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The Possible Role of Dermal Lymphatics in the Dissemination of Breast Cancer

K. Kett, I. Kádas, L. Tabár, L. Lukács

I. Surgical Clinic and the Roentgenological Clinic of the University Medical School Pécs and the Pathological Department of the County Hospital in Pécs, Hungary

Summary

The authors studied the role of the dilated cutaneous lymphatic capillaries, which function as a subsidiary draining system in advanced breast cancer in 7 patients. They selected the material by using the Patent blue dye test, then administered P^{32} isotope preoperatively for autoradiographic detection of tumour cell emboli in the mammary skin, excised by mastectomy. In half of the cases the histological follow-up of autoradiographically positive skin-samples showed the existence of cancer-cell nests in the minute lymphatics. They call attention to the fact, that the skin-area in question will not be removed totally by mastectomy, so that tumour cells which have become lodged in its dilated lymphatics may serve as a starting-point for local renewal and late dissemination. In support of their statement they bring some of their own observations.

The results of recent research in such fields as cytochemical assay, lymph circulation and tumour-immunology have added considerably to our knowledge of the pathways of dissemination and of the dynamics of cancer cells. Although anatomists of the past century showed that metastases may avoid normal pathways of regional drainage even in distant regions and be established via aberrant lymphatics (2), their findings were obtained at autopsy and not from studies of lymph flow in the living patient. The knowledge concerning the lymphatic drainage of the breast therefore, remained defective for decades. Several authors made use of former experiences and failed to reveal the importance of the minute collateral lymphatics under pathological conditions. *Gray* was the first who got closer to the core of the problem, by injecting Thorotrast interstitially (3). He was successful in demonstrating the increased importance of the superficial cutaneous capillary network of lymphatics after blockade of the focal drainage – which having no rectifying valve system, comes to a more accentuated role as „subsidiary drainage". More over, he had admitted that tumour cell embolization might occure frequently but these emboli would be rapidly propagated by the lymph flow. *Willis* (11) was quite accurate in depicting changed lymph circulation in cancer patients and gave an up-to-date explanation for the origin of back-flow and the rise of satellite nodules!

In a series of direct mammalymphographic investigations we were able to demonstrate different stages of lymph flow alterations. In the course of these investigations we noted that the lymph stagnation, the formation of collateral lymphatic vessels and the consecutive rise of back-flow led to an extremely widened and widespread lymphatic

network in the skin of the tumorous breast, which took up the role of blocked collectors (5, 6, 7). On the basis of these observations we supposed that the skin would play an important role not only in the changed lymph circulation but very likely in the dissemination of cancer cells, too.

Material and Methods

0,5 ml of a mixture containing equal parts of 11 percent Patent blue violet dye[1] and one percent Lidocaine was injected intradermally into the areolar field of mamma, in order to obtain visible lymphatics for lymphography. Some minutes following the injection, there appeared in 7 patients a characteristic reticular pattern on the mammary skin, more over, in the surrounding skin area, too, delineating the dilated collateral network of dermal lymphatics (Fig. 1). All the 7 patients received 24 hours before mastectomy 500 μC P^{32} isotope i. c. diluted with Lidocaine, injected at the same site where the dye was administered. Following operation the dermis was stripped off the specimen, then stretched out and fixed for 6 hours in 10 percent formaline. Subsequently the specimens have been placed on 8 × 10 inch high-speed double emulsion non-screen films in light-tight paper casettes for 24 hours. Visible positive spots on the autoradiogramms were then identified with identic points of the specimens by marking them with a dermographic pencil (Fig. 2). Then small pieces of 1 cm^2 were excised from the

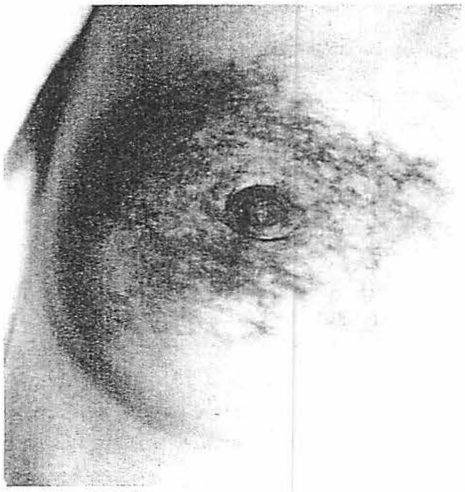

Fig. 1 A widespread reticular pattern indicating retrograde lymph flow and dilated cutaneous lymphatic capillaries in the skin of the breast and the chestwall.

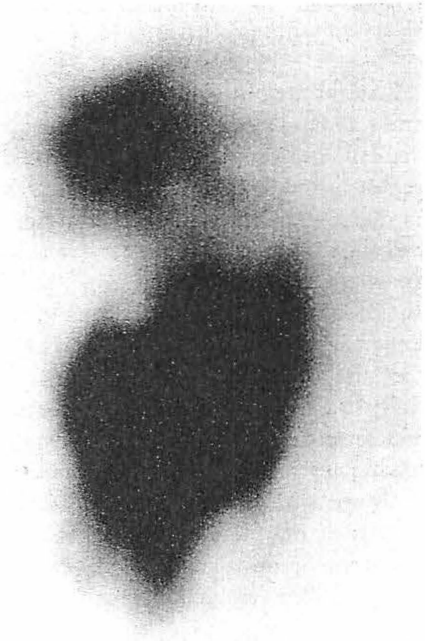

Fig. 2 Autoradiogramm of the removed skin.

[1] Bleu Patente V á 2,5% Laboratoires André Guerbet, St. Quen-Seine, France.

preparation at the marked spots (Fig. 3), embedded in paraffine, sectioned 10 μ thin, parallel to the skin-surface and finally stained with haematoxyline-eosin. Excisions made simultaneously from negative areas served as controls.

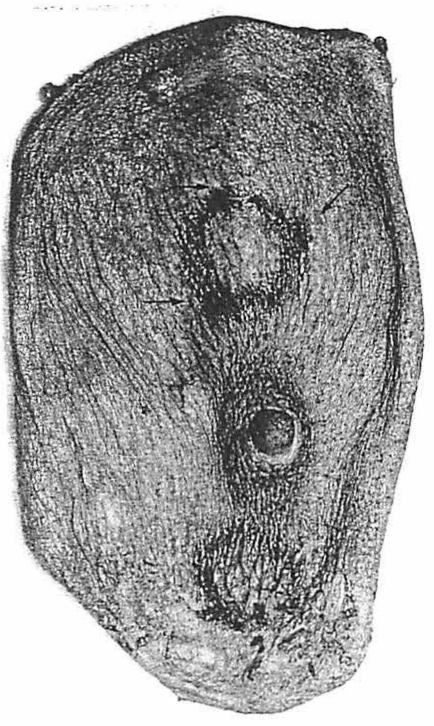

Fig. 3 Removed skin; the marked sites correspond with the positive spots of the autoradiogramm.

Results

Macroscopic signs of tumour infiltration could not be observed in either of the cases. In 3 of the 7 patients marked and excised pieces did not show any suspicious alterations by serial-sectioning, while 3 other cases presented in all of the samples tumour emboli in the lymphatic slits of the deeper cutis layers either in a free environment or surrounded by plasmacells and lymphocytes. In one of the excised pieces from the 7th patient, the histological investigation revealed a remarkable nest of plasma cells and lymphocytes, very similar to those seen around the tumour cell emboli.

It seems to be noteworthy that the average distance of the samples to be excised has been 7 cm from the tumour (6–8 cm). If we put the primary tumour as the center and draw a circle with a radius of 6–8 cm, supposing that tumour emboli may be concealed theoretically anywhere within this circle, we can easily realise, that certain nests of cancer cells will get locked out of the operation field.

One must keep in view that this method of investigation is not adequate for detecting all tumour cell emboli, more over it is incapable to give information about the skin area excluded from the operation field and so to settle the limits of tumour infiltration (Fig. 4).

Discussion and Conclusions

The lymphatic capillary system of the cutis visualized by Patent blue violet dye does not respect the limits of the operation field; it surpasses it far along the chestwall. Even an accountable part of the territory in question escapes the usual irradiation

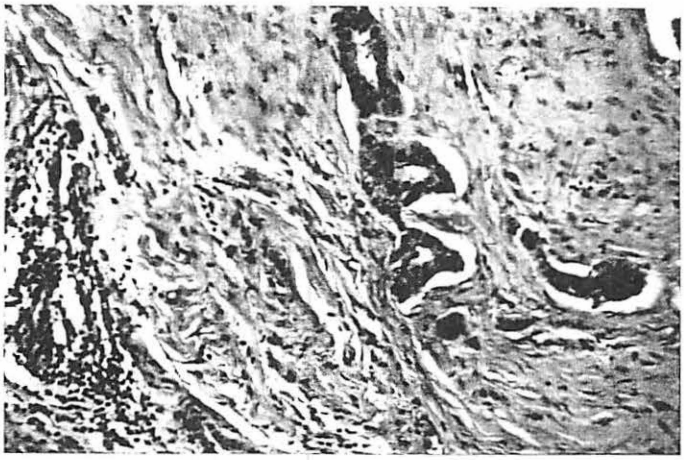

Fig. 4
Histological view of a tumour embolus. Cancer cells are located in the lumen of a lymphatic and surrounded by plasmacells and lymphocytes.

areas. However, the choice of skin-samples to be excised for histological serial-sectioning will be made not after the dye-pattern and so one may expect with good reason the excluded skinfield to be infected by tumour cells, *Roth* (10) has failed to find a widespread dissemination at autopsy in 6 of 23 cases and in only one of these there has been a tumour-rest in the chestwall.

But, besides a general dissemination he has found in all 17 cases tumour rests in the tissues of the chestwall involving all its layers. As to whether they were spread by the lymphatic or by the haematogen means he could not prove. However, he omitted the latter possibility as unlikely. *Handley* assumes haematogenous spread causing late dissemination (4). *Fisher* and *Prochnov* (1, 9) believe the hypoxically damaged operative field be a so called "fertile soil" for circulating cancer cells of the blood. They suppose that tumour cells torn off preoperatively and existing metastases, form the sources of local recurrences and are also responsible for late disseminations. Many authors are searching after the source of tumour cells dormant often for years and decades. Circulating cancer cells have been already identified (8), but quoting *Roth's* statement it seems to be more likely that they will be disseminated from the primary onset-site than in a retrograde way from another site backwards into the lymphatics of the chestwall (10).

On base of our data we are inclined to suppose that in the dilated, subsidiary lymphatic capillaries of the skin-areas "dropping" out of the field of mastectomy, cancer cells may get caught and may serve as a starting-point for late local recurrences and distant metastases. We have some clinical observations supporting this idea:

Lymphangitis carcinomatosa in the presternal region 6 years after mastectomy → regression after irradiation therapy; subsequent mammalymphography showed contralateral pectoral nodes affected; the patient died one year later with widespread metastases.

Four patients underwent plastic surgery because of postmastectomy edema 2, 3, 7 and 12 years after the first intervention. All 4 cases presented 1–1½ years later regional and distant lymphnode metastases.

Our observations underline the tumour-cell-reservoir function of the widened lymphatic capillary system of the skinfield around the mastectomy scar:

1. Six to 8 cm from the tumour cancer cell emboli can be demonstrated by histological investigation in the lymphatic capillaries of the mammary skin.
2. Patent blue violet dye-test delineates an extended subsidiary draining system of cutaneous lymphatics in advanced cases with breast cancer, surpassing the usual operation field;
3. Lymphangitis carcinomatosa in the postoperative area may precede late dissemination;
4. Surgical interventions performed a new even some years later, in the environment of the mastectomy scar may set off rapid dissemination.

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K. Kett, I. Kádas, L. Tabár, L. Lukács, 1. Surgical Clinic and Roentgenological Clinic of the University Medical School, Pécs, Pathological Department of the County Hospital in Pécs, Hungary