CASE REPORT

Reversal reaction occurring 16 years after beginning antibacterial treatment

THOMAS H. REA
Division of Dermatology, Keck School of Medicine,
University of Southern California and the Los Angeles County/
University of Southern California Medical Center,
1200 North State St., Room 8440, Los Angeles, CA 90033, USA

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Introduction

Reversal reactions [type I reactions or delayed-type hypersensitivity (DTH) reactions if
named by their putative mechanism] are important sources of morbidity in patients with
leprosy, especially because of their propensity to cause nerve injury. Reversal reactions may
be the presenting manifestation of the illness, may occur in association with antibacterial
treatment, or may occur after treatment has been completed.1,2 Their incidence varies
considerably from group to group,1,2 but, in association with treatment, the incidence is
most common in the first year, and then declining in each subsequent year.1 Reversal
reactions have been reported to begin as long as 7 years after initiating treatment.1 The
present report details a patient with the onset of a reversal reaction beginning 16 years after
the start of treatment.

Case report

The patient, a Filipino woman, then 45 years old, sought care in July of 1984 because of a
progressive skin eruption of 1 year’s duration and numbness in one foot of recent onset. A
skin biopsy showed changes of multibacillary leprosy, and the patient was referred to Dr
Robert Gelber at the Regional Hansen’s Disease Center in San Francisco for further
evaluation. Dr Gelber’s clinical impression of borderline lepromatous (BL) leprosy, based
upon the skin eruption, and a mild sensory nerve deficit in the left heel (could feel the 10 g
Weinstein filament), was confirmed by the two independent histologists who reviewed the
skin biopsy specimen. Both of the latter described a heavily bacillary lesion with many globi,
but a bacillary index (BI) was not determined, (the specimen now not available for review). Prior to beginning treatment the patient’s bacilli were tested for dapsone sensitivity in a mouse footpad, and were determined to be fully sensitive to dapsone, i.e. responding to the lowest dietary concentration used, 0.0001% dapsone, this patient being included in a reported study of dapsone susceptibility or resistance in California.3 (With this patient’s bacilli, in the control mice the bacilli increased from \(5 \times 10^3\) to \(6.7 \times 10^5\) in 8 months’ time, but in the mice receiving the least amount of dietary dapsone, the bacilli fell from \(5 \times 10^3\) to less than \(5 \times 10^3\) at 8 months).

To summarize the patient’s antibacterial chemotherapy, in August of 1984 she was started on dapsone 100 mg daily and rifampin 600 mg daily, the combination being continued until September of 1986, and, subsequently, she was maintained on 100 mg dapsone daily until October of 2002.

In November of 1984, the patient moved to the Los Angeles area, receiving her care in the Hansen’s Disease Clinic of this institution since that time, the move not interrupting her chemotherapy. In December of 1984 the patient returned to clinic ahead of schedule because of a new skin eruption of 3 days duration, associated with chills but no fever. On the trunk and extremities were erythematosus, warm, well defined plaques and nodules. The clinical impression was that of either a reversal reaction or erythema nodosum leprosum (ENL). A biopsy specimen was characteristic of ENL, showing a patchy infiltrate of foamy macrophages in both the papillary and reticular dermis extending into the subcutis, with a mild, superimposed infiltrate of both neutrophils and lymphocytes (see Figure 1) of similar density through out the dermis. In addition, the epidermis was thickened and the BI was 5.5.

![Figure 1. A photograph of a haematoxylin and eosin stained tissue section demonstrating confluent foamy macrophages, with a few lymphocytes, as well as intravascular and infiltrating neutrophils. ×90 objective.](image_url)
The course of the patient’s ENL was protracted and marked by frequent, debilitating exacerbations. Treatment of the ENL began in December of 1984 and continued in one form or another to May of 1999. From December of 1984 through August of 1986, treatment of the ENL consisted of prednisone, up to 60 mg daily, sometimes supplemented by intramuscular triamcinolone 40 mg as often as every 2 weeks, but a satisfactory remission was only occasionally obtained. Because of continuing exacerbations the patient elected to have a tubal ligation in September of 1986, enabling her to receive thalidomide therapy, as required at that time by our investigative protocol. With thalidomide, 100 mg daily, good control of her ENL was obtained, but exacerbations continued to occur within 3 months or less of stopping thalidomide, until it was successfully discontinued in May of 1999. Throughout this prolonged course of ENL, the exacerbations had the same clinical picture as in the initial presentation, and were difficult to distinguish between reversal reactions and ENL on clinical grounds alone. Hence biopsies were performed periodically, and these showed the same histological pattern as the one obtained in December of 1984, but with a slowly declining BI. (In June of 1985 the BI was 5.2, in June of 1986 4.6, and in June of 1991 1.8.) Other features of the exacerbations included chills, fever, leukocytosis, and anaemia. The prolonged course of her ENL was associated with further peripheral nerve damage, specifically weakness in the right hand, and a loss of protective pain sensation in some areas on the left plantar surface. The sensation in the right foot remained normal.

In January of 2001, the patient returned to clinic ahead of schedule because an erythematous eruption of 4 weeks duration associated with sudden worsening in cutaneous numbness. Sharply margined, erythematous, and moderately indurated plaques, up to 8 cm in diameter, were present in largest numbers on the trunk, but involved all four extremities as well. Sensory examination revealed loss of protective pain sensation over half of the right, and most of the left plantar surfaces. Absent were chills, fever, and leukocytosis. Tissue sections showed sparse, small tuberculoid granulomata at all levels of the dermis, characterized by oedema, epithelioid differentiation of macrophages, and some giant cell formation (see Figure 2). No acid-fast bacilli were found. Based upon the clinical and histological changes, a working diagnosis of reversal reaction, not relapse, was made. In a 6 mm punch biopsy specimen, fixed in 70% ethanol, the 360 bp fragment of the gene for the 18-kD protein of *Mycobacterium leprae* was not found, further more sensitive evidence, but not proof, that a bacteriologic relapse was not the problem. A lymphocyte transformation test performed on the patient’s peripheral blood mononuclear cells, obtained in June of 2002, showed a 6-fold greater response to *M. leprae* stimulation as compared to media alone, a finding consistent with a previous reversal reaction.

The patient was treated with prednisone, initially 40 mg daily, with slow tapering of the daily dose for 3 months, followed by slow tapering of alternate day prednisone until discontinued in February of 2002. Supplemental therapy consisted of calcium carbonate, 600 mg twice daily, calcitriol, 0.5 mcg daily and doxipen 25 mg daily.

**Discussion**

The 16 year time span between the onset of antibacterial treatment and the occurrence of a reversal reaction raises the question of the frequency of their late onset.

The original classification of the patient as BL was never in doubt by a seasoned clinician or two experienced histologists. Based upon histological changes and the response to
thallidomide, the diagnoses of ENL was not in doubt. Similarly, based upon histological\textsuperscript{1} and peripheral nerve changes, the diagnosis of reversal reaction was also firm.

There are many unusual, but not rare, features in this case, which make it conceivable to dismiss the late onset of the patient’s reversal reaction as one more feature of a unique syndrome, and consequently of little or no relevance to the general problem of reversal reactions. For example the patient had a high BI, 5.5 after 4 months of treatment, but BIs of this magnitude are not rare in our BL patients,\textsuperscript{6} and Ridley found that the typical BI in untreated BL patients ranged from 4 to 5.5.\textsuperscript{7} Also, the histological changes were not that of the common ENL pattern, i.e. with the most extensive involvement in the deep dermis or subcutis, but the pattern found was one of the recognized variants of ENL.\textsuperscript{8} In addition, the duration of the ENL, 14 years, was well beyond our median duration of 5 years, but is not rare in our patients. Finally, any difficulty with distinguishing between ENL and a reversal reaction on clinical grounds alone is uncommon, but not rare, especially in BL patients, in our experience. Consequently, this case is not considered to be a unique syndrome.

Another possible explanation is that of a bacteriological relapse followed by a reversal reaction, which destroyed evidence of bacilli, or bacilli were too few to detect with the methods used. This explanation cannot be excluded, but is considered to be less likely than that of a reversal reaction without relapse for the following reasons. The patient’s bacilli were fully sensitive to dapsone at the onset of treatment, she received daily dapsone and rifampin for 2 years, and was on daily dapsone until the time of the reversal reaction. Also, other patients with ENL followed by a reversal reaction have been observed in our clinic, but in each the reversal reaction was associated with demonstrable, solid staining bacilli.\textsuperscript{6}
Furthermore, the patient has been observed for nearly 3 years following the onset of her reversal reaction and no sign of relapse has appeared.

This report is not submitted to establish a record, or to begin a contest for a record, but to suggest that late occurring reversal reactions may be more common than generally thought. Several factors may obscure the diagnosis of late reversal reactions. For example, the diagnosis may be difficult to distinguish from bacteriological relapse. Furthermore, because of the remoteness from the time of chemotherapy, it may be hard to even consider the possibility of a reversal reaction. Also, because ‘cured’ patients may be dropped from leprosy registers, late occurring reactions are apt to be well beyond the ken of the health care system and any consulted physician. In addition, patients are often reluctant to admit to a previous diagnosis of leprosy, thus preventing exploration of the possibility of a leprosy related condition. Finally, a late reaction is difficult to diagnose, or even to consider, without benefit of histological examination, which may not be readily available in the areas of the world with greatest need.

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References