Inflammatory Changes of Skin in Lymphedema of Extremities and Efficacy of Benzathine Penicillin Administration

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All types of inflammatory changes of skin in lymphedema as crysipelas, cellulitis, lymphangitis have been recently been given the name dermato-lymphangio-dermatitis (DLA). DLA is the most common complication of lymphedema.

Clinical signs of DLA are circumscribed erythema of skin in the swollen extremity (red, inflamed areas), often a rash or red blisters and warmth; in some cases, red streaks along the superficial lymphatics and enlarged painful regional lymph nodes. The changes develop first in the skin, then in lymphatics and nodes. This sequence of events (1), documented by our group, prompted us to coin the condition "DLA." Malaise, fever and chills accompany the local changes. The fully developed clinical picture is, today, less frequently seen. This is attributed to the effect of antibiotics given already at the prodromal* stage of DLA. The inflammatory changes persist after an acute episode, at a subclinical level, and occasionally undergo exacerbations. Chronic inflammatory changes can be observed in skin biopsy sections (1). Bacteria can be cultured from the tissue fluid, lymph, and lymph nodes (2).

The episodes of DLA are most frequently observed in the postsurgical, posttraumatic, and postdermatitis types of lymphedema, as well as in the late and advanced stages of congenital forms. Clinical observations indicate that there is a time lag between the clinical appearance of lymphedema and the first episode of DLA, lasting for months or years. Once DLA occurs, its recurrence is almost certain, and the frequency of attacks increases in the course of lymphedema. Each episode of DLA is followed by an increase of swelling. The statistics based on reports obtained from 40 researchers from all continents point to at least 50% of lymphedema patients to be affected by DLA (3). This data is higher in tropical countries (4). The frequency and duration of DLA episodes depend on the stage and duration of lymphedema (4).

There is a general agreement, based on clinical observations, that antibiotics are highly effective in therapy of acute DLA (3). It is also known that after cessation of administration of antibiotics, recurrent episodes of DLA again become frequent. The question arises as to whether a long-term antibiotic administration will prevent recurrences of DLA and consequently slow down the process of skin fibrosis and lymphatic obliteration.

We evaluated the clinical course of lymphedema of lower limbs with respect to the prevalence of DLA in an open trial in 45 patients given long-term parenteral penicillin. The frequency of DLA episodes in the pretreatment year served as a control in each patient.

Definition of DLA and Inclusion Criteria

Common criteria for diagnosing DLA were established, both for doctors and patients. These were acutely appearing circumscribed tender, warm, and erythematous areas on the skin of lymphedematous extremity as a separate entity, or together with dermal red streaks along lymphatics, sometimes with tender and enlarged inguinal lymph nodes, occasionally prodromal malaise, fever and chills. In chronic cases there was focal redness, tenderness and an increase in skin temperature. Patients with three attacks of DLA in their past history were included.

Exclusion Criteria

Excluded were cases with arterial insufficiency, post-thrombophlebitic syndrome, congenital malformations, lipedema, recent trauma of limbs, and dermatological diseases.

Patients

The group consisted of 45 randomly selected patients, age 23-65 years. Diagnosis of secondary lymphedema was based on clinical investigation, X-rays of soft tissues of limb (skin & subcutis/muscles ratio), and lymphoscintigraphy. Extirpation of inguinal lymph nodes was the cause of lymphedema in four, hip operation with immobilization in two, limb trauma in six, hysterectomy and radiotherapy in two, acute dermatitis in the past in 15, no identified factor in 16 patients.

Penicillin administration protocol

a) A routine skin test for allergy to penicillin was made.
b) For prevention of DLA attacks Benzathine penicillin, 1,200,000 u. (Trade name Dipecoline, in USA Bicillin) was given intramuscularly, at 3-week intervals, in a few more advanced cases, at 2-week intervals. The site of injection was anesthetized prior to injection with 2% Xylocaine or penicillin suspension was mixed with Xylocaine in the syringe and subsequently injected.
c) In case of recurrence of acute episode of DLA during the period of prophylactic administration of Benzathine penicillin, patients received oral antibiotics (Erythromycin or Ampicillin, 1.5 g, daily, for 7 days). Oral administration of antibiotics was superimposed on regular Bicillin injections.
Inflammatory Changes...  Cont.

In our study, each patient received injections of Benzathine penicillin for a period of one year. After this period of time, administration of Benzathine penicillin was reinstalled in a regular one-year protocol when cessation of penicillin therapy was accompanied by tendency for recurrences. The prodromal symptoms of recurrent DLA were malaise with tenderness of skin, or sudden exacerbation of skin inflammatory changes, or circumscribed erythematous, warm skin areas and tender inguinal lymph nodes.

Results

All 45 patients received Benzathine penicillin for a period of one year, at 2-3 week intervals. In this group only four patients experienced attacks of DLA (9%). Their frequency was from 1-3 per year. Interestingly, cessation of penicillin administration after one year observation was followed in each of the 45 patients by recurrence of either subclinical or acute DLA. The time interval between the end of penicillin administration and recurrence was 3-6 months. In all these patients, the prophylactic injections of penicillin were resumed. They were given for periods from two to ten years (Table 1).

Some patients deliberately interrupted taking injections, with hope of no recurrences. However, all of them had to resume injections upon the first symptoms of recurrence.

During the one year follow up, there was no evident increase in the calf and thigh circumference in any of the investigated cases.

Discussion

This study has shown that administration of Benzathine penicillin for a period of one year in a group of 45 patients with secondary lymphedema of lower limbs with recurrent episodes of DLA was accompanied by a decrease of the rate of attacks by 90%. These data confirm the numerous statistically undocumented observations, that penicillin is extremely effective in prevention of occurrence of inflammatory complications of lymphedema and recurrent skin infections (5-10). To objectify the data, frequency of DLA episodes prior to and during penicillin administration period was compared in each patient.

We noted that progression of skin changes and increase in size of the affected part of extremity, compared with the pretreatment period, slowed down. So far, this has not been objectively documented. However, in three patients, skin biopsies were made after three months of penicillin therapy, and resolution of mononuclear infiltrates could be observed (unpublished observations). Patients reported subsidence of feelings such as skin tension and tenderness with less limitation of movement in ankle and knee joints; previously erythematous skin regained normal color.

Three-week intervals between prophylactic penicillin injections seemed to be sufficient for protection against recurrences. Longer periods without systemic penicillin were burdened with reappearance of inflammatory skin changes and systemic symptoms. No complications of protracted penicillin administration have been observed. In the very few cases of allergy to penicillin, erythromycin or ampicillin were recommended in a dose of 0.5 g daily for a period of one year.

Taken together, the presented data indicate that Benzathine penicillin, given periodically at low doses, may be an effective drug preventing recurrences of DLA. Moreover, it may slow down progression of skin inflammatory changes typical for progressive lymphedema.

References

Table 1

Administration of Benzathine penicillin in 45 patients with secondary lymphedema of lower limbs and prevalence of DLA episodes. The follow-up was from one to ten years. Each patient experienced at least one, two or three attacks of DLA prior to entering the trial.

<table>
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<th>Duration of penicillin*</th>
<th>Number of Patients</th>
<th>Number of patients with recurrence of DLA</th>
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<tr>
<td>1</td>
<td>45</td>
<td>4* (9%)</td>
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<tr>
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<tr>
<td>5</td>
<td>14</td>
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<tr>
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<td>9</td>
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<td>8</td>
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<tr>
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</table>

\* 1,200,000 u, i.m., every 3 weeks, no clinically detectable side-effects,
\* number of patients with recurrence of DLA during the first year of penicillin administration,
\* number of patients with recurrence of DLA during the second year of penicillin administration, etc.