Necrobiotic Granuloma: An Update

Achyut Pokharel, Isha Poudel Koirala

Department of Dermatology, Bakulahar Hospital, Tandi, Chitwan, Department of Dermatology Kathmandu Clinic of Cosmetic Surgery, Kathmandu, Nepal

Abstract

Granulomatous disorders comprise a large family sharing the common histological denominator of granuloma formation. Collagenolytic or necrobiotic granuloma is one in which a granulomatous infiltrate develops around a central area of altered collagen and elastic fibers. The altered fibers exhibit new staining patterns, becoming either more basophilic which gives blue appearance (“blue granuloma”) or eosinophilic giving red appearance (“red granuloma”). Conditions which exhibit blue granuloma include granuloma annulare, Wegener’s granulomatosis, and rheumatoid vasculitis, whereas red granulomas include necrobiosis lipidica, necrobiosis xanthogranuloma, rheumatoid nodules, Churg-Strauss syndrome, and eosinophilic cellulitis (Well’s syndrome).

Keywords: Blue granuloma, necrobiotic granuloma, red granuloma

INTRODUCTION

Granulomatous disorders comprise a large family of unrelated conditions sharing the common histological denominator of granuloma formation. Collagenolytic or necrobiotic granuloma is one in which a granulomatous infiltrate develops around a central area of altered collagen and elastic fibers. The altered fibers exhibit new staining patterns, becoming either more basophilic or eosinophilic. Within the area of altered collagen, there may be deposition of acellular substances such as mucin (blue) or fibrin (red), or there may be neutrophils with nuclear dust (blue), eosinophils (red), or flame figures (red). Depending on the deposition, these granulomas are distinguished as red granulomas and blue granulomas.[1]

Hence, blue granulomas as of explanation above include granuloma annulare (GA), Wegener’s granulomatosis, and rheumatoid vasculitis (RV), whereas red granulomas include necrobiosis lipidica (NL), necrobiosis xanthogranuloma, rheumatoid nodules (RN), Churg-Strauss syndrome (CSS), and eosinophilic cellulitis (Well’s syndrome).

BLUE GRANULOMAS

Granuloma annulare

GA is a benign inflammatory dermatosis of unknown etiology. It was first described in 1895 as ringed eruption.[2] It is relatively common skin disease; hence, it is important that we get familiar with the clinical variants as well as be able to recognize it microscopically. GA can arise in all age groups and present as asymptomatic grouped papules in an enlarging annular shape. The eruption can occur anywhere on the body, and most often they are seen on the lateral or dorsal surfaces of the hands and feet. The etiology of GA remains unknown, and several systemic associations have been proposed including diabetes mellitus, malignancy, thyroid disease, and dyslipidemia.[3,4] The diagnosis of GA relies on clinicopathological correlation, with a skin biopsy confirming the histological features of the disease, including palisading granulomas, collagen degeneration, mucin deposition, and a lymphohistiocytic infiltrate.

Clinical presentation

GA has several clinical presentations, and the lesions are usually asymptomatic. Localized form is the most common type of GA in children, which starts as small red to flesh-colored papules gradually increasing in diameter with central involution and peripheral spread, seen commonly in dorsal surfaces of hand and feet [Figure 1a]. Mainstay of treatment is steroid either topical or intralesional injection.[5] More than 50% of these patients will have spontaneous

Address for correspondence: Dr. Achyut Pokharel, Department of Dermatology, Bakulahar Hospital, Tandi, Chitwan, Nepal.
E-mail: pachyut@gmail.com

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resolution within 2 years,\(^6\) approximately 80% of patients do not report a recurrence.\(^1\)

Disseminated or generalized GA is similar to the localized variant but is more widespread, having ten or more lesions. The papules may fuse to form annular lesions on the extremities, trunk, and neck. In contrast to the localized form, these lesions may persist for 3–4 years or longer.\(^6\)

Subcutaneous GA also known as deep GA occurs predominantly in children and is characterized by firm or hard asymptomatic nodules in the deep dermis or subcutaneous tissues. It occurs usually on the shin, ankles, dorsal feet, buttocks, and hands; rarely, it can be seen on forehead and scalp.\(^2\) Other uncommon clinical variants are shown in Table 1.

**Histopathology of granuloma annulare**

GA typically belongs to blue granulomas because of hypocellularity and presence of mucin which displays blue color histologically. The histopathologic findings are independent of clinical presentation. Thus, localized annular lesions or disseminated macules are histologically indistinguishable.\(^7\) Three histological patterns may be seen in GA – necrobiotic (collagenolytic) granulomas, an interstitial or “incomplete” form, and granulomas of sarcoideal or tuberculoid type; the interstitial type is the most common histopathological variant, whereas sarcoideal variant is the least common type. Necrobiotic (collagenolytic) granulomas are characterized by, one or more areas of necrobiosis in the superficial and mid dermis, surrounded by histiocytes and lymphocytes. The peripheral rim of histiocytes may form a palisading pattern [Figure 1b]. The lesions of subcutaneous or deep GA have areas of necrobiosis which are often larger than in the superficial type. In the disseminated form GA, the granulomatous foci are often situated in the papillary dermis. Necrobiosis may be inconspicuous. There is some superficial resemblance to lichen nitidus.\(^8\)

Perforating GA typically has transepidermal elimination of altered materials. Compared to classic GA, actinic GA of O’Brien and annular elastolytic giant cell granuloma have more superficial and horizontal infiltrations and contain more giant cells. The histologic pattern of the interstitial variant of GA may also be interstitial instead of palisading and hence need a clinicopathological correlation for the diagnosis. An important histologic feature of GA is the presence of mucin in areas of connective tissue degeneration, stained by alcian blue and/or colloidal iron.\(^7\) The presence of reticulin fibers surrounding and permeating the histiocytic cluster seen in reticulin stain suggests the presence of sarcoideal type of granuloma.\(^9\)

**Differential diagnosis**

GA must be distinguished from NL, rheumatoid nodule, and actinic granuloma.\(^9\) The histology of NL in contrast to GA involves the entire dermis with no intervening normal zones, prominent collagen bundles’ degeneration, no deposits of mucin, two or three tiers of granulomatous inflammation, and often, extending to the subcutaneous septa are the

### Table 1: Clinical and histological variants of granuloma annulare

| Type of GA               | Clinical Presentation                                                                 | Histopathology                                                                 |
|-------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Localised GA            | Firm flesh colored to erythematous papules, coalescing to form annular plaques       | No epidermal envolvement with degenerated connective tissue surrounded by slightly elongated epithelioid cells.|
|                         | Uncommon\(^1\)                                                                        |                                                                             |
|                         | a) Papular                                                                           |                                                                             |
|                         | b) Umbilicated                                                                       |                                                                             |
|                         | c) Follicular Pustular                                                               |                                                                             |
| Generalised GA          | Similar to localised GA with extensive involvement                                    | Granuloma are situated in papillary dermis. Necrobiosis may be inconspicuous\(^10\) |
| Deep/Subcutaneous GA\(^5\) | Subcutaneous nodules, misdiagnosed as rheumatoid nodules\(^6\)                       | Necrobiosis is larger and wider and are distributes in deep dermis and subcutaneous layer\(^10\) |
| Interstitial GA         | Erythematous patches, misdiagnosed as Morphea, Mycosis Fungoides, EM                 | Bust dermis with subtle histological changes and best seen under low power\(^10\) |
| Perforating GA          | Umbilicated papules with keratotic core 2 varients\(^5\)                             | Central epidermal perforation which communicates with underlying necrobiotic granuloma\(^10\) |
|                         | a) Papular                                                                           |                                                                             |
|                         | b) Ulcerated                                                                         |                                                                             |
| Actinic GA              | Anular lesions, more on sun exposed areas                                            | Granulomas are more superficial and contain more giant cells\(^7\)          |
| Synonym: Annular Elastolytic Giant Cell Granuloma\(^5\) |                                                                     |                                                                             |
major differences. Differentiating subcutaneous GA from a rheumatoid nodule is not always possible on histologic grounds, but subcutaneous GA is more likely than rheumatoid nodule to show prominent mucin and less likely to show foreign-body giant cells or prominent stromal fibrosis.\textsuperscript{[10]}

**Granulomatosis with Polyangiitis**

Antineutrophilic cytoplasmatic antibodies (ANCA)-associated vasculitis (AAV) is defined as a necrotizing vasculitis with few or no immune deposits, predominantly affecting small blood vessels (i.e., capillaries, venules, and arterioles), associated with the presence of circulating autoantibodies (ANCA) that are usually directed against myeloperoxidase (MPO) or proteinase 3 (PR3). ANCA-AAVs are multisystemic diseases and include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly known as Wegener’s granulomatosis), and eosinophilic GPA (EGPA, formerly known as CSS).\textsuperscript{[11]} CSS is considered the eosinophilic variant of the Wegener’s granulomatosis.\textsuperscript{[12]}

**Clinical presentation**

GPA is a systemic granulomatous disease which is more common among children, predominantly in Caucasians and in females.\textsuperscript{[13]} In a study by Cabral et al., median age at diagnosis was 14 years.\textsuperscript{[13]}

GPA is a triad of symptoms that include necrotizing granulomas of the upper or lower airway respiratory tracts, in conjunction with a focal necrotizing glomerulonephritis, and systemic vasculitis of the arteries and veins. Limited GPA refers to the disease when only one or two organ systems are involved.\textsuperscript{[11]}

Many other organs may be affected including the skin, the nervous system, the eyes, and musculoskeletal. A retrospective study done in year 2016, the most commonly involved organs were the upper respiratory tract (72.7%), lower respiratory tract (81.8%), and kidneys (72.7%).\textsuperscript{[14]} Cutaneous lesions are more common in generalized GPA than in limited GPA.\textsuperscript{[11]}

Skin lesions are variable and nonspecific and usually affect lower extremities. Common cutaneous manifestations are palpable purpura and papulonecrotic ulcer (45%).\textsuperscript{[15]} Less common manifestations can be petechiae, livedo reticularis, pustules, vesicles, hemorrhagic bullae, and subungual splinter hemorrhage. Rarely, GPA may manifest in the form of acneiform lesions, nonhealing surgical incisions, auricular chondritis, and penile ulcers.\textsuperscript{[11]} Mucocutaneous involvement occurs in approximately 40% of patients, and it can be a presenting sign in 10% of patients.\textsuperscript{[16]}

**Histopathology of granulomatosis with polyangiitis**

GPA is characterized by leukocytoclastic vasculitis and necrotizing granulomatous inflammation.\textsuperscript{[17]} Histopathological features of cutaneous lesions reveal a variety of features including necrotizing vasculitis, in which small or medium-sized dermal vessels display fibrinoid necrosis, a neutrophil polymorphonuclear infiltrate, and nuclear dusts.\textsuperscript{[18]} Special stains are noncontributory; however, immunofluorescence microscopy will sometimes show C3 and immunoglobulins related to vessels in early lesions.\textsuperscript{[19]} A study of 17 patients with Wegener’s granulomatosis showed that those patients with skin lesions are likely to have positive c-ANCA/PR3-ANCA serologic test results.\textsuperscript{[20]}

According to the 1999 international consensus on ANCA testing, indirect immunofluorescence (IIF) should be used to screen for ANCAAs, and samples containing ANCAAs should then be tested by immunoassays for proteinase 3 (PR3)-ANCAAs and MPO-ANCAAs.\textsuperscript{[20]} PR3-ANCA is most specific for GPA.\textsuperscript{[21]}

**Differential diagnosis**

Histological picture of early lesions of GPA, before the formation of vasculitis, may mimic sarcoidosis and infective (myological and fungal) conditions. Granulomatous vasculitis may also be seen in lymphomas and leukemias. In MPA and Wegener’s granulomatosis, only the involvement of lung favors the latter. A high eosinophils’ count favors the Churg-Strauss disease than Wegener’s granulomatosis and still is not diagnostic. Therefore, distinction of Wegener’s granulomatosis from other forms of granulomatous inflammation requires a careful clinicopathological correlation.\textsuperscript{[18]}

**Rheumatoid Vasculitis**

RV is a serious complication of long-standing rheumatoid arthritis (RA). It is immune complex-mediated process that develops in approximately 0.7%–5.4% of the RA patient population.\textsuperscript{[21]} A number of predisposing factors have been recognized including certain human leucocyte antigen haplotypes, male sex, smoking, and long-standing seropositive nodular erosive disease.\textsuperscript{[22]}

**Clinical presentation**

RV can involve any organ of the body; skin and peripheral nerves being the most common and affected in 80% of RV patients.\textsuperscript{[23]} Other organs involved in RV are cardiac, pulmonary, renal, and gastrointestinal (GI) system. Cutaneous manifestations are characterized by the presence of purpura, digital ischemia, cutaneous ulcers, and nail-fold changes.\textsuperscript{[22]}

**Histopathology of rheumatoid vasculitis**

The changes are similar to those seen in leukocytoclastic vasculitis, which is nonspecific to a single condition, although there is usually prominent edema of the upper dermis in RV.\textsuperscript{[24]} Hence, the most suggestive appearances are medial necrosis with proliferating intimal and adventitial cells organized in a radial manner; necrosis may involve the whole circumference of the vessel wall.\textsuperscript{[25]} One study explains three patterns of histological features such as leukocytoclastic vasculitis type, polyarteritis nodosa type, and combination features of dermal vasculitis and atrophic blanche.\textsuperscript{[26]}

**Red Granulomas**

**Necrobiosis Lipoidica**

NL is a chronic granulomatous skin disorder that affects 0.3% of diabetic patients.\textsuperscript{[27]} Microangiopathy associated with
diabetes is one of the leading etiologic factors of NL. Hence, it was formerly named NL diabeticorum. However, nondiabetic cases of the condition were reported, and hence, the term diabeticorum was removed. The other reported correlations are with celiac disease and elevated thyroid antibodies.\[28\]

Clinical presentation
Average age of onset is 30–41 years.\[29\] Patients commonly present with multiple sclerotic plaques with elevated violaceous borders over the pretibial area [Figure 2]. There are reports of involvement of scalp, upper extremities, abdomen, penis, nipple area.\[27,29,30\] Ulceration can occur and is often slow to heal. Koebnerization is common over the site of trauma.

Histopathology of necrobiosis lipoidica
NL is classified under red granulomas due to the presence of densely packed sclerotic collagen degeneration. The Epidermis is usually flat. The dermis displays a “sandwich” or “cake layering” appearance with alternating layers of degenerated and sclerotic collagen and layers containing granulomatous infiltrates.\[17\] Histologic changes may extend into the subcutaneous septae.\[31\] Occasionally, histopathological changes are confined to the upper dermis.\[22\] The granulomatous component is usually conspicuous, and the histiocytes may or may not be arranged in a palisade. Occasionally, there are just a few scattered epithelioid histiocytes and giant cells.\[10\] Electron microscopic examination shows degenerative changes in collagen and elastin with loss of cross-striation in collagen fibrils. Collagen synthesis by fibroblasts is diminished.\[13\] Direct immunofluorescence studies have shown that necrobiotic foci contain fibrinogen. Deposits of immunoglobulin and C3 have been found in the vessel walls, but this is not a consistent finding.\[34,35\]

Differential diagnosis of necrobiotic lipoidica
The principle differential diagnoses are subcutaneous GA, epithelioid sarcoma, rheumatoid nodule, and necrobiotic xanthogranuloma (NXG). Differentiation of NL from GA is discussed above. Occasionally, NL shows discrete collections of epithelioid cells that may resemble those seen in sarcoidosis. However, significant alteration of the collagen is usually present in NL and absent in sarcoidosis.\[36\] Histological features of NXG show more dense and diffuse infiltrate with greater number of foamy histiocytes, Tufton giant cells and extensive inflammation with more disruption of subcutaneous architecture than in Necrobiotic Lipoidica.\[37\]

Necrobiotic Xanthogranuloma
NXG is a rare, chronic, progressive, non-Langerhans histiocytosis that is strongly associated with hematologic malignant conditions. The etiology remains uncertain. NXG is found to be associated with monoclonal gammopathy (in approximately 80%–90% cases), multiple myeloma (10%), and plasmacytosis.\[38\] IgG kappa is the most frequently discovered monoclonal gammopathy (65%), followed by IgG lambda (35%) and less commonly IgA.\[38\]

Clinical presentation
NXG is usually occurred in middle-aged patients; there is no gender predilection.\[20\] It presents as asymptomatic, indurated, yellow papules, nodules, or plaque, in the periorbital region. Thus, clinical picture may sometime mimic xanthomas. Less commonly, it can affect other areas of face, trunk, and proximal extremities.\[19\] Uncommon manifestations include telangiectasias, ulcers, and scars.\[40\] Patients with extensive periorbital involvement can present with vision changes, diplopia, proptosis, episcleritis, keratitis, iritis, conjunctivitis, and corneal perforation.\[29\]

Histopathology of necrobiotic xanthogranuloma
It reveals broad zones of hyaline necrosis as well as granulomatous inflammation composed of histiocytes, foam cells, and multinucleate cells [Figure 3]. However, necrobiotic foci with degenerated and sclerotic connective tissue are much more extensive and deeper.\[41\] It is surrounded by palisade-like infiltrates of epithelioid and foamy histiocytes;
giant cells, usually of Touton type, can be recognized. Lymphoplasmocellular infiltrates are usually seen in the perivascular compartment.[62]

**RHEUMATOID NODULES**

RNs are the most common and specific cutaneous manifestation of seropositive RA seen in approximately 25% of patients.[43] These are the most common extra-articular lesions of this disease. Risk factors for RNs are smoking and elevated level of serum RF. Rarely, it can also be associated with diseases such as rheumatic fever and some connective tissue diseases.[46] Recently, RN formation has been reported following etanercept and adalimumab therapy. RNs which crop up mostly in the hands and feet in patients without RAs or joint complaints include a condition known as rheumatoid nodulosis (“benign RNs”).[45]

**Clinical features**

Classic RNs are usually asymptomatic and clinically present as firm-to-hard subcutaneous, mobile nodules. It is usually seen in areas of repeated trauma such as extensor surface of the elbow, olecranon, and extensor tendons of the hands, proximal ulna, sacrum, occipital region, and sole.[46] The most common noncutaneous location for RN is lung; rarely, it can be seen in the heart, central nervous system, spine, and GI tract.[44,45]

**Histopathology of rheumatoid nodule**

The histological changes of RN are typically located in the subcutaneous fat; occasionally, it may extend upward into the deeper reticular dermis.[46] It exhibits a central area of necrosis surrounded by palisading epithelioid macrophages enclosed by granulation tissue containing lymphocytes and histiocytes, and occasionally, neutrophils, mast cells, and foreign body giant cells.[45,47]

**Differential diagnosis**

Histological picture of RN must be differentiated from subcutaneous GA, rheumatic fever nodule, and RA with palisading granuloma with neutrophilic infiltrate. Granulomatous inflammation with central necrobiosis is seen on both RN and subcutaneous GA but palisading mononuclear cells and perivascular inflammatory cells are seen more in RN than subcutaneous GA with positive mucin stains and less fibrin.[46,48]

**EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

EGPA, formerly known as CSS, is an eosinophil-rich, necrotizing granulomatous inflammation, often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small vessels and associated with asthma and eosinophilia.[49]

A diagnosis of EGPA is made in patients who have at least four of the following six objective features which are (1) asthma, (2) eosinophilia >10% on differential white blood cell count, (3) mononeuropathy (including multiplex) or polyneuropathy, (4) nonfixed pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) extravascular eosinophils.[50]

Although EGPA belongs to the spectrum of ANCA-AAVs, <50% of EPGA patients are ANCA positive, usually of ANCA-MPO type. Incidence of EPGA ranges from 0.5 to 2.7 cases per million. It is slightly more common in females; the median age at diagnosis was 50 years (range: 17–80 years).[51,52]

**Clinical presentation**

Clinically, EGPA develops into three sequential phases. First phase is characterized by allergic rhinitis, asthma, and sinusitis. Second phase is characterized by peripheral eosinophilia; eosinophilic organ infiltrates specially in lungs, heart, and GI. Third phase is the sequelae of systemic necrotizing vasculitis with granulomatous inflammation in different organs including the skin, renal, and peripheral nervous system.[53] Cutaneous manifestations include subcutaneous nodules, purpura [Figure 4], urticaria, livedo racemosa, retiform purpura, and papulonecrotic lesions.[53]

**Histopathology of eosinophilic granulomatosis with polyangiitis**

The typical histopathological changes include extravascular granulomas, small-to-medium-sized-vessel vasculitis, and tissue eosinophilia. Extravascular granulomas show a center of necrotic eosinophils surrounded by palisading lymphocytes and multinucleated giant cells.[54] Pronounced perivascular inflammatory infiltrates dominated by eosinophils but also macrophages and lymphocytes infiltrated in the arterioles, venules, and capillaries. A study of 37 biopsies of 29 patient’s biopsy show extravascular necrotizing granuloma and leukocytoclastic vasculitis as most common findings.[55] Well’s Syndrome could be the starting point of a pathogenic process that might evolve to CSS.[56]

**EOSINOPHILIC CELLULITIS**

Eosinophilic cellulitis also known as Well’s syndrome was first described by Wells et al. in 1971 in a report of four cases as recurrent granulomatous dermatitis with eosinophilia,
and it was renamed as eosinophilic cellulitis in 1979. It is seen in relatively young patients with mean age of onset, at 27.4 years (23–40). [37] Etiology of EC remains unknown, but various triggers such as insect bite, bacterial or viral infections, drug eruptions, hematological disorders, lymphoproliferative malignancies, and carcinoma may initiate the pathological process. [38]

**Clinical presentation**

Natural course of the disease can be divided into two stages: first stage clinically manifests as cellulitis/erysipelas such as redness and edema of extremities [Figure 5] but would not respond to antibiotics. There are also reports of papular and nodular presentations. [59] Second stage occurs over a period of 2–8 weeks. It is characterized by progressive involution of the lesions giving the appearance of morphea-like skin atrophy and hyperpigmentation.

**Histopathology**

Histological picture of Well’s syndrome has three stages. The first acute stage shows eosinophilic cellulitis with subepidermal edema and masses of eosinophils throughout the dermis, the second subacute stage of granulomatous dermatitis with typical “flame figures,” and the third final stage of resolution. [56] The flame figures consist of eosinophil granule major basic protein (MBP) encrusted on otherwise normal collagen. [56] IIF studies have shown that flame figures contain extracellular eosinophil granule MBP. [61]

**Differential diagnosis**

Similar features may be seen in arthropod bite reactions, spider bites, onchocerciasis, drug hypersensitivity reactions, diffuse erythema, tinea infection, atopic eczema, allergic contact dermatitis, urticarial vasculitis, eosinophilic pustular folliculitis, bullous pemphigoid, herpes gestationis, the hypereosinophilic syndrome, and cutaneous mastocytoma. [61]

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Nil.

**Figure 5:** Cellulitis or erysipelas such as redness, edema, and erythema on lower leg

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**Conflicts of interest**

There are no conflicts of interest.

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