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Histopathological Features of Cutaneous Tuberculoid Granuloma Disorders

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ABSTRACT

Tuberculoid granulomas consist of epithelioid histiocytes, Langhans giant cells and rarely foreign bodies with lymphocytes, plasma cells and caseous necrosis. The granulomatous reaction pattern is defined as a typical inflammatory pattern that is characterized by granulomas. Various etiologies can lead to granulomatous reactions. The histopathological features of cutaneous disorders with tuberculoid granuloma include cutaneous tuberculosis, tuberculids, Morbus Hansen, syphilis and rosacea. There are various clinical manifestations of tuberculoid granuloma with similar appearances which makes it difficult to establish a definitive diagnosis. The histopathological features of cutaneous tuberculoid granuloma disorders can support the diagnosis. Therefore, the clinician can determine the appropriate treatment with the right diagnosis.

1. Introduction

A granulomatous reaction pattern is defined as a typical inflammatory pattern characterized by granuloma.¹ Granuloma is a collection of histiocytes or epithelioid histiocytes with multinuclear giant cells and other inflammatory cells such as lymphocytes, plasma cells, and macrophages in the dermis.^{2,3} The studies of Kumbar et al. and Chakrabarti et al. showed that tuberculoid granuloma is the most common granulomatous reaction.^{4,5}

Various etiologies may underlie the tuberculoid granuloma reaction.⁵ In some countries, up to 90% of granulomas are caused by chronic infection.³ The most frequent cutaneous disorders often found with granulomatous reactions are Morbus Hansen (66.4%),

lupus vulgaris (8%), scrofuloderma (5.1%), and syphilis (1.5%). Tuberculoid granulomas are more common in women (52.7%) and mostly develop in the second to third decades of life.⁴

Histopathological examination is the gold standard for the definitive diagnosis of various granulomatous skin lesions.⁵ A definitive diagnosis is important to determine the proper treatment. Tissue culture examination and histopathological examination with special stains can also help identify the causative organism.^{2,5} Determining the definitive diagnosis of cutaneous disorders with granulomatous reactions aims to prevent complications such as tissue damage that may cause atrophy, fibrosis, and scarring.^{3,6}

In daily practice, various clinical manifestations of cutaneous disorder with tuberculoid granuloma infection troubled clinicians in determining a diagnosis according to the histopathological features. This literature review aims to determine the clinical manifestations of cutaneous disorders that are histologically characterized by tuberculoid granulomas, including etiology, clinical manifestations and histopathological features.

Definition and classification

Tuberculoid granuloma is characterized by epithelioid histiocytes (especially Langhans giant cell) (Figure 1) and giant cells surrounded by lymphocytes, plasma cells, and central caseous necrosis.³ Langhans giant cells are more dominant although foreign body giant cells can also be identified.^{5,6} It is also commonly seen in the form of a horseshoe shape.^{6,7}

In general, tuberculoid granulomas are caused by chronic infection.^{3,8} The histopathological features also depend on the stage of the disease and previous treatment history.³ Tuberculoid granulomas occurred in cutaneous tuberculosis, tuberculid, leprosy, late-stage syphilis, rosacea, leishmaniasis, perioral dermatitis, lupus miliaris disseminatus faciei, and Crohn's disease.^{3,6} The most common causes of tuberculoid granulomas are cutaneous tuberculosis, leprosy, late-stage syphilis and tuberculid.⁴

Histopathological examination with special stains can also help identify the causative organism. Some of the stains that are often used are Ziehl-Neelsen and Fite-Faraco staining, which are used to examine *Mycobacterium tuberculosis*.^{2,5,7} Meanwhile, Warthin-Starry staining can identify the organism *Treponema pallidum*.⁵ When an organism is difficult to identify in staining, a Polymerase Chain Reaction (PCR) examination can be performed to identify *Mycobacterium*.^{3,8}

Pathogenesis of tuberculoid granuloma

The pathogenesis of cutaneous disorders with granulomatous reactions is still incomprehensible. Granulomas are organized collections of histiocytes.

There are two groups of histiocytes, namely dendritic cells and macrophages. The main roles of tissue macrophages are mainly for phagocytosis, elimination of microorganisms, and presentation of antigens.^{9,11} Macrophages also play a role in the induction and production of cytokines, chemokines, and lipid chemotaxis.^{6,11}

In an inflammatory reaction, macrophages interact closely with complement to recognize and phagocytose antigens. Cell membrane receptors such as toll-like receptors (TLRs) and cytoplasmic receptors such as NOD (nucleotide-binding oligomerization domain) -like receptors are the main roles of innate immunity which acted as microbial recognition proteins.^{6,11} The inflammatory cascade is triggered by the release of proinflammatory cytokines resulting in the activation of neutrophils, macrophages, and dendritic cells. Macrophages secrete cytokines and chemokines such as tumor necrosis factor (TNF) or interleukin-1 (IL-1) and interleukin-12 (IL-12).^{4,6,9}

These inflammatory mediators stimulate the response of T helper 1 (Th1) cells which have strong microbicidal activity. Macrophages are activated by cytokines, such as interferon-gamma (IFN- γ) and TNF- α , which lead to positive feedback loops that often lead to chronic inflammation. In this way, macrophages interact with lymphocytes to form granulomas (Figure 2) and ultimately lead to fibrosis.^{4,9,10} Granuloma can be palpated as a solid mass under the surface of the skin (dermal infiltrates).^{3,12}

Various infectious diseases may cause tuberculoid granuloma reactions, though only the inflammatory reaction displayed without a granuloma feature. This depends on the stage of the disease and the individual's immune status. This reaction is formed when the immune system eliminates pathogens.^{10,12}

Granulomas usually cause damage to existing tissues, specifically the elastic fibers and collagen, causing atrophy, fibrosis, and scar tissue. Tissue damage results in necrobiosis or fibrinoids, caseous necrosis, or liquefaction and forms abscesses or fibrohistiocytic infiltrates and fibrosis.^{3,6}

Disease associated with tuberculoid granuloma formation

Cutaneous tuberculoid granuloma disorders including cutaneous tuberculosis, tuberculid, leprosy, and late-stage syphilis.

Cutaneous tuberculosis

Mycobacterium tuberculosis is the causative agent in cutaneous tuberculosis (TB). Skin manifestations of mycobacterial infection are seen in the inoculation of primary tuberculosis (tuberculous chancre), tuberculosis verrucosa cutis, scrofuloderma, cutaneous miliary tuberculosis, tuberculosis cutis orificialis, and lupus vulgaris.¹⁰ Scrofuloderma is the most common cutaneous tuberculosis. The differences of some cutaneous tuberculosis are displayed in Table 1. Acid-and alcohol-fast bacilli (AAFB) can be found in special staining (Ziehl Neelsen: ZN and Fite-Faraco).² If the organism is not identified by this method, culture or molecular examination is needed to confirm the diagnosis.^{12,13}

Primary cutaneous tuberculosis (chancre)

The clinical symptoms of primary tuberculosis may be in the form of papules, pustules with indurations on the margins that evolve into indolent ulcers with erosions and undermined edge. Lesions are formed 1-3 weeks after penetration of the organism. Regional lymphadenopathy is common in chancre.^{12,14} Histopathological examination of early chancre revealed inflammatory cells such as neutrophils, lymphocytes and plasma cells, followed by superficial necrosis and ulcers. After a few weeks, a distinctive tuberculoid granuloma formed and occasionally formation of caseous necrosis (Figure 3).^{8,13} Acid-fast bacilli (AFB) can be found in dermis.⁸

Scrofuloderma

Scrofuloderma results from contiguous extension of organs under the skin that is infected by *Mycobacterium*, mostly from the lymph nodes, joints and bones.³ The clinical manifestations of

scrofuloderma vary depending on the duration of the disease. In the early stage, only a few lymph nodes were infected, then multiple reddish-blue nodules appeared and partially confluent.⁸ Then it will gradually soften, resulting in a supple and tender consistency (cold abscess). Scrofuloderma may evolve into ulcers or sinuses with indurations around it and red-black discoloration.^{3,12,13} The sites of predilection are usually areas with many superficial lymph nodes, the most common being the neck, submandibular, axilla, and occasionally the thigh.^{1,8,12} The histopathological features of scrofuloderma include epidermal atrophy with underlying abscess or caseous necrosis to significant fibrosis involving the dermis and subcutis (Figure 4). At the border of the necrotic tissue, there are fewer tuberculoid granulomas and lymphocytes than the chancre, indicating a weak cell-mediated immune response. Acid-fast bacilli are usually identified on the blood smear.^{6,13}

Tuberculosis verrucosa cutis

Infection in tuberculosis verrucosa cutis occurs exogenously. *Mycobacterium tuberculosis* penetrates directly into the skin, thus the lower limbs and feet that are often traumatized are the sites of predilection (Figure 5a). The typical clinical manifestation of tuberculosis verrucosa cutis is a crescent-shaped lesion due to its serpiginous distribution.^{3,12} The rash consists of lenticular papules on erythematous skin that evolve into verrucous plaques and scars may be present.^{3,13} Histologically, it is characterized by hyperkeratosis, epidermal hyperplasia, acanthosis, mainly papillomatosis and occasionally pseudoepitheliomatosis. In addition, there is a caseous granuloma in the mid dermis (Figure 5b). Acid-fast bacilli are usually found in deep layers of the skin.^{13,14}

Lupus vulgaris

The spread of the disease occurs directly from the mucous membrane that has been infected with *M. tuberculosis* and by lymphatic spread. Lesions are typically solitary and more than 90% arise on the head and neck area, which are small, well-defined, red-

brown papules with a gelatinous consistency (apple-jelly nodules) and slowly extend peripherally into large plaques with atrophy at the center.^{3,8} Histologically, it is characterized by tuberculoid granulomas with lymphocytes in the dermis and multinuclear giant cells, while caseous necrosis is rare or absent. A moderate amount of Langhans cells is present in granulomas. Atrophy or hyperplasia may occur in the epidermis, but pseudoepitheliomatous hyperplasia is rare. When a lesion appeared especially on the face, it is necessary to consider granulomatous rosacea. AFB is usually rare and difficult to find on staining.^{8,13}

Tuberculid

Tuberculid is a group of cutaneous disorders resulting from a response to tuberculosis infection elsewhere in the body. This is caused by hematogenous spread to people with moderate or high immunity and allergies to *M. tuberculosis*. Organisms are not present in skin lesions but *M. tuberculosis* DNA can be detected by polymerase chain reaction (PCR) in some cases. Lichen scrofulosum, papulonecrotic tuberculids and erythema induratum (nodular vasculitis) are the cutaneous disorders included in this group.³

Lichen scrofulosorum

Lichen scrofulosorum is a lichenoid eruption associated with hair follicles and sweat glands caused by the hematogenous spread of mycobacteria due to *M. tuberculosis*. It is associated with chronic tuberculosis of the lymph nodes and bones.^{6,13,14} The lesion is usually confined to the trunk and often occur in children and adolescents with active tuberculosis. It may appear as pink or yellowish papules, 0.5–3 mm in size, sometimes with fine and hard scales, and asymptomatic on follicular and perifollicular.^{3,8} Lesions persist for months, but will spontaneously resolve without leaving scar tissue.^{6,12,13} Histopathological examination reveals non-caseous tuberculoid granulomas associated with hair follicles in the upper dermis and tuberculoid granulomas are formed around hair follicles and eccrine glands. *Mycobacteria* are not visible and cannot be cultured on biopsy.^{13,14}

Papulonecrotic tuberculid

Papulonecrotic tuberculid is a symmetrical eruption of necrotic papules, which is a paucibacillary form of tuberculosis that spreads hematogenously, often affects children and young adults with active tuberculosis.^{8,13,14} The primary lesions consist of dark erythematous papules with a size of 1-5 mm which will form pustules, ulcers with crusts, and necrosis.^{8,14} The sites of predilection are predominantly extensor areas of the extremities in a symmetrical distribution.^{13,14} Histologically, it reveals the involvement of granulomas, inflammatory cells such as lymphocytes, and typical vascular damage (obliterative vasculitis) that can lead to thrombosis and occlusion of the blood vessels. Subsequently, there is a distinctive wedge-shaped necrotic area in the upper dermis extending into the epidermis.^{3,14}

Erythema induratum (nodular vasculitis)

Clinically, erythema induratum has a painless bluish erythematous plaque or nodule with a soft consistency and it often recurs. Ulceration often causes scarring. The most common sites are the calf and anterolateral part of the foot, thighs and rarely on the arms and face.^{3,14} The histopathological features including lobular and mixed panniculitis. In the initial lesion, fatty lobules contain aggregates of inflammatory cells dominated with neutrophils. Adipocyte necrosis occurs and yield foamy macrophages.³ The collection of epithelioid histiocytes, multinucleated giant cells, and lymphocytes produce the appearance of tuberculoid granulomas in the lesion.¹⁶ Vascular damage is followed by extensive caseous necrosis. The overlying dermis may be involved in the caseous necrosis resulting in ulceration.^{1,8,12}

Leprosy

Leprosy is still frequently found in Asian countries, especially around India and Pakistan.^{17,18} Leprosy or Morbus Hansen is caused by *M. leprae*, which is an AFB that attacks peripheral nerves, skin, and other organs such as the mucosal surface of the upper

respiratory tract, liver, and bone marrow, but not the central nervous system.^{3,10}

Histopathological finding is one of the features in Ridley and Jopling's classification.⁸ Tuberculoid granuloma can be observed in tuberculoid (TT), borderline-tuberculoid (BT), and borderline-borderline (BB) leprosy.^{1,3,6} This is thought to be due to the good immune system in these patients as strong granulomatous response is involved in TT, BT and BB leprosy, whereas this reaction is not well-formed in lepromatous leprosy.^{6,13} Collection of skin biopsy specimens should include the dermis and subcutaneous tissue when possible. After the hematoxylin and eosin staining has been performed, special stains can be used to increase diagnostic sensitivity, namely Ziehl-Neelsen or Fite-Faraco stains.¹⁹ On histopathological examination of tuberculoid leprosy, granulomas are seen along the nerve fibers, inside and around the sweat glands and musculus arrector pilli, as well as around the superficial vascular plexus.^{3,20} Ziehl-Neelsen and Fite-Faraco staining can show red smears of AFB, mostly in raft or globi form. Bacilli can be found in nerves, Schwann cells, eccrine glands, and vascular endothelium.¹⁷

Tuberculoid leprosy (TT)

The clinical manifestations of TT leprosy include one or more erythematous brown anesthetic plaques with dry scales and well-defined borders. The number of lesions ranges from one to five and is accompanied by overt anesthesia. Complaints of dry skin and alopecia in the lesion. Thickened local peripheral nerves can be found.¹⁷ Histopathological examination on TT reveals dermal tuberculoid granulomas consisting of macrophages or epithelioid histiocytes, lymphocytes, Langhans giant cells in the dermis and subcutis, and there was no subepidermal clear zone (Grenz zone) (Figure 6). Tuberculoid granulomas are present in the neurovascular vicinity, cellular infiltration of the sweat glands and invasion of the arrector pili muscles.^{3,8} The dermal nerves may be absent or enclosed until they are destroyed by a collection of inflammatory cells, also

there are caseous necrosis and damage in the basal layer. Acid-fast bacilli are rare even in peripheral nerves.^{6,14}

Borderline-tuberculoid leprosy (BT)

In the clinical manifestations of borderline-tuberculoid leprosy (BT), there may be several lesions in the form of erythematous macules, dry scaly papules or plaques, and hypopigmentation. The difference between BT leprosy with TT leprosy is that the border of the lesion in BT is less well-defined than TT. The number of lesions ranges from one to five with clear anaesthesia. Thickened local peripheral nerves can also be found.^{6,12,17} The histopathological features of BT leprosy can be distinguished from TT leprosy by the presence of subepidermal Grenz zone with tuberculoid granulomas, lymphocytes and lesser Langhans cells. Little or no AFB are present and neither caseous necrosis nor epidermal damage can be found.^{3,8,17}

Borderline borderline leprosy (BB)

The clinical manifestations of BB leprosy comprise an erythematous patch with punched-out lesions, a slightly rough and shiny surface, and lesions that have ill-defined borders. The lesions of BB leprosy are fewer in number and less symmetrically distributed than in lepromatous leprosy (LL). More than one thickened peripheral nerves can be found in this type of leprosy.^{3,8} Histologically, BB leprosy is characterized by formation of Grenz zone (Figure 7a), irregular-shaped tuberculoid granulomas, along with the presence of epithelioid histiocytes and a few lymphocytes that invade nerves (Figure 7b). There is numerous AFB, while Langhans giant cell is not found (Figure 7c).^{6,17}

Syphilis

Syphilis is a sexually transmitted infection with various clinical stages caused by the spirochaete *Treponema pallidum*. Acquired syphilis is divided into early and late-stage syphilis. Early syphilis consists of primary, secondary, and early latent syphilis.^{2,3}

Histopathological examination is not the main workup to diagnose syphilis as it can be confirmed by clinical findings, serological tests, and dark-field microscopy when available. However, in unusual cases, a histopathological examination may be useful.^{3,21} Tuberculoid granuloma reactions may be seen in late secondary and tertiary syphilis.^{1,3,8} Various and occasionally nonspecific results may be found on the histopathological examination.^{1,3}

Secondary syphilis

Secondary syphilis usually presents as papulosquamous eruptions and can also affect mucous membranes.^{22,23} The secondary stage is caused by hematogenous and lymphogenous spread of treponemes over several weeks or months.⁹ Rash is a clinical manifestation in almost all cases of secondary syphilis. Macular eruptions (roseola syphilitica) are mainly located on the trunk and flexors of the upper limbs followed by palms and soles of the feet but rarely on the face.^{6,14,23} The histopathological features of secondary syphilis are more dominant with papular lesions and fewer macular lesions.²³ There are presence of psoriasiform hyperplasia, parakeratosis, dermal papillary edema and perivascular or periadnexal infiltrates consisting of lymphocytes or histiocytes, and sometimes tuberculoid granulomas can be found in the dermis especially in the dermal papillae. Plasma cells

are present in almost all cases. The diagnosis must be confirmed by serological examination because the organism *T. pallidum* is seen in only one-third of cases, it is typically located in the epidermis, less often in the dermal vessels.^{3,16,23}

Tertiary syphilis

The manifestations of tertiary syphilis appear years after the initial infection and are rare.¹⁶ Syphilitic granulomas are generally found in the tertiary stage of the disease, although they are uncommon in the secondary phase.²² This infection involves the cardiovascular system, central nervous system, and skeletal system. However, lesions can also occur in the testes, lymph nodes, and skin. There are 2 types of skin lesions in tertiary syphilis, namely nodular and chronic ulcers with gumma. Lesions are generally solitary.^{1,12,23} Extensive areas of gummatous necrosis surrounded by tuberculoid granulomas with superficial or deep dermal infiltrates, plasma cells, Langhans giant cells and epithelioid histiocytes, accompanied by epidermal atrophy (Figure 8).^{12,23}

Treponema pallidum is rarely found on the histopathological examination.^{1,3,12} Furthermore, spirochaetes can be identified using silver-based stains. However, these histopathologic features are nonspecific and has low sensitivity and specificity, thus laboratory test should be carried out.²⁴

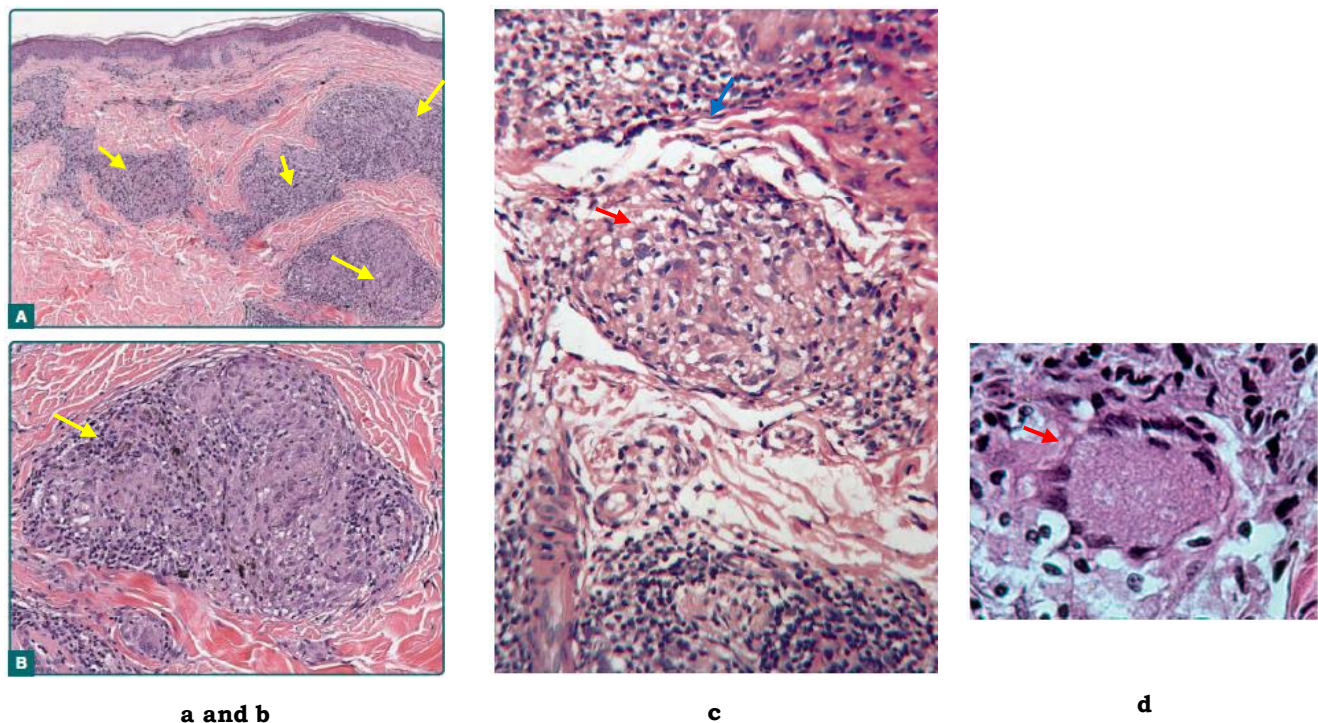


Figure 1. Granuloma (a) Histopathologic of granuloma with lymphocytes, histiocytes and multinuclear giant cells forming nodules (b) large enlarged granulomas² (c) tuberculoid granulomas (blue arrows) with Langhans giant cells (red arrows)³ (d) Langhans giant cells (horseshoe nucleus)¹

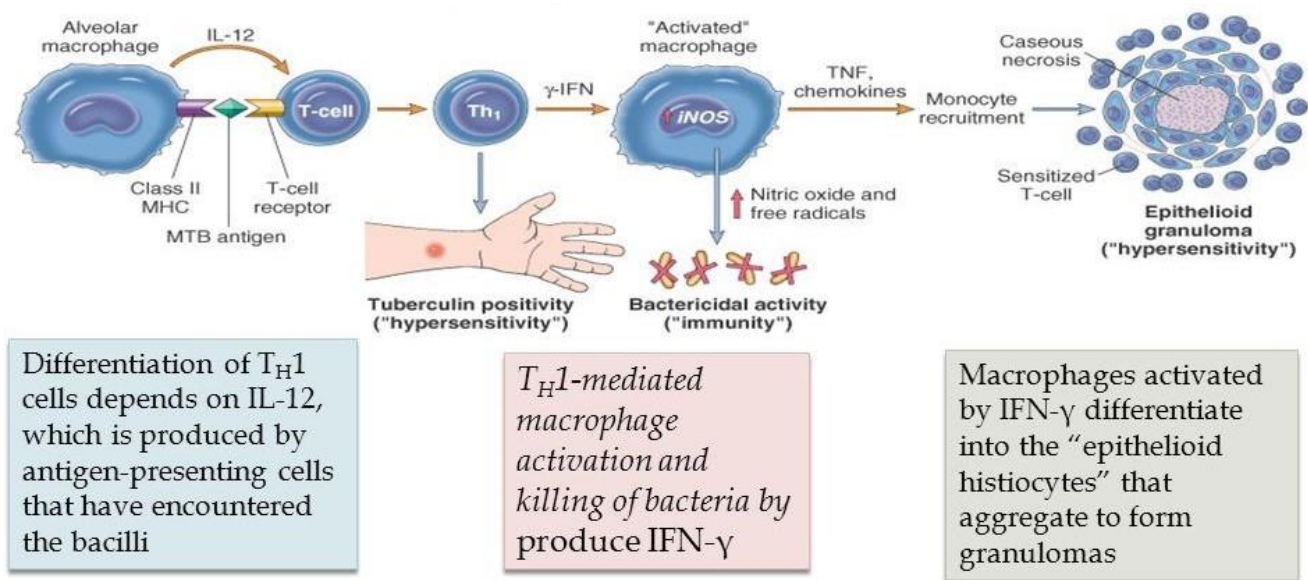


Figure 2. Pathogenesis of epithelioid granuloma formation⁹

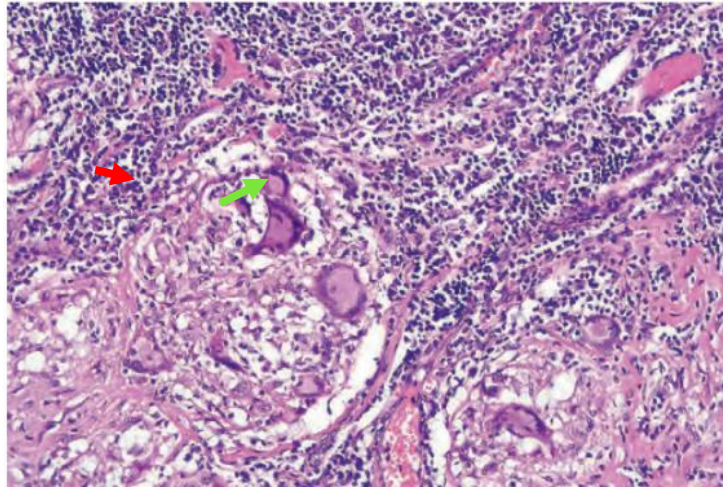


Figure 3. Primary cutaneous tuberculosis. Histopathologic of tuberculoid granuloma (red arrow), lymphocytes, and Langhans giant cells (green arrow)⁸

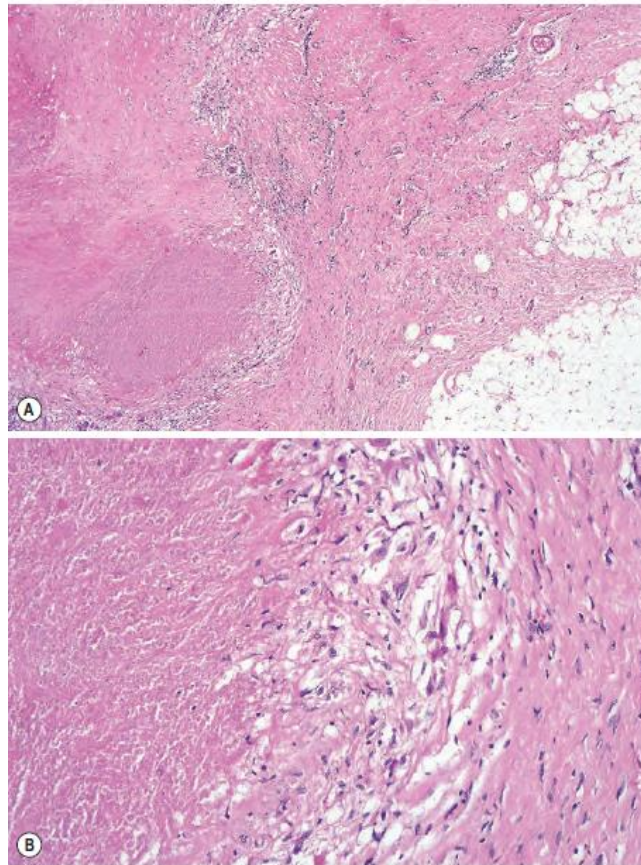


Figure 4. Scrofuloderma. Histopathologic of extensive caseous necrosis⁸



a



b

Figure 5. Tuberculosis verrucosa cutis (a) Clinical manifestations of verrucous plaque on the back of the hand¹³ (b) Histopathologic of hyperkeratosis (green arrow), acanthosis (black arrow), papillomatosis (blue arrow)⁸

Table 1. Summary table of cutaneous tuberculosis⁸

Variant	Infection Route	Relationship with other tuberculosis	Depth of Infection	Histopathological feature	Presence of AFB
Primary Cutaneous Tuberculosis (chancre)	Inoculation	Absent	Dermal	Neutrophil abscess, granuloma tuberculoid, caseous necrosis	Present
Scrofuloderma	Extends from underlying infection	Active Infection	Subcutaneous and dermal	Mixed inflammation, granuloma and significant fibrosis	Might be present in deep layers of the skin
Tuberculosis Verrucosa Cutis	Inoculation	Previous or current infection	Dermal	Little granuloma, acanthosis papillomatosis	None or little
Lupus Vulgaris	Inoculation or hematogenous	Previous or current infection	Superficial dermal	Granuloma with slight caseous necrosis, epidermal atrophy	Might be present in deep layers of the skin

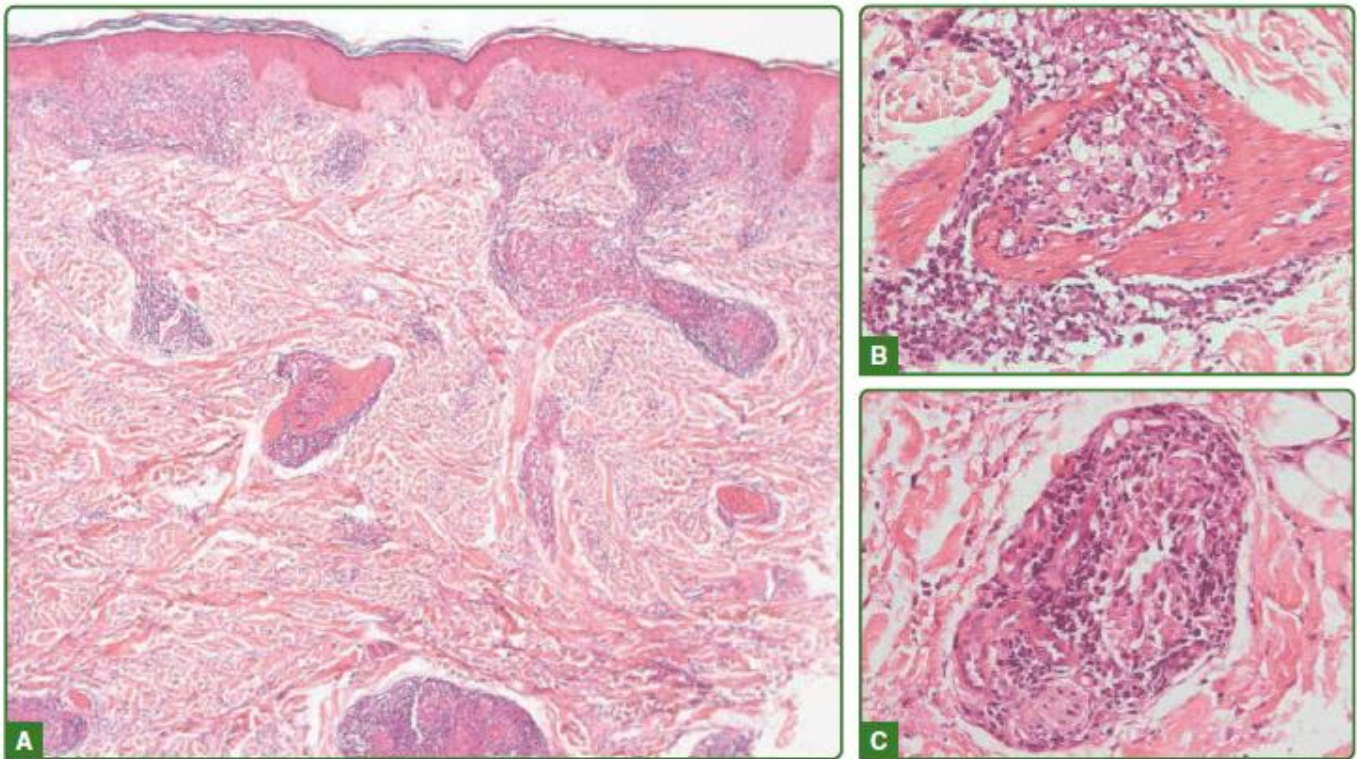


Figure 6. Tuberculoid leprosy (a) Histopathologic of superficial and deep granuloma (b) lymphocyte infiltration surrounds, attacks and damages skin adnexa such as nerves, musculus arrector pili (c) or sweat glands ¹⁷

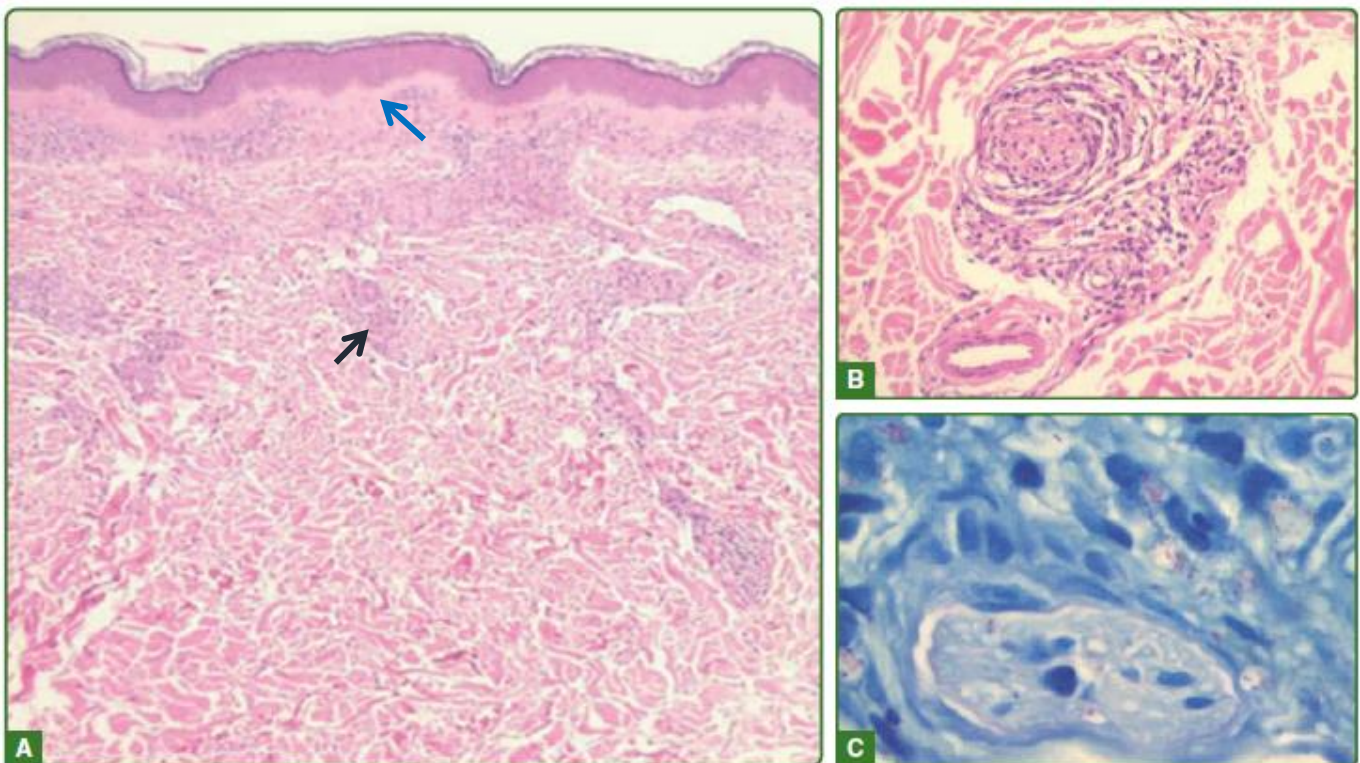
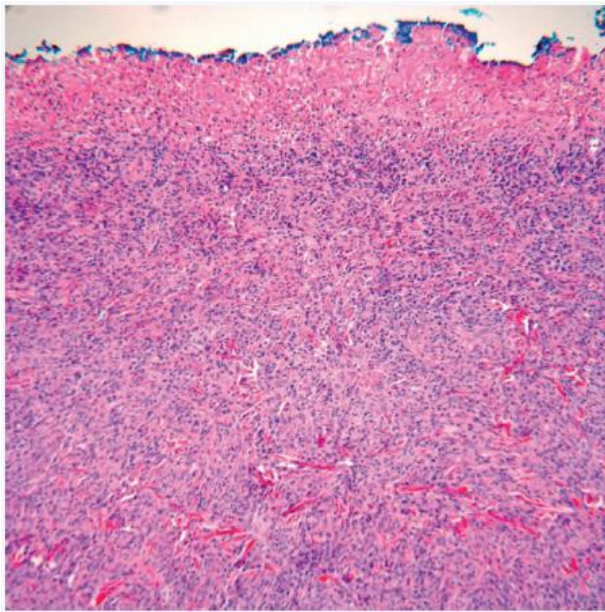
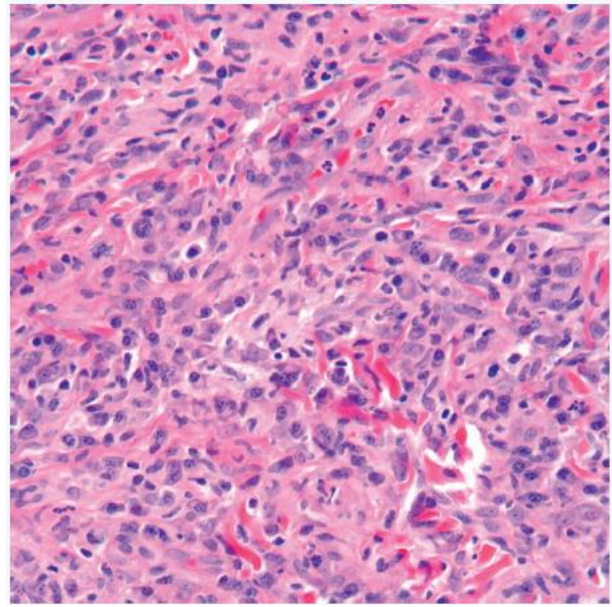


Figure 7. *Borderline leprosy* (a) Clinical Manifestations (b) Histopathologic of tuberculoid granuloma (black arrow) and Grenz zone (blue arrow) (c) inflammatory cells invade nerves (d) AFB and globi ¹⁷



a



b

Figure 8. Tertiary syphilis (a) Histopathologic of solid lymphocyte infiltrates with orthokeratosis and parakeratosis (b) solid lymphocyte infiltrates¹

2. Conclusion

The inflammatory reaction pattern of tuberculoid granuloma in cutaneous disorders is an inflammatory reaction characterized by the presence of granulomas consisting of epithelioid histiocytes, giant cells especially Langhans giant cell, lymphocytes, plasma cells and occasionally central caseous necrosis. Most of these reactions are caused by chronic infection. The most common incidence of cutaneous disorders with tuberculoid granuloma reactions are leprosy and cutaneous tuberculosis. The staining method on histopathological specimens can be used to assist the identification of the causative organisms. In addition, the collaboration between clinicians and pathologists is important in determining the diagnosis thus the objectives of the biopsy can be achieved.

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