Review
Derleme

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Granulomatous skin infections

Granülomatöz deri enfeksiyonları

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Abstract

Granulomatous skin disorders are a heterogeneous group of disorders characterized by granuloma formation on histopathology. They may be triggered by various stimuli, including infectious and non-infectious stimuli (foreign bodies, malignancy, metabolites, and chemicals), of different etiological origins. Although pathophysiological mechanisms are still poorly understood, infectious granuloma formation may occur if the patient's immune system could not eliminate an agent. Clinically, localized or disseminated infectious granuloma formation can be related to the infectious agent's pathogenicity or the patient's immunity. Typical infectious agents causing infectious granulomatous reactions are mycobacteria, fungal infections, or parasites, such as leishmaniasis. This review aims to summarize granulomatous skin diseases encountered more frequently in our clinical experience because of infectious causes.
Keywords: Granulomatous, skin, infection

Öz

Granülomatöz deri hastalıkları histopatolojisinde granülom oluşumu ile karakterize heterojen bir hastalık grubudur. Etiyolojik olarak, enfeksiyöz ve enfeksiyöz olmayan da (yabancı cisim, malignite, metabolitler ve kimyasallar) dahil olmak üzere çok çeşitli uyaranlarla tetiklenebilirler. Her ne kadar patofizyolojik mekanizmalar hala yeterince anlaşılamasa da, hastanın bağışıklık sistemi bir ajanı ortadan kaldıramadığında enfeksiyöz granülom oluşumu meydana gelebilir. Klinik olarak lokalize veya dissemine enfeksiyöz granülom oluşumu, ajanın patojenitesi veya hastanın bağışıklığı ile ilgili olabilir. Enfeksiyöz granülomatöz reaksiyonlara neden olan tipik ajanlar: Mikobakteriler, mantar enfeksiyonları veya layşmanya gibi parazitlerdir. Bu derlemede, klinik deneyimimizde daha sık karşılaşılabilecek enfeksiyöz nedenli granülomatöz deri hastalıklarını özetlemeyi amaçladık.
Anahtar Kelimeler: Granülomatöz, deri, enfeksiyon

Introduction

The classification of granulomatous skin diseases is mainly based on their pathogenic properties. For this reason, granulomatous skin diseases are examined in two groups as infectious and non-infectious in many resource books. In contrast to non-infectious granulomas, the factors are relatively well known in infectious granulomas[1]. This review aims to summarize granulomatous skin diseases with infectious etiology, which may be encountered more frequently in our clinical experience.

The clinical and histological appearance may vary depending on the immunity of the patient. Since the infectious microorganism may be perceived as both an antigen and a foreign body simultaneously, it can trigger granuloma formation in both ways. Granuloma formation occurs because of the inability of the infectious agent to be eliminated by the immune system. The granulomatous reaction is mainly directed by Th1 lymphocytes. In the case of Th2 dominance, the ability to form granulomas is impaired. The presence of the pathogen that cannot be eliminated stimulates

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the immune system through Th1 cells, B cell activity, and circulating immune complexes[1-3].

The histomorphological findings of many granulomatous diseases are similar, and a definitive diagnosis is often possible by identifying the pathogen. Some pathogens can be detected with special tissue dyes. Granulomatous skin diseases because of infectious agents and pathogens are summarized in Table 1.

Protozoan infections

Leishmaniasis

Leishmaniasis is caused by the transmission of protozoan parasites by phlebotomes living in tropical and subtropical regions. Phlebotomes cannot survive in areas where the outdoor temperature is below 10 °C. The types of pathogens vary by region, and travel history to endemic sites is essential in the diagnosis[1]. Cutaneous leishmaniasis (Figure 1) can be examined in two groups: Localized and generalized "anergic cutaneous leishmaniasis." Also, the localized form is divided into two groups as acute and chronic. Granuloma formation is often observed in chronic forms[1,4]. Chronic cutaneous leishmaniasis (CCL) is one of the major imitative diseases because of its wide variety of clinical presentations. CCL is divided into three groups as papulonodular, plaque, and ulcerative types. Papulonodular and plaque-type lesions are frequently observed on the face. The papulonodular type is characterized by multiple erythematous papules and/or nodule-like lesions and may be confused with sarcoidosis or granulomatous rosacea. There are three unique subtypes of the papulonodular type: tumoral, verrucous, and sporotrichoid. The tumoral subtype can be confused with eccrine poroma, amelanotic melanoma, and lymphoma; the verrucous subtype can be confused with warts, deep mycoses, and tuberculosis verrucosa cutis; and the sporotrichoid subtype can be confused with sporotrichosis.

Plaque-like lesions are differentially diagnosed from lupus vulgaris, sarcoidosis, granuloma faciale, Sweet's syndrome, psoriasis, and pseudolymphoma. The ulcerative type of CLL is seen most commonly on the lower extremities, and is involved in the differential diagnosis of chronic venous ulcer. CCL is among the great imitators not only clinically but also histologically. Histologically, it can be confused with other granulomatous and neoplastic diseases, such as squamous cell carcinoma and mycosis fungoides[4]. It is characterized histologically by diffuse infiltrating lymphocytes, macrophages, and plasma cells in the acute phase. There are numerous neutrophils, especially in the upper dermis. Following the pathogen's transfer into the host by phlebotomes, promastigotes are phagocytosed by macrophages, where they transform into mature amastigotes. Amastigotes within macrophages can be readily displayed with Giemsa staining. The epidermis is often acanthotic, and pseudoepitheliomatous hyperplasia can be observed in some cases.

While small tuberculoid granulomas predominate in leishmaniasis, sarcoidal, and palisadal granulomas are also rarely observed. In advanced stages, amastigotes may not be shown because of the scarcity of the pathogen. A polymerase chain reaction (PCR) of Leishmania may be required in suspicious granulomatous inflammatory reactions. It is important to identify Leishmania subspecies as it may affect the treatment plan. However, the morphological distinction of subtypes is not possible with hematoxylin and eosin staining. Fresh

Table 1. Classification of granulomatous diseases because of infectious agents[1-4]

Granulomatous diseases	Pathogen
Protozoa	
Leishmaniasis	*L. tropica, L. major,* etc.
Bacteria	
Mycobacterial diseases	
Cutaneous tuberculosis	*M. tuberculosis, M. bovis*
Leprosy	*M. leprae*
Atypical mycobacterial infection	*M. avium, M. marinum,* etc.
Sexually transmitted bacterial diseases	
Granuloma inguinale	*Klebsiella granulomatis*
Lymphogranuloma venereum	*Chlamydia trachomatis*
Other bacterial diseases	
Cat scratch disease	*Bartonella hanselae*
Tularemia	*Francisella tularensis*
Actinomycosis	*Actinomyces israelii*
Nocardiosis	*Nocardia asteroides*
Botryomycosis	*Staphylococcus aureus*
Spirochetes	
Syphilis second and third stages	*Treponema pallidum*
Fungal infections	
Kerion	
Majocchi granuloma	
Candida granuloma	
Deep fungal infections	
Sporotrichosis	Sporothrix schenckii
Coccidioidomycosis	
Cryptococcosis	Cryptococcosis neoformans
Histoplasmosis	Histoplasma capsulatum
Blastomycosis	Blastomyces dermatitidis
Aspergillosis	Aspergillus fumigatus, A. niger
Parasitic infections	
Demodicosis	D. folliculorum, D. brevis

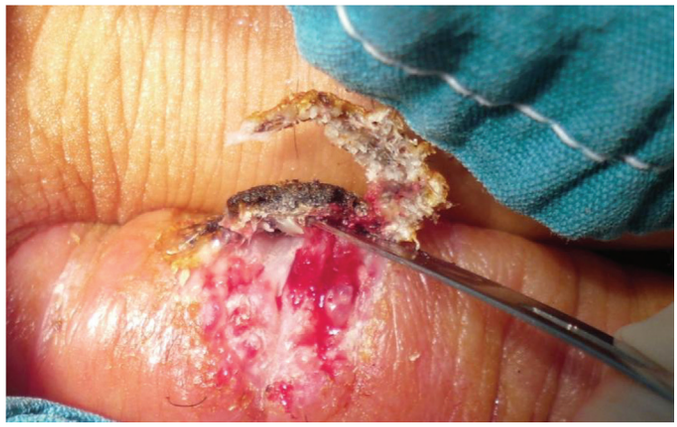

Figure 1. Leishmaniasis (archive of Assoc. Prof. Dr. Didem Dinçer Rota)

tissue culture is superior to PCR in detecting subtypes, although PCR is a more practical method.

Bacterial infections

Mycobacterial infections

Mycobacteria are Gram-positive, acid-fast resistant bacteria difficult to stain with Gram stain because of their cell walls' structure. Mycobacteria are taxonomically classified into three groups. The first group consists of the *Mycobacterium tuberculosis (M. tuberculosis)* complex consisting of *M. tuberculosis* and *M. bovis*. The second group contains *M. leprae*, the pathogen of leprosy. The third group includes *M. marinum*, *M. chelonae*, *M. abscessus*, and *M. fortuitum*, called non-tuberculosis mycobacteria[1].

Cutaneous tuberculosis

Cutaneous tuberculosis is one of the most common causes of infectious granulomas[3]. Cutaneous tuberculosis is frequently caused by *M. tuberculosis* and rarely by *M. bovis*. The development of cutaneous tuberculosis depends on many factors, including the route of infection, duration of exposure, pre-sensitization, and cell-mediated immunity. If the cellular immune response is high, the number of bacilli is low, making it difficult to detect them in culture. Many mycobacteria can be detected using Ziehl-Neelsen stain if the cellular immune response is compromised. The presence of many acid-fast bacilli suggests low cellular immunity and non-tuberculosis disease, such as leprosy[5]. In cases where cellular immunity is high, tuberculosis verrucosa cutis, lupus vulgaris, and tuberculids can be observed. However, in cases where immunity is weak, the patient may present with tuberculosis chancre, scrofuloderma, tuberculosis cutis orificialis, miliary tuberculosis, or tuberculosis gummas (Table 1)[5]. *M. tuberculosis* granuloma is characterized by caseous necrosis in the center called the tubercle. Typically, there is amorphous granular debris with many acid-fast bacilli at the center in which cellular details are lost. This area is surrounded by epithelioid cells, lymphocytes, histiocytes, fibroblasts, and sometimes Langerhans-type giant cells (Figure 2a, b). If acid-fast bacilli cannot be detected in the granuloma, a culture of the biopsy material may be helpful. PCR is currently used to identify specific species and play an essential role in excluding non-tuberculous mycobacteria. In immunocompromised individuals, the histopathological features of tuberculosis may vary. While granulomas are well-circumscribed in the early periods of AIDS, less pronounced granuloma formation, more necrotic appearance, and more bacillus content can be observed in the advanced stages[3].

Leprosy

The causative agent is *M. leprae*. It does not grow in culture. It is an obligate intracellular bacillus with a very slow division time. Unlike *M. tuberculosis*, *M. leprae* is difficult to stain with Ziehl-Neelsen. It is mostly negative. *M. leprae* is stained with Fite-Faraco stain. It is the only bacterium that damages the peripheral nerves[1,3,5]. It is generally examined in three groups; tuberculoid, borderline, and lepromatous leprosy. At one end of the spectrum, lepromatous leprosy is found. In lepromatous leprosy, immunity is low with multiple lesions, diffuse skin, and visceral involvement, diffuse infiltration with multiple leprotic bacilli. At the other end of the spectrum, in tuberculoid leprosy, a few hypopigmented macules or plaques have nerve involvement of the active lesions where immunity is high. Lesions in tuberculoid leprosy are often scaly, with accompanying hypoesthesia and hair loss. Initially, in lepromatous leprosy, lesions are in the form of hypopigmented or erythematous macules. Subsequently, they transform into erythematous papules or nodules[3,4]. On the other hand, tuberculoid leprosy skin biopsies show few acid-resistant bacilli, giant cell granuloma, true granulomatous invasion, dermal nerve damage, and very rarely, caseous necrosis[3].

Atypical mycobacterial infections

The best known mycobacterial infections are swimming pool granuloma and Buruli ulcer. The causative agent of swimming pool granuloma is *M. marinum*. It is a single, blue-red nodule or pustule most commonly seen on the hands, feet, knees, and elbows. It can be ulcerated. The causative agent of Buruli ulcer is *M. ulcerans*. It is often characterized by a rapid, widening ulcer on the arms and legs. There are also reported cases on the face. Another clinical form of atypical bacteria is cervicofacial lymphadenitis. It occurs because of *M. avium* complex and *M. haemophilum*. This disease is common in children aged 1-5 years. It is characterized by submandibular, cervical, and periauricular

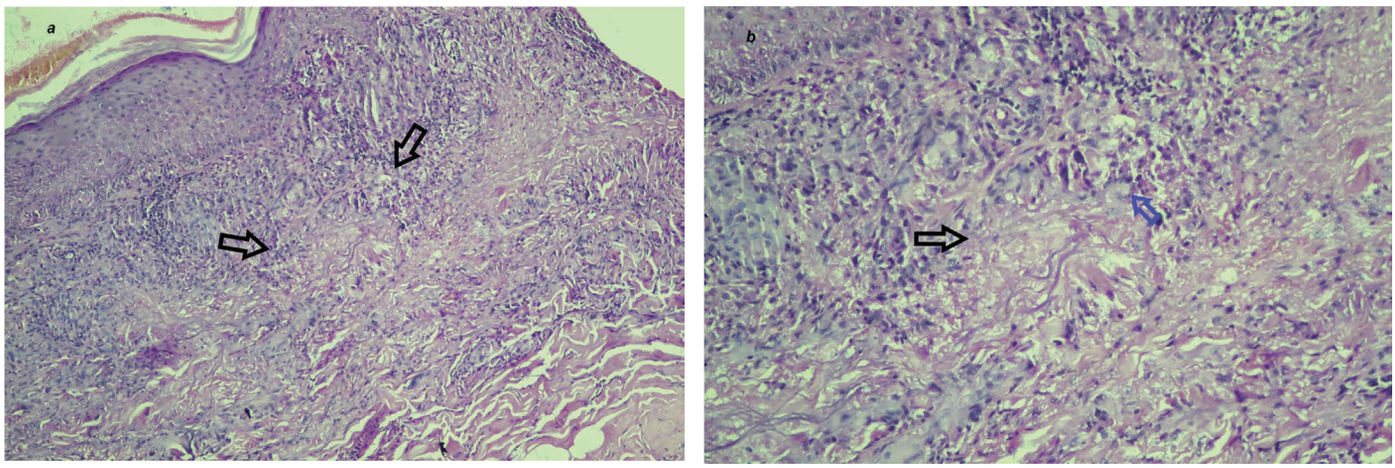

Figure 2. (a) Cutaneous tuberculosis (Lupus vulgaris). Granuloma formation (marked with a black arrow) is characterized by caseous necrosis (marked with a black arrow). **(b)** Multinuclear giant cells (marked with a blue arrow) surrounding the granulomas (archive of Prof. Dr. Haldun Umudum)

lymphadenopathy. Enlarged lymph nodes have violet-erythematous color. Atypical mycobacterial infections have also been reported after plastic surgery, such as breast implantation, tattooing, and fractional CO_2 laser applications[4].

Histologically, neutrophil accumulation (suppurative granuloma) is observed in the epidermis and upper dermis following the emergence of macrophages and granuloma formation in the acute phase. The granuloma border is often unclear and difficult to discern. Classical tuberculoid granulomas, sarcoidal, and rheumatoid granulomas were also reported. In epidermis acanthosis, partial pseudoepitheliomatous hyperplasia is present. In addition, although less specific, lichenoid granulomatous dermatitis, interstitial granulomatous dermatitis, and small vessel proliferation may also occur[1].

As there are many mycobacteria species causing infection in humans, in some cases, the primary organism may not be detected just by clinical features and acid-fast staining. Only one-third of the cases stain positively with Ziehl-Neelsen. PCR and culture should be performed. When biopsy material obtained from a lesion is cultivated in the Löwenstein-Jensen medium, atypical mycobacteria can grow in a 2-4 week period. PCR should be performed on fresh tissue as a priority. With the development of molecular technique applications such as PCR, it will be possible to make more accurate and precise diagnoses[1,3,4].

Sexually transmitted diseases

Granuloma inguinale

Granuloma inguinale, also known as donovanosis, is a rare, sexually transmitted disease characterized by chronic genital ulcers. The causative agent is *Klebsiella granulomatis*, a Gram-negative bacillus. It is often seen in tropical regions. The incubation period varies from a few days to a few weeks (50 days on average). It starts as a single or multiple papules or nodules. Then, the ulcer develops and may spread to the surrounding tissue[2,6]. Histologically, many plasma cells and macrophages, and some neutrophils are observed in the dermis. In 80% of cases, the typical Donovan body can be detected with Wright or Giemsa stain. It cannot be cultivated using routine microbiological media[1,6].

Lymphogranuloma venereum

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis*. Of the 15 known types of *C. trachomatis*, only L1, L2, and L3 subtypes can cause the disease. It is frequently observed in tropical regions and homosexual men. It is thought that the organism enters through minor skin cracks in the external genital area. The infection primarily attacks the lymphatic tissue and regional lymph nodes through the lymphatic system. It causes systemic disease by multiplying in macrophages in the regional lymph nodes. Transmission usually occurs during sexual intercourse and rarely can be transmitted by non-sexual contacts. The clinical course is correlated with the immunity of the patient. While the agent enters the body through the penis in men, drainage occurs through the lymph nodes in the inguinal region. In women, the entrance is through an intravaginal or cervical route. The drainage occurs through the intrapelvic, anal, and rectal lymph nodes. While the disease manifests with swelling in the groin in men, it causes elephantiasis in the genital, anal, and rectal areas in women[1,2,7].

C. trachomatis can be demonstrated by direct microscopy on samples taken from primary lesions, ulcers, or bubo fluid. It is also possible to stain and show the microorganism in the biopsy material with Giemsa or fluorescent methods. Plasma cells, and lymphocyte infiltration and rarely epithelioid macrophages are observed on microscopy[1,7].

While the "Frei test" that measured delayed-type hypersensitivity was used in the past, serological tests have gained importance today. A complement fixation test is the most commonly used serological test. Another test that can be used is the microimmunofluorescence test. If the detected immunoglobulin G titration is higher than 1:128, it suggests LGV. PCR is another method with high sensitivity that helps to diagnose LGV[7].

Other bacterial diseases

Cat scratch disease

Benign lymphoreticulosis, also known as cat scratch disease, is the most common *Bartonella* infection. *B. henselae*, together with *B. clarridgeiae* and *Afipia felis*, are causative agents of cat scratch disease. The reservoirs of *B. henselae* are domestic cats. It is common in humid and hot areas, especially in children and young adults[8].

The primary skin lesion appears as a papule or pustular lesion at the bite or scratch site after approximately 1-10 days[4]. The lesion site is crusted in approximately 1-23 days. Lymphadenopathy is generally regional and unilateral and occurs 1-2 weeks after the primary lesion. Upper epitrochlear and axillary lymphadenopathy are the most common (50%) sites, followed by the cervical (25%) or inguinal (18%) region. Lymphadenopathy is usually solitary, mobile, and sensitive. Fever, weakness, headache, and anorexia may accompany the clinical picture. Granulomatous inflammation with stellate necrosis is observed in the center of the affected lymph nodes and skin lesions. Lymphoid hyperplasia with arteriolar proliferation can be seen in the early period. As the disease progresses, angiolymphoid nodules may contain microabscess accompanied by granulomatous inflammation and central necrosis. Histopathological features are not diagnostic, and Warthin-Starry staining is useful in showing *Bartonella* in the early stage before granuloma formation and in the granulomatous stage[3,8].

Recently, indirect fluorescence technique, ELISA, tissue culture, and PCR from samples taken from lymph node aspirate or biopsy material are used[3,8].

Tularemia

Tularemia is a zoonotic infection caused by an aerobic Gram-negative bacteria, *Francisella tularensis*. People get infected by being bitten by infected arthropods, being in contact with infected animal tissues, drinking contaminated water, ingesting contaminated food, or inhaling the bacteria. The disease is usually transmitted by drinking contaminated water in our country. For tularemia, small rodents are considered the primary natural host, and blood-sucking ectoparasites are the most important vectors[9].

Tularemia can be seen in six main clinical forms: Ulceroglandular, glandular, oropharyngeal, oculoglandular, typhoidal, and pneumonic, depending on the route of entry of the agent (Figure 3). Although the incubation period may vary between one and 20 days, it is usually two to six days. Generally, sudden onset of high fever, chills, headache, weakness, myalgia, and arthralgia are observed in all forms. The disease

severity may vary according to the subtype of the bacteria, the number of bacteria taken, and the host's immune status[10]. It may be confused with cat scratch disease histopathologically[3].

Routine laboratory tests are not diagnostic in the diagnosis of tularemia. Direct microscopic examination, culture, serology, antigen detection, and molecular methods are used in the diagnosis. The definitive diagnosis is made by culturing the bacteria in special cysteine-rich media. The most common method used for diagnosis is serology. With serological tests, antibodies against bacteria can be detected by tube agglutination, microagglutination test, hemagglutination, and ELISA tests. Antibodies become positive after the second week of tularemia and reach their highest level in the fourth to fifth weeks. Therefore, the diagnostic value of serology in the early phase of the disease is limited. The PCR has been used in the early disease stages as a rapid diagnosis in recent years[11].

Actinomycosis

Actinomycosis is a chronic, suppurative, granulomatous disease mainly caused by *Actinomyces israelii. A. israelii* is a Gram-positive, non-acid-fast, anaerobic, or microaerophilic, filamentous branching bacterium. It is found in the normal flora of the oral cavity. It is generally harmless. However, it can be dangerous in the presence of mucosal damage and the presence of another pathogen[1,4,12]. Actinomycosis mainly includes cervicofacial, thoracic, abdominal, and pelvic forms. The cervicofacial form is the most common. The infection is seen after trauma, especially after tooth extraction, as a submandibular or supramandibular nodule or swelling. The skin is purple and warm with palpation. Subsequent fistula or ulceration with yellow exudate with characteristic sulfur granules may be seen[4,12]. Primary cutaneous actinomycosis is an extremely rare form as actinomycosis penetrate the skin because of external trauma[4].

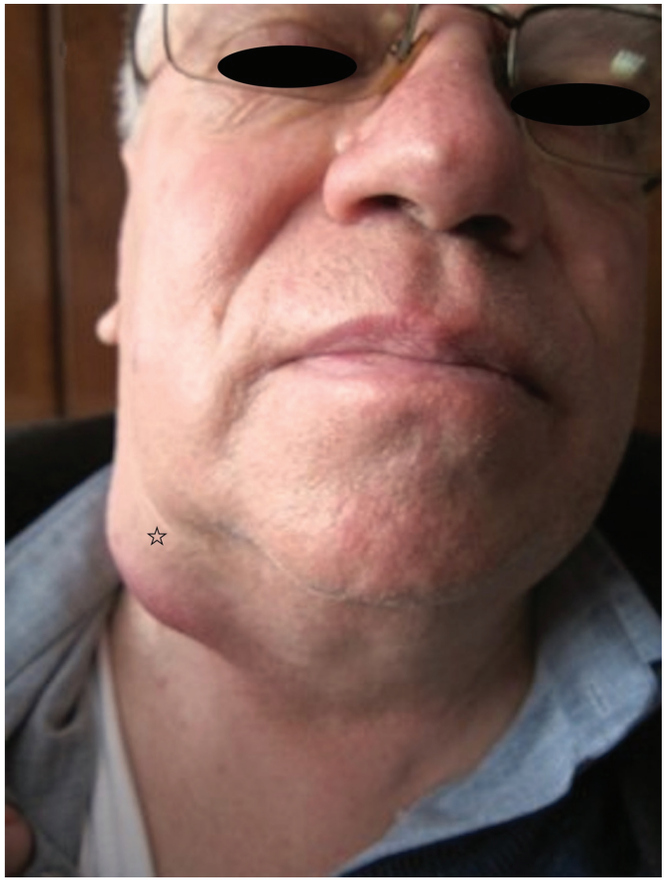

Figure 3. Tularemia (archive of Assoc. Prof. Dr. Didem Dinçer Rota)

The diagnosis is made histopathologically or by growing the bacteria in culture. Diagnosis is often difficult, and it can be confused with tuberculosis, nocardiosis, fungal infections, and other chronic granulomatous diseases[12].

Nocardiosis

Nocardia is an aerobic, filamentous Gram-positive, atypical acid-resistant bacteria. It causes localized or systemic infections in immunocompromised patients. The genus of Nocardia has several species of clinical significance. *N. brasiliensis* is the main pathogenic organism for primary cutaneous infection, and *N. asteroides* is usually the cause of fulminant systemic infection. Isolation and subspecies determination of Nocardia from clinical samples are difficult.

There are three clinical variations of primary cutaneous nocardiosis: Acute superficial skin and soft tissue infection, lymphocutaneous infection, and deep infection, such as mycetoma[13]. The superficial type occurs after superficial inoculation and is manifested by pustules, abscesses, or cellulitis. The deep type, mycetoma, occurs after deep inoculation into the subcutaneous tissue and has many drainage sinuses. It has a chronic course[4,14]. Mycetoma is more common than the other two variants. Mycetoma is common in adult men who walk barefoot. A papule or pustule is observed in the inoculation area of lymphocutaneous or sporotrichoid type. The infection then spreads through the lymphatics. Thus, subcutaneous erythematous nodules and deep regional lymphadenopathy are observed throughout the lymphatic spread. This type is often seen on the upper extremities of gardeners and farmers. Secondary cutaneous nocardiosis occurs with visceral, particularly pulmonary, nocardiosis by the hematogenous or direct spread. In immunocompromised patients, it is characterized by solitary or multiple subcutaneous abscesses and numerous pustules[4].

Botryomycosis

Botryomycosis is a rare chronic bacterial infection. Gram-positive organisms, especially *Staphylococcus aureus*, are the most common causative agents. In addition, *Pseudomonas aeruginosa*, *Bacillus, Proteus*, *Peptostreptococcus* species, *E. coli*, alpha-hemolytic *Streptococci* and *Neisseria catarrhalis* are also reported to be isolated from botryomycosis lesions. Two known forms of the disease affect the skin and internal organs. Cutaneous lesions are characterized by solitary nodules, ulcers, or draining sinuses, but some diffuse cases have also been reported.

The predisposing factors for developing botryomycosis are not fully understood. It has been reported that alcoholism, diabetes mellitus, trauma, AIDS, and immunosuppressive treatments may have a role in the emergence of the disease.

Histopathological examination of the lesions reveals abscesses rich in neutrophils in the dermis and surrounding granulation tissue and fibrin. There are granules in the abscess that resemble a bunch of grapes, giving the disease its name. It is the non-filamentous bacteria that comprise these granules. A dense eosinophilic material stands out around the granules. This is called the "Splendore-Hoeppli phenomenon." It is not specific to botryomycosis.

Filamentous bacteria and fungi can cause chronic local skin infections with drainage. These infections, which are clinically and histopathologically similar, are grouped under "mycetoma." It is called actinomycetoma when caused by filamentous bacteria and eumycetoma when caused by fungi. Mycetomas are characterized by the appearance of sulfur granules in suppurative granulomas in the dermis or subcutaneous tissue. Botryomycosis is also clinically and pathologically similar to mycetomas, which should be differentially diagnosed from actinomycosis, especially in the skin. Non-filamentous bacteria seen in the Gram stain is the most critical criterion in diagnosing and differentiating botryomycosis from other diseases. Bacterial cultures are necessary for the agent's precise identification and isolation[15].

Spirochetes

Among the spirochetes, the agent of syphilis, *Treponema pallidum*, and non-venereal Pinta disease, *T. carateum*, can form chronic granulomatous disease. They should be differentially diagnosed from other granulomatous diseases[3]. The granulomatous reaction is observed in both the secondary and tertiary stages of syphilis. Secondary syphilis is characterized by macular, papular, or pustular lesions. Early lesions that are widespread and separate tend to group and become localized in the later stages. Although granuloma formation is often seen in older syphilis lesions, the granulomatous reaction may also be observed in early lesions. The face is the most common localization for secondary syphilis lesions. Lesions can be annular, acneiform, serpiginous, polycyclic, and large in shape[4].

Tertiary syphilis lesions are syphilitic, tuberculid, and gumma. A tuberculid is a pink-purple papule or nodule. It leaves atrophy and a scar in the center and turns into a plaque with peripheral spread within weeks and months. A gumma begins as a pink-reddish, firm, subcutaneous nodule. After softening, scar-like retraction or ulcers covered with a sticky yellowish membrane may occur. The most common localization for a tuberculid and gumma is the face[4].

The histopathology of secondary syphilitic lesions ranges from minimal infiltration to granulomatous infiltration along with the dermis. Granulomatous infiltration shows endothelial proliferation with mononuclear cell infiltration (Figure 4a, b). In the histopathology of tertiary syphilitic lesions, extensive gumma necrosis is surrounded by lymphocytes, giant cells, fibroblasts, and plasma cells. In addition, endothelial edema with small vascular proliferation is observed. The detection of the pathogen is often unsuccessful. In a few cases where pathogens are detected, PCR can be performed. In case of doubt, serological tests are necessary[1,3].

Fungal infections

Fungal infections are among the most common causes of granulomatous reactions and manifest as localized or systemic diseases. Serial tissue sections are required to detect fungal elements stained with Periodic acid-Schiff or Grocott's stain. Identifying the pathogen's histological subclassification is difficult. Most of these fungal infections can be diagnosed by PCR or cultivation[1,3].

Kerion

Kerion is a dermatophytosis frequently caused by Trichophyton verrucosum and T. mentagrophytes. The intensive immunological response to fungal antigens plays a role in its etiopathogenesis. It presents with pustules, abscesses, ulcers, painful plaques with scales and masses. There is often regional lymphadenopathy without fever. Although it can be localized in any area, it is most frequently observed on the scalp. If the scalp cases are not treated, they may cause cicatricial alopecia. Diagnosis can be confirmed by direct examination with a native preparation (potassium hydroxide) or culture. In culture, they can grow in 3-4 weeks on Sabouraud dextrose agar medium. A histopathological examination is rarely required[4,16].

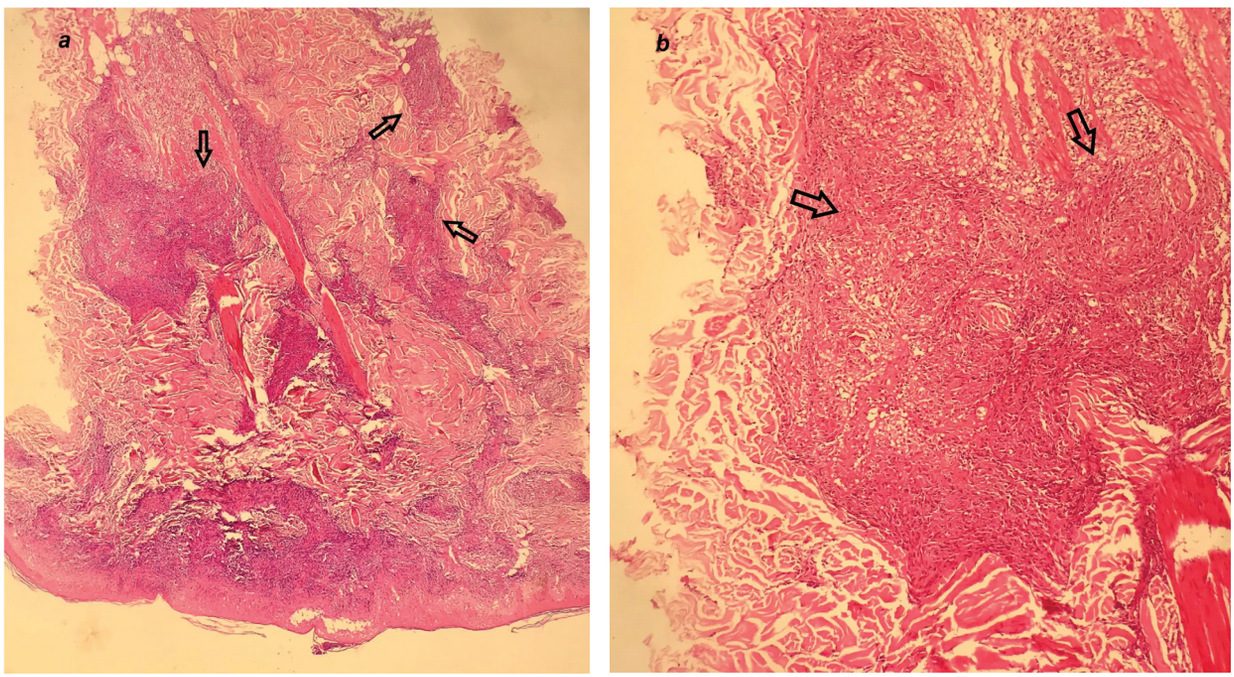

Figure 4. (a, b) Secondary syphilis. Non-caseating granuloma formations (marked with black arrow) with interstitial and perifollicular localization in the deep dermis (archive of Prof. Dr. Haldun Umudum)

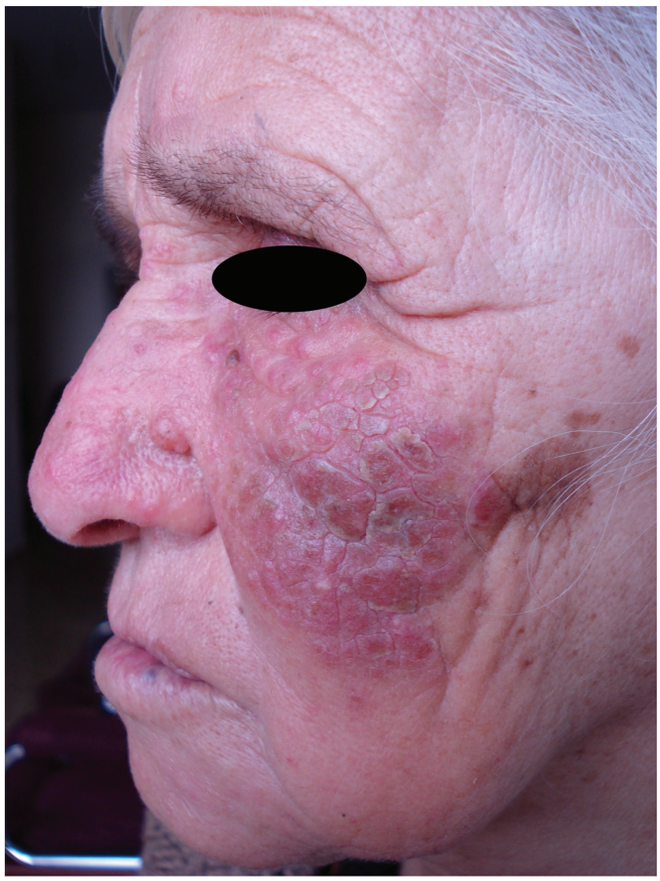

Figure 5. Granulomatous rosacea-like demodicosis (archive of Assoc. Prof. Dr. Didem Dinçer Rota)

Majocchi granuloma

Majocchi granuloma, also known as granuloma trichophyticum, is a rare deep fungal infection often caused by Trichophyton rubrum. It begins as suppurative folliculitis, resulting in granuloma formation, unlike other inflammatory tinea infections. It can occur in any area with hair, such as the face and extremities[4,17]. There are two clinical types: The follicular type is often observed in young women who shave their legs. On the other hand, the subcutaneous type is observed as a plaque, subcutaneous nodule, or abscess in immunocompromised people. A mycological examination is required to identify the causative organism. A histological examination can also help in the diagnosis[17].

Candida granuloma

Candida often infects keratinized tissue and can also infect subcutaneous tissue in immunodeficient, diabetic, or traumatized skin. Deep cutaneous candidiasis occurs mainly by the invasion of candida and secondarily by the spread of candidemia. Candida albicans is the most common pathogen detected. Clinical manifestations range from an ulcer or nodule to subcutaneous induration. It is most commonly observed in the face and scalp region[18].

Deep fungal infections

Blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis are deep fungal infections with cutaneous manifestations. These dimorphic fungi affect immunocompromised and immunocompetent individuals, but the infection is more severe in immunocompromised individuals. They can cause both localized and systemic diseases. Deep fungal infections other than sporotrichosis can also be transmitted by inhalation.

Traveling to endemic areas poses a risk in blastomycosis. B. dermatitis causes infection in all organs, lungs in the first place, and skin in the second.

Sporotrichosis is caused by Sporothrix schenckii. It is often found in soil and plants. Unlike others, it causes disease after entering the skin. It has been reported that each deep fungal infection causes nodular, papular, ulcerative, and verrucous lesions. The lesions grow slowly and often start as papules or nodules, then turn into plaques, and finally ulcerate. Lesions heal by scar formation. The initial lesion is in the inoculation site. Other lesions appear along the same lymphatic vessel. Culturing on Sabouraud dextrose agar is the gold standard in the diagnosis. Direct microscopy can be performed, but it is less sensitive. Showing the causative agent of sporotrichosis is not easy. However, asteroid bodies can be demonstrated, especially in the lymphocutaneous form. Serological tests are available for coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. The urine antigen test for histoplasmosis has a high sensitivity. The latex agglutination test has 90% sensitivity and specificity for cryptococcus[18].

Parasitic infections

Demodicosis

Demodex mite, a saprophytic ectoparasite, has two types: D. folliculorum and D. brevis, located in the follicular infundibulum and sebaceous/meibomian glands, respectively.

These mites are colonized in areas where sebaceous glands are concentrated, such as the face, scalp, and neck. They increase in number with age from the neonatal period to the elderly. Demodex density above five per square centimeter is defined as demodicosis even though it is colonized in 80%-100% of all adults. Demodicosis, which can be confused with many diseases, especially rosacea, can cause many clinical pictures, such as folliculitis (pityriasis folliculorum), papulopustular erythema (rosacea-like demodicosis), blepharoconjunctivitis (demodectic blepharitis), and granulomatous rosacea-like demodicosis (demodicosis gravis)[19].

In granulomatous rosacea- like demodicosis (Figure 5), the parasite (mostly D. brevis) may cause granulomatous foreign body reaction by invading the subdermis. In its pathology, dermal granulomas with caseous necrosis in the center and remnants of mites phagocytosed by foreign body giant cells are seen[20].

Conclusion

Granulomatous skin infections have an important place in the etiopathogenesis of granulomatous skin diseases. They should be considered among the broad spectrum of differential diagnosis of granulomatous skin diseases.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D.R., M.C.E., Concept: D.D.R., Design: D.D.R., Data Collection or Processing: D.D.R., M.C.E., Analysis or

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