

## Histopathological features of reversal reactions in Morbus Hansen

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### Abstract

The reversal reaction on Morbus Hansen is a type IV hypersensitivity reaction to *M. leprae* antigens. The clinical symptoms of a reversal reaction are that some or all of the existing lesions become more numerous and active in a short time. Hypopigmented lesions become more erythematous, erythematous lesions become increasingly erythematous, macular lesions become infiltrating, and old lesions increase in size. The histopathological feature of the reversal reaction showing dermal edema, stretching of the granulomas followed by loss of the well form granuloma arrangement, and predominance of lymphocytes are described as the hallmarks of a reversal reaction. Several additional characteristics were obtained in the form of an increase in the number of Langhans giant cells, as well as pyknosis/shrinkage of the lymphocyte nucleus. Although not a diagnostic criterion for a reversal reaction, histopathological examination of a lesion biopsy is needed to differentiate a reversal reaction in Morbus Hansen from other differential diagnoses.

**Keywords:** Reversal reaction; Morbus Hansen; Histopathology; Differential Diagnosis

### 1. Introduction

Morbus Hansen (MH), also known as leprosy, is a chronic infection caused by *Mycobacterium leprae*. Leprosy involves various organs ranging from peripheral nerves, skin, and eyes to the respiratory tract [1,2]. Until now, leprosy is still a health problem, especially in developing countries. From the 2020 WHO new leprosy case report results, Indonesia is still the country with the third highest number of new leprosy case reports after India in first place and Brazil in second place. Based on the case report in 2020, in Indonesia, 11,173 new cases were reported. In Indonesia, several areas are more vulnerable to leprosy transmission, including Madura, East Nusa Tenggara / *Nusa Tenggara Timur* (NTT), Maluku, Sulawesi, North Sumatra, and Papua [3].

Leprosy reaction is an acute episode of leprosy with symptoms of constitution, activation, and the emergence of new efflorescence on the skin in the otherwise chronic course of the disease. Leprosy reactions can occur before, during, or after leprosy treatment with Multi Drug Therapy (MDT). The leprosy reaction is divided into three types: type 1 or reversal reaction, type 2 or Erythema Nodosum Leprosum (ENL), and Lucio phenomenon. The prevalence of reversal reactions varies between 8%-33% of all leprosy patients. Clinical symptoms of type 1 reactions can include redness, swelling, pain, and heat on the skin, which is more severe than before the reaction occurred. Other clinical manifestations in the nerves include pain or impaired nerve function [4,5].

The diagnosis of the reversal reaction in Morbus Hansen must be done correctly to determine the appropriate therapy given to the patient's condition because proper treatment of the patient can cause disability or morbidity in the reversal reaction. This literature review was created to help establish the diagnosis of reversal reaction in Morbus Hansen and

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eliminate differential diagnoses that might be considered based on microscopic images from histopathological examination.

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## 2. Material and Methods

This literature review was prepared by collecting 20 library sources, consisting of 14 international journals searched using search engines (Google, Google Scholar), 5 textbooks, and 1 citation from a website. The process of compiling this literature review began by searching for scientific journals related to Morbus Hansen, such as how to approach the diagnosis of Morbus Hansen and reversal reactions, differential diagnosis of reversal reactions, and histopathology of reversal reactions. Based on the journal data obtained, an analysis was carried out, and a literature review manuscript was arranged regarding the histopathological description of the reversal reaction along with the differential diagnosis.

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## 3. Literature Review

This literature review is divided into four subtopics. The first subtopic will discuss the classification and how to diagnose Morbus Hansen. The second subtopic explains immunological reactions in the form of leprosy reactions. The third subtopic will discuss the type 1 leprosy or reversal reaction in more detail. The fourth subtopic explains reversal reactions with other differential diagnoses.

### 3.1. Classification and Diagnosis of Morbus Hansen

Morbus Hansen's classification is divided based on criteria according to Ridley and Jopling, which consists of six types, namely Tuberculoid (TT), Borderline Tuberculoid (BT), Intermediate (I), Mid Borderline (BB), Borderline Lepromatous (BL), and Lepromatous (LL). Meanwhile, for treatment purposes, Indonesia uses clinical diagnoses based on the WHO (World Health Organization), namely the paucibacillary (PB) and multibacillary (MB) types. The cellular immune system provides protection for leprosy sufferers. When a specific cellular immune system effectively controls infections in the body, the lesion will disappear spontaneously or give rise to paucibacillary (PB) type leprosy. If the cellular immune system is low, the infection spreads uncontrollably and causes multibacillary (MB) type leprosy [6,7].

The leprosy diagnosis is based on clinical, bacterioscopic, and histopathological features. The main signs include white patches or skin redness accompanied by numbness (anesthesia). Apart from that, there is a thickening of the peripheral nerves accompanied by nerve disorders in the form of numbness or paralysis of the muscles of the eyes, hands, and feet, dry skin (dehydration), and disturbed hair growth (alopecia) in the lesions. On bacterioscopic examination, skin tissue scrapings or swabs of the nasal mucosa show the presence of *M. leprae* bacteria. Histologically, a picture appears in diffuse granulomas in the dermis, and bacilli are found in large numbers [8,9].

### 3.2. Leprosy Reaction

During a long disease process, leprosy reactions can occur, which is an immunological phenomenon that can occur before, during, or after complete therapy with Multi-Drug Treatment (MDT). Leprosy reactions can be divided into three types, namely [10]:

- Type 1 reaction, a reverse reaction, is a type IV hypersensitivity reaction to *M. leprae* antigens.
- Type 2 reaction, also called erythema nodosum leprosum (ENL), is a reaction related to destroyed bacteria, antigens, and the intensity of antibody production.
- Type 3 reaction, also called the Lucio phenomenon, is a reaction that arises due to dermal ischemic infarction, which is triggered by the proliferation of endothelial cells and thrombosis of small skin blood vessels, which is clinically indicated by bleeding, thrombosis, and skin infarction.

### 3.3. Reversal Reaction

#### 3.3.1. Pathogenesis of Reversal Reactions

Increased cellular immune responses in the form of delayed-type hypersensitivity reactions to *Mycobacterium leprae* antigens in the nerves and skin cause type 1 reactions. The dead bacillus product antigens will react with T lymphocytes, accompanied by rapid changes in cellular immunity. This reaction occurs due to changes in the balance between cell-mediated immunity (CMI) and bacteria. The final result of this reaction can be upgrading/reversal or downgrading; if there is an increase in the CMI response to *M. leprae* antigen, it will lead to a tuberculoid clinical form; if there is a decrease in the CMI response to *M. leprae* antigen, it will lead to a lepromatous clinical form [2,4].

3.3.2. Clinical Manifestations of Reversal Reactions

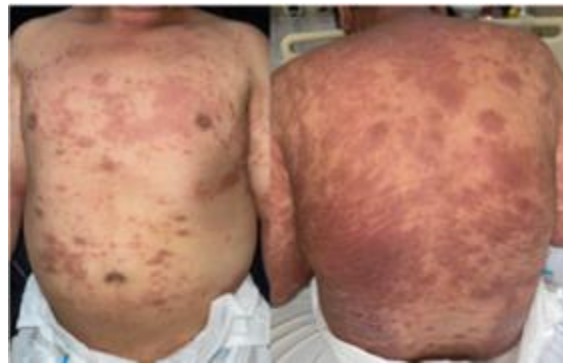
Clinical symptoms often found in reversal reaction patients are increased inflammation in some or all pre-existing skin spots or plaques. There are diagnostic criteria to establish a clinical reversal reaction, namely by obtaining one major criterion or at least two minor criteria (without signs of ENL) according to the following table:

**Table 1** Diagnostic Criteria for Reversal Reactions [6]

<b>Major</b>	<b>Existing and/or new skin lesions become inflamed, red, and swollen.</b>
<b>Minor</b>	One or more nerves become thick and may become swollen Appearance of new lesions (painless) Sudden edema of the face and extremities Loss of sensation in the hands and feet or signs of recent nerve damage (loss of sweat, sensation, muscle strength) in areas supplied by specific nerves.

Reversal reactions can occur as mild or severe. A mild reversal reaction can be characterized by the presence of several skin lesions with a clinical picture of the reaction (without nerve pain or loss of function). Meanwhile, severe reversal reactions can be characterized by nerve pain or paresthesia, increasing loss of nerve function, fever or discomfort, edema of the hands and feet, reactions lasting more than six weeks, skin lesion reactions on the face, and the presence of ulcerative skin lesions [6].

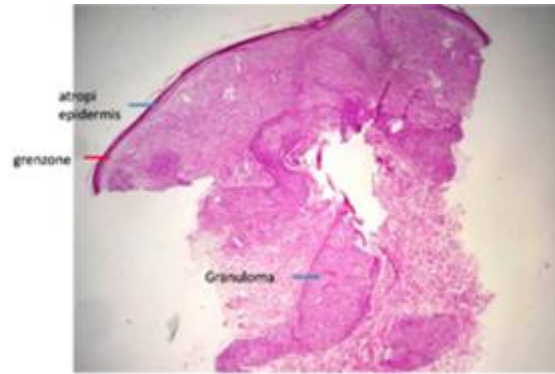
Apart from mild or severe reversal reactions, there can also be upgrading or downgrading reversal reactions. However, upgrading reactions are more common, characterized by occurring  $\leq 6$  months after therapy, where the current lesion can become enlarged, erythematous, and itchy, but new lesions usually do not appear. Meanwhile, downgrading reactions can occur  $\geq 6$  months after therapy, where old skin lesions become swollen and painful, new lesions appear, and nerve damage is often progressive and extensive [11].



**Figure 1** Clinical Manifestations of Upgrading Reversal Reactions. (RSSA DV Dept. Private Collection).

3.4. Histopathology of Reversal Reactions

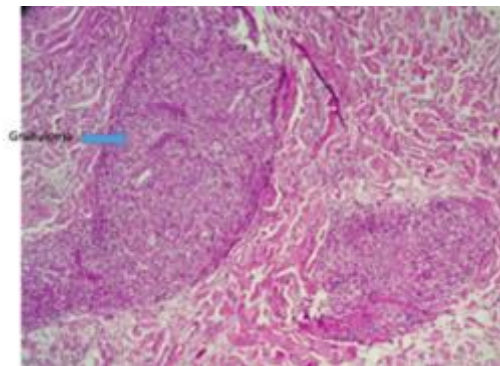
The histopathological examination of the reversal reaction shows edema within the granuloma with dense lymphocytes in the dermis. Edema of the dermis, stretching of granulomas followed by loss of well formed granuloma arrangement, and predominance of lymphocytes are described as characteristic features of reversal reactions. Several additional characteristics were found in the form of an increase in the number of Langhans giant cells and reduction in thw number of lymphocytes, which is sometimes difficult to obtain [12].



**Figure 2** Histopathology of Reversal Reaction

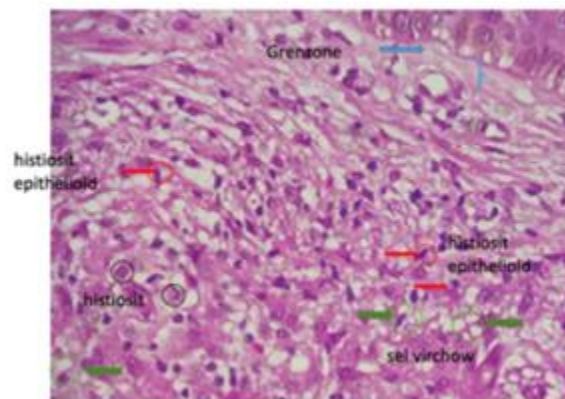
A piece of atrophic epidermal tissue. at the dermo-epidermal junction, grenzone is found. There is a granulomatous reaction, with inflammatory cells infiltrating the superficial and deep dermis (HE, 40x).

The difference between the reversal upgrading and downgrading reactions is that histopathologically, in the upgrading reaction, there will be edema, an increase in lymphocytes and well-formed granuloma. Meanwhile, in the downgrading reaction, there was a decrease in lymphocytes and epithelioid histiocytes, replaced by macrophages, fibrosis, and many bacteria. Comparison of previous biopsy specimens is helpful when determining whether the reaction is type 1 upgrading or downgrading [12].



**Figure 3** Histopathology of Reversal Reaction

The tissue showed a granulomatous reaction, consisting of inflammatory cells, lymphocytes, epithelioid histiocytes, and foamy macrophages, among fibro-collagenous tissue (HE, 100x). (Private Collection Dept DV – PA RSSA)



**Figure 4** Histopathology of Reversal Reaction

In the basal layer of the epidermis, a grenzzone appears. In the dermis, granulomas were found consisting of lymphocytes, epithelioid histiocytes, and foamy macrophages (Virchow cells) (HE, 400x). (Private Collection Dept DV – PA RSSA).

### 3.5. Differential Diagnosis of Reversal Reactions

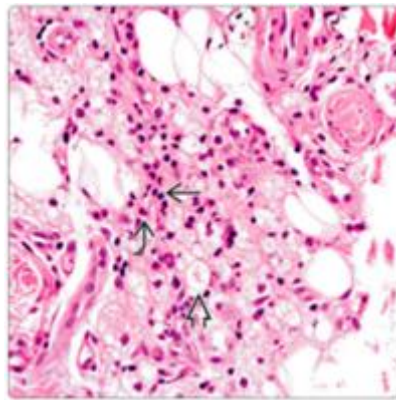
#### 3.5.1. Erythema Nodosum Leprosum (ENL)

##### Clinical Manifestations

Type 2 reaction or erythema nodosum leprosum (ENL) occurs in leprosy with a vast number of bacteria. ENL can manifest as an inflammatory skin reaction in the form of erythematous nodules and papules, accompanied by pain that can progress to ulceration. Nodules in ENL can persist and cause fibrosis and scarring. Systemic symptoms that can appear in ENL include fever, edema, and malaise. ENL can manifest in other organs such as joints, lymph nodes, eyes, liver, testicles, kidneys, respiratory system, muscles, nerves, and even psychiatric disorders. [13] The severity of ENL can be assessed with the ENLIST ENL Severity Scale questionnaire, which consists of 10 component questions with a score of 0-3. Mild ENL if the total score is  $\leq 8$ , severe ENL if the total score is  $> 8$  [14].

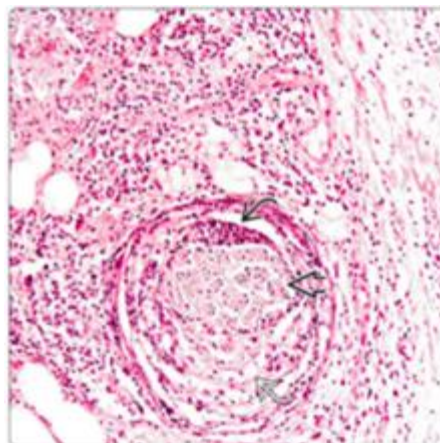
##### Histopathological Features

ENL's typical pathological histological features are edema and mixed inflammatory infiltration in the dermis and subcutis, especially neutrophils with eosinophils, lymphocytes, foamy aggregates of macrophages, plasma cells, and mast cells. Mixed lobular and septal vasculitis and panniculitis were present in most cases. Large amounts of bacilli, usually in granular form, are easy to find. The predominant lymphocytes found in ENL are T-helper cells, while T-suppressor cells dominate in lepromatous leprosy [15].



**Figure 5** Histopathology of ENL [15]

ENL shows an intense inflammatory infiltrate consisting of neutrophils, lymphocytes, and Virchow cells that extend into the surrounding subcutaneous fat.



**Figure 6** Histopathology of ENL [15]

ENL shows an intense inflammatory infiltrate consisting of neutrophils, lymphocytes, and Virchow cells that extend into the surrounding subcutaneous fat and surround the nerve.

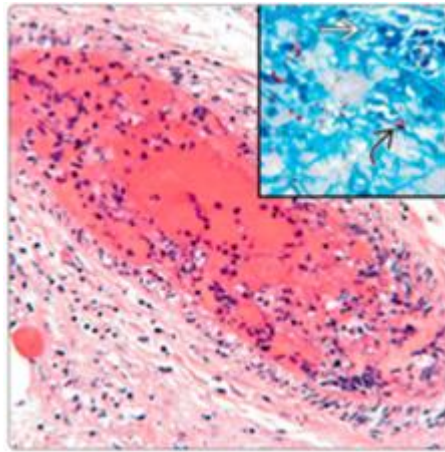
### 3.5.2. Lucio Phenomenon

#### Clinical Manifestations

Lucio's phenomenon is called "Pretty Leprosy," also known as Bonita Leprosy, because its manifestation is diffuse with a facial appearance that looks healthy and smooth, usually accompanied by madarosis. The atypical features mean that Lucio leprosy is often undiagnosed and develops into the Lucio phenomenon, a manifestation of diffuse cutaneous infiltration without nodules in the initial phase and then expanding into reddish spots as a sign of hemorrhagic infarction. If left untreated, plaque and blisters will form and develop into extensive ulcers with necrotic tissue [16].

#### Histopathological Features

The microscopic features of the Lucio phenomenon are necrotizing vasculitis of the skin or subcutis and also the presence of fibrinoid necrosis of small and medium vessels. Other histological features include necrosis of the epidermis and superficial dermis, micro-abscess formation, angiogenesis, endothelial swelling, vascular occlusion caused by luminal thrombi, and fibrin deposits in the walls of small blood vessels of the dermis and subcutis. There is a mixed dermal and/or subcutaneous infiltrate of neutrophils, eosinophils, lymphocytes, and nuclear dust. Bacillus is found in endothelial cells, blood vessels, nerves, arrectores pylorum muscle, follicular epithelium, sebaceous glands, and sweat glands [17].



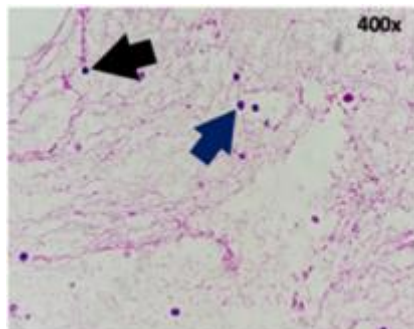
**Figure 7** Histopathology of Lucio's Phenomenon [20]

Lucio's phenomenon shows a pattern of thrombotic vasculopathy with a large thrombus in the vessels, surrounding mononuclear inflammation, and mild endothelial proliferation that is sometimes quite striking. Staining of this biopsy showed positive BTA staining within the thrombus and vessel wall.

### 3.6. Scrofuloderma

#### 3.6.1. Clinical Manifestations

Scrofuloderma is a clinical form of secondary cutaneous TB, which can be caused mainly by *Mycobacterium tuberculosis* but can also be caused by atypical mycobacteria. Scrofuloderma begins with a lesion in the form of a painless subcutaneous nodule, slowly enlarging, fluctuating, then softening, then breaking and finding a way out by penetrating the overlying skin to form a fistula. The fistula opening then confluent until it becomes an ulcer. The characteristics of the ulcer are linear and irregular; the surrounding area is bluish-red (livid) and oozing, with a base of granulation tissue covered by seropurulent pus. Sometimes, cordlike scars or scar tissue form as the ulcer heals. This scar tissue connects the ulcerated area or pulls on normal skin with a healing process that takes a long time. Above the scar tissue, skin bridges can also be found [18].



**Figure 8** Histopathology of Scrofuloderma

Histopathology of ulcers in scrofuloderma appears to be fatty tissue accompanied by a suppurative inflammatory process: lymphocyte inflammatory cells (black arrow) and neutrophil inflammatory cells (blue arrow). (Private Collection Dept. DV – PA RSSA)

### 3.6.2. Histopathological Features

Histopathological examination of scrofuloderma showed a granulomatous inflammatory infiltrate, accumulation of epithelial-like histiocytes, Langerhans giant cells among them, and an infiltrate of mononuclear cells around them. In the middle part, caseous necrosis can be found. This picture is usually seen in the deeper dermis. With Ziehl Neelsen (ZN) staining, acid-fast bacteria (AFB) can be found, but AFB may not be detected in lesions that have occurred for a long time [19].

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## 4. Conclusion

Histopathological examination in cases of reversal reaction in Morbus Hansen is needed to help establish the diagnosis and rule out other differential diagnoses. Appropriate histopathological examination in cases of reversal reactions can ideally be carried out before and when the reversal reaction appears.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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