An Overview of Suppurative Granuloma

Mary Thomas, Raghavendra Rao¹, G. Nanda Kumar²

Department of Dermatology, Poornima Hospital, Bengaluru, ¹Department of Dermatology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, ²Department of Pathology, Government Medical College, Thiruvananthapuram, Kerala, India

Abstract

Suppurative granulomatous inflammation is a common histopathological reaction pattern that is encountered in the tropical countries including India. It occurs usually due to infective etiology and identification of the causative pathogen is crucial to initiate appropriate treatment. In this review article, we discuss about certain common and uncommon condition which may present with this reaction pattern.

Keywords: Fungal infections, histopathology, suppurative granuloma

Introduction

The suppurative (or “mixed cell”) granuloma is a common and important pattern of granulomatous inflammation, especially in the Indian context as it is seen in several tropical diseases. It is characterized by a collection of epithelioid histiocytes with scattered multinucleated giant cells with a central neutrophilic infiltrate.[1] The various conditions where this pattern of inflammation can be seen are given in Table 1.[2]

Although a broad diagnosis of “suppurative granuloma” can be made by pattern analysis even with sections stained with hematoxylin and eosin (H and E) on low magnifications, more often than not, the dermatopathologist has to rely on special stains to come to a definite diagnosis. Stains can be classified as follows:[1]

Broad-spectrum stains

The most common stain that is used in the diagnosis of suppurative granulomatous conditions is the periodic acid-Schiff’s (PAS) stain that stains the cell walls of the fungi purple. Another such stain is the Grocott’s stain which contains methenamine silver. This stains the fungi black against a green background. Although these stains are very useful, they may also stain several other structures other than the fungi creating a lot of artifact.

Narrow spectrum stains

These stains are very specific and stain only certain organisms, e.g., mucicarmine and Masson-Fontana stain for Cryptococcus.[3]

Fluorescence

Although technically not a stain, this technique can help make a diagnosis when special stains are not available. There are certain fungi that exhibit autofluorescence when stained with H and E and viewed under ultraviolet light. Some common examples are Cryptococcus, candidial spores, and Aspergillus. Frozen sections of Cryptococcus can also be stained with calcofluor-blue and viewed under a fluorescent microscope.

Understanding the pathogenesis and the differentiating features of the several diseases that present with this pattern of inflammation is of paramount importance. The characteristic features of the conditions discussed in this article are summarized in Table 2.

Chromomycosis (Syn: Chromoblastomycosis)

Chromomycosis is a common tropical mycosis caused by dematiaceous fungi. It manifests as asymptomatic, slowly spreading verrucous plaques or nodules.[4] The infection develops following minor trauma. The most commonly implicated organisms include Fonsecaea pedrosoi, Fonsecaea compacta, Phialaphora verrucosa, Rhinocladiella aquaspersa, and Cladosporium (Cladophialophora) carrionii. These

Address for correspondence: Dr. Mary Thomas, Department of Dermatology, Poornima Hospital, 200/A, 6th A Main Road, HMT Layout, 9 Block, RT Nagar, Bengaluru, Karnataka - 560 032, India. E-mail: mary_thomas121@yahoo.com

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organisms are saprophytes and can be found growing in decaying plant material.[5]

**Clinical features**
The classical initial lesion is a small, verrucous papule found on the exposed parts of the body with blackish dots on the surface. It gradually increases in size to form a large hyperkeratotic verrucous plaque with central scarring, ulceration, and cystic areas [Figure 1].[6,7] Occasionally, autoinoculation can cause the spread the infection to atypical cutaneous sites.[8] Other forms described in literature include the nodular, tumoral, plaque, and cicatricial variants. Most of the etiologic agents produce only localized disease restricted to skin and subcutaneous tissue. However, some agents such as *Cladosporium* species (*C. carrionii* and *Cladosporium trichoides*) are known to disseminate hematogenously to distant sites including brain to produce so-called “brain abscess syndrome.”[9]

**Laboratory diagnosis**
Standard diagnosis is based on the presence of Medlar bodies in the potassium hydroxide-cleared specimen obtained from skin scrapings or histopathologically. Histopathology shows hyperkeratosis, pseudopapillomatous hyperplasia [Figure 2], and a tuberculoid granulomatous inflammatory pattern in the upper and mid dermis. The dermal infiltrate consists of epithelioid histiocytes and multinucleated giant cells. Small neutrophilic abscesses may be present, but caseation is never observed. Fungi are seen as single or clustered thick-walled rounded golden-brown bodies within macrophages and lying freely in the dermis. These are known as sclerotic bodies, muriform cells, or Medlar bodies that are 5–12 µm in diameter [Figures 3 and 4]. The organisms are easily identified on H- and E--stained sections. Transepidermal elimination of the fungal spores may be clinically visualized as black dots on the surface of the lesion.[10]

Late lesions or treated, healing lesions are characterized by prominent dermal fibrosis.

**Differential diagnosis**
The differential diagnosis includes phaeohyphomycosis, which is characterized by pigmented hyphae. Other differentials that may resemble chromomycosis include sporotrichosis and blastomycosis.[11] Occasionally, the prominent pseudopapillomatous hyperplasia may resemble squamous cell carcinoma, tuberculosis verrucosa cutis, and viral warts.[12,13]

**Sporotrichosis**
Sporotrichosis is caused by *Sporothrix schenckii*, a dimorphic fungus that is found in soil, decomposing material, on thorned
plants such as roses, sphagnum moss, and animals. This organism exists as a filamentous fungus at room temperature and as pleomorphic yeast in tissue or at temperatures >37°C. It is commonly seen in the tropics. Infection follows minor trauma leading to inoculation.

Clinical manifestations
Sporotrichosis can have variable presentations. Three patterns of presentation have been described: Fixed cutaneous sporotrichosis, lymphocutaneous sporotrichosis, and the disseminated form. Fixed cutaneous sporotrichosis occurs in patients who have been previously inoculated with S. schenckii. Lesions are seen on exposed areas, especially the face as a single subcutaneous nodule or ulcer. It may be accompanied by satellite pustules. Lymphocutaneous sporotrichosis is the most common presentation of sporotrichosis and accounts for 80% of cases. It is seen in patients who have not been exposed to sporotrichosis in the past. The initial lesion is a small hard, painless nodule at the site of inoculation. It may gradually enlarge and ulcerate. The infection ascends along the lymphatics leading to the formation of small secondary nodules along the course of the lymphatic channels. This is associated with regional lymphadenopathy. Extracutaneous and disseminated sporotrichosis is seen in immunocompromised individuals, especially HIV-seropositive patients. Dissemination may occur either through the inhalation or from a primary cutaneous lesion. Patients may present with widespread cutaneous ulcers. Systemic involvement may present with pulmonary, meningeal, joint, or generalized infection.

Diagnosis
The sensitivity of histopathological identification is low because S. schenckii is normally absent or rarely found in smears or biopsies. The characteristic findings are the asteroid bodies and the Splendore-Hopelli phenomenon which are described below. These, unfortunately, are neither sensitive nor specific for the histological diagnosis of sporotrichosis.

The lesions of fixed cutaneous sporotrichosis demonstrate a central ulceration of epidermis surrounded by a hyperkeratotic edge with pseudoepitheliomatous hyperplasia. A mixed granulomatous infiltrate is seen in the upper and mid dermis. Neutrophilic abscesses may be seen. In lymphocutaneous sporotrichosis, three concentric zones may be identified: a central necrotic zone of chronic suppuration, a middle tuberculoid granulomatous zone composed of tuberculoid granulomas, and an outer syphiloid zone of plasma cells, lymphocytes, and fibroblasts with prominent capillary hyperplasia and proliferation. The fungal elements, when present, are seen as globose, budding yeast-like cells measuring 3–8 µm in diameter (in 84% cases), cigar-shaped cells sized 1–2 µm × 4–5 µm (in 33% cases), or oval to round or single budding forms of the yeast within the cytoplasm of giant cells or in the center of asteroid bodies.

Asteroid bodies, sized 15–35 µm in diameter, are fungal cells surrounded by the Splendore-Hoeppli phenomenon, wherein the fungal elements are enveloped by an eosinophilic material radiating centrifugally in a “sunburst” pattern representing
an immunologic reaction. This phenomenon is not specific to sporotrichosis and can be observed surrounding parasitic ova, actinomycotic granules [Figure 5], eumycotic granules, and foreign bodies. It may also be seen in other fungal infections, for example, *Coccidioides immitis*, *Aspergillus*, and *Candida*.\[22\] Definitive diagnosis is made with culture to illustrate the characteristic appearance and dimorphic nature of the fungi.

**Differential diagnosis**

Although the Splendore-Hoeppli phenomenon usually helps make the diagnosis of sporotrichosis, it is seen in several other conditions including mycetoma, *Aspergillus*, *Coccidioides* and occasionally, intradermal foreign bodies.\[23,24\]

Another close differential is sporotrichosis in which microabscesses are more prominent. There is transepithelial elimination of fungal bodies and inflammatory debris. Dermal fibrosis is prominent in treated cases.

**Mycetoma**

Mycetoma is a chronic subcutaneous infection characterized by multiple abscesses and discharging sinuses that contain grains which are large aggregates of fungal or actinomycete filaments. It can be caused by about twenty different fungi and actinomycetes. Infections caused by fungi are called eumycetoma and by actinomycetes are actinomycetoma. Infection follows a penetrating skin injury.\[25,26\] Actinomycetoma is more common than eumycetoma worldwide, and around 75% of mycetoma are actinomycotic in parts of India.\[27\]

**Clinical features**

Eumycetoma and actinomycetoma have similar clinical features except that actinomycetoma can spread more rapidly.\[20\] Mycetoma begins as small, firm, painless subcutaneous plaques or nodules, usually at the site of injury. The most commonly affected site is the feet. Gradually, the lesions increase in number. The lesions ulcerate to discharge a seropurulent material with the characteristic grains [Table 3]. The infection tracks along the fascial planes and invades the deeper tissues associated with induration of the surrounding tissue associated with deformities. The condition is asymptomatic but may become painful when there is osseous involvement and secondary infection.\[29\]

**Diagnosis**

Histological examination of the affected skin shows extensive granulation tissue with abscesses that may lead to sinus formation. In the early stages of the disease, there is a lymphoplasmacytic infiltrate with histiocytes and a few fibroblasts.\[30\] In the later stages of the disease, the fibroblasts predominate. In eumycetoma, the grains are surrounded by a narrow zone of polymorphs and further surrounded by a mixed inflammatory infiltrate consisting of mononuclear cells, histiocytes, and a few foreign body giant cells and occasional xanthomatous cells. In actinomycetoma, a wider zone of polymorphs and mixed inflammatory infiltrate with a few giant cells surround the grains. In most cases, the affected area shows fibrosis with lymph spaces within it. The granules of both eumycetoma and actinomycetoma stain with methenamine silver and PAS.\[30\]

Histopathological characteristics of grains of the common organisms are described.

**Eumycetoma**

**Madurella mycetomatis**

Under low power, the grains were large and uniformly brown, but under high power, they reveal an outer cortex and central medulla. The hyphae in the cortex show an almost regular radiating pattern; the grains may be filamentous or vesicular in nature. The brown pigment is more prominent at the periphery.\[21\]

**Leptosphaeria senegalensis**

The grains in this species are also large with a dark brown peripheral zone made up of multiple vesicles immersed in
cement material. Toward the center, vesicles are less apparent and filamentous hyphae are more prominent, but very lightly pigmented.

**Pale-grain fungi**
The grains in these species are large, but cement is absent. They are eosinophilic with a deeper color at the periphery.

**Actinomycetoma**

*Streptomyces somaliensis*
The grains are large, rounded, kidney-shaped, and multilobed in a few cases. They are basophilic, but mildly eosinophilic at the periphery, and have a homogeneous appearance with cracks in places and radiating filaments at the margins.

**Nocardia species**
The grains are small, rounded or oval, appear pale blue with H and E stain, and are surrounded by an eosinophilic band.

Definitive diagnosis is made by visualization of grains. Culture on Sabouraud’s dextrose agar polymerase chain reaction and ribosomal DNA detection are also used in the diagnosis of mycetoma. Evidence of later bone involvement, such as periosteal thickening, bone lytic lesions, and increased bone density, can also be seen radiologically.

**Differential diagnosis**
The differential diagnosis of mycetoma includes actinomycosis, botryomycosis and osteomyelitis, chromoblastomycosis, and scrofuloderma. It can be differentiated by the presence of the characteristic grains.

**Cutaneous Leishmaniasis**
Cutaneous leishmaniasis (CL) is one of the most common forms of leishmaniasis worldwide. The disease is a protozoan infection caused by various species of the genus leishmania, which is transmitted by the bite of an infected sandfly. With its myriad presentations, it poses considerable difficulty in diagnosis. Familiarity with clinical features and histopathology findings enable one to suspect the condition which can be confirmed by doing newer investigations. In places where the disease is not endemic, this is all the more important.

**Clinical features**
Clinical spectrum of leishmaniasis includes localized CL, diffuse CL, mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis. Localized (acute) CL is characterized by the development of small papule at sites of sandfly bite. It progresses into nodule which might ulcerate and heal subsequently in several weeks with scar formation. Diffuse CL manifests as multiple nonulcerative nodules and plaques which resolve slowly leaving a hypopigmented area. MCL follows localized CL with a latent period of 2–30 years. The mucosal surfaces of nose, oral cavity-pharynx, and larynx are affected leading on to destructive mucosal inflammation.

**Histopathology**
Diagnosis of leishmaniasis can be made by doing a slit and scrape smear of lesion, which will show Leishman-Donovan (LD) bodies, the amastigote form of the protozoan within macrophages and histiocytes [Figure 7]. Biopsy from an early lesion shows an atrophic epidermis and dense infiltrate in the dermis composed of macrophages, histiocytes’ few epithelioid cells, and good number of lymphocytes. This stage where suppurative granulomas can be seen. Many of the macrophages would be seen to harbor the LD bodies which have a tendency to orient toward the periphery of the cytoplasm, referred to as “Marquee sign.” LD bodies are visible in hemotoxylin and eosin sections but can be highlighted by Giemsa stain. In the older lesions, there is gross epidermal hyperplasia, occasionally, to the extent of pseudoepitheliomatous hyperplasia. Well-developed noncaseating tuberculoid granulomas develop with both Langhan’s as well as foreign body type giant cells. There is very little chance of identifying LD bodies at this stage. Down in the deep dermis, granulomas may orient around nerve bundles.

Histopathological changes of CL have to be differentiated from other infective granulomatous conditions. Histoplasmosis can be distinguished by the presence of clear halo and absence of marquee sign. Toxoplasmosis may mimic early CL; morphology and special staining characteristics help to differentiate the two. Late lesions of CL have to be differentiated from other conditions showing tuberculoid granuloma including lupus vulgaris and borderline tuberculoid (BT) leprosy. The absence of epidermal hyperplasia and the absence of background inflammation in the BT leprosy are differentiating features.

**Scrofuloderma**
Scrofuloderma (SD) (also known as tuberculosis cutis colliquativa) is a type of cutaneous tuberculosis that results from direct extension from an underlying tuberculosis focus in lymph nodes and bones to the overlying skin. It begins as a painless subcutaneous nodule, which subsequently...
suppurates (“cold abscesses”). It then breaks down to form an irregular, superficial ulcer with undermined cyanotic edges. Sometimes, sinuses may develop between deep foci of the infection. Ulcers heal with retracted, cordlike, irregular scars. The most commonly affected areas are the neck, armpits, chest wall, and groin.

Histologically, SD is characterized by a dermal abscess (accumulation of neutrophils) with pronounced caseating necrosis underneath an ulceration. There are macrophages, lymphocytes, and plenty of acid-fast rods (Ziehl–Neelsen stain). Tuberculoid granulomas may be seen in the deeper portions or at the lateral borders of the abscess.

**Atypical Mycobacterial Infections**

Atypical mycobacteria are *Mycobacteria* species other than *Mycobacterium tuberculosis* and *Mycobacteria leprae*. They are ubiquitous in nature and are widely distributed in water, soil, and animals. The most familiar atypical mycobacterial infection which reveals suppurative granuloma histopathologically is swimming pool granuloma (PPG). It is caused by *Mycobacterium marinum* which is the most common variant of atypical mycobacterial infection affecting human. The disease typically affects immunocompetent individuals with occupational or recreational (aquarist) contact with fresh or salt water. An erythematous papule develops at the point of entry of the organism that subsequently progresses into a violaceous, verrucous, or ulcerating plaque. The site of predilection is the hand or forearm. Uncommonly, there may be a sporotrichoid distribution of lesions along the lymphatics. Deeper structures (tendons, bones, and joints) are involved in about one-third of cases. Histologically, the acute stage is marked by an accumulation of neutrophils in the dermis (suppurative dermatitis). Subsequently, poorly circumscribed epithelioid granuloma develops. Occasionally, sarcoidal and necrobiotic granulomas have also been described. The epidermis is typically acanthotic, partly showing pseudoepitheliomatous hyperplasia. Other uncommon histopathological changes include lichenoid granulomatous dermatitis, interstitial granulomatous dermatitis, and small vascular proliferations with granulation. Organism can be detected by Ziehl–Neelsen staining only in one-third of cases.

Besides *M. marinum* infection, suppurative granuloma may also occur with other atypical *Mycobacterium* infections such as *Mycobacterium fortuitum*. It is a rapidly growing *Mycobacterium* in soil and water. It has been reported to cause infections of postsurgical wounds, soft tissue, skin, and lung. Disseminated disease has been reported in immunocompromised patients.

**Cutaneous Cryptococcosis**

Cryptococcosis is caused by four serotypes (A–D) of *Cryptococcus neoformans*. Immunosuppressed individuals are more commonly affected. The spores are 4–12 μm in size and form a mucous capsule. Cutaneous cryptococcosis (CC) may be either primary or secondary. The former is a result of direct inoculation after an injury and may be seen in healthy individuals. It is characterized by a single nodule, ulcer, cellulitis, panniculitis, or abscess. Secondary CC is the result of hematogenous spread from pulmonary infection and is usually seen in immunocompromised patients. It presents with multiple erythematous or skin-colored, umbilicated, papulonodular lesions on the face and neck, mimicking molluscum contagiosum. These lesions are often the first presenting symptom of the fatal systemic disease; therefore, recognition of them is crucial to start an early treatment.

Two types of histopathological reactions have been described irrespective of the type of skin lesions in CC – gelatinous and granulomatous. Gelatinous reactions show very subtle inflammation but abundant organism. Latter, on the other hand, is characterized by suppurative granulomatous inflammation with scant organism. Special stains are often required to demonstrate the fungus; these include mucicarmine, PAS, Alcian blue, and methenamine silver. Mucicarmine positivity may help to differentiate CC from other fungal infection such as histoplasmosis and blastomycosis which might share clinical features.

**Histoplasmosis**

Histoplasmosis is caused by *Histoplasma capsulatum* which is normally found in the soil, contaminated by feces from bats or birds (chickens, turkeys, and geese). The infections usually occur in the setting of immunosuppression including HIV infection, and histoplasmosis is an AIDS-defining diseases. Cutaneous involvement is extremely uncommon and almost always occurs in disseminated disease. The manifestations may be polymorphic and include papules (sometime umbilicated), pustules, nodules, ulcers, and verrucous plaques. The histological pattern in all of these pathogens ranges from suppurative to granulomatous dermatitis and is associated with the formation of various types of granulomas. Suppurative features are seen frequently in the ulcerated lesions. The
Blastomycosis (North American Blastomycosis)

Blastomycosis is caused by Blastomyces dermatitidis. Although initially thought to be confined to North America, it has been reported from around the world including India.[41] The infection is acquired through the respiratory route and presents in three forms—pulmonary, disseminated, and primary cutaneous blastomycosis. Disseminated cutaneous blastomycosis starts as papulopustules that progress to form either verrucous or ulcerated plaques. As the disease progresses peripherally, the center of the lesions may heal with atrophy and scarring.[37] The face, neck, and limbs are commonly involved in disseminated cutaneous blastomycosis. Primary cutaneous blastomycosis is extremely rare and follows inoculation of the organism as a solitary, nodule, or ulcer. Lymphangitis and painful lymphadenopathy may accompany them.

Biopsy from the active border will often show neutrophilic abscess in the dermis. Subsequently, granulomatous reaction develops with plenty of multinucleated giant cells and epithelioid cells; occasionally, this may result in tuberculoid granuloma. The fungal spores can be seen within the giant cells as well as free in the connective tissue. Use of fungal stains facilitates their visualization. The epidermis is acanthotic and painful lymphadenopathy may accompany them.

The vacuolation occurs because of the presence of bacteria within the macrophages. The spores are 2–4 µm in size and exhibit a halo. Despite its name, H. capsulatum is not capsulated and the clear halo is due to the presence of granular material which separates the cell wall from the cytoplasm. Histological features may sometimes be confused with leishmaniasis, donovanosis, and rhinoscleroma. Special stains for fungus such as PAS and methenamine silver often help to distinguish these conditions from histoplasmosis. Fontana-Masson stain is useful to distinguish histoplasmosis from cryptococcosis as the latter stains black with this staining technique.[10,40]

Paracoccidioidomycosis (South American Blastomycosis)

Paracoccidioidomycosis is caused by Paracoccidioides brasiliensis. It typically affects the skin around the mouth, as a result of direct extension from the so-called muriform or mulberry-like stomatitis.[41] The lips may be diffusely swollen or a plaque may be seen. Rarely, multiple skin lesions may develop following hematogenous dissemination. They may present as erythematous papular, papulopustular, ulcers covered with fine hemorrhagic dots. Lymphadenopathy may accompany perioral or disseminated skin lesions. Multiple enlarged lymph nodes may be seen in the cervical and submandibular regions. Histologic picture resembles that of blastomycosis. The spores of P. brasiliensis resemble marine “pilot wheel” with protrusion of peripheral buds from the spores and said to be diagnostic of this condition.[40]

Coccidioidomycosis (Valley Fever)

It is caused by a dimorphic fungus, C. immitis; cutaneous lesions are uncommon and almost always due to dissemination. They appear as verrucous papules, nodules, and plaques. There may be subcutaneous abscesses which break open to form sinus tracts. Histological pictures are similar to other infections mentioned above. The spores of C. immitis are larger and are round, thick walled, and have a granular cytoplasm.[59]

Granuloma Inguinale (Donovanosis)

Donovanosis is caused by Klebsiella granulomatis, Gram-negative bacilli. It is characterized by an ulcerating lesion in the genital or perianal region. The ulcers are typically covered with exuberant granulation tissue which gives them a “beefy red” appearance. Affected individual may have multiple, usually painless ulcers which bleeds easily on manipulation. This condition is predominantly found in tropical regions. Histologically, there is an abundance of plasma cells and macrophages in the dermis; small neutrophilic abscess is scattered throughout the dermis. The pathognomonic feature of donovanosis is the demonstration of vacuolated macrophages. The vacuolation occurs because of the presence of bacteria which exhibit handle appearance due to bipolar condensation of the chromat atin when stained with Wright or Giemsa stain and are found in up to 80% of all cases. The epidermis often exhibits pseudoepitheliomatous hyperplasia.[39]

Lymphogranuloma Venereum

Lymphogranuloma venereum is caused by Chlamydia trachomatis (serovars L1, L2, L3). It is predominantly found in tropical regions; it is characterized by a self-healing genital ulcer. Subsequently, the organism colonizes the lymphatic system, vessels, and lymph nodes, leading to inguinal lymphadenitis. Initial histopathological features are nonspecific. The lymph nodes show stellate neutrophilic abscess surrounded by palisading granulomatous reaction. The pathogen can be identified using antibodies directed against C. trachomatis.[37]

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