Late reversal reaction after 10 years of adequately treated leprosy

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Summary
Differentiation between a relapse or late reversal reaction following completion of regular drug therapy in patients with leprosy is often difficult, though it has definite therapeutic implications. The present case documents a late reversal reaction occurring an unusually long time after the completion of multi-drug therapy.

Keywords: leprosy, multi-drug therapy

Nerve damage in active leprosy is a reflection of cellular immune response to mycobacterial antigen. Whereas the dermal lesions of leprosy affect patients cosmetically, it is the neural damage and the resultant deformities which serve as constant reminders of the disease. The introduction of multi-drug therapy has brought new hope to the management of leprosy. However, exacerbations of the disease are reported at variable times following completion of therapy. Distinguishing relapse from a reaction is often difficult on clinical grounds and sometimes even after bacteriologic and histopathologic investigation. This is particularly true in paucibacillary disease. Such exacerbations, attributed to increases in the leprosy antigen, have been well recognised up to two years after completion of treatment in paucibacillary and up to five years in multibacillary leprosy. We report a case that illustrates how leprosy antigen may cause reversal reactions as late as 10 years after completion of multi-drug therapy.

Case report

A 35-year-old man with borderline Hansen's disease received World Health Organisation multi-drug therapy for two years from 1983. The diagnosis and classification of leprosy was based on clinical and histopathological features of skin lesions and demonstration of acid-fast bacilli on slit and scrape skin smear. There was no neurological deficit, although the nerve trunks were enlarged and tender. Regular therapy led to complete clearance of skin lesions and he remained symptom-free for 10 years. Thereafter, he complained of numbness and paraesthesiae in both hands rapidly progressing to both lower limbs as well. This was followed over the next three weeks by fever, malaise and the rapid development of weakness in both feet and hands over three days. He did not give any history of recent major illness nor any drug therapy for these symptoms. He did not have clinical indicators of immunosuppression nor had he received recent blood transfusion. Examination revealed a slim young man with no skin lesions. Neurological findings were confined to the limbs. He had bilateral foot drop with clawing and distal amyotrophy of both hands. There was glove and stocking hypo-aesthesias for touch, pain and temperature, relatively more marked over the distribution of ulnar and peroneal nerves bilaterally. Deep tendon reflexes were normal and the plantars were equivocal. Ulnar and peroneal nerves of both sides were thickened and were markedly tender.

The slit and smear examination did not show any acid-fast bacilli (AFB). Full blood count and blood biochemistry for sugar, creatinine, liver functions were normal. The motor nerve conduction study revealed inexorable median, ulnar and peroneal nerves on both sides. No sensory nerve action potentials could be recorded along these nerves. Biopsy of the sural nerve showed dense mononuclear cell infiltration of the nerve fascicles with perineurial fibrosis. No foamy histiocytic cells were seen. Perivascular lymphocytic infiltrates were present (figure). The slides stained for AFB were negative.

The patient was diagnosed as having a reversal reaction and was kept on prednisolone 60 mg/day for one week, then tapered off over a period of six weeks. His sensory symptoms rapidly subsided and the foot drop improved remarkably. However, the clawing of the hands and hypo-aesthesia along the distribution of ulnar and peroneal nerves persisted. A repeat nerve conduction study after an interval of

Figure Sural nerve microphotograph showing intraneural inflammation with mononuclear cells with lymphocytic perivascular infiltration (H&E, original × 280)
eight weeks revealed persistence of inexcitability along the peroneal and ulnar nerves. The median nerve conduction improved (motor conduction velocity 20.7 m/s, distal latency 2.7 m/s, dispersion 10.8 m/s, evoked response amplitude 5.3 mV, F-conduction velocity 35.3 m/s, F-latency 39.8 m/s, F-wave amplitude 0.1 mV).

Discussion

The clinical, electrophysiological and histopathological pointers, supported by the response to steroid therapy, favour a reactional state of leprosy in this patient occurring 10 years after completion of multi-drug therapy. Reversal reactions observed within two years of completion of multi-drug therapy have been labelled as late reversal reactions. These result from an enhanced immune reactivity directed against the remnants of Mycobacterium leprae antigens or the host's own antigenic determinants with structures similar to those of M. leprae. While drugs in multi-drug therapy only kill the bacteria, antigenic clearance is probably related to competence of the phagocytic system of the individual, which is deficient in tuberculoid leprosy and absent in the lepromatous form.

Remnants of dead myobacteria or their remultiplication, may incite late reversal reactions or relapse with reaction, respectively. Unfortunately, the means to differentiate between antigens of nonviable and viable bacilli are not yet readily available. This has therapeutic implications as the former need immunosuppression alone while the latter also require multi-drug therapy. Immunohistology for anti-M. leprae monoclonal antibodies and DNA or RNA-based detection methods may demonstrate antigenic determinants of live M. leprae.

Quantification of antigenic load in patients at the end of chemotherapy may predict the future risk of reversal reaction. The clearance of antigens released from dead bacilli takes at least five years in tuberculoid and is never complete in lepromatous leprosy. Pregnancy, vaccination, major illnesses, surgical procedures, emotional stress, blood transfusion, etc., may precipitate the development of reversal reactions, if bacterial or antigenic clearance is not complete. Contrary to expectations, concurrent infection with human immunodefiency virus (HIV) appears to have little effect on the clinical manifestation or natural course of leprosy. However, HIV infection ought to be kept in mind in leprosy patients with worsening of symptoms. There was no obvious precipitating factor in our patient. Continuation of dapsone therapy has been shown to prevent late reversal reactions in patients with paucibacillary leprosy. Dapsone seems to possess immunosuppressive properties as well as having bacteriostatic activity. Immunotherapy with M. leprae or BCG vaccination during or at the end of chemotherapy may reduce the risk of such reversal reactions by enhancing antigenic clearance. Clear therapeutic guidelines for these exacerbations, and not extermination of M. leprae alone, should be an important step in the fight against leprosy.

Learning points

- reversal reactions in leprosy may present years after multi-drug therapy, particularly in immune compromised states like AIDS
- rapid neurological worsening after completion of multi-drug therapy in leprosy may reflect relapse or reaction
- differentiation between the two may be difficult but it is vital for planning therapy (multi-drug therapy in the former and immunosuppression in the latter)

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*Postgrad Med J* 1997 73: 741-742
doi: 10.1136/pgmj.73.865.741

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