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ERYTHEMA INDURATUM LEPROSUM, A DEEP NODULAR FORM OF REACTION IN LEPROMATOUS LEPROSY

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One of the more noticeable effects of the sulfone treatment of leprosy, as seen among the patients at the Central Luzon Sanitarium, is the increase of frequency of erythema nodosum leprosum and also an apparent modification of the course of that condition in some cases. Among a group of moderately and markedly advanced lepromatous cases dealt with in this report, 83 per cent developed acute lepra reaction, chiefly of the erythema nodosum type, over a period of 2 years under sulfone treatment. With so many cases of reactions to observe, and with re-awakened interest in these acute skin manifestations of the lepromatous type, it has been surprising to discover how many interesting features of this familiar phenomenon we have glossed over or missed in the past.

No attempt will be made here to describe in detail the manifestations of typical erythema nodosum leprosum. This article deals only with a certain heretofore little-noticed phase of both the acute and the recurrent forms of lepra reaction in lepromatous leprosy, here called "erythema induratum leprosum." This form of reaction is characterized by acute, deep-seated subcutaneous nodules and chronic fibrous masses called by our patients *tolondron*, a Spanish word meaning contusion or bump. The histology of these nodules during their various stages suggests that they may occupy a unique place in the unfolding of the infection in the skin in the lepromatous type of the disease.

CLINICAL FEATURES

The recurrent efflorescences of lepra reaction may continue to be mild from start to finish of an attack, or they may become so severe and protracted as to last many months or years, accompanied by more or less marked constitutional symptoms. Many patients with the severe and protracted condition sooner or later become bed-ridden, and if they do not terminate in rapidly-progressing pulmonary tuberculosis, or in

nephritis, or in some other intercurrent illness, they eventually develop anorexia and asthenia leading to death directly attributable to leprosy itself.

Between these two extremes of mild recurrences and pernicious protracted attacks, many of our more advanced lepromatous cases under sulfone treatment pass through a stage of clinical instability characterized by attacks of a special form of lepra reaction of moderate severity, which is here considered as an erythema induratum form.

Among the cases which experience erythema induratum leprosum, it has been observed that most have first the erythema nodosum type of reactional eruptions. After a few bouts of that condition—or some other form of acute lepra reaction, or towards the end of a prolonged exacerbation—some of the acute papules and nodules become distinctly larger and deeper than the preceding ones, ranging in diameter from 1 to 3 cm. The ordinary small erythema nodosum papules and nodules, including those developing on pre-existing lesions, either gradually diminish in number or quite suddenly fail to recur. Usually the nodules of the new type appear only in certain definite regions of the body.

In the later attacks the larger, deeper-seated nodules or "tolondrons" predominate in the clinical picture. They are confined exclusively to the following regions, given in their order of frequency as sites:

1. Extensor surfaces of forearms and/or backs of hands
2. Antero-lateral aspect of thighs
3. Anterior and lateral surfaces of arms
4. Front and sides of legs
5. Dorsal aspect of feet
6. Forehead (very rare)

Over 90 per cent of these large subcutaneous nodules are located on the dorsal aspects of the forearms and hands and on the anterolateral surface of the thighs.

At these sites, some of the tolondrons develop close to one another and fuse to form irregular subcutaneous groups. On subsidence of such a group, a hard, fibrous, residual mass remains. Subsequent fresh nodules develop over or around this fibrous mass and, becoming attached to it, add their own fibrous residues to the original masses, thereby producing irregularly elongated nodulations pursuing a jagged course along the long axis of the limb.

If a cross section were to be made of this mass during the reactive phase, it would show a central fibrous core with nodules in various stages of development all around it. On the other hand, during the intervals of latency or quiescence the whole mass diminishes in volume, and the overlying skin which has become attached to it may show wrinkles and creases due to these areas of attachment; the rest of the overlying integument is smooth, darkly pigmented and glistening.

In our observed cases of erythema induratum reaction the active phase has lasted an average of 8 to 10 months, with a range of 1 to 19 months,

starting from the appearance of the first large subcutaneous nodules or tolontrons to the final failure of fresh new nodules to reappear. The fibrous residual masses usually persist much longer, usually for years.

The average case going through this process usually manifests successive active and quiescent phases, as follows:

(a) During the active phase, acute subcutaneous nodules appear in crops at the sites of predilection. The patients have irregular fever, and they often complain of a chilly sensation. However, they do not feel ill enough to enter the infirmary, and almost always they will resist all efforts to hospitalize them. Because of the location of the nodules on the extremities and their tenderness the gait of the patients is affected, and this condition can be detected even at a distance. The patients thus affected are wasted and sickly in appearance, and they walk with a distinct crouch, with a slow-motion movement of both extremities due to the pain. Sitting down or standing up is accomplished with much difficulty in this stage.

The individual nodules are deep-seated and are not well delimited. During the acute stage, which lasts for 1 to 7 days for each nodule, the overlying skin is deep-red in color; as the nodule subsides the skin becomes darker. Occasionally some of the nodules come to a point during the acute stage, and they are exquisitely tender. Later, a small pustule forms at the top which dries to produce a grayish crust; they never break down to form ulcers.

(b) In the quiescent periods there may appear only an occasional acute tolontron, in relation to the distinctive lumpy fibrous masses under hyperpigmented skin of the forearm and thighs. The patients are able to go about their usual activities, although they do not feel up to their usual strength and will not tolerate their previous doses of the sulfones.

Variations in the course of an attack of erythema induratum leprosum occur. In some cases, in the reaction period there may be an accompanying eruption of the ordinary erythema nodosum nodules, with or without exacerbation of the original leprosy lesions. During such attacks the pigmentations and the subcutaneous fibrous masses are the only indications that the patient is having or has had an erythema induratum form of reaction. Sooner or later, however, the character and location of the acute lesions revert back to the tolontron type, followed by extension of the fibrotic masses.

Again, the typical subcutaneous nodules or tolontrons may appear at the very outset of the attack, without there having been preliminary bouts of ordinary erythema nodosum. This happened in 10 out of 47 cases of erythema induratum studied. When this occurred, the attacks as a rule were mild and of short duration.

Finally, the subcutaneous nodules may likewise appear without a preliminary attack of the ordinary lepra reaction but be quite different in appearance from the usual tolontron, being more superficial and more diffuse. This condition was noted in 2 instances, both of them occurring in

early lepromatous cases with extensive areas of skin that showed no visible leprotic lesions. There was a tendency in these cases for some of the lesions to develop along the course of nerves—the medial brachial cutaneous and the superficial branch of the radial. The portions of the nerves under the nodules became thickened and tender, causing the patient much pain and discomfort. In both cases, when the reactions subsided the involved nerves remained thickened and paralysis of the lumbrical muscles followed.

Incidence of erythema induratum leprosum reactions.—In the course of this study a special group of 148 lepromatous cases under sulfone treatment for two years was particularly observed for the occurrence of the erythema nodosum and erythema induratum reactions. Of this group, only 17 were regarded as slight with respect to advancement of the disease (L_1), the other 131 being of moderate to marked severity (L_2 and L_3). During the period of observation no less than 123, or 83 per cent, developed one or the other of those forms of lepra reaction, of varying degrees of severity and duration, from very mild attacks with only a few papules of brief duration, without constitutional symptoms, to very protracted series of exacerbations which required hospitalization for months. Of those reacting cases 6 were among the 17 early cases, while 117 occurred among the 131 advanced cases. The incidence rates were therefore 35 per cent for the slight cases and 90 per cent for the more advanced ones.

One group of 57 reacting cases showed erythema nodosum of relatively brief duration, and of them 14 developed lesions of the erythema induratum type within three months after the outset of the attack. The other group, comprising 56 reacting cases, had prolonged or recurrent attacks of erythema nodosum, and 23 showed late appearance of tolonidrons. In 10 instances the erythema induratum form of lesions appeared at the very outset of the attack, preceding the erythema nodosum lesions. In other words, the erythema induratum type of lepra reaction occurs both in acute and in long-standing attacks of erythema nodosum, and the name is not merely another term for prolonged or recurrent erythema nodosum. There appears to be some additional element or elements leading to the occurrence of this special condition.

With regard to age, few children exhibit this stage or reaction. For one thing, advanced lepromatous cases are not common among children below 15 years of age. As for sex, the tolonidrons appeared with about equal frequency in both sexes.

With reference to the sulfone drug used, while the incidence of erythema nodosum is about the same among those receiving promin as among those taking DDS or diasone (diamidin), the deep subcutaneous nodules are somewhat the more frequent in the DDS and diasone groups.

Comparison with nonsulfone cases.—An attempt was made to follow, as virtually untreated controls, a group of 50 patients receiving only occasional injections of chaulmoogra oil as their sole antileprosy treatment.

It was not possible, however, to keep as good records of the occurrence of erythema nodosum in this group during the two years that the sulfone group was being observed, and the figures are perhaps not directly comparable for other reasons. At any rate, it can be safely stated that the occurrence of erythema induratum leprosum is at least 50 per cent less frequent among the untreated patients than in the sulfone-treated group.

Results of skin and serological tests.—Groups of erythema induratum patients were subjected to the lepromin and tuberculin skin tests, and the Kahn serological test. The results are consolidated in Table 1.

TABLE 1.—*Results of lepromin and tuberculin skin tests, and Kahn serological test, in representative groups of erythema induratum cases.*

Lepromin (47 cases)		Tuberculin ^a (31 cases)		Kahn (18 cases)	
Result	Cases	Result	Cases	Result	Cases
Negative	41	Negative	10	Negative	8
Pos., 1+	5	Pos., 1+	3	Doubtful	4
Pos., 2+	1	Pos., 2+	10	20 KU	2
—	—	Pos., 3+	6	80 KU	1
—	—	Pos., 4+	2	160 KU	1
—	—	—	—	320 KU	2

^a Results with 1 TU. The 10 negatives when retested with 10 TU all gave positive reactions (see text).

Lepromin test: Of the 47 patients subjected to the lepromin test, all of them lepromatous, 6 gave positive reactions, 5 of them 1+ and the other 2+. The 2+ reactor was an improved case with marked atrophies; of the 5 weak reactors, 2 also had atrophies of the extremities, but the other 3 had predominantly advanced cutaneous nodular lesions. All the rest were Mitsuda negative.

No relationship was found between positivity to the test and the severity of the erythema induratum lesions. However, the only case moderately positive to lepromin had only a few tolondrons, and the active stage lasted less than 2 months.

Tuberculin test: Thirty-one cases which had just passed through the active status reactionalis stage, or which still had active tolondrons, were tested with PPD. As shown in Table 1, all but 10 of the 31 reacted to the first dose (0.00002 mgm., or 1 TU). The 10 negatives were retested with the intermediate dose (0.0002 mgm., or 10 TU), and all then reacted—only 2 of them weakly (1+).

Thirteen other erythema induratum cases were tested but with the intermediate dose directly. Of these, 3 were negative while the other 10

gave strong reactions. In fact, in 6 instances the reactions may be said to have been violent, both locally and constitutionally, for there was bleb formation with chills and high fever lasting 1-2 weeks. Four of these 6 were in the active phase, and they had marked exacerbations of the cutaneous leprotic lesions as well as the constitutional symptoms, and the 2 who were in the latent phase developed typical acute erythema nodosum nodules.

Only 12 patients with ordinary acute lepra reaction could be tested with PPD (first dose). No difference in their response to tuberculin was noted as compared with those in the erythema induratum phase.

Kahn test: The blood sera of 18 patients with tolondrons were examined by the Kahn test, with results also shown in Table 1. One of the strongly positives, having a titre of 320 KU, gave a history of possible syphilis. All the others denied ever having had either syphilis or yaws, and none of them showed active lesions or scars of those diseases. Of course this lack of positive history does not necessarily completely eliminate such infections. Most of the patients, moreover, had malaria.

Bacteriology.—Smears of scrapings from the tolondrons and from the subcutaneous fibrous masses showed numerous bacilli with globi, although perhaps not as many as in corresponding smears from ordinary lepromata. Furthermore, in many of the smears there were more beaded than solid forms.

In sections stained for bacilli, the frequency with which they were found in the endothelial cells of the small blood vessels was notable.

TREATMENT

The main consideration in the management of the erythema induratum reaction is the conservation of the strength of the patient, with due attention to the diet. Recourse is had to the routine measures commonly employed in the management of lepra reaction, such as alkalinization, use of anti-pyretics and analgesics, calcium chloride or calcium gulconate intravenously, occasional injections of adrenalin, etc.

Our results with antihistaminics have been extremely disappointing. Not only was there no improvement of the acute skin lesions or of other symptoms, but the side effects were frequent and disagreeable. It would require a lot of convincing to make any of these patients try any anti-histaminic drug again. In common with experience elsewhere, penicillin has been found to be ineffective.

The intravenous administration of dilute novocaine solution, as advocated by Horan (1), was tried in a few cases. There was temporary relief of the usual attendant nerve, muscle, and joint pains. On the whole, however, the results were not particularly effective, and recurrence of the attacks was the rule.

Cortisone, hydrocortisone, prednisone, prednisulone and ACTH preparations were unavailable during the period of this study, but other cases of the erythema induratum form of lepra reaction were subsequently

treated with these drugs. There was rapid subsidence of the acute manifestations in practically all cases, and the improvement was continued under adequate maintenance dosage, but there was a return of all the active manifestations after the administration of the corticosteroids was discontinued. Suppression of the acute phase has been maintained for as long as four years with prednisone and/or prednisulone, but there was reactivation within a few days after discontinuance of the drug.

Of all the drugs tried, streptomycin was found to produce the most lasting improvement. Injections of this drug were given to 10 patients, with total doses ranging from 15 to 30 grams. Except in 1 case, there was a definite clinical improvement of the lesions, but there was recurrence of about the same intensity as before treatment in 2 instances, with milder recurrences in 3 others. In the exceptional case, the active lesions became much more severe after a few injections. In 4 of these streptomycin cases there was no recurrence of the acute phase. The period of observation covered four months, during and after treatment.

In another group of 12 patients observed at that time but not given streptomycin injections, the tolondrons subsided in only 2 of them within an observational period of six months.

HISTOLOGY OF THE TYPICAL TOLONDRON

The architecture of a typical tolondron in the reactive stage may be summarized as follows:

Epidermis: There are either no noticeable changes, or, more usually, there is slight acanthosis.

Papillary layer: There is slight dilatation of capillaries with some perivascular infiltration and slight edema of the tissues. Microlepromata are usually present.

Upper reticular layer: Microlepromata are numerous around the hair follicles, with tendency to giant-cell formation.

Deeper reticular layer: Practically all of the sweat glands are involved, with marked leprotic deposits between the follicles. The lepromata in this layer extend down to the deepest layers of the mesoderm.

Hypoderm: This layer is extensively involved, with marked lepromatous and lymphocytic infiltration. Severe leprotic involvement of practically all the deeper blood vessels of the hypoderm is characteristic. Three stages of the vascular involvement may be noted: (1) In the most acute lesions, lymphocytic and lepra-cell infiltration of all coats—the intima, media, and adventitia—with obliteration of the lumen in many cases. (2) In less acute lesions, some infiltration of the adventitia and media. (3) In the least acute lesions, no marked cellular infiltrate in any of the coats, but fibrotic changes in the adventitia.

In the inactive stage the characteristic changes consist of the presence of a large number of poorly-nucleated vacuolated cells in all the layers of the cutis, and very marked leprotic involvement of the fatty layer produc-

ing a veritable leprotic panniculitis. The arterioles and veins show thickening of the adventitia and media, with fibroblastic infiltration of the adventitia. There is sometimes seen a recanalization of the lumen of some of the previously occluded blood vessels.

A biopsy specimen of apparently involved skin taken three inches from an active lesion on the forearm showed the ordinary slight degree of leprotic involvement of the skin found in moderately advanced lepromatous cases. The blood vessels showed no infiltration of their walls, even when they were completely surrounded by leprotic deposit. Involvement of the panniculum was minimal.

DISCUSSION

Although it is believed that the causes of all acute reactions in lepromatous leprosy are basically the same, the reactions being essentially allergic in nature, the morphological characteristics and development of the clinical manifestations may vary greatly in different cases, due perhaps to the site of the shock tissue and to other factors not understood. Thus, an erythema multiforme type of acute lepra reaction has been described, while pemphigoid and pustular varieties are also recognized. A more or less generalized erythematous reaction is sometimes seen, with or without exfoliation. At other times the skin is quite clear of acute lesions and the acute reactional manifestations occur in the testis or the mammary gland in the male, or in the nerves, lymph glands, or the ciliary body of the eye.

The possibility that some of the more unusual manifestations of acute lepra reaction may be due to the existence of concomitant disease of widespread distribution has probably to be taken into consideration also. Association with tuberculosis was considered in connection with the present study, but unfortunately it was not possible to diagnose the coexistence of tuberculosis of the lungs through x-ray examinations. However, pieces of tolondron were removed, ground, and injected into guinea-pigs by Dr. C. Manalang, with negative results. Of 18 patients with tolondrons whose sera were examined by the Kahn test, 6 gave positive results with titers of over 20 KU. Only 1 of them, however, gave a history of syphilis; none had had yaws.

The form of reaction that has been described here is reminiscent of erythema induratum of the variety not showing any tubercles, designated by O'Leary and Barber as nodular vasculitis. Some of the sections are similar in histology to the Parkes Weber-Christian disease. The morphology and site of the lesions as well as the constitutional manifestations also show some similarities to those syndromes.

SUMMARY

A chronic form of nodular lepra reaction in the lepromatous type of leprosy is described, characterized clinically by the presence of deep coalescing nodules on the forearms, hands, and thighs, and histologically

by a proliferative vasculitis involving both arteries and veins of the hypoderm. There is also a massive leprotic panniculitis, more exaggerated than that commonly seen in the typical lepromatous nodule or in erythema nodosum leprosum.

RESUMEN

Se describe una forma crónica de reacción leprosa nodular en la lepra de forma lepromatosa, que se caracteriza clínicamente por la presencia de nódulos coalescentes profundos en los antebrazos, manos y muslos, e histológicamente por una vasculitis proliferante que afecta tanto las arterias como las venas de la hipodermis. Hay además una paniculitis leprótica masiva, más exagerada que la observada comúnmente en el típico nódulo lepromatoso o en el eritema nudoso leproso.

ACKNOWLEDGEMENT

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DESCRIPTION OF PLATES

PLATE (19)

FIG. 1. Acute subcutaneous nodules appearing over fibrotic masses on the back of the hands, and also on the extensor surfaces of forearms.

FIG. 2. Fibrous masses on the extensor surfaces of the forearm and dorsum of hand during the later part of the active phase, which is beginning to subside.

FIG. 3. Subsiding fibrous masses on the extensor surfaces of both forearms and the dorsum of one hand. The pigmented, thickened, lumpy skin closely adherent to the underlying contracting mass shows characteristic irregular depressions. (Below the large fibrous masses on the left forearm are a few typical small subcutaneous lepromatous nodules, not of reactional nature.)

FIG. 4. Atrophic, scarred, shiny, almost translucent skin of front and lower half of both thighs, after complete subsidence of tolongons and fibrous masses. The subcutaneous tissue is also reduced to a very thin layer. Duration of the reactive phase in this case was 5-½ years.

