BRIEF COMMUNICATION

LIPOPEROXIDE IN THE DERMIS OF PATIENTS WITH LYMPH STASIS

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ABSTRACT

Lipoperoxide has been detected in the thoracic duct lymph of the dog. This finding suggests that lipoperoxides are normally transported in lymph and with impaired lymph drainage may be deposited in the skin and contribute to the soft tissue changes characteristic of chronic lymphedema. Accordingly, after obtaining skin specimens taken from 8 patients (7 with obstructive lymphedema) with lower extremity lymph stasis we determined dermal malondialdehyde (MDA) content (after conversion to fluorescent thiobarbituric acid or TBA), a marker of lipoperoxide. In all 7 patients with obstructive lymphedema, the MDA levels were increased compared to control dermis (p<0.05). We suggest that inability to clear lipoperoxides from the dermis with lymphatic insufficiency may contribute to the pathogenesis and structural skin derangements of chronic lymphedema.

In an earlier paper (Lymphology 22:150, 1989), we demonstrated that lipoperoxide was present in thoracic duct lymph and suggested that this agent may contribute to the soft tissue changes associated with chronic lymphedema. Hyperoxidation of unsaturated fatty acids such as linoleic, linolenic, and arachidonic acid produces endoperoxide or hydroperoxide. Lipid superoxide is generated by a potpourri of stimuli including irradiation, ultraviolet light, hyperthermia, hyperoxia, nitric oxide, iron, chlorophyll, pyridine, tri-o-cresyl phosphate, vitamin E antagonists, thiogroup (SH) inhibitors, carbon tetrachloride, hexobarbital, superoxide dismutase inhibitors, codeine, tolbutamide, aminopyrine, phenobarbital, 3-methylcholoranthrene, and alcohol (1). Deposition of lipoperoxides in tissues has been implicated in necrosis, inflammation, cataracts, atherosclerosis, cancer, hemolysis, and aging (1). In the skin, lipoperoxide is a normal constituent (3,4) and may be responsible for pigmentation, wrinkling, alopecia, and bullae formation (2).

We suspect that in lymphedema (i.e., lymph stasis), lipoperoxide deposition in the skin increases as its transport through lymphatics is impaired. Indeed, Okada et al have demonstrated that lipid superoxide rises in cardiac muscle in conjunction with myocardial edema after experimental ligation of draining lymphatics (6). To pursue circumstantial evidence along these lines, we examined the lipoperoxide content in the skin of patients with lymph stasis.

MATERIALS AND METHODS

Seven patients with unilateral secondary extremity lymphedema (6 arms, 1 leg) and one patient with bilateral leg primary lymphedema (precox) (Table 1) underwent biopsy of the skin under local anesthesia. Skin specimens from the edematous extremity were immersed in liquid nitrogen, the epidermis
### TABLE 1
Demographics of Lymphedema Patients

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (Yr)</th>
<th>Sex (M/F)</th>
<th>Involved Limb</th>
<th>Duration</th>
<th>Primary Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>RLE</td>
<td>11 years</td>
<td>radical hysterectomy, irradiation (uterine CA)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>F</td>
<td>LUE</td>
<td>6 weeks</td>
<td>modified radical mastectomy (breast CA)</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>F</td>
<td>RLE</td>
<td>10 years</td>
<td>hysterectomy(uterine leiomyoma)</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>RLE</td>
<td>10 weeks</td>
<td>radical prostatectomy (prostate CA)</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>F</td>
<td>LLE</td>
<td>4 weeks</td>
<td>radical hysterectomy, irradiation (uterine, CA)</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>F</td>
<td>LLE</td>
<td>24 weeks</td>
<td>radical hysterectomy, irradiation (uterine, CA)</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>LLE</td>
<td>12 weeks</td>
<td>radical hysterectomy, irradiation (uterine, CA)</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>F</td>
<td>LLE,RLE</td>
<td>20 years</td>
<td>lymphedema precoc</td>
</tr>
</tbody>
</table>

M/F=male/female
RLE, right lower extremity; LLE, left lower extremity; LUE, left upper extremity;
CA=cancer

### TABLE 2
The Level of Dermal Malondialdehyde (MDA) in Lymphedema Compared with Non-Edematous (Control) Skin (nmol MDA/mg tissue)

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Lymphedema</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.317</td>
<td>0.087</td>
</tr>
<tr>
<td>2</td>
<td>0.394</td>
<td>0.218</td>
</tr>
<tr>
<td>3</td>
<td>0.153</td>
<td>0.094</td>
</tr>
<tr>
<td>4</td>
<td>0.240</td>
<td>0.130</td>
</tr>
<tr>
<td>5</td>
<td>0.149</td>
<td>0.077</td>
</tr>
<tr>
<td>6</td>
<td>0.203</td>
<td>0.083</td>
</tr>
<tr>
<td>7</td>
<td>0.185</td>
<td>0.082</td>
</tr>
<tr>
<td>8</td>
<td>0.110</td>
<td>0.160*</td>
</tr>
</tbody>
</table>

\[
\bar{x} = 0.219^{**} \\
\text{SD} = 0.095 \\
^*\text{control specimen from skin of breast} \\
^{**}p<0.05 \text{ (paired t test)}
\]

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scraped off, freeze-dried and examined for lipoperoxide content after the method of Ohkawa et al (7). Control skin specimens from the uninvolved limb or the skin of the breast in the patient with bilateral lymphedema precox (controls) were handled similarly.

RESULTS

In 7 patients with secondary lymph stasis, levels of MDA (malondialdehyde), a byproduct of linolenic acid metabolism was consistently higher in the edematous limb than MDA in the uninvolved extremity (Table 2). In the patient with primary lymphedema of both legs, the edematous dermis MDA was similar to that of the control site (breast skin).

DISCUSSION

Unsaturated fatty acids, namely linoleic, linolenic and arachidonic acid are hyperoxidized to endoperoxide or hydroperoxide. Lipid superoxide is quantified by the amount of malondialdehyde (MDA) which is converted to fluorescent TBA (thiobarbituric acid) pigment by the addition of thiobarbituric acid. Because other aldehydes such as propionaldehyde or crotonaldehyde also react with TBA forming a fluorescent pigment, the MDA value is not solely indicative of lipoperoxide. In our study, the epidermis was scraped from the specimen, because the skin surface lipid is converted into lipoperoxide by ultraviolet rays and the MDA value varies after sun exposure (8-10).

Skin melanin is transported by lymphatics to regional lymph nodes (11). Accordingly, it is important to determine whether a similar dermis-lymph nodal connection exists with dermal lipoperoxide, and whether the latter substance is important in the pathogenesis of lymphedema. In somewhat related disorders such as scleredema adutorum Buschke (12), dermal burns (13,14), psoriasis and atopic dermatitis (15), lipoperoxide skin levels are increased.

Lipoperoxide in normal skin is probably transported to regional lymph nodes via dermal lymphatics. If this pathway is impaired as in lymphedema, lipoperoxide may be deposited in skin and contribute to lymphatic dysfunction thereby initiating a vicious circle with progressive worsening of lymph stasis. If this supposition is correct, then a lipoperoxide reducer or inhibitor may help alleviate chronic lymphedema. The serum level of lipoperoxide is not consistently elevated with lymphedema (16), as a metabolic barrier may exist between the blood serum and dermis. In patient #8 with bilateral lymphedema precox, lipoperoxide (TBA positive) was not increased, in part, because the patient had primary lymphedema and, in part, because the control specimens were taken from the breast skin. We avoided taking a control specimen from the arms in that this area is typically exposed to the sun (ultraviolet light) and may yield a factitiously high value.

Although these data are preliminary they suggest that accumulation of lipoperoxide contributes to the pathogenesis of lymph stasis. The findings need to be corroborated because of the 7 patients with positive findings each had secondary lymphedema and moreover 5 had lymph stasis for only 6-24 weeks after radical operation and irradiation.

REFERENCES


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