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Chapter 5

Leprosy Reactions

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Abstract

Sudden changes in immune-mediated response to Mycobacterium leprae antigen are referred to as leprosy reactions. The reactions manifest as acute inflammatory episodes rather than chronic infectious course. There are mainly two types of leprosy reactions. Type 1 reaction is associated with cellular immunity and particularly with the reaction of T helper 1 (Th1) cells to mycobacterial antigens. This reaction involves exacerbation of old lesions leading to the erythematous appearance. Type 2 reaction or erythema nodosum leprosum (ENL) is associated with humoral immunity. It is characterized by systemic symptoms along with new erythematous subcutaneous nodules.

Keywords: leprosy, type 1 reaction, reversal reaction, type 2 reaction, erythema nodosum leprosum

1. Introduction

Sudden changes in immune-mediated response to Mycobacterium leprae antigen are referred to as leprosy reactions. The reactions manifest as acute inflammatory episodes rather than chronic infectious course [1]. These reactions account for about 30–50% of cases with leprosy [2]. Both patients with low and high load of leprosy bacilli are at risk of developing leprosy reactions. Leprosy reactions can occur at any time before, during, or after the treatment. Patients with fewer skin lesions and without nerve involvement are less likely to develop leprosy reactions. The presence of multiple lesions in close proximity to peripheral nerves, facial involvement, and presence of nerve thickening without functional impairment are risk factors for the development of leprosy reactions. Patients developing leprosy reactions are more likely to develop sequelae or deformities [3]. There are mainly two types of leprosy reactions. Type 1 reaction involves exacerbation of old lesions leading to the erythematous appearance. Type 2 reaction is an immune complex-mediated reaction. It is characterized by systemic symptoms along with new erythematous subcutaneous nodules [4].

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Type 1 reaction is a delayed hypersensitivity reaction. It mostly occurs in borderline patients as well as in patients with lepromatous leprosy (LL) and those with tuberculoid leprosy (TL) receiving therapy. Reaction can be the first sign of the disease and it often persists for a few weeks or months [5]. Classically, two subtypes of type 1 reactions have been described; first subtype is called reversal reactions, false exacerbation reaction or upgrading reactions and this type of reaction is reversible. Second subtype is called downgrading or downgrading reaction and it is associated with disease worsening. Upgrading (reversal) reactions occur in patients receiving therapy, and downgrading reactions occurs in patients who do not receive therapy. Due to decrease in bacterial load, borderline patients receiving therapy progress to tuberculoid phase of the disease spectrum. Bacterial load increases in patients who do not receive therapy and clinical appearance shifts to the lepromatous phase of the disease spectrum due to impaired cellular immunity [6].

2.2. Pathogenesis
These reactions are associated with cellular immunity and particularly with the reaction of T helper 1 (Th1) cells to mycobacterial antigens. It has been demonstrated that cytokines derived from Th1 cells such as interleukin-$\text{1}\beta$ (IL-$\text{1}\beta$), tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-2 (IL-2), and interferon gamma-$\gamma$ (IFN-$\gamma$) play a more prominent role. High levels of TNF-$\alpha$, soluble IL-2 receptors, and adhesion molecules also reflect severity of local inflammation. Borderline leprosy patients with type 1 reaction show increased expression of TNF-$\alpha$ mRNA in peripheral nerves and skin. Type 1 reactions are mediated by Th1 lymphocytes and secreted proinflammatory cytokines IFN-$\gamma$ and IL-12, and free oxygen radicals [4, 5]. It was demonstrated that macrophages could initiate neural inflammatory process even in the absence of bacilli in the neural tissue [7].

2.3. Clinical features
Reversal reaction episodes often occur within the first 6 months of multidrug therapy (MDT) [8]. After initiation of therapy, skin lesions with manifestations of regression or lesions appearing as hypochromic macules become erythematous and edematous, and these lesions, then, become scaled and rarely become ulcerated [9]. The existing lesions show signs of inflammation, but no new lesions occur. Previously unnoticed or invisible patches may become prominent. This may give the impression of the development of new lesions. The lesions are often painless, but tenderness may sometimes be found. The lesions are often accompanied by edema and neuritis in the extremities [6]. Edema in the hands and feet may be sometimes the main symptom of reversal reaction. There may be burning pain in the lesions, pain in the face and extremities, and decrease in muscle strength. Isolated neuritis is commonly observed within the first 12 months of therapy. Nerve thickening and pain may occur and preexisting peripheral neuropathy may become prominent (sensory, motor, or autonomic). Ulnar, median, posterior tibial, fibular, radial, and facial nerves are the most
commonly involved nerves. The patients may present with the symptoms of neural dysfunction such as loss of sensation, facial palsy, claw hand, and drop-foot. Hyperesthesia may occur in palmar and plantar areas, associated with widespread nerve damage [1]. The ability to close eyelids is lost due to damage in the facial nerves (lagophthalmos) [10]. Neural damage is important, as it is considered the main cause of deformities and sequelae in the course of reversal reactions. Neuritis episodes may be severe; however, it sometimes has an insidious and even painless course, which is called silent neuritis. Silent neuritis is defined as sensory or motor dysfunction in the absence of skin lesions observed in type 1 and type 2 reactions [11]. It may cause inflammatory eye diseases, including iritis and scleritis, and it may even result in blindness. Systemic symptoms such as weakness, fever, bone pain, lymphadenomegaly, joint pain, and generalized edema are rarely observed and these symptoms indicate the severity of clinical condition. Furthermore, systemic symptoms are minimal in patients close to the TL pole of the spectrum and more commonly observed in patients close to the LL pole. Fever is usually absent and patients’ general condition is good [6, 10].

2.4. Risk factors
The risk of type 1 reaction may increase with vaccination, MDT, pregnancy, puerperality, infections, stress, trauma, and oral contraceptive use. The extensiveness of skin lesions has been described as an important risk factor both in patients with low and high bacilli load [1]. It has been shown that the risk of developing neural damage, along with the risk of developing reversal reaction, is 10-fold higher in patients in whom three or more body segments are affected [11]. Facial involvement is a risk factor for the development of reversal reaction, as it is for lagophthalmos [12]. Although factors which can induce type I reactions are not clearly known, recent studies have pointed to genetic factors [5]. Identification of the risk factors, therefore, allows more meticulous follow-up of patients and early treatment [1].

2.5. Histopathology
The type 1 reaction is characterized by edema in the upper dermis and disorganized granulomas. The foreign body giant cells, Langhans giant cells accompanied by epidermal erosion and spongiosis, and fibroplasia appear in the dermis. The necrosis, ulcer and inflammatory infiltration by neutrophils may be observed in severe reaction [13]. The cytology of preexisting granulomas is differentiated by the presence of large epitheloid cells and decreased number of bacilli. Inflammatory cells often infiltrate epidermis and increased neural destruction is observed. The edema inside and around the granulomas results in the damage of surrounding tissues and nerves [1].

2.6. Treatment
The main goal of treatment in type 1 reaction is to suppress the cellular immunity. Prevention of nerve damage required early diagnosis and early institution of anti-inflammatory medications. MDT must be continued during the reactions. Corticosteroids are the most effective drugs used to treat reversal reaction. Their main effects are to inhibit activation of cellular immune response and suppress inflammatory response against M. leprae.
and nerves. Corticosteroids increase vasodilation by inhibiting the release of mediators such as arachidonic acid (prostaglandins) metabolites and platelet activating factor (PAF), vasoactive amines, neuropeptides, interleukin-1 (IL-1), TNF-\(\alpha\), and nitric oxide (NO). They inhibit adhesion of neutrophils, eosinophils, and lymphocytes to the endothelial cells, their migration to the inflammation site, and decrease vascular permeability. They inhibit phagocytosis and production of oxygen-free radicals [1].

Clinically, corticosteroids change the course of reversal reactions in many ways. They decrease intraneural and cutaneous edema and promote rapid recovery of the symptoms [1]. Earlier initiation of corticosteroid treatment can eliminate the risk of permanent neural dysfunction [3]. Corticosteroids must be continued at immunosuppressive doses for prolonged periods. A prednisolone dose of 40 mg has been suggested as the start dose to control many of the type I reactions. However, patients with neural involvement require a dose of 1 mg/kg (60 mg) or sometimes higher doses (2 mg/kg). [14] Prednisolone dose must be reduced only after observing clinical recovery and tapering the dose to 20 mg/day. Recovery is often occurs within 3 months but may sometimes exceed 6 months. Intravenous methylprednisolone pulse therapy has been used to control reactions. Pulse therapy is indicated in severe reversal reactions and in cases of acute or chronic neuritis who have previously received oral corticosteroid therapy for prolonged periods. The therapy involves administration intravenous methylprednisolone at a dose of 1 gr/day for consecutive 3 days in the first week and this is followed by a dose of 1 gr/week for consecutive 4 weeks, and finally 1 gr/month for consecutive 4 months. Prednisone 0.5 mg/kg/day is administered between the cycles of pulse therapy [15]. The treatment should be modified with a return to the previous dose in case worsening of clinical condition. Correct start dose and dose tapering regimen for prednisone must be determined on a patient basis, and this decision must rely on the follow-up of the loss of sensory functions and motor examination findings. The recommended duration of treatment is often 4–9 months in patients with borderline tuberculoid (BT) leprosy, 6–9 months in patients with borderline-borderline (BB) leprosy, 6–18 months in patients with borderline lepromatous (BL) leprosy; however, the treatment may last 24 months or longer. Patients with recent neural lesions and particularly those with less than 6-month duration better respond to therapy compared with patients in whom therapy is initiated in late periods [1].

Immunosuppressive medications such as azathioprine and cyclosporine can be used alone or in combination with corticosteroids [16]. Thalidomide is an effective drug used as an alternative to corticosteroid therapy and it allows long-term disease control [17]. Nerve decompression surgery has a limited place and it is recommended for patients with permanent pain after corticosteroid therapy. Surgery can be performed in patients with TL and BT leprosy with neuralgia and nerve abscesses in whom therapy with immunosuppressive is not feasible [1].

3. Type 2 reaction

3.1. Introduction

Type 2 reaction or erythema nodosum leprosum (ENL) occurs in patients with high bacilli load as in patients with multibacillar type leprosy (BL and LL) [5]. Type 2 reaction is considered to
be more complicated than type 1 reaction due to systemic nature and recurrent episodes [4]. The differences between type 1 and type 2 reactions are summarized in Table 1 [1, 3, 4, 6, 10, 13]. Type 2 reaction course is 1 – 2 weeks, but may occur multiple recurrences over several months [5]. ENL is identified by Pocaterra et al. as single acute (one ENL episode lasting less than 6 months, recurrence is not), multiple acute (repeated discrete episodes) or chronic (an episode lasting for more than 6 months, continuous episodes) [18].

| Parameter          | Type 1 reaction | Type 2 reaction |
|--------------------|-----------------|-----------------|
| **Immunological**  |                 |                 |
| Response           | Type 1 helper cells | Type 2 helper cells |
| **Pathogenesis**   |                 |                 |
|                    | Type IV hypersensitivity reaction (delayed cell-mediated) | Type III hypersensitivity reaction (immune complex formation and deposition) |
| **Type of reaction** |                 |                 |
| Reversal reaction  |                 |                 |
| Downgrading reaction |                 |                 |
| Erythema nodosum leprosum |                 |                 |
| Lucio's phenomenon |                 |                 |
| Erythema multiforme-like reaction |                 |                 |
| **Clinical phenotype** |                 |                 |
| Tuberculoid, borderline tuberculoid, borderline-borderline |                 |                 |
| Previous treatment (except in downgrading reactions) |                 |                 |
| Borderline lepromatosis, lepromatosis |                 |                 |
| Previous treatment or not |                 |                 |
| **Cutaneous features** |                 |                 |
| Acute onset of erythema and swelling of previous lesions |                 | New painful subcutaneous nodules in previously unaffected skin |
| No new lesions |                 |                 |
| **Neurological features** |                 |                 |
| Painful neuritis with or without loss of nerve function |                 | Pain or tenderness in one or more nerves |
| Muscle weakness in the hands, feet, or face |                 | Muscle weakness in the hands, feet, or face |
| **Systemic manifestations** |                 |                 |
| Rarely |                 | Common (Fever, weakness, lymphadenitis, iridocyclitis, neuritis, arthritis, dactylitis, orchitis) |
| **Risk factors** |                 |                 |
| Multidrug therapy |                 | Vaccination |
| Vaccination |                 | Pregnancy |
| Pregnancy |                 | Puerperality |
| Puberty |                 | Infection |
| Infection |                 | Stress |
| Stress |                 | Trauma |
| **Histopathology** |                 |                 |
| Tuberculoid granuloma |                 | Superficial dermal edema |
| Disorganized granuloma and necrosis or ulceration in severe reactions |                 | Dermal fibroplasia |
| Neutrophilic infiltrate in the mid-deep dermis and subcutaneous tissue |                 | Leukocytoclastic vasculitis of the small and medium vessels |
| **Treatment** |                 |                 |
| Nonsteroidal anti-inflammatory drug |                 | Systemic corticosteroids |
| Systemic corticosteroids |                 | Acetylsalicylic acid, pentoxifylline |
| | Clofazimine | Thalidomide |
3.2. Pathogenesis

Type 2 reaction is associated with humoral immunity. This is a type 3 hypersensitivity reaction associated with the deposition of immunocomplexes produced by binding of antigens released by the destruction of bacilli with antibodies [6]. Immunocomplexes cannot be phagocytosed by the macrophages, cleared by the kidneys, and they are deposited on the vessel walls [19]. This reaction is also associated with increased levels of proinflammatory cytokines. Release of inflammatory cytokines and followed by neutrophilic infiltration contribute to the development of variable characteristic clinical findings depending on the involved organ. In type 2 reaction, vasculitis and/or concurrent panniculitis occurs with inflammatory infiltration by neutrophils [5].

3.3. Clinical features

Type 2 reaction may occur in the early periods of therapy and even after completion of therapy, as it takes long time for the body to eliminate dead bacilli in the macrophages. It often occurs in the first three years after initiation of leprosy treatment. Sudden deterioration in clinical condition may be observed in patients with LL and rarely in patients with BL leprosy [6]. This reaction can involve multiple organs and systems. Immunocomplexes accumulate in the circulation and they are deposited in the skin, eyes, joints, lymph nodes, kidneys, liver, spleen, bone marrow, endothelium, and the testes. The lesions are multiple, bilateral, erythematous, firm, painful, subcutaneous nodules resembling erythema nodosum that are distributed symmetrically. Pustular, bullous ulcerated, and necrotic types have also been reported. Some nodules may persist as a chronic painful panniculitis and lead to scar. The target lesions of erythema multiforme may occur in any region [4, 6]. The lesions more often occur in external surfaces of the body [20]. General symptoms such as fever, weakness, edema, myalgia-arthralgia, dactylitis, bone tenderness, and lymphadenomegaly are observed prior to the occurrence of or concurrent with ENL lesions. Iridocyclitis, episcleritis, eye pain (photophobia), orchitis, liver, or kidney damage can be observed. Neuritis, painful enlarged nerves and nerve function impairment may occur [4, 5]. Necrosis can occur as a result of vascular thrombosis and ischemia. Vascular occlusion is probably associated with vasculitis caused by immunocomplex deposition on the vessel wall and leukocytoclasia. This should not be confused with Lucio’s phenomenon observed with classical LL. In Lucio’s phenomenon, the majority of the bacilli infect capillary endothelium, leading to endothelial proliferation, thrombosis, and vascular occlusion [21]. Laboratory tests show elevated levels of acute phase reactants such as C-reactive protein (CRP), α1-antitrypsin, α1-acit glycoprotein (AGP), and γ-globulins [22].

3.4. Risk factors

Lepromatous leprosy forms with high bacilli load, vaccination, infection, puberty, pregnancy, puerperality, with significant hormonal changes occurring in women are risk factors for the development of type 2 reaction. Emotional and psychological stress and associated immunological and hormonal changes have been regarded to trigger these reactions; however, this has yet to be confirmed [4, 10].
3.5. Histopathology

Two different histopathological variants have been described in ENL. First variant has been reported by Ridley as "the pink nodule type" or classical ENL (or mild ENL form). Typically, there are clusters of neutrophils accumulated around the foamy macrophages at the center of small granulomas. Eosinophils, plasma cells, and mast cells are present. Classical characteristics of vasculitis affecting small- or medium-sized vessels, necrotizing changes, and thrombosis formation have been reported in almost 25% of the patients. Indeed, vasculitic changes mostly occur in early lesions. Vasculitic changes involving neutrophilic infiltration, hemorrhage, and thrombus formation may be severe in necrotizing ENL. Necrosis in epidermis and dermis, collagen degeneration can be observed and this may result in dermal fibrosis [13]. Intact acid resistant bacilli (ARB) are found in the lesions of untreated patients, whereas granular and fragmented ARB are often found in patients receiving therapy. Lucio's phenomenon must be histopathologically differentiated from real erythema nodosum, Sweet syndrome, pyoderma gangrenosum, and deep micotic infections [13, 23].

3.6. Treatment

Type 2 reaction often regresses with addition of clofazimine to the MDT. After the use of clofazimine-containing MDT, type 2 reaction prevalence has decreased in leprosy patients under therapy. Suppression of inflammation is the basis of therapy. Bed rest and drugs such as acetylsalicylic acid, corticosteroids, nonsteroidal anti-inflammatory drug (NSAID), chloroquine, antimony compounds, pentoxifylline, and thalidomide are used in the treatment [4, 24, 25]. Corticosteroids and thalidomide are still considered the mainstay of therapy in severe cases of type 2 reaction presenting with orchitis, iridocyclitis with glaucoma, and neuritis that cause neural dysfunction [14]. Administration of high doses of corticosteroids with pulse therapy and rapid dose tapering within 2–3 weeks have been deemed appropriate as type 2 reaction is an episodic disease. If maintenance therapy must be avoided particularly in patients with chronic recurrent ENL, as long term therapy with prednisolone causes dependence to corticosteroid therapy and side effects. Thalidomide seems to be the choice of drug in maintenance therapy. Action mechanism of thalidomide is not clear. It is thought to be effective in the inhibition of TNF-α. It has some side effects which do not necessitate discontinuation of therapy. Neuropathy has been reported in approximately 20–30% of patients. It is often masked by leprosy neuropathy [26]. It is well tolerated at a dose of 100–300 mg/day in cases with recurrent disease and it provides prolonged remission [4]. Clinical trials have shown that thalidomide rapidly controls ENL and it is superior to acetylsalicylic acid and pentoxifylline therapy. On the other hand, thalidomide is teratogenic when used in early periods of pregnancy [25]. Thalidomide analogs chemically resemble thalidomide, but side effects are not the same. Revlimid and aktimid are promising drugs in this category [27].

Clofazimine is recommended in the treatment of chronic recurrent reactions. Clofazimine is administered for 12 weeks together with corticosteroids at doses of 100 mg tid, 100 mg bid, or 100 mg/day. Clofazimine is less effective than corticosteroids and it often takes 4–6 weeks to be fully effective. Addition of clofazimine to the therapy is extremely beneficial in reducing corticosteroid doses or discontinuation of corticosteroid therapy in patients who have become
dependent on corticosteroids. The total duration of clofazimine therapy should not exceed 12 months [18].

Corticosteroids and thalidomide are the mainstay of therapy in the control of type II reaction. Selective cytokine inhibitors and phosphodiesterase type-4 inhibitors with potential TNF-alpha activity but without T-cell activating effect are new drugs [17].

4. Differential diagnoses

In general, cutaneous drug reactions, local skin infections, relapses, diabetes, Bell’s palsy, rheumatoid arthritis, rheumatic fever, and disc prolapse must be taken into consideration in differential diagnosis. It may manifest as various cutaneous drug reactions such as urticarial, lichenoid, exanthematous reactions, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. The patients usually suffer from itching and burning in some of these lesions, whereas these symptoms are not observed in patients with leprosy. Furthermore, new skin lesions do not resemble preexisting lesions. Localized skin infections developing in patients with leprosy are often confined to a particular body site. The lesions do not occur bilaterally and medical history is often remarkable for trauma or insect bites that could cause an infection. New lesions appear if relapse occurs, and this often has an insidious course rather than a severe clinical course. Reaction often occurs within the first 3 years after initiation of leprosy therapy and old lesions exhibit acute pain and tenderness. Diabetic patients are prone to infections and development of peripheral neuropathy. Furthermore, regulation of blood glucose is impaired upon administration of corticosteroids. All patients must be screened for diabetes and referred to an advanced facility if diabetes is diagnosed. Bell’s palsy may mimic facial paralysis caused by leprosy reactions. These patients do not have nerve thickening, sensory loss along the nerve projection, and hypopigmented skin lesions. This condition is better evaluated by the ophthalmologists. In Bell’s paralysis, widening of palpebral fissure is not associated with the drop of lower eyelid. It occurs in women at childbearing age with rheumatoid arthritis, joint pain, joint deformities, fever, skin rash, and multiple organ involvement. Rheumatoid factor is almost always found to be elevated. However, referral to an advanced facility may be sometimes required to differentiate rheumatoid arthritis from leprosy reaction. Patients with rheumatic fever are usually young patients with fever, joint pain, and skin rash for a short period. These patients have high antistreptolysin O titers and valvular involvement can be found that cause murmur on auscultation. Patients with disc prolapse may present with acute onset of neuropathy in the extremities. Patients often report weight lifting in the early periods or stretching in the back. These patients do not show skin lesions or nerve thickening [23, 28].

5. Conclusion

The reactions can contribute to further deterioration of the quality of life in leprosy. Early diagnosis of reactions can prevent nerve damage and provide early intervention to systemic complications.
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