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Giant Reactions to Tuberculin in Lepromatous Leprosy Patients[1]

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Among the many immunological anomalies observed in lepromatous leprosy patients is the phenomenon known as giant reaction to tuberculin. This has received very little attention, and except for passing mention by Waters and Ridley ([12]) and by Rees ([1]) and paragraphs describing its salient features in a recent book ([5]) and review ([7]), we know of no account of it in the literature. The phenomenon appears to have been first observed by one of us (MW) in 1959, and by the other in 1972. Only shown by occasional lepromatous patients who have usually received antileprosy drugs, giant reactions are accelerated and exaggerated responses to tuberculin.

In this paper, we first define and then give an account of our experience with giant reactions and record all our available observations.

Of the 28 instances of giant reactions which we have observed, all but one occurred among patients with lepromatous (LL or BL) leprosy. The single exception was in a case of quiescent, treated, borderline-tuberculoid (BT) leprosy.

The reaction commences as erythema and edema at the skin test site between six and 12 hr after injection. This rapidly increases in size to a swollen area, perhaps 70–90 mm or more longitudinally and 40–50 mm or more transversely, across the forearm and, occasionally, involves the full circumference of the arm. It is usually accompanied by local pain, fever, headache, and often by lymphangitis and/or a painful, swollen axillary lymph node. Maximal between 24 and 48 hr, the reaction is sometimes already resolving by 72 hr and disappears within one to four weeks. Usually the central area around the injection site becomes further raised and indurated. This central area, which often vesiculates but less commonly ulcerates yet which need not be larger than a large reaction of the more usual type observed among such patients, may become more prominent as the edema and erythema recede. A giant reaction sometimes precipitates the patient into an episode of erythema nodosum leprosum (ENL), and it usually recurs if the patient is again tested with tuberculin. A remarkable observation is that the reaction is directed against specific antigens of *Mycobacterium tuberculosis* and never occurs with reagents made from other mycobacterial species which may have been tested at the same time. The phenomenon is quite unlike anything observed among tuberculosis patients.

In this paper (for reasons given below), we have classified as giant reactions all responses to 1 or 2 TU of PPD RT23 or to 0.2 μg New tuberculin which measure 40 mm or more in overall diameter.

MATERIALS AND METHODS

Malaysia. One hundred untreated or minimally treated lepromatous patients with active leprosy were serially admitted to two controlled clinical trials over the space of five years ([10, 11]). Patients were classified by clinical, bacteriological, and histological criteria, the last being given the most weight, into lepromatous (LL) and borderline-lepromatous (BL) leprosy ([2,3]). Lepromin and tuberculin tests and chest X-rays were performed before commencing treatment, after six months, and at one year. The tuberculin used was 1 TU of RT23, injected intradermally into the flexor surface of the right forearm; the lepromin test, using Dharmendra lepromin, was given on the left forearm. Reactions were read at 48 hr and at 72 hr, the lepromin also being read weekly for four weeks. If the tuberculin response was negative (<5 mm diameter of induration), the patient was retested, usually one week later, with 20 TU of RT23.

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Patients were paired—one member of each matched pair received parenteral dapsone twice weekly; the other, dapsone plus the trial drug, namely, macrocyclon in the first trial and ditophal (Etisul) in the second trial. Most patients were studied as inpatients for one year, although the last three pairs admitted to Trial 1 were followed for only six months. Ten patients, however, of whom five had shown giant reactions and five normal tuberculin reactions, were retested 25–37 months after commencing antileprosy chemotherapy.

Patients were checked regularly for ENL; severe ENL was treated with steroids.

Uganda. As part of a skin-test study carried out in 1972, 61 leprosy patients in the Buluba leprosarium, Busoga, were injected intradermally with 2 TU of RT23 on one forearm, and with 0.2 μg protein of the new tuberculin Duvalin (prepared from *M. duvalii* [4]), and a second new tuberculin, on the other forearm. Forty-one patients received Burulin (prepared from *M. ulcerans*), 10 received Ranin 1 (prepared from *M. fortuitum*-type subspecies), and 10 received Chelonin (prepared from *M. chelonei*-type subspecies) as the third reagent ([4]). Tests were read as diameters of induration after 72 hr. Twenty-three of the 61 patients were classified as lepromatous, and all were receiving chemotherapy.

Additionally, 39 patients on treatment for pulmonary tuberculosis in Mulago Hospital, Kampala, were skin tested with 2 TU of RT23 and three new tuberculins. Data on these patients are included for comparison. Although not age matched with the leprosy patients, they were in the same age range of 20–40 years.

Spain. In association with an immunotherapy study in the Sanatorio de Fontilles, Alicante, and in Almeria in Spain, 140 patients with lepromatous leprosy were injected intradermally with New tuberculin (0.2 μg of protein in 0.1 ml) and Leprosin A (1 μg) on the left forearm, and with Scrofulin (0.2 μg) prepared from *M. scrofulaceum*, and Vaccin (2 μg) prepared from *M. vaccae* on the right forearm ([4]). On each arm, the injection sites were at least 10 cm apart. Reactions were read after 72 hr. Some patients (87) were first tested in 1982, some (34) in 1983 and some (24) in 1984. Patients were re-tested when possible at yearly intervals. However, tuberculin was excluded from subsequent tests in individuals producing large reactions to it on the first occasion.

London. A small group of 20 leprosy patients, 16 presumed untreated (6 BT, 1 BB, 7 BL, and 6 LL), were injected intradermally with Mitsuda lepromin (4×10^6 bacilli in 0.1 ml), New tuberculin (0.2 μg in 0.1 ml), Scrofulin (0.2 μg), Leprosin A (1 μg), and Vaccin (2 μg). Three tests about 5 cm apart were given on the left and two tests on the right forearm. All of the reactions were read at 72 hr, and the lepromin reaction was again read after four weeks.

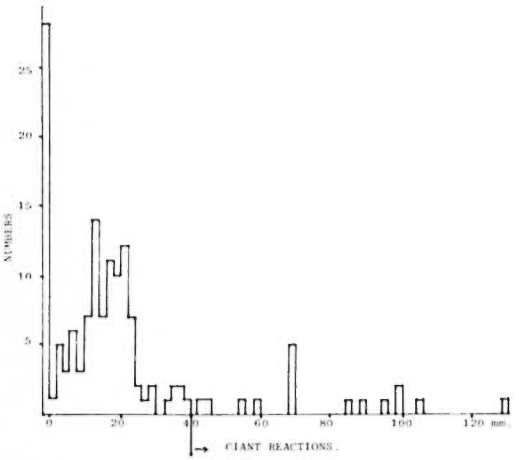
RESULTS

Malaysia. Serial tuberculin test results were available from 96 of the 100 patients. Of these, 76 were LL, including 54 Chinese, 10 Indians, and 12 Malays; 6 of the Chinese were females. The 20 BL patients included 15 Chinese, 3 Indians (one female) and 2 Malays. Re-testing was done after six months for 73 LL and 19 BL patients, and after 12 months for 69 LL and 18 BL patients.

No patient on admission was considered to show X-ray evidence of active tuberculosis. One Indian BL patient developed symptoms of pulmonary tuberculosis, confirmed by chest X-ray at five months, and a review of his pre-trial X-ray revealed a scarcely discernable small localized lesion. No other patient developed clinical or X-ray evidence of active tuberculosis during the course of the trial, although one subsequently suffered a relapse of apparently healed tuberculosis.

Of the 76 LL patients, 19 developed giant reactions with diameters of 40 mm or more; 12 were in trial 1 and 7 in trial 2. Fifteen were Chinese (including two females), two were Malay and two were Indian.

The size of their reactions, compared with normal reactions, is shown in The Figure and in Table 1. Fifteen of the 19 reactions were 50 mm or more, and 12 were 70 mm or more, in diameter along the long axis of the forearm, the largest measuring approximately 130 mm. The raised inner area, when visible and palpable, measured about 25 mm in diameter. Lymphangitis commonly occurred, with or without axillary lymphadenitis, and sometimes the raised



THE FIGURE. Distribution of tuberculin responses by diameter of induration at 72 hr among our patients studied in Malaysia. The results obtained after 6 and 12 months of chemotherapy are included. Thus, two results are incorporated for most individuals.

central area vesiculated, but was only once recorded as having ulcerated.

Only one patient had a giant reaction (measuring 40 mm) in the pre-trial test. He and 11 others had giant reactions at six months; the other 11 were re-tested at one year, and four continued to have giant reactions. Seven other patients developed giant reactions for the first time at 12 months.

The five patients who had giant reactions at six months, and who volunteered for re-testing at 25–37 months after commencing trial therapy, included the one who giant-reacted pretreatment but who was not re-tested at one year and two others who did not exhibit giant reactions at one year, although both were then receiving steroids for ENL. All five had giant reactions, measuring between 45 and 80 mm. The five patients who had not shown giant reactions at each of their three routine tuberculin tests, who also volunteered for re-testing after 2–3 years when two were suffering from severe ENL, did not develop giant reactions at the latest test.

Twelve (63%) of the 19 patients who developed giant reactions suffered from ENL during the study period compared with 27 (48%) developing ENL among the 56 patients without giant reactions. This difference is not significant at the 5% level. Despite this, there was a clinical impression that giant reactions could precipitate episodes of ENL in patients liable to reactions.

TABLE 1. *Tuberculin results obtained in Malaysia, Uganda, and Spain.*[a]

"Normal" reactors		Giant reactors	
No. (% positive)[b]	Mean positive size reaction ± S.D.	No. (% positive)[b]	Mean positive size reaction ± S.D.
Malaysia			
Initial results			
48 hr 33/58 (56.9%)	12.5 ± 5.1 mm	16/18 (88.9%)	16.75[c] ± 9.7 mm
72 hr 32/58 (55.2%)	12.5 ± 5.1 mm	15/18 (83.3%)	16.05[c] ± 6.8 mm
Results after 6 months' treatment			
48 hr 42/54 (77.8%)	16.0 ± 7.7 mm	18/18 (100%)	55.7 ± 30.4 mm
72 hr 42/54 (77.8%)	15.8 ± 7.1 mm	18/18 (100%)	55.4 ± 36 mm
Results after 12 months' treatment			
48 hr 46/52 (88.5%)	14.7 ± 8.1 mm	17/17 (100%)	47.1 ± 28.8 mm
72 hr 37/52 (71.2%)	16.3 ± 7.0 mm	16/17 (94.1%)	43.9 ± 25.4 mm
Uganda			
72 hr 15/22 (68.2%)	19.0 ± 4.8 mm	1	100+ mm
Spain			
72 hr 91/136 (67%)	14.8 ± 5.4 mm	4	47.5[d] ± 11.8 mm

[a] In each case, those producing conventional reactions are shown on the left and those producing giant reactions on the right.

[b] Positive reactions to RT23 are defined as having a diameter of induration ≥5 mm in Malaysia and in Uganda. For New tuberculin in Spain, positive reactions are ≥2 mm.

[c] Patients who developed giant reactions at subsequent testing.

[d] Central indurated area; swollen areas much larger.

Only one of the 13 LL patients who developed giant reactions at six months was found subsequently (at 12 months) to be tuberculin negative (4 mm at 48 hr and 0 mm at 72 hr); the only BL patient who developed a giant tuberculin reaction (at six months, measuring 65 mm in diameter at 48 hr) was the one found to be suffering from early active pulmonary tuberculosis.

Uganda. Of the 23 lepromatous patients tested with RT23 and Duvalin at Buluba, one patient developed a giant reaction to the PPD within 12 hr of injection. An ENL reaction was precipitated within 48 hr, and the patient was in bed and receiving steroid treatment when the reactions were read at 72 hr. The entire diameter of the arm was swollen, and the patient had a tender, enlarged, axillary lymph node.

It was not possible to measure accurately the inner area of induration distinctly from the surrounding edema, but it was between 30 mm and 40 mm in diameter. The reaction subsided over the next few days without ulceration. On his other arm, the patient produced induration of 10 × 12 mm to Duvalin, and he did not react at all to Burulin. The mean positive response size plus standard deviation for each reagent in the 22 other lepromatous patients were PPD (2 TU), 19.0 ± 4.8 mm; Duvalin, 10.1 ± 6.5 mm; Burulin, 5.0; Ranin 1, 7.3 ± 2.1; Chelonin, 8.5 ± 3.5 mm.

Although some of the tuberculosis patients produced large reactions to PPD, the two largest being 34 mm and 43 mm in diameter, none of them resembled the giant reactions of leprosy. The mean positive reaction sizes were PPD, 23.5 ± 5.4 mm; Burulin, 7.9 ± 3.7 mm; Ranin 1, 5.6 ± 1.7 mm; and Chelonin, 5.1 ± 2.3 mm.

Spain. Among the 140 lepromatous patients tested in Spain, four developed giant reactions to New tuberculin, one in 1982 and three in 1984. The first of these was a long-term resident in the Sanatorio de Fontilles. First diagnosed in 1950, she had been on treatment since diagnosis and, at the time of testing, was receiving dapsone monotherapy and had a negative bacterial index. Some 10 hr after testing, she had a very tense and tender arm, with aching in the left axilla, headache, and mild pyrexia. Aspirin was prescribed and steroid cream was applied to the tuberculin test site. Within 24 hr of testing, all symptoms except the aching and swollen forearm had gone. At 72 hr, edema was in excess of 120 mm in longitudinal diameter, and there was a central indurated plaque measuring 35 × 40 mm. Reactions to the other three reagents were within normal limits. This patient was re-tested with Leprosin A, Scrofulin, and Vaccin, but not tuberculin, in 1983 and 1984 without any sign of excessive response.

TABLE 2. *Skin test results for individual patients producing giant reactions in Spain and London.*

Patient no.	Tuberculin[a]	Leprosin A	Vaccin	Scrofulin
		Spain		
1	38	0	0	0
2	55	0	0	0
3	63	0	15	11
4	34	0	0	0
		London		
5 (BL)	23	0	3	11
6 (BL)	23	0	0	11
7 (BT)	20	16	11	9

[a] Measurements are of the central indurated area of much larger overall reactions.

The three patients producing giant reactions in 1984 were outpatients, one at Fontilles and two in Almeria, who had not previously been tested. All three had received several years of chemotherapy, but two still had positive bacterial indices. Their stories were typical of the reaction which in each case was resolving by 72 hr. Their reaction sizes were all in excess of 60 mm, with central indurated plaques measuring 34 mm, 63 mm, and 55 mm. The sizes of responses to the other reagents tested at the same time in the four patients with giant reactions to tuberculin are shown in Table 2. They were not different from those occurring in the patients with normal tuberculin reactions.

London. One untreated Northern Indian patient, clinically and histologically unstable active BL leprosy, developed a notable giant reaction. After 8 hr, he complained of pain in his left arm, and by 24 hr the lesion was already very swollen, approaching its full size. Despite the local application of steroid ointments, the lesion was painful, and the patient developed a mild fever and axillary lymphadenopathy. Central bullae occurred, which subsequently ulcerated slightly. At three days the reaction mea-

sured 82 × 65 mm, the central plaque being 21 × 24 mm. It took about ten days to resolve. At the height of the reaction, the Scrofulin reaction, measuring 11 mm, could be easily identified on the edge of the tuberculin reaction from which it was separated by a narrow margin. The lepromin was negative, and on the right arm the Leprosin A and the Vaccin were negative. His chest X-ray was normal. About two months after his diagnosis and these tests were performed, his wife was found to be suffering from active open pulmonary tuberculosis.

One other untreated BL patient, from Pakistan, had a giant reaction, measuring 40 mm at 48 hr and 44 mm at 72 hr when the raised central area measured 23 mm. One fully treated, quiescent Chinese BT patient, who had completed chemotherapy and was in the hospital for reconstructive surgery, also developed a giant reaction which at 75 hr measured 46 × 36 mm, with a central raised area 20 mm in diameter.

DISCUSSION

We have chosen a 40 mm or more diameter of swelling at 48 and/or 72 hr as the definition of a giant tuberculin reaction for three reasons: a) A review of The Figure and Table 1 suggests that there are two separate peaks of reactions to tuberculin, namely, the "normal" group of reactions and the "giant" reactions, the two distribution curves meeting at about a 40 mm diameter size. (These must not be confused with the two types of responses to New tuberculin observed in Ethiopian school children by Stanford and Eshetu Lema [8]). b) Secondly, 40 mm is the smallest size at which there is any likelihood of finding an inner, more elevated area, so typical of the giant reactions. c) When reactions reach about 40 mm in diameter, patients begin to complain of local symptoms of pain and discomfort.

Giant reactions have been found to occur in many different races, including overseas Chinese, Malays, southern and northern Indians, Ugandans, and Spaniards. Although our number of female patients is small, we have not detected any obvious sex difference.

With a single exception, all of the giant reactions we have seen have been in lepromatous patients. In Malaysia and London, where there was clear categorization between BL and LL disease, the difference in occurrence of giant reactions among them was not statistically significant (3/26 BL and 19/82 LL). However, in two of the BL giant reactors, there was an association with tuberculosis which may have influenced the results. One treated BL patient in Malaysia had normal positive reactions at 0 and 12 months but had a reaction of 65 mm at six months, one month after he had been diagnosed as suffering from active pulmonary tuberculosis. One untreated BL patient in London had a normal chest X-ray; two months later his wife was diagnosed as suffering from active, sputum–positive, pulmonary tuberculosis. One untreated BL patient (in London) with a normal chest X-ray produced a reaction measuring 44 mm. She, and the single quiescent BT patient, are under continuing observation. We have not observed giant reactions in any other BT patients, although treated (as compared with untreated) BT patients were seldom tuberculin tested in Malaysia, and no more than 10 were tested in Spain.

The prevalence among untreated BL and LL patients was 3 out of 108 (2.8%) tested (Malaysia 95, London 13), as compared with 20 out of 95 (21%) tested in Malaysia between 6 and 12 months after starting chemotherapy. This difference is highly statistically significant ($p < 0.0001$).

The lack of giant reactions in untreated LL patients concurs with their general lack of reaction to tuberculins which has been called "non-specific skin test unresponsiveness" ([6]), and which may be associated with the high levels of the phenolic glycolipid of *M. leprae* origin present at that time.

Only in Malaysia were serial tests performed on previously untreated patients. Although it was shown that giant reactions could persist for up to three years after the start of treatment, patients treated for longer than 37 months were not tested, and the majority were still bacteriologically strongly positive. The only Malaysian patient to develop a giant reaction at six months and to be negative to 1 TU of RT23 at one year (Case no. 5 of Reference no. 12) showed a marked fall in the bacterial index during the first year of treatment, and at 18 months her histological classification had "reversed" to BB.

The prevalence among long-term treated patients in Spain and Uganda was 5 out of 163 tested, which does not differ significantly from the results in untreated patients in Malaysia and London, but is very significantly different from the recently treated Malaysian patients ($p < 0.0001$).

Although we cannot be sure that the latter difference is unassociated with racial or geographical variations, at the moment it seems probable that giant reaction to tuberculin is a phase through which a proportion of lepromatous patients (perhaps one fifth) pass during the early years of their chemotherapy. Possibly it reflects changes associated with a rapid reduction in levels of the specific phenolic glycolipid, or some other change in antigenic load which is later compensated by homeostatic mechanisms in all but 3% of the patients. Interestingly, despite their years of treatment, 2 of the 4 Spanish giant reactors still had positive bacterial indices at the time of skin testing.

Two other skin-test studies of lepromatous patients have been carried out (by JLS) which are not reported in detail here since giant reactions were not encountered. In one of them, 50 lepromatous (BL or LL) patients, all on chemotherapy, the majority for many years, were tested in Iran with New tuberculin and three other reagents. In the other study, 23 LL patients and 8 BL patients undergoing their first two years of treatment in Agra, India, were tested with New tuberculin, Scrofulin, Leprosin A and Vaccin. Only the earliest stigmata of disease were visible in these Indian patients, and this may explain the lack of giant reactions among them.

Although New tuberculin has not been formally compared with PPD in inducing giant reactions, it is likely that both types of reagent are similarly active. Indeed, a few patients known to produce giant reactions to PPD in Malaysia were subsequently tested with New tuberculin and, again, they produced giant reactions (Laing and Stanford, unpublished observations). Unfortunately, only PPD and lepromin were used in Malaysia, so that one cannot be certain that reagents from other species would not induce giant reactions there. Nevertheless, our experience to date indicates that giant reactions occur exclusively to skin test reagents made from *M. tuberculosis.*

If this assumption is correct, the exclusiveness of the reaction suggests that a particular antigen, or antigens, must be responsible. If so, it is unlikely to be from among those shared with other species (groups i, ii and iii antigens of Stanford and Grange [9]). Rather, it must be among the relatively few species-specific (group iv) antigens withstanding the preparative techniques for PPD. Similarly, the reaction is unlikely to be due to antigen altered or degraded by these techniques, since it is equally present in the unheated sonicate preparation New tuberculin.

The cause of giant reactions is obscure, as is also their apparent specificity to *M. tuberculosis.* Infection with this organism is common in Uganda and India, as well as in Malaysia, so that frequency of contact with it would not seem a rational explanation.

The timing of the onset of the reaction suggests that it might be associated with antibody or perhaps with degranulation of basophils or eosinophils in an uncontrolled way. The indurated plaque, although large, is not usually unduly so in giant reactions, suggesting that infiltration with monocytes and lymphocytes is not the sole cause. Thus, the giant reaction may be a concurrence of tuberculin-type delayed hypersensitivity with a humoral or some less-delayed type of cellular response.

Another possibility is that persons of a particular genotype tend to produce these exaggerated responses because of incompetent or perturbed immune mechanisms. Studies of these possibilities are progressing on our Spanish and London patients.

In conclusion, giant reactions are abnormally large and accelerated skin responses to specific antigens of *M. tuberculosis,* the majority occurring in treated, bacteriologically positive cases of multibacillary leprosy. The mechanism by which they occur remains unknown.

SUMMARY

A detailed account and definition is given of the previously inadequately described "giant reactions" to tuberculin occasionally seen in leprosy patients. The reaction is an accelerated and exaggerated response to species-specific antigens of *Mycobacterium tuberculosis* found in both PPD and New tuberculin. Our studies were performed in

Malaysia, Uganda, Spain, and England. There was a significantly higher incidence of the phenomenon in Malaysia than in the other centers, but this may have been because there alone previously untreated lepromatous (LL and BL) patients were serially tested for up to three years after starting chemotherapy. Of the 28 patients exhibiting giant reactions, 27 occurred among lepromatous patients (24 LL and 3 BL), of which only 3 (1 LL and 2 BL) were untreated. One treated BL patient had developed, and one untreated BL patient was a family contact of, active tuberculosis.

Giant reactions are uncommon in untreated and in very long-term treated LL patients, but may occur in up to a fifth of those receiving their first 1–3 years of chemotherapy. Although the mechanism is not yet understood, it appears to be a coincidence of delayed hypersensitivity of the tuberculin type and a less-delayed phenomenon of excessive local edema associated with local lymphadenopathy and short-lasting symptoms of malaise and pyrexia. It is suggested that the majority of giant reactions occur during a period of temporary lack of immune regulation associated with changing levels of antigenic load.

RESUMEN

Se hace una descripción detallada de las ocasionales "reacciones gigantes" hacia la tuberculina descritas previamente, de manera inadecuada, en los pacientes con lepra. La reacción es una respuesta acelerada y exagerada contra los antígenos específicos del *Mycobacterium tuberculosis* encontrados tanto en el PPD como en la tuberculina nueva. Los estudios se hicieron en Malasia, Uganda, España e Inglaterra. En Malasia la incidencia del fenómeno fue significativamente mayor que en los otros sitios aunque ésto pudo estar relacionado con el tiempo de tratamiento. Dentro de los 28 pacientes que exhibieron reacciones gigantes, 27 fueron lepromatosos (24 LL y 3 BL) de los cuales sólo 3 (1 LL y 2 BL) estaban sin tratamiento. Un paciente BL tratado había desarrollado tuberculosis activa y un paciente BL sin tratamiento era un contacto familiar de un paciente con tuberculosis activa.

Las reacciones gigantes son raras en los pacientes LL sin tratamiento y en aquéllos con muchos años de tratamiento, pero pueden ocurrir hasta en ⅓ de los pacientes que reciben sus primeros 1 a 3 años de quimioterapia. Aunque el mecanismo no está bien entendido, la reacción parece deberse a la coincidencia de un estado de hipersensibilidad retardada tipo tuberculinica y un fenómeno menos tardío de excesivo edema local, asociado con linfadenopatía local y síntomas transitorios de malestar y pirexia. Se sugiere que la mayoría de las reacciones gigantes ocurren durante un período temporal de falta de regulación inmune asociado a los cambiantes niveles de la carga antigénica.

RÉSUMÉ

Cet article décrit en détail et fournit une définition de ce que l'on a précédemment décrit de manière incorrecte comme "réactions géantes" à la tuberculine, telles qu'elles sont observées à l'occasion chez les malades de la lèpre. Cette réaction est une réponse accélérée et exagérée à des antigènes spécifiques pour l'espèce *Mycobacterium tuberculosis*, que l'on observe à la fois dans le PPD et dans la tuberculine nouvelle. Cette étude a été réalisée en Malaysie, en Ouganda, en Espagne, et en Grande-Bretagne. L'incidence de ce phénomène était significativement plus élevé en Malaysie que dans les autres centres; la raison toutefois peut en être que c'est dans ce pays seulement que l'on a étudié des malades lépromateux non traités au préalable (LL et BL) auxquels on a appliqué cette épreuve jusqu'à 3 ans après le début de la chimiothérapie. Parmi les 28 malades qui ont témoigné de réactions géantes, 27 étaient des patients lépromateux (24 LL et 3 BL), dont seulement 3 (1 LL et 2 BL) n'étaient pas traités. Un malade BL traité avait développé une tuberculose active; il en était de même chez un malade BL non traité présentant des contacts dans la famille.

Les réactions géantes étaient peu communes chez les malades LL non traités ou traités pour une très longue période; elles peuvent survenir chez environ un cinquième des patients pendant les 3 premières années de la chimiothérapie. Quoique le mécanisme de ce phénomène ne soit pas élucidé, il semble qu'il soit du à la coincidence d'une hypersensibilité retardée du type tuberculinique et d'un phénomène moins tardif d'oedème local excessif associé à une lymphadénopathie locale et à des symptômes temporaires de malaises et de pyrexie. On suggère que la majorité des réactions géantes surviennent pendant une période transitoire d'absence de régulations immunitaires, associées avec des taux changeants de la charge antigénique.

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