Original Article

Infectious Granulomatous Dermatitis: Clinicohistopathological Study with Some Unusual Clinical Presentation

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Abstract

Introduction: Granulomatous dermatitis has a varied differential diagnosis ranging from infectious etiology to immune mediated diseases. In tropical countries like India, infectious etiology forms an important cause of granulomatous dermatitis with tuberculosis (TB) and leprosy being the major contributing factors. The present study was carried out with the aim to determine the frequency of various etiological agents causing infectious granulomatous dermatitis in our hospital setup and to see clinicohistopathological correlation in these cases. **Materials and Methods:** This is a hospital based retrospective study conducted in the department of pathology over a period of 1 year. All the skin biopsy cases diagnosed as infectious granulomatous dermatitis were retrieved from the histopathology record section for analysis and were categorized based on the causative etiological agents. Special stains were applied wherever necessary in addition to routine hematoxylin and eosin stain. **Results:** A total of 40 cases of infectious granulomatous dermatitis were included in the present study. Most common diagnosis was leprosy (57.5%), followed by TB (30.0%), actinomycosis (5.0%), dermatophytosis (2.5%), histoplasmosis (2.5%), and cysticercosis (2.5%). Gender wise distribution showed male predominance with 57.5% of cases and age wise distribution showed a peak in the age group of 41–60 years (32.5%). Clinicohistopathological correlation was found in 87.50% of the cases. The unusual clinical presentations were seen in cases of cysticercosis, actinomycosis, and histoplasmosis. **Conclusion:** Histopathological examination of the skin biopsies is an important diagnostic tool providing definitive diagnosis as well as clinicohistopathological correlation in cases of infectious granulomatous dermatitis.

Keywords: Actinomycosis, cutaneous tuberculosis, cysticercosis, granulomatous dermatitis, histoplasmosis, leprosy

Introduction

Granulomatous inflammation is a distinctive form of chronic inflammation. It is characterized by the formation of granuloma consisting of discrete collection of epithelioid histiocytes admixed with variable numbers of multinucleate giant cells of varying types and other inflammatory cells.[1] Granulomatous dermatitis can be classified according to the type of granuloma present in it which, in turn, is classified according to the arrangement of cells, presence or absence of central necrosis, suppuration, and foreign material or organisms into the following different seven types tuberculoid, sarcoidal, necrobiotic, suppurative, foreign body, xanthogranulomatous, and miscellaneous.[1]

Granulomatous dermatitis has a varied differential diagnosis ranging from infectious etiologies to immunologically mediated diseases. Thus, reporting of these cases becomes a diagnostic challenge for a general histopathologist without any specialized training in dermatopathology.

In tropical countries like India, infectious etiology forms an important cause of granulomatous dermatitis and it should be ruled out in all the cases.[1,2] Leprosy and tuberculosis (TB) form the most common cause of infectious granulomatous dermatitis.[2,3] Despite reports of global elimination of leprosy in the year 2000, it still continues to be a social stigma with new cases being reported from different parts of the world.[4,5] According to the 2016–2017 annual report submitted by the National Leprosy Eradication Program in

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India, the prevalence rate of leprosy was 0.66 per 10,000 population.[6]

As per the 2017 Global TB report, India accounts for about a quarter of the world's TB cases.[7] Although cutaneous TB accounts for only 1%–2% of all TB cases, in countries with high prevalence, the absolute number of cases becomes significant.[8] Cutaneous TB has a varied clinical presentation depending on the mode of infection and immune response of the host. Previously, cutaneous TB was mainly classified based on its pathophysiology. However, recently, a more widely acceptable method of classification based on the route of propagation and bacterial load is used.[9,10]

Other causes of infectious granulomatous dermatosis are fungal infections, actinomycosis, and parasitic infestation like leishmaniasis.

The present study was carried out with the aim to determine the frequency of various etiological agents causing infectious granulomatous dermatitis in a tertiary care hospital setup and to see clinicohistopathological correlation in these cases.

Materials and Methods

Study design and setting

This is a hospital-based retrospective study conducted in the department of pathology, in a tertiary care hospital from North India.

Subjects and methods

A total of 300 skin biopsy cases were retrieved from the histopathology laboratory record section for analysis over a period of 1 year from August 2019 to July 2020. The cases diagnosed as infective granulomatous dermatitis were included in the study. Routine histopathological analysis was done on slides stained with hematoxylin and eosin stain. Special stains such as Ziehl–Neelsen (ZN), Fite Faraco (FF), periodic acid Schiff (PAS), and Gram stain were applied where ever necessary. Relevant clinical data were retrieved from requisition forms.

Statistical analysis

Data analysis was done using Microsoft Excel sheet.

Results

A total of 40 cases of infectious granulomatous dermatitis were included in the study. Leprosy was the most common etiological factor found in 23 cases (57.5%). Further distribution of cases according to the etiological factors is shown in Table 1. Clinicohistopathological correlation was seen in 35/40 cases (87.50%) as shown in Table 1.

Gender-wise distribution showed males were 57.50% (23 cases) and females were 42.5% (17 cases). Both cases of actinomycosis and a single case of cysticercosis occurred in females. Age-wise distribution showed a maximum number of cases in the age group of 41–60 years (13 cases, 32.5%) as shown in Table 2.

Leprosy

In the present study, the clinical correlation was seen in all 23 cases of leprosy. On histopathological examination, leprosy cases were subdivided into the groups based on the Ridley and Jopling classification as shown in Table 3. Histopathological findings such as involvement or destruction of the nerve by granuloma, lack of fibrosis, absence of caseous necrosis, and associated atrophy of epidermis were used to differentiate cases of tuberculoid leprosy from cutaneous TB as shown in Figure 1. One case each of type 1 and type 2 lepra reaction was reported as shown in Figure 2. FF stain was positive in 10 cases (43.47%).

Cutaneous tuberculosis

All the 12 cases of cutaneous TB were correlated clinically. These were further classified based on bacterial load into paucibacillary and multibacillary groups as shown in Table 4. Cutaneous TB was differentiated from tuberculoid leprosy by observing associated changes seen in the epidermis like hyperplastic reaction or areas of ulceration, absence of nerve involvement, and significant fibrosis in addition to the presence of tuberculoid granuloma with the occasional area of caseous necrosis [Figure 3]. The maximum number of cases (10, 83.33%) belonged to the paucibacillary group and lupus vulgaris was the most common subtype seen in six cases (50.0%). ZN stain for acid-fast bacilli was positive in three cases of cutaneous TB, i.e., one case each of lupus vulgaris, tubercular ulcer, and tubercular abscess.

Table 1: Distribution of infectious granulomatous dermatitis cases according to the etiological factor and their clinical correlation

Infectious granulomatous dermatitis	Number of cases ($n=40$), *n* (%)	Clinicohistopathological correlation, *n* (%)
Leprosy	23 (57.50)	23 (100)
Cutaneous tuberculosis	12 (30.0)	12 (100)
Actinomycosis	2 (5.0)	0
Dermatophytes	1 (2.5)	0
Histoplasmosis	1 (2.5)	0
Cysticercosis	1 (2.5)	0
Total	40	35 (87.50)

Table 2: Age group-wise distribution of infectious granulomatous dermatitis

Age-wise group	Leprosy	Tuberculosis	Actinomycosis	Cysticercosis	Fungal	Total ($n=40$), n (%)
0-20	5	5	1	1	0	12 (30.0)
21-40	4	4	1	0	1	10 (25)
41-60	10	3	0	0	0	13 (32.5)
>61	4	0	0	0	1	5 (12.5)

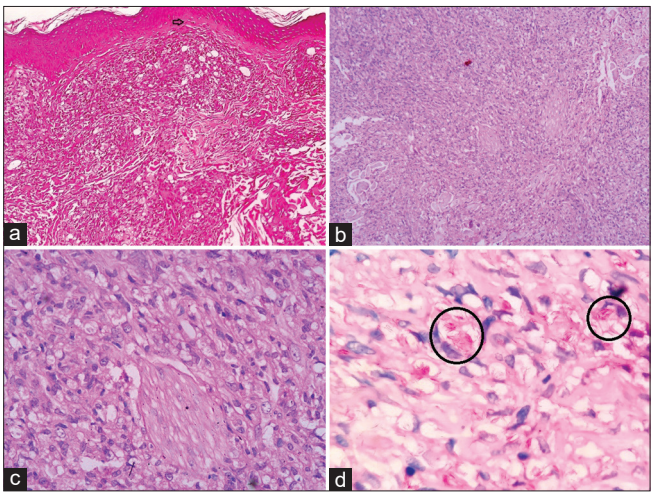

Figure 1: Cases of lepromatous leprosy: (a) Diffuse sheets of foamy histiocytes (Virchow's cells) in the dermis and separated from the epidermis by Grenz zone (arrow) (H and E, ×5); (b) Virchow's cells surrounding the nerve fibers (H and E, ×10); (c) Virchow's cells surrounding the nerve fibers (H and E, ×40); (d) Macrophages distended with large groups (globi) of magenta-colored rod-shaped leprosy bacilli (circles) (Fite Faraco stain for acid-fast bacilli, oil immersion, ×100)

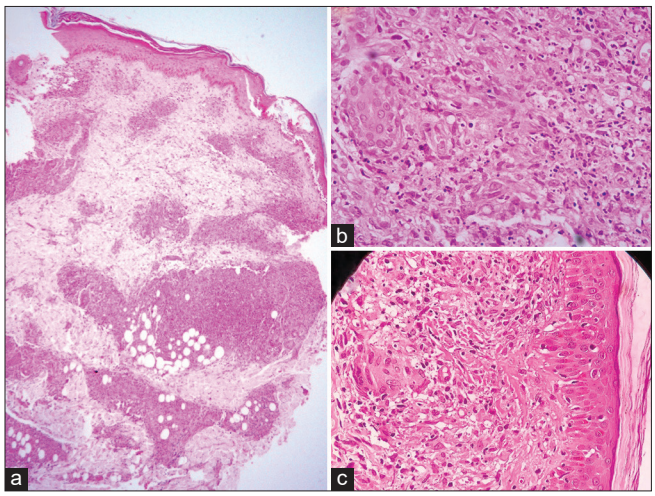

Figure 2: (a and b) Case of erythema nodosum leprosum: (a) Dermis and subcutaneous tissue show dense inflammatory infiltrate consisting of foamy histiocytes admixed with neutrophils, panniculitis (H and E, ×5); (b) Collection of histiocytes and neutrophils surrounding the dermal appendages (H and E, ×40); (c) Case of Type 1 Lepra reaction shows edema within and surrounding the granuloma and these granulomas are seen encroaching the lower epidermis (H and E, ×40)

Actinomycosis

In the present study, two cases (5.0%) of actinomycosis were reported in young females who presented with swelling over the lower limb. In the case of a 15-year-old female, the provisional diagnosis was a sebaceous cyst. In another case of a 22-year-old female, who presented with swelling and discharging sinus, the provisional diagnosis was soft-tissue tumor. Microscopic examination in both the cases revealed suppurative granuloma with purple-colored bacterial colonies/grains showing the Splendore–Hoeppli phenomenon [Figure 4]. The diagnosis of actinomycosis was confirmed by PAS and Gram stain.

Parasite

In the present study, one case (2.5%) of cutaneous parasitic infestation was reported in a 10-year-old female who presented with swelling over the eyelid. The provisional diagnosis in this case was a dermal lipoma. On histopathological examination, a cystic cavity containing the irregular membranous structure of a parasite surrounded by fibrous tissue and granulomatous inflammation was observed [Figure 4]. The parasite was identified as cysticercosis based on the characteristic appearance of the scolex of the cysticercus larva.[11]

Fungal infection

In the present study, one case (2.5%) each of dermatophytosis and histoplasmosis was reported. A case of dermatophytosis was reported in a 22-year-old male who presented with a nodular growth in the right axilla. The provisional clinical diagnosis in this case was cutaneous TB. Histopathological examination showed a perifollicular granulomatous inflammation along with fungal hyphae and spores. PAS stain demonstrated fungal hyphae and spores while ZN stain was negative.

A case of histoplasmosis occurred in a 64-year-old male who presented with swelling over the chest and forearm. His clinical diagnosis was an epidermal cyst. Histopathological examination showed a well-circumscribed granulomatous lesion consisting of histiocytes, epithelioid cells, Langhans, and foreign body type of giant cells surrounded by mantle of lymphocytes. The histiocytes showed the presence of round to ovoid bodies surrounded by clear halo in the cytoplasm on routine H and E stained slide [Figure 4]. Further PAS stain revealed magenta-colored round to oval bodies surrounded by a halo. thereby confirming the diagnosis of histoplasmosis.

Discussion

Various etiological agents such as bacteria, parasites, and fungal infections affecting the skin can cause granulomatous inflammation. Different types of granulomas can be seen in infective granulomatous dermatitis depending on the causative agent and host's immune response. In the present study, we

classified infective granulomatous dermatitis cases based on their causative etiological factor.

The present study showed a male predominance with 23 (57.5%), which is in concordance with other studies from India,[12-15] Southeast Asia,[3,16] and Egypt,[17] whereas a study from India by Kumbar *et al*.[18] reported female predominance.

In the present study, the maximum number of cases (32.5%) belonged to the age group of 41–60 years. Studies from India by Potekar *et al*.[12] and Agrawal *et al*.[15] reported a maximum number of cases in the younger age group of 21–30 years and 21–40 years, respectively. Studies from other tropical southeast Asian countries found the maximum number of cases in the fourth decade of life.[3,16]

Leprosy

In the present study, leprosy was the most frequent etiological factor found in 57.50% of cases. By Ridley and Jopling classification, borderline tuberculoid leprosy was the most frequent subtype (7 cases, 30.43%). Similar findings were reported by other studies from India[2,12,13,18] and Nepal.[16] In contrast to our findings, a study from Pakistan[19] reported cutaneous leishmaniasis as the most common form of granulomatous dermatosis and no case of leprosy was reported by them. A study from Egypt[17] reported borderline lepromatous leprosy as the most common subtype.

In the present study, FF stain was positive for lepra bacilli in 43.47% of cases of leprosy. This is in concordance with the study done by Bal *et al*.,[2] whereas Chakrabarti *et al*.[13] and Kumbar *et al*.[18] reported lower percentage of positivity for lepra bacilli.

Tuberculosis

Lupus vulgaris is the most common form of cutaneous TB resulting from hematogenous spread.[20] In the present study too, lupus vulgaris was the most common form of cutaneous TB (6 cases, 50.0%). Similar findings were reported by other studies from India[2,13,14,21] and Egypt.[17] A study from Nepal[16] reported equal number of lupus vulgaris and TB cutis orificialis cases, whereas a study from Brazil[10] reported erythema induratum of Bazin as the most common form of cutaneous TB.

In the present study, cutaneous TB was most frequent in the age group of 0–20 years (5 cases, 41.66%). Similar findings were reported by Kannan *et al*.[14] and Jayanthi *et al*.[21] In

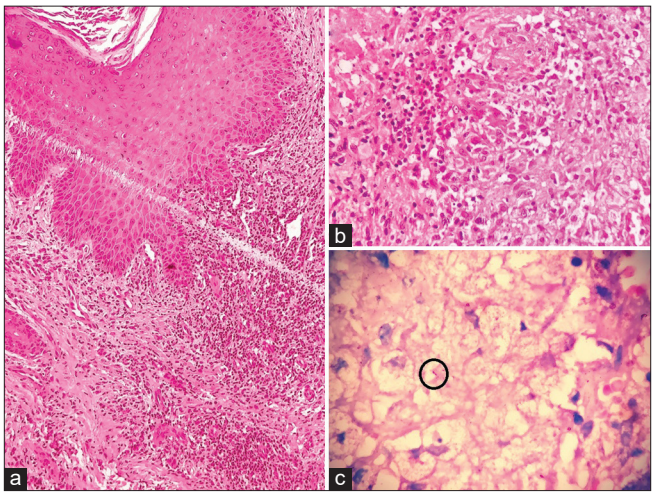

Figure 3: Lupus vulgaris: (a) hyperplastic stratified squamous epithelium and multiple epithelioid cell granuloma in the dermis (H and E, ×5); (b) tuberculoid granuloma composed of epithelioid histiocytes, scattered Langhans' type of giant cells, and lymphocytic infiltrate. There is minimal caseation necrosis (H and E, ×40); (c) Ziehl–Neelsen stain for acid-fast bacilli demonstrates magenta-colored rod-shaped bacilli (circle) in the lesion (oil immersion, ×100)

Table 3: Ridley Jopling classification of leprosy cases

Leprosy cases	Total (*n*=23), *n* (%)	Number cases positive by Fite-Faraco stain (*n*=10)
Indeterminate	3 (13.04)	0
Tuberculoid	4 (17.39)	0
Borderline tuberculoid	7 (30.43)	1
Mid-borderline leprosy	1 (4.34)	1
Borderline lepromatous	3 (13.04)	3
Lepromatous leprosy	3 (13.04)	3
Type 1 lepra reaction	1 (4.34)	1
Erythema nodosum leprosum	1 (4.34)	1

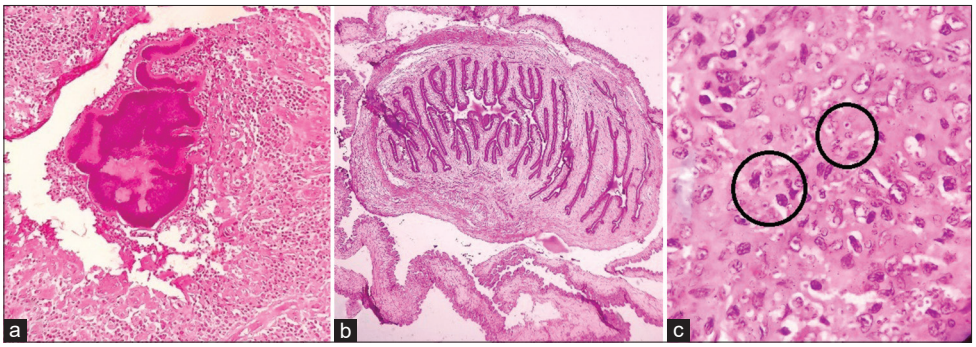

Figure 4: (a) Actinomycosis: Suppurative granuloma with purple-colored bacterial colonies showing the Splendore–Hoeppli phenomenon (H and E, ×10). (b) Cysticercosis: The cystic cavity containing scolex of the cysticercus larva surrounded by fibrous tissue and granulomatous inflammation (H and E, ×10). (c) Histoplasmosis: The histiocytes show the presence of round to ovoid bodies surrounded by clear halo (circles) in the cytoplasm (H and E, ×100)

Table 4: Classification of cutaneous tuberculosis cases

Category of cutaneous tuberculosis	Pattern of cutaneous tuberculosis	Number of cases, *n* (%)	Total (*n*=12), *n* (%)
Paucibacillary	Lupus vulgaris	6 (50)	10 (83.33)
	Verrucosa cutis	1 (8.33)	
	Sinus	2 (16.66)	
	Abscess	1 (8.33)	
Multibacillary	Abscess	1 (8.33)	2 (16.66)
	Ulcer sinus	1 (8.33)	

the present study, the gender-wise distribution of cutaneous TB showed male predominance, which is similar to the other studies from India,[14,21] whereas Chakrabarti *et al*.[13] reported female predominance.

In the present study, the most frequent site of lupus vulgaris was the face, which is in concordance with the study from Egypt,[17] whereas Kannan *et al*.[14] from India reported lower limbs and buttocks as the most common site for lupus vulgaris.

Actinomycosis

In the present study, two cases of primary cutaneous actinomycosis affecting the lower extremities were reported Actinomycosis is a rare chronic suppurative and granulomatous bacterial infection caused by Gram-positive organism belonging to the Actinomyces genus. The most commonly affected sites are the cervicofacial, thoracic, and abdominopelvic regions. It presents with a clinical triad of swelling, sinus tract, and discharging grains. Primary cutaneous actinomycosis of the lower extremities is quite rare and it mainly occurs due to traumatic implantation of the organism on the exposed skin. In the present study, actinomycosis was not suspected in both the cases due to lack of history of trauma and discharging grains. In the present study, both the cases were reported in young females. However, other studies from India reported cases of primary cutaneous actinomycosis in middle-aged patients.[22-24] In the present study, the incidence of actinomycosis was 5.40%, which is comparable to the previous studies from India,[13,18] whereas a study from Egypt reported a lower incidence.[17]

Parasite

Cysticercosis is a parasitic infestation caused by Taenia solium larvae. Humans are an accidental intermediate host. It presents as asymptomatic small subcutaneous nodule. It most commonly affects the central nervous system, followed by striated muscles, eyes, and subcutaneous tissue. A review of the literature shows only a few cases of eyelid cysticercosis reported in the past with its incidence being 0.6%.[25-27] In the present study, a case of eyelid cysticercosis was reported in a young girl. She had no other complaints except for a longstanding painless swelling over the upper eyelid and excision was done for cosmetic reasons. These findings are comparable to the previous studies from India.[26,27] In the present study, there was no clinical suspicion of cysticercosis due to the absence of any other signs or symptoms. This can occur due to the varied incubation period of cysticercosis. Such longstanding benign eyelid masses are commonly misdiagnosed as dermoid cysts or benign soft-tissue tumors.[25-27] In the present study, the clinical diagnosis was dermal lipoma. While in other studies, the cases were misdiagnosed as sebaceous or dermoid cysts.[25-27]

Fungal

Histoplasmosis is a systemic mycosis that can present as cutaneous lesion. It is caused by Histoplasma capsulatum, a dimorphic fungus found in soil. Skin lesions can occur in few cases of disseminated histoplasmosis or rarely as primary cutaneous histoplasmosis. Although it mainly affects immune-compromised individuals, some cases are reported in immune-competent patients.[28] In the present study, a case of primary cutaneous histoplasmosis occurred in an elderly male patient in form of a skin nodule over the upper extremity and trunk. He had no other signs or symptoms, however his immune status was unknown. As opposed to this, previous studies from India by Raina *et al*.[28] and Nair *et al*.[29] reported it in a younger immunocompetent patients with a history of nonhealing ulcer over extremities.

Dermatophytosis can be caused by fungi belonging to genera of Trichophyton, Microsporum, or Epidermophyton The major etiological agent for dermatophytic or Majocchi's granuloma is Trichophyton rubrum.[30] Dermatophytic granuloma presents in two forms based on the patient's immune status. In immunocompetent patients, it usually presents as a perifollicular papule over lower extremities, often accompanied by a history of trauma or use of topical steroids. In immunocompromised patients, it can present either in form of nodule or perifollicular pustule, usually involving the upper extremities.[30] In the present study, it presented as a perifollicular nodule in the axilla of a young patient, however his immune status was unknown. The provisional clinical diagnosis in our case was cutaneous TB which is the most common differential diagnosis for dermatophytic granuloma.

Conclusion

Histopathological examination of skin biopsies is an important diagnostic tool in determining definitive diagnosis and clinicohistopathological correlation of infectious granulomatous dermatitis. In our study, leprosy and cutaneous TB were the most frequent type of infectious granulomatous dermatitis. Although major efforts are being made toward controlling TB and eradicating leprosy through various national programs, these diseases still continue to be a serious public health problem in various parts of India. Some

unusual clinical presentation was seen in the rare cases of cysticercosis, actinomycosis, and histoplasmosis causing infectious granulomatous dermatitis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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