite)		negative
RBC	$\times 10^4/mm^3$	452
Ht	%	44
Hb	g/dl	15.2
Platelet	/10HPF	59
WBC	$/mm^3$	5300
Differential	%	
Neutrophile		34
Lymphocyte		64
Monocyte		1
Eosinophile		1
Basophile		0

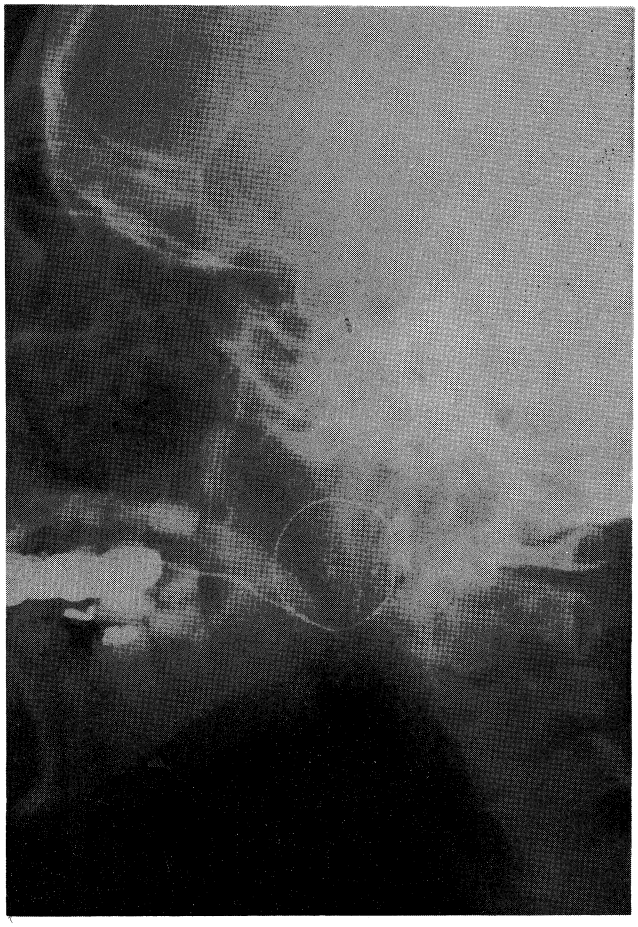

Fig. 4. Case 2-Sialogram
The area shown by the wire corresponds to the location of the tumor. Areas of leakage of contrast media can be seen.

Histological examination showed cellular infiltration of the connective tissue, particularly strong infiltration of eosinophils, fibrous hyperplasia and lymph follicle formation, and in some areas there was extension of infiltration into the salivary gland tissue. The diagnosis was eosinophilic lymph-follicular granuloma (Fig. 5). It seems probable that the tumors which had developed in the anterior region of the left ear and subjected to surgery on three occasions were of similar nature.

Following the surgical procedure, 3000 rad of ^{60}Co was adminstered to the surgical wound and the right cervical region, after which the lymph nodes became no longer palpable.

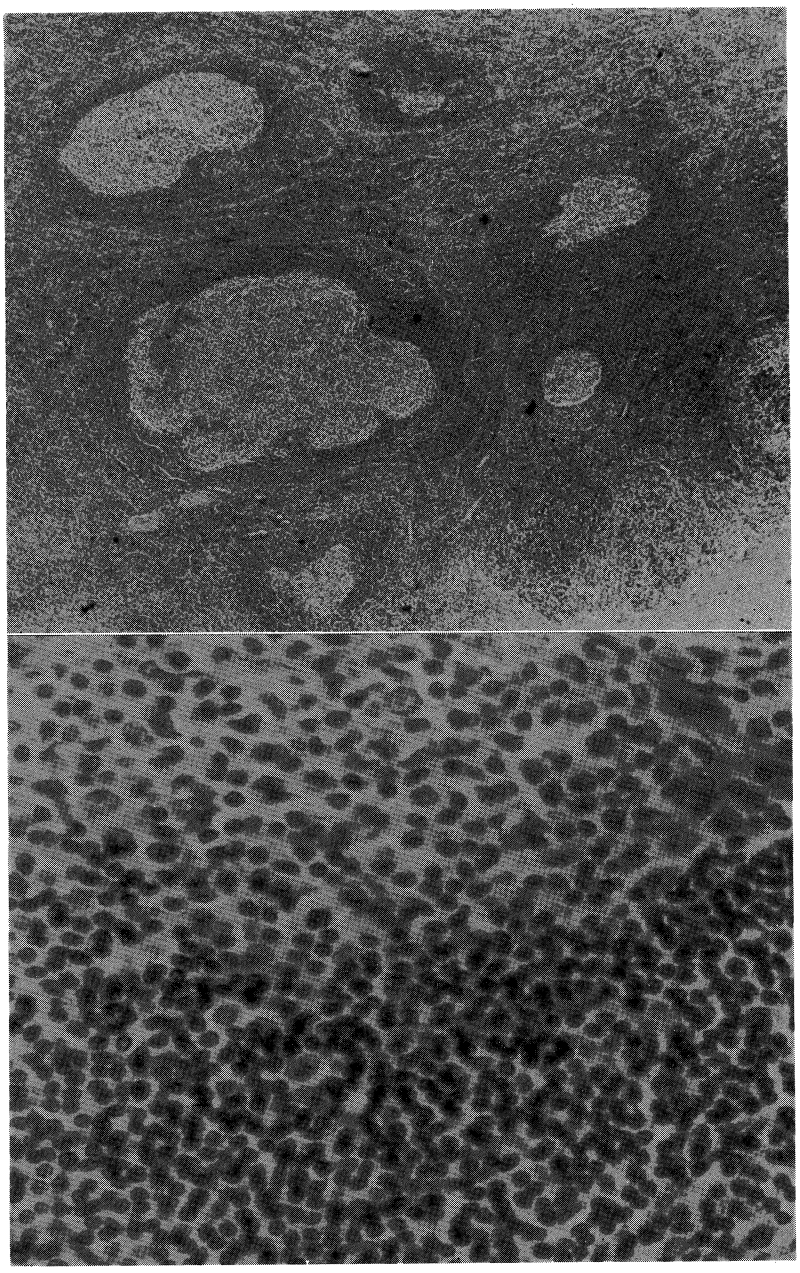

Fig. 5. H-E stain, upper: ×10, lower: ×134

DISCUSSION

A characteristic of this disease is that reports of this disease are found to be completely lacking or very rare in western countries whereas it tends to be rather prevalent in the eastern part of Asia. There are almost two hundred reported cases in Japan, about fifty cases in China and also about twenty in Indonesia[4]. This disease has been reported under a variety of names in Japan such as Mickliz's disease, Mickliz's syndrome, Kimura's disease, eosinophilic lymphadenitis, eosinophilic folliculokentric syndrome[5] and eosionophilic lymph folliculoplastic panniculitis (-losis)[6]. Such confusion results from the fact that the true nature of this disease is yet unknown.

Iizuka[2], in 1959, advocated that this disease had the characteristics to be considered a clinical disease entity, and proposed that it be named Kimura's disease after Kimura who was the first to describe it in Japan.

Next, in 1962 Watanuki *et* al[7] provided a general description based on 12 cases of his own and 35 cases reported in literature. He stated that it is an eosinophilic granuloma which is an independent clinical entity that develops in the subcutaneous lymphatic tissue. Therefore, it was inappropriate to call it Mickliz's disease. In other words, the independence of Mickliz's disease as a disease entity was questioned. Signs of bilateral swelling of the lacrimal glands and salivary glands which are associated with lymphatic leukemia, Hodgkin's disease, lymphosarcoma and tuberculosis are called Mickliz's syndrome. On the other hand, only entities which meet Mickliz's description completely are now being called Mickliz's disease proper[8]. Godwin[9] regards the latter as a benign lymphoepithelial lesion, and Skarpil considers it to be Lymphom der Speicheldrüse while Morgan[10,11] feels it is identical with Sjögren's disease. Further, according to Geiler[12] and Key[13], the above three may be considered to be practically identical. Their description of the histological picture mentions that ducts can be seen in the lymphocyte population which had expanded extensively so as the replace lacrimal and salivary gland tissue. They described further that there was narrowing and even obstruction of the duct lumen resulting from degeneration and proliferation of epithelial cells, and such duct epithelium and gland epithelial cells could be seen scattered in insular fashion in the lymphatic tissue. Granuloma formation which is a histological characteristic of this disease could not be seen nor was there any description of eosinophilic infiltration. On the basis of these findings, this disease was considered an independent entity different from Mickliz's disease.

Nasu *et al*[14] prepared a comprehensive report which included 59 cases found subsequent to the series reported by Watanuki *et al*[7] and Kawada *et al*[15], covering the period up to 1969, brought the total to 165 cases. They summarized the characteristics of this disease as follows.

1. It is a chronic disease found chiefly in young males, but its nature is yet unknown.
2. The main signs are development of masses in the subcutaneous soft tissues and generalized enlargement of superficial lymph nodes independently or in combination.
3. The histological picture of such masses or lymph nodes shows neoplastic or hyperplastic lymph follicular structure accompanied by a large, well defined germination centers, and at the same time marked infiltration of eosinophils can be seen in the inter-follicular tissue.
4. Leukocytosis and eosinophilia are found in the majority of the cases.
5. The prognosis is good, but appropriate therapeutical procedures have not yet been established.

According to the reports of various workers, subcutaneous masses and enlarged lymph nodes are frequently noted in the head and neck. In many instances, findings resemble those of malignant tumors like our Case 1, in whom there masses in the parotid gland and enlarged lymph nodes in the cervical region on the same side. We found at the time of surgery that granulomas do not have a capsule, and they proliferate not by expansion but by infiltration. There is strong fibrosis and when it develops around the facial nerve, detachment of the nerve is difficult. Therefore, it is important to make distinction from malignant tumors.

In 1973, Yamaguchi *et al*[16] have reported on 14 cases in whom this disease had developed in the parotid gland and cheek region. According to the report, 6 had unilateral swelling of the parotid gland, 5 with bilateral involvement and 3 with unilateral cheek swelling, and of the 14 cervical lymph node enlargement was noted in 10. Further, in many cases, there were complaints of pruritus and pigmentation at the site of swelling. In 7 patients out of 14 in their report, there were complaints of local pruritus at the site of enlargement and generalized itchiness in 2. Localized pigmentation was noted in 2. Both of our cases had localized itchiness, and Case 2 also had pigmentation.

As for the therapeutic procedures, Nasu *et al* reviewed 59 cases in previous reports, 19 of which had been treated with corticosteroids followed by 13 who had undergone radiation therapy while 11 had surgical removal.

Watanuki *et al*[7] claimed that the first choice should be radiation therapy, but admitted that there are nonresponsive cases. Cannon *et al*[17] cautioned the use of radiation therapy on benign tumors as there was a risk that it could cause transition into malignancy and thus stated that careful consideration should be given to its use in this disease[18,19]. Even when surgical removal is performed, there are only a few cases who are completely cured by this procedure alone. Ishikawa *et al*[20] state that emphasis should be placed on surgery, but Tsukamoto *et al*[20] reported that whereas the recurrence rate is 15% in those treated with radiation, it is 50% among those in whom the tumor has been extirpated.

Corticosteroids has been becoming more frequently used in recent years. According to reports, in practically all cases there had been rapid decrease in size of the tumor and in the number of eosinophils in peripheral blood. No decrease in eosinophils is seen after surgery and radiation therapy. However, one of the difficulties with corticosteroids is that the effects produced are only temporary, and once administration is discontinued, the condition recurs. Yamaguchi *et al*[16] have attained good results by making the enlargement first disappear by administering corticosteroids followed by radiation therapy. They report a dose of 3,000～4,000 rad appropriate.

The etiology of this disease is as follows. As eosinophilia is observed in many of the cases, an allergic disease and parasitic infestation were suspected and studied in this direction, but there have been no reports signifying the presence of parasites.

At present there are many who advocate the allergy theory. Arakawa *et al* (1973)[22] in their treatment of a male 40 years of age with steroids, noted that his RA test turned negative, there was complication of Burger's disease and his toxo test results were strongly positive. They feel these finding strongly support the allergy theory.

Recently, the increase of serum Ig E[16,23,24] and the increase of mast cells have been added as special characteristics of this disease. Thus, there are many reports which consider it to be an atopic allergy[26] or a Type I allergic reaction[16] whose allergen is candida[16,23,24,27].

It is only recently that the etiology of this disease has been subjected to such scruting close and thus the number of cases so studied is yet few. The need for further investigation is indicated.

As the chief complaint of this disease is tumor, during early years most of the reports were made by surgeons, but in recent years more

reports being made by internists. On the bases of our experience, we feel that as this tumor proliferates and increases in size by infiltration, total extirpation is difficult, the frequency of recurrence following surgery is high and, although temporary, the response to corticosteroids and radiation therapy is good, this disease falls in the realm of internal medicine rather than surgery.

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