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SHORT REPORT

Decongestion improves cell-mediated immunity in postmastectomy arm lymphoedema: a pilot study

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Abstract

Background Chronic lymphoedematous limbs have an increased propensity for infections and primary or secondary malignant tumours. It has been attributed to suppressed delayed-type hypersensitivity measured in lymphoedemas related to Stewart–Treves syndrome, Kaposi's sarcoma or breast cancer treatment. Cell-mediated immunity is an effective defence mechanism against bacteria, fungi, viruses and tumour cells.

Objective We aimed to examine whether decongestive lymphoedema therapy could improve cell-mediated immunity in breast cancer treatment-related lymphoedema (BCRL).

Methods Eight women with unilateral BCRL were included in this study. At baseline, tuberculin skin test (TST) was performed on the volar surfaces of the forearms of the affected and non-affected sides using 0.5, 1 and 5 tuberculin units in the form of three consecutive injections with 3-cm spaces in-between, and arm volumes were measured using the Kuhnke's disc model. Decongestive lymphatic therapy was given to swollen arms in 10 consecutive working days. At the end of intensive decongestion, TST on affected side and bilateral volumetry were repeated.

Results Baseline test using undiluted (5 units) and fivefold diluted (1 unit) tuberculin solutions has shown significant differences ($P < 0.05$) between the mean sizes (11.81 ± 2.32 and 7.75 ± 1.92; 7.12 ± 1.12 and 5.12 ± 0.91 respectively) in favour to healthy arms. Post therapeutically, the mean sizes were significantly increased ($P < 0.05$) in the dilutions of 1 : 1 and 1 : 5 (7.75 ± 1.92 and 10.56 ± 1.23 mm, 5.12 ± 0.91 and 5.93 ± 1.74 mm respectively).

Conclusion Significant increase in TST sizes suggests that decongestive lymphatic therapy is able to partially restore impaired cellular immune function in BCRL.

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Conflict of Interest

None

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Introduction

The lymphatic system plays multiple roles in the maintenance of homeostasis: fluid and protein balance of the interstitium, fat transport, immune surveillance and waste scavenging. In case of lymph stasis these functions are perturbed, and among others lymphoedema becomes a local site of altered immuncompetence. It was supported by a study demonstrating impaired dendritic cell and lymphocyte trafficking in 14 patients with lymphoedema of mechanical causes.[1] Lymphoedematous limb has a high propensity for bacterial, fungal and viral infections, and is also at risk for the onset of malignant tumours and their metastases.[2,3] As Ruocco *et al.* and Mallon *et al.* have shown in their clinical studies in lymphoedemas with Stewart–Treves syndrome,[4] Kaposi's sarcoma (KS)[5–7] or breast cancer treatment,[8] such susceptibility to malignancy seems to have close relationship with an altered cell-mediated immunity measured with standard antigens and dinitrochlorobenzene (DNCB). Clinical observations and retrospective analyses well reported that proper oedema control might be able to reduce the frequency of erysipelas, which might reflect the improvement of defence mechanism against infectious bacteria.[9]

Therefore, we aimed to measure the cell-mediated immunity with tuberculin skin test (TST), prior and subsequent to decongestive lymphatic therapy[10] (DLT)-based standard care of breast cancer treatment-related secondary lymphoedema (BCRL). As control we used contralateral healthy arm for TST. Because of the concern on possible DNCB genotoxicity,[11] we decided to use purified protein derivative (PPD) of *Mycobacterium tuberculosis*,

which has been known to serve as a reliable model for delayed hypersensitivity with no biohazard activity.

Methods

Eight women [mean age: 58 years (range: 51–77 years)] with BCRL [mean duration: 27.5 months (range: 12–52 months)] were included in our prospective study after a written informed consent. This study was approved by the local Ethical Committee of the University of Szeged.

All patients had previously undergone excisional breast surgery, axillary block dissection and radiotherapy. Seven of eight patients also received postoperative chemotherapy. All participants were proved to be tumour-free in complete cancer screening conducted within the last 3 months.

Limb volumes of both affected (mean value: 3463 cm^3 in range 2650–4230 cm^3) and healthy arms (mean value: 2998.75 cm^3 in range 2318–3830 cm^3) were determined using Kuhnke's method.[12] Mean oedema volume (volume difference between affected and non-affected arm) measured as the baseline was 464.25 cm^3 (range: 197–798 cm^3).

TST was performed on the volar surfaces of both forearms with three consecutive injections of 0.5, 1 and 5 international units (IU) of 0.1 mL PPD solution (Teva, Debrecen, Hungary) prior to DLT. Serial injections were administered with 3-cm spaces among each inoculation to avoid a false positivity.

DLT was given daily for 10 consecutive weekdays, and comprised manual lymph drainage (MLD) of Vodder's method performed along the neck, breast, abdomen and then affected arm using light pressure (~20–30 mmHg) for 60 min, followed by skin moisturization and multilayered (~50% overlap) and multicomponent short-stretch bandaging with appropriate padding.[13] The pressure of the bandage system was set to the values between 30 and 39 mmHg in vertical position with dangling arm.

TST was repeated exclusively in lymphoedematous forearms after completing the full course of the DLT. The reading of the test results was regularly performed by two independent examiners for 72 h with measurement of the size of induration given in millimetres,[14] thus each final value represents the mean of two single measures.

To rule out boosting effect (increased test reactions), two-step TST was performed using 5, 1 and 0.5 tuberculin units on one selected forearm of eight healthy individuals (mean age 32, range: 24–52 years) on days 1 and 16. No significant difference was measured in the diameters of inflammatory reactions of the identical dilutions ($P > 0.05$) revealing no false conversions in repeated course of TST.

Statistical analysis

Statistical analyses were performed using the Student's *t*-tests for paired samples and differences were accepted as significant when $P < 0.05$. Statistica 9.1 software (Stat Soft, Tulsa, OK, USA) was used for data analysis.

Results

As shown in Table 1, baseline test using undiluted (5 units) and fivefold diluted (1 unit) tuberculin solutions has shown significant differences ($P < 0.05$) to be measured between the mean diameters of reactions (11.81 ± 2.32 and 7.75 ± 1.92; 7.12 ± 1.12 and 5.12 ± 0.91 respectively) in favour to healthy limbs. At the end of DLT course, the mean diameters of the reactions were significantly increased ($P < 0.05$) in the dilutions of 1 : 1 (5 units) and 1 : 5 (1 unit) (7.75 ± 1.92 and 10.56 ± 1.23 mm, 5.12 ± 0.91 and 5.93 ± 1.74 mm respectively).

At baseline, we measured limb volumes of both affected (mean value: 3463 cm^3 in range 2650–4230 cm^3) and healthy arms (mean value: 2998.75 cm^3 in range 2318–3830 cm^3), as well as mean oedema volume calculated as volume difference between affected and non-affected arm (mean value: 464.25 cm^3 in range 197–798 cm^3). DLT resulted in a significant decrease ($P < 0.05$) in the mean values of lymphoedematous limb (pretreatment:

Table 1 Tuberculin skin test diameters

Patient	Healthy arm TST diameter (mm)			Affected arm before decongestion TST diameter (mm)			Affected arm after decongestion TST diameter (mm)		
	5 TU	1 TU	0.5 TU	5 TU	1 TU	0.5 TU	5 TU	1 TU	0.5 TU
1	10	8	7	9	6.5	5	9	8	5
2	12.5	7	6	6	4.5	4	11.5	7	5
3	17	6	4	11	4.5	4	12	4	4
4	10	6	3	5.5	4.5	3	9	6.5	4
5	10	6	2	6	6	3	10	5	3
6	11	9	7	7	5	5	10	7	4
7	12	8	6	8.5	4	4	12	7	2
8	12	7	5	9	6	5	11	3	3
Mean ± SD	11.81 ± 2.32	7.12 ± 1.12	5.00 ± 1.85	7.75 ± 1.92	5.12 ± 0.91	4.12 ± 0.83	10.56 ± 1.23	5.93 ± 1.74	3.75 ± 1.03

Two independent examiners accomplished single measurements at each TST and the values are expressed as means of these two results.
TU – tuberculin unit.

Table 2 Arm volumes

Patient	Healthy arm volume (cm^3)	Affected arm volume before decongestion (cm^3)	Affected arm volume after decongestion (cm^3)	Oedema volume before decongestion (cm^3)	Oedema volume after decongestion (cm^3)
1	2318	2650	2470	332	180
2	3580	4230	3765	650	465
3	3112	3910	3403	798	507
4	3830	4027	3905	197	122
5	3008	3551	3170	543	381
6	2514	2741	2635	227	106
7	2898	3580	3110	682	470
8	2730	3015	2835	285	180
Mean ± SD	2998.75 ± 510.25	3463 ± 598.87	3161.62 ± 510.25	464.25 ± 232.02	301.37 ± 170.56

The same examiner implemented single volume measurements on affected arms at baseline and after decongestive lymphoedema therapy and on healthy upper extremities.

3463 cm^3, posttreatment: 3161.625 cm^3) and oedema volumes (pretreatment: 464.25 cm^3, posttreatment: 301.375 cm^3), whereas healthy limbs remained unchanged (Table 2).

It is noteworthy that TST exerted a mild volume increase in involved arms in three cases, which was restored with an additional 5-day cycle of DLT.

Discussion

Lymphoedema is often featured by complications such as recurrent erysipelas, fungal or even herpes virus infections. Lymphoedematous limbs are prone to develop primary or more commonly secondary malignancies. Several attempts have been made to identify the underlying causes. The link between lymph stasis and disturbed immune function was first described in 1982, when intradermal skin tests to common allergens in a patient with unilateral Stewart–Treves syndrome of the right leg showed weak reaction on the involved limb and normal skin reactions on both arms and contralateral leg.[4] In 1984, the same finding was detected in a lymphedematous leg with classical KS.[5,6] As the disease progressed and involved more limbs with KS in conjunction with lymphoedema, it resulted concomitantly impaired immune response on the affected extremity. Finally, each limb developed KS and secondary lymphoedema with negatively conversed skin tests.[5,6] In DNCB-sensitized classical KS patients, the rechallenge showed impaired immune response on involved limbs.[7] Further clinical trials involving arms with chronic lymphoedema showed a disturbed trafficking of immune cells after DNCB rechallenge. In their study on postmastectomy lymphoedema, Mallon *et al.* found that both the afferent and efferent loops of immune response were compromised with decreased hypersensitivity reactions.[8] These data clarified that lymph stasis directly causes immunostasis.

While trying to elucidate the permanent weakness of cell-mediated immunity of lymphoedematous limbs, we observed that intensive and later maintenance phases of DLT reduce the frequency of cellulitis. This empirical body of knowledge and the finding of a clinical report[9] promoted us to conduct a clinical trial to study the effect of decongestion on immune status of lymphoedematous limbs in the belief that the less frequent attack of this severe bacterial infection might be attributed to an improved defence mechanism.

Prior and subsequent to DLT, TST was performed on involved forearms. Repeated TST can result in boosting, because it might evoke a recall of delayed-type hypersensitivity to mycobacterial antigens that has waned. Singh *et al.* reported that the retest reading after 72 h did not prove any significant change in the size of reaction hence ruling out the boosting effect.[15] In a separate study, healthy volunteers were subjected to TST in a repeated fashion and no significant changes of TST induration sizes were detected. Following the completion of DLT course, we intentionally did not retest healthy arm with PPD injections so as to exclude the possible influences of MLD on the lymphatic circulation of healthy arm.

Our study has revealed that cell-mediated immune response was weaker at the two lowest dilutions of tuberculin inoculums in the lymphoedematous arms compared with healthy ones. This finding is quite compatible with the previous results of Mallon *et al.*[8]

Significant increase in tuberculin reactions to 1 or 5 tuberculin units proved that DLT had immunomodulatory effect and could partially restore the cellular immune status of the arm with BCRL.

To our knowledge no previous study examined the effect of DLT on lymphoedematous limbs from the cellular immunity point of view.

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