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A Study on the Pathogenesis of Postmastectomy Lymphedema

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ABE, R. *A Study on the Pathogenesis of Postmastectomy Lymphedema.* Tohoku J. exp. Med., 1976, 118 (2), 163-171 —— In order to study the causes of postmastectomy lymphedema, venography, lymphangiography and RISA absorption test were performed on the patients following radical mastectomy. Venous obstruction was a rare cause of postmastectomy lymphedema. Edema patterns in arm lymphangiography were observed in the patients with lymphedema and even in some of the non-edematous upper extremities. The finding of axillary lymphangiography was correlated with the degree of edema of the upper extremity. The absence of adequate lymphatic pathway across the axilla (type 2, collateral and type 3, blocking) was thought to provide the pathologic base for the postmastectomy lymphedema. RISA absorption test also provided precise information of the lymphatic flow in the extremity. It was lower in the patients with edema, as compared with the patients without edema. ——— postmastectomy lymphedema; venography; lymphangiography; RISA absorption test

Lymphedema of the upper extremity is frequently observed in patients who had radical mastectomy, and it is one of the major problems after surgery for both patients and surgeons. None of the therapeutic procedures for chronic lymphedema described in the literature were satisfactory and on rare occasion an occurrence of malignant tumor was even reported, which has resulted from chronic lymphedema following mastectomy. Therefore, chronic postmastectomy lymphedema should be avoided before, during and after radical operation. Postmastectomy lymphedema is grossly classified into two types, i.e. transient and persistent. Transient or acute lymphedema appearing soon after surgery is not uncommon and usually disappears within a few months after mastectomy. On the other hand, persistent or chronic lymphedema may not disappear even after a few months.

Pathophysiological changes responsible for postmastectomy lymphedema are not completely understood. Generally, postmastectomy lymphedema is considered to be caused by obstruction of the lymphatic pathways secondary to axillary dissection. However, edema is also considered to be of venous origin. In order to elucidate the pathophysiology of the edematous extremity, the knowledge of lymph flow in the upper extremity after radical mastectomy seems mandatory.

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Method

Lymphangiography

According to the technic described by Kimmonth, 0.4 ml Patent blue V was injected into the subcutaneous tissue between the index and middle fingers. A skin incision, 1.0 cm long was made at the proximal portion in the dorsum of the hand and a needle inserted into a lymphatic vessel. 5 to 6 ml contrast medium (Lipiodol ultra fluid) was injected with an automatic injector. Lymphangiograms of the whole upper extremity and the ipsilateral axilla were taken immediately and 24 hr after injection. These lymphangiographies were performed at least three months after the operation.

Venography

Venography was performed by injecting contrast medium into the dorsal vein of the hand. The axillary, subclavian and cephalic veins were visualized.

RISA absorption test

0.1 ml solution (25 μCi) of human serum albumin labeled with ^{131}I (RISA) was injected into the subcutaneous tissue of the dorsum of the hand. When the injection was made, the use of a sharp needle was regarded as essential in order to minimize a local tissue injury. The patient was placed on an oral intake of potassium iodide tablets 5 days before and during the test in order to minimize the uptake of radioiodine by the thyroid gland.

1.0 ml serum was obtained from the opposite cubital vein 2, 6, 12, 24, 48 and 72 hr after RISA injection.

Radioactivity of the serum was measured, using a Well type scintillation counter. Absorption rate was calculated, and expressed as percentage of the administered dose of RISA.

Results

Lymphangiography

Findings of the arm lymphangiography. The lymphedema patterns, i.e., dilated, tortuous, varicose lymph vessels and dermal back flow of the upper and/or the forearm, were demonstrated on lymphangiograms at the termination of the injection of contrast medium in all 6 cases of postmastectomy lymphedema. Delay in disappearance of contrast medium in the lymph vessels and the extravasation frequently observed in the 24 hr arm lymphangiography of postmastectomy edema. In one of these, the injected contrast medium did not reach the axilla, and lymph flow of the proximal part was not visible at any time during the period of one week (Fig. 1). However, various types and degrees of the edema patterns of the arm lymphangiography were also seen in some of the patients without clinically detectable lymphedema. Dilated and tortuous lymph vessels, dermal back flow and extravasation were shown in the upper arm of the patient without lymphedema, as shown in Fig. 2. Although the arm lymphangiographical findings did not always present the degree of the swelling of the upper extremity, patients who showed almost normal findings of arm lymphangiograms did not have any clinical edema.

Findings of axillary lymphangiography. On the basis of lymphangiographic findings in the axilla, the patterns of lymph flow were classified into three types: type 1 (crossing pathway), type 2 (collateral pathway), and type 3 (blocking pathway).

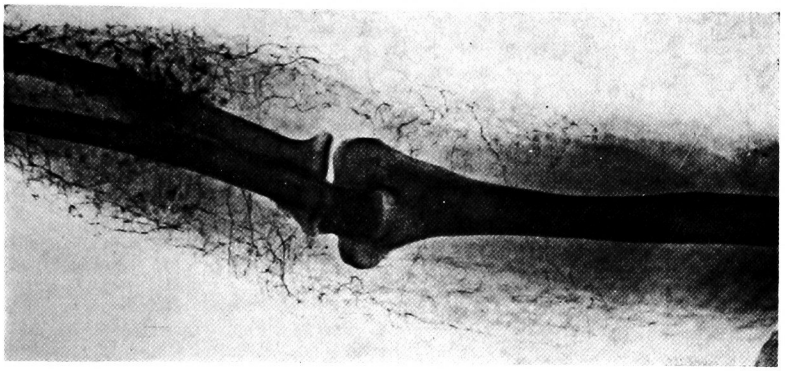

Fig. 1. Tortuousity of lymph vessels and dermal back flow on arm lymphangiography.

Fig. 2. Lymph vessels crossing the axilla (type 1) and lymphedema pattern in non-edematous extremity.

The type 1 indicated that lymph vessels passing along the original route in the axilla could be demonstrated at the termination of the injection of contrast medium (Fig. 2) and lymph nodes in the supraclavicular region were visualized on the 24 hr lymphangiogram. In the type 2, no lymph flow crossing the axilla could be proved, and stasis of the contrast medium in the axilla forming an irregular figure and collateral lymph flows toward the shoulder or the lateral chest wall could be seen at the termination of the injection (Fig. 3). Delay in visualization of lymph nodes was rarely observed in the mediastinum and opposite axilla. In the type 3, only stasis of the contrast medium was seen in the axilla, and lymph flow crossing

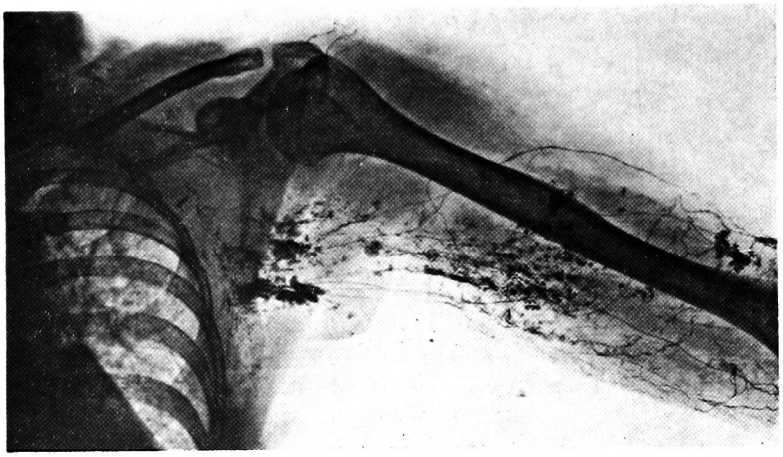

Fig. 3. No lymph vessels crossing the axilla and collateral lymph vessels toward the shoulder (type 2) in moderately edematous extremity.

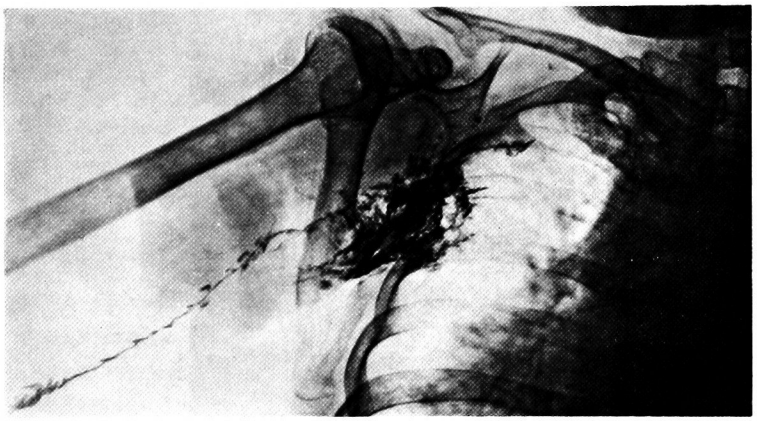

Fig. 4. Stasis of the contrast medium in the axilla, no lymph vessel crossing the axilla and no collateral lymph flows (type 3) in severe edematous extremity.

the axilla and collateral pathways were not proved in axillary lymphangiogram at any time during the observation period (Fig. 4).

Of 19 patients who underwent postmastectomy lymphangiography, 13 patients were placed into type 1, 3 into type 2 and 2 into type 3, exclusive of 1 patient whose axillary lymphangiography failed to visualize.

Each type of axillary lymphangiogram well represented the degree of clinical lymphedema of the upper extremity, whereas arm lymphangiogram was not relevant to it. In spite of the pathologic findings of arm lymphangiography, the case showing type 1 revealed clinically little lymphedema of the upper extremity. Those belonging to type 2 revealed moderate lymphedema of the upper extremity. Lymphangiogram (Fig. 4) showing type 3 was taken 5 years after radical mastectomy and postoperative irradiation. In this film, any lymph

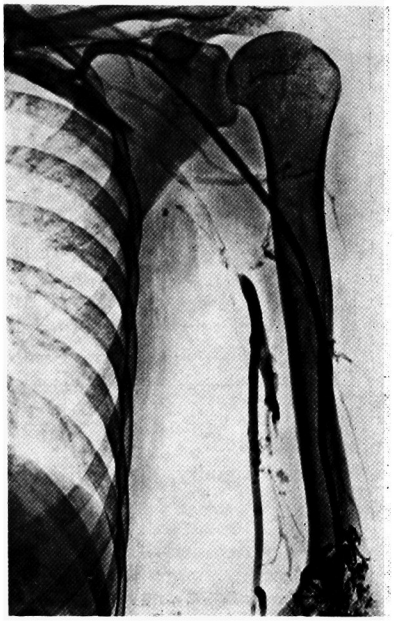

Fig. 5. Venogram showing axillary vein occlusion in non-edematous extremity.

flows crossing the axilla or collateral circulations were not demonstrated, lymph vessels decreased in number, and no dermal back flow was seen in the swollen arm. The two cases of the type 3 revealed clinically severe lymphedema of the upper extremity.

Venography

Venography was performed in 24 patients, of whom 9 were with edema and 15 were without edema. A narrowing of the axillary or cephalic vein was often observed in either swollen or not-swollen arm after radical mastectomy. In some patients, no abnormal findings of the axillary or cephalic veins were seen in those with lymphedema of the upper extremity. On the other hand, some without lymphedema of the upper extremity showed obstruction of the axillary vein (Fig. 5). Since no collateral venous circulation was seen in this case an adequate venous return may have been obtained via the cephalic vein.

Total obstruction of both the axillary and cephalic veins was not found in all of 24 cases. In most cases venous obstruction was not thought to be the pathologic cause for the postmastectomy lymphedema.

RISA absorption test

This test was carried out in 11 patients, of whom 4 were with edema and 7 without edema of the upper extremity. In most of the cases radioactivity of the circulating serum gradually increased with time and reached the maximum rate in 48 hr. In general, RISA absorption rates of the swollen arm were apt to be lower

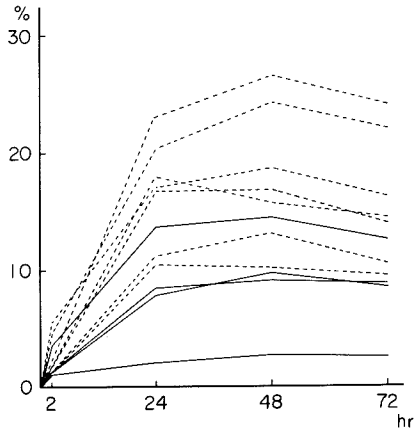

Fig. 6. RISA absorption rates.
The dotted line is in edematous extremity, the solid line is in non-edematous one.

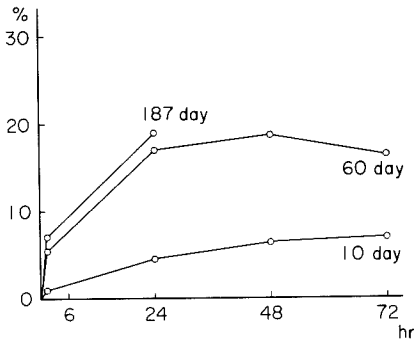

Fig. 7. RISA absorption rate in a 53-year-old postmenopausal woman without edema of the extremity.

than that in the not-swollen arm as shown in Fig. 6. These findings indicated that lymphatic circulation in the swollen arm was impaired, as compared with that in the not-swollen arm.

RISA absorption rates which were repeatedly measured in the same patient at different intervals after mastectomy were shown in Figs. 7 and 8. The first case was a 53-year-old postmenopausal woman without clinically detectable edema of the upper extremity. In this case the second and third absorption rates were higher than that of the first one (Fig. 7). It might be indicated that the lymphatic circulation improved with lapse of time. The second case was a 32-year-old premenopausal woman with swollen extremity. On the contrary, the absorption rate did not change for 5 months after surgery (Fig. 8). The lymphatic circulation might not be improved in this case.

The difference of RISA absorption rate between the groups of the swollen and not-swollen upper extremity was not determined because of the following two reasons; the repeated tests in one patient did not always show the same value as

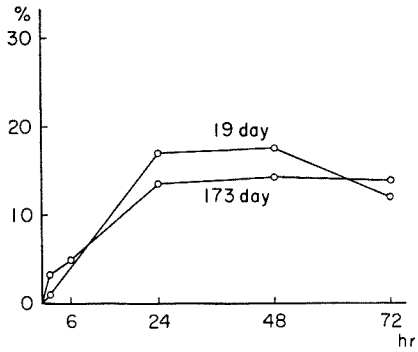

Fig. 8. RISA absorption rate in a 32-year-old premenopausal woman with edema of the extremity.

TABLE 1. *Edema of upper extremity after radical mastectomy*

Circumferential difference	Number of cases	per cent
0–1.0 cm	85	68
1.1–2.0 cm	19	15
2.1–5.0 cm	16	13
5.1– cm	5	4
Total	125	100

Of 125 patients, 17 per cent had edema of circumferential difference of more than 2.1 cm.

indicated in Fig. 7 and the test of the individual was performed at various intervals after radical mastectomy.

DISCUSSION

In our series of 125 patients without distant metastasis and recurrence, 21 presented with postmastectomy lymphedema which showed the maximum circumferential difference between both arms more than 2.1 cm (Table 1).

The causative factors concerning lymphedema which were previously reported by the present author were age, obesity, grade of cancer growth, method of surgery, postoperative complication (i.e., infection, necrosis of the skin and prolonged collection of fluid in the axilla), and postoperative irradiation (Abe et al. 1970). Of these factors, postoperative irradiation was thought to be the most important cause of edema. It was impossible to explain, however, that postmastectomy lymphedema was a sequela of these factors.

In arm lymphangiography, dilated, tortuous, varicose lymph vessels and dermal back-flows were observed on the upper extremity either in the patients with edema or in some of the patients without edema. The findings of axillary lymphangiography showed a close correlation with clinical edema and it might be useful to predict whether edema will persist or improve in the future. Tsangaris

and Yutzy (1966) divided the lymphangiographic findings in the axilla into 2 basic groups on the basis of lymph flow. Lymph flow across the axilla could be demonstrated in group 1, but did not occur in group 2. Into group 1 were placed 22 patients in whom lymph flow across the axilla was demonstrable without lymphedema. The remaining 5 patients were placed into group 2. Clinically significant lymphedema was present in 3 patients in whom lymph flow across the axilla could not be demonstrated and in 2 patients with long lymphatic pathways to the contralateral axillary lymph nodes.

From these lymphangiographic studies it appeared that the occurrence of postmastectomy lymphedema was primarily depending upon the postoperative regeneration of lymphatic pathway in the axilla. This potential of lymphatic regeneration was also proved by RISA absorption test. The case which demonstrated the improved RISA absorption rate as compared with the previous test did not show persistent lymphedema of the upper extremity. It was likely that the blocked lymphatic pathway by surgery might be reestablished by the regeneration of lymphatic vessels. Lymphangiogram of the patient who indicated improved absorption rate showed adequate lymphatic pathways resembling the preoperative route in the axilla. Regeneration of the lymphatic vessels had been experimentally observed to be established about 1 month after lymphadenectomy (Dettman et al. 1966; Kocandile et al. 1966). They observed that the lymphatics have a tremendous capacity for regeneration.

A change of the radioactivity at the site of the ^{131}I albumin injection revealed the rate of the disappearance of labeled albumin. Tissue clearance of ^{131}I albumin was shown by the period to reach half value as much as the locally injected labeled albumin (Emmett et al. 1967; Jepson et al. 1953; Taylor et al. 1957). In the normal individual, the protein in the tissue fluid was transported by way of the lymphatic pathway to the general circulation and did not enter directly into it. In the experimental dog it was shown by Drinker (1946) and Seki et al. (1968) that the majority of the protein in tissue fluid was transferred into the lymphatic system.

Labeled albumin and globulin, however, could also disappear from the injection site by diffusion other than the lymphatic transportation. After the interdigital dye injection in the case of obvious lymphedema, dye diffusion into the dermal lymphatics was used to demonstrate both in the neighborhood of injection site and in the distant area. Jepson et al. (1953) used a narrow collimeter to measure the removal rate of the labeled protein from the injection site, with results suggesting a rapid rate of removal. Taylor et al. (1957) suggested that the effect of the local diffusion might give rise to major errors in the tissue clearance test.

If the local diffusion was dominant and if the diffused area was wider than the area of the collimeter, the detector in use might have picked up only a part of the radioactivity of the labeled protein in the tissue. In these circumstances, the value of ^{131}I protein clearance would give the results suggesting a rapid rate of disappearance. However, it was not identified whether a rapid rate of disappea-

rance was depending upon the lymphatic transportation or the local diffusion. To avoid this error, Emmett et al. (1967) measured the radioactivity remaining at or near the injection site by inserting the entire limb into perspex cylinder with large γ-ray counter tubes.

Threefoot and Kossover (1966) showed actually lymphaticovenous anastomosis to be present in various parts in man. He considered this findings to be a safety valve in the cases of disturbance of the lymphatic flow. Ohara and Taneichi (1973) reported lymphaticovenous anastomosis at the inguinal area in a patient of 53-year-old male with primary lymphedema of the lower extremity.

If the local diffusion of the labeled protein would be dominant and if lymphatico-venous anastomosis would be open, measurement of the radioactivity in the circulating serum at various intervals after subcutaneous RISA injection could be regarded to represent a more reliable value of the lymph flow in the swollen extremity.

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