Case 6.1
A 61-year-old Thai female from Nonthaburi

Chief complaint: Multiple erythematous non-scaly annular plaques on both elbows for 5 years

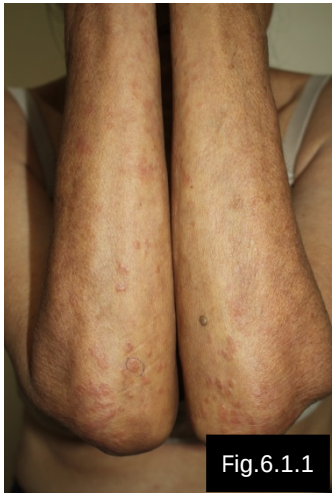
Fig.6.1.1

Present illness:
She presented with a 5-year history of recurrent non-pruritic erythematous rash on both elbows and extensor surface of upper extremities (Fig.6.1.1). She was diagnosed with chronic eczema and treated with topical corticosteroids. Lesions were partially subsided but somehow recurred on the original sites.

Past history: She has hypertension and dyslipidemia
Family history: Unremarkable

Physical examination: Systemic examinations otherwise normal

Dermatological examination:

Multiple discrete ill-defined, non-scaly, erythematous, annular and arcuate plaques on both elbows and extensor surface of both forearms.

Histopathology (S18-025101, forearm):
- Palisading granuloma composed of histiocytes and lymphocytes with central degenerative floating collagen and mucin deposition (Fig.6.1.2)

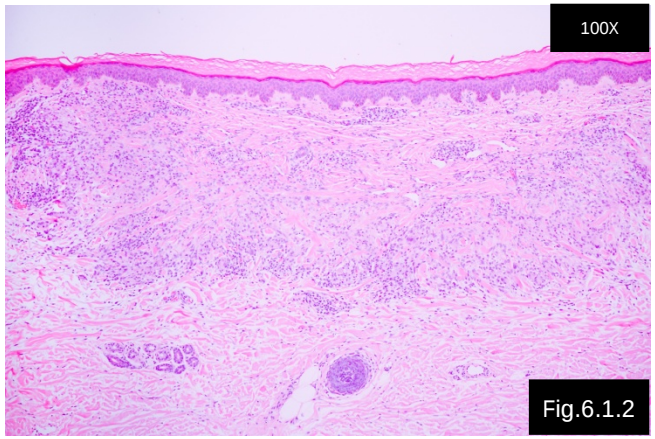

Fig.6.1.2

Laboratory investigations:
- CBC: Hb 12.4 g/dL, Hct 37.7%, Plt 292,000/mm^3
- WBC 5,090/mm^3 (N 63%, L28%, M 7%, E 2%, B 0%)
- AST/ALT: 16/15 U/L
- BUN/Cr: 13/0.56 mg/dl
- FBS: 81 mg/dl

Diagnosis: Classic granuloma annulare

Treatment:
- Hydroxychloroquine 200 mg po once daily
- 0.05% clobetasol propionate cream apply lesion twice daily

Case 6.2
A 49-year-old Thai female from Bangkok

Chief complaint: Erythematous annular plaque on left elbow for 2 years

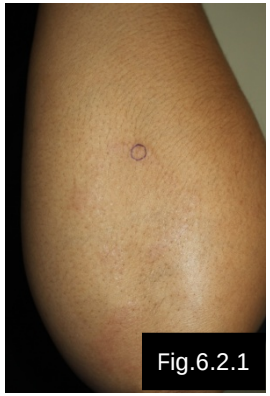
Fig.6.2.1

Present illness:
She presented with a 2-year history of pruritic, persistent, expanding erythematous annular plaques on left elbow (Fig.6.2.1). The original lesion was mild pruritic, small and confined to left elbow. She has been treated as chronic eczema and was prescribed topical corticosteroids. Topical treatment partially relieved her symptom but lesions were not completely subsided. During the past two years, lesions were more coalescing and expanding with worsening and intractable pruritus.

Past history: She had been diagnosed with invasive lobular carcinoma (T1N0M0) of the right breast since 2016 and underwent modified radical mastectomy. She has been treated with tamoxifen since 2017.

Family history: Unremarkable

Physical examination:
- Breast: Rt. MRM scar, Lt. – impalpable mass
- Abdomen: Soft. Not tender. Impalpable mass.
- Lymph nodes: Impalpable (supraclavicular, axillary, inguinal node)

Dermatological examination:
An erythematous to brownish non-scaly annular plaque on left elbow (Fig.6.2.1)

Histopathology (S19-019780, Lt. elbow):
- Superficial and deep perivascular lymphocytic infiltrate with interstitial lymphohistiocytic infiltration (Fig.6.2.2)
- Focal mucin deposition among interstitial infiltrate (Fig.6.2.3)

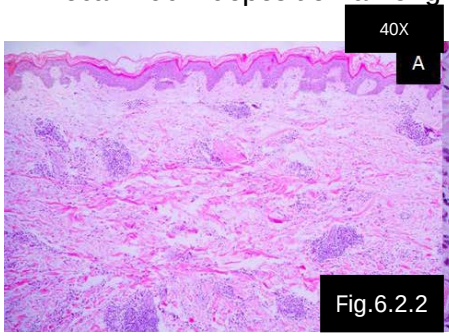

Fig.6.2.2

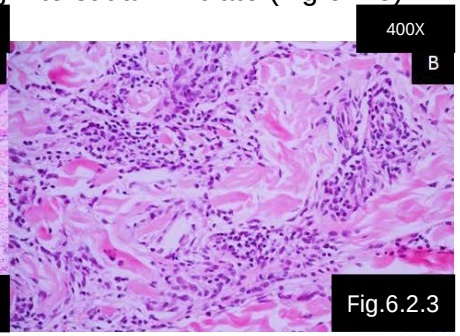

Fig.6.2.3

Laboratory investigations:
- CBC: Hb 12.1 g/dL, Hct 36.8%, Plt 196,000/mm^3
  WBC 6,100 /mm^3 (N 39%, L 59%, M 1%, E 1%)
- AST/ALT: 22/16 U/L
- TB/DB: 0.7/0.3 mg/dl
- Serum Cr: 0.60 mg/dl
- FBS: 93 mg/dl

Imaging:
- CXR: no active chest disease

Diagnosis: Interstitial granuloma annulare

Treatment:
- 0.1% betamethasone valerate cream apply lesion twice daily

Case 6.3
A 24-year-old Thai female from Bangkok

Chief complaint: Multiple erythematous oval plaques on both lower legs for 3 months

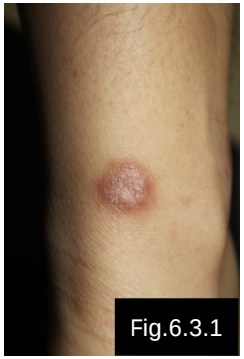
Fig.6.3.1

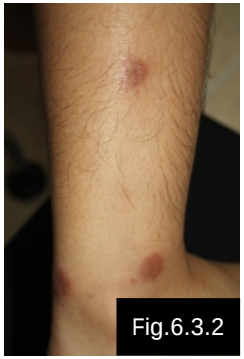
Fig.6.3.2

Present illness:
She presented with a 3-month history of multiple discrete well-defined erythematous round plaque on both anterior lower legs (Fig.6.3.1). She complains of intractable pruritus and progressive thickening of lesions over few months (Fig.6.3.2). She denied history of fever, anorexia or weight loss. No history of contact exposure or newly prescribing medications before the onset of lesions was noted.

Past history: She has been diagnosed with bipolar disorder, currently on quetiapine, trazodone, bupropion, flupentixol and melitracen.

Family history: Unremarkable

Physical examination: Otherwise normal

Dermatological examination:
Multiple discrete well-defined erythematous oval plaques with overlying scale-crust on top of some lesions on both anterior aspects of both lower legs.

Histopathology (S18-030339, Rt. leg):
- Superficial and deep perivascular, interstitial and nodular infiltrate of lymphocytes and histiocytes (Fig.6.3.3)
- Multinucleated giant cells in the deep dermis to subcutaneous tissue (Fig.6.3.4)

Special stain (S18-032255, Rt. leg):
- Mucin deposition highlighted by alcian blue pH 2.5 is noted in the deep dermis to subcutaneous tissue (Fig.6.3.5)

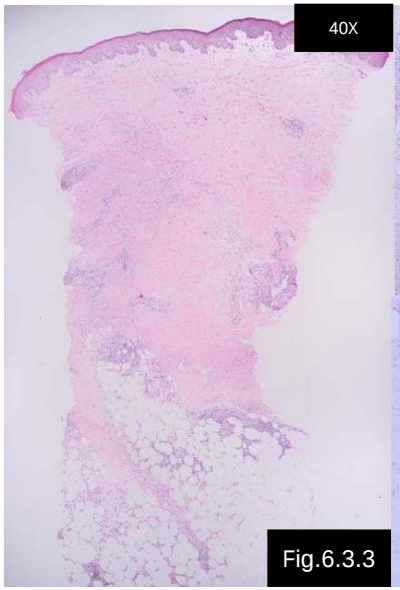

Fig.6.3.3

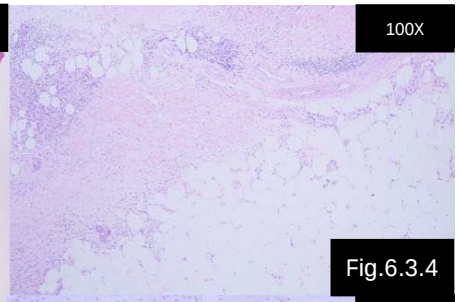

Fig.6.3.4

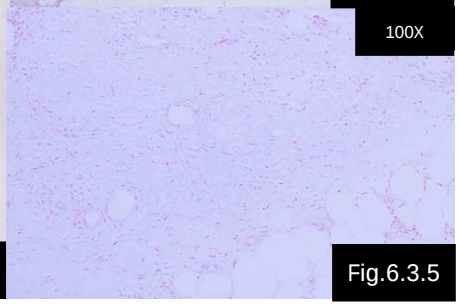

Fig.6.3.5

Laboratory investigations:
- CBC: Hb 13.4 g/dL, Hct 41.4%, Plt 291,000/mm^3, WBC 4,100/mm^3 (N 47.3%, L 36.9%, M 7.9%, E 6.6%, B 1.3%)
- Serum TSH 3.006 IU/mL, serum FT3 1.72 pg/mL, serum FT4 0.98 ng/dL
- BUN/Cr: 12/0.65 mg/dl

- Lithium level 1.11 mmol/L (0.5-1.02 mmol/L)

Diagnosis: Subcutaneous granuloma annulare

Treatment:
- 0.05% clobetasol propionate ointment apply lesion twice daily

Discussion

Granuloma annulare (GA) was first described by Thomas Colcott Fox in 1895 and Radcliffe-Croker in 1902. It can occur in all age groups but generalized form is more common in adult population especially the first 3 to 5 decades of life.[1] Subcutaneous and localized forms are more common in pediatric and young adult. Possible associated conditions including diabetes mellitus, dyslipidemia, thyroid disease, HIV, immune checkpoint inhibitors and other conditions.[2, 3] Recently, case-control study demonstrated that generalized GA can be associated with solid organ malignancy such as lung cancer.[4] Familial cases of GA have been reported with the association between generalized GA and HLA-Bw35.[5]

Multiple clinical variants of GA have been described. The common variants are localized GA (LGA), generalized GA (GGA) and subcutaneous GA (SGA). However, new and rare clinical variants have been described such as perforating, patch, palmoplantar GA and annular elastolytic giant cell granuloma (AEGCG).[1, 6] LGA is classified as localized annular erythematous non-scaly papules and plaques on distal extremities especially hands and feet. On the contrary, GGA is considered a widely distributed form with involvements of trunk and extremities. The clinical setting of GGA can be both coalescing erythematous annular papules and plaques or non-annular papules scattered on trunk. The deeper form, subcutaneous GA, occurs exclusively in pediatric population with painless subcutaneous nodules on extremities.[7] Perforating GA is less commonly diagnosed variant presents with umbilicated papules with central crusting. Disseminated perforating GA should raise clinical suspicion of acquired immunosuppression especially HIV infection. Patch or macular GA presents with large flat erythematous to brownish macules or patches on extremities more than trunk. Lastly, AEGCG is considered actinic form of GA variant that found on sun-exposed area, sometimes called actinic granuloma. Palmoplantar GA is another rare form manifested with painful acral papules on the palms.[6]

Characteristic histological examination of GA includes granulomatous inflammation with abundant mucin deposition that can be found in either palisading or interstitial patterns. Palisading pattern composes of palisading histiocytes and lymphocytes surrounding central necrobiotic collagen in upper dermis. Meanwhile, histiocytes infiltrates between collagen bundles and blood vessels in interstitial pattern. Both patterns can be found in both LGA and GGA. However, SGA demonstrates deeper collection of granuloma in both palisading and interstitial pattern and more eosinophilic infiltration comparing to the latter variants.[8] Perforating GA reported to have transepidermal elimination of collagen with palisading granulomatous pattern. Patch GA histology is compatible with interstitial pattern.[9] The histological differential diagnoses of GA include palisaded neutrophilic and granulomatous dermatitis (PNGD) and interstitial granulomatous dermatitis (IGD). PNGD differs by lack of mucin deposition and abundant neutrophilic infiltration with or without vasculitis. Meanwhile, IGD demonstrates focal interstitial histiocytic infiltration surrounding deformed collagen in a typical “rosette” pattern with minimal mucin deposition.[7, 10]

Localized form of GA is a self-limiting and do not require aggressive treatment. Topical or intralesional corticosteroids can be used for cosmetic concern. Topical immunomodulators such as tacrolimus or pimecrolimus can be used as well. However, generalized GA usually requires systemic medication or physical modalities. Reported literatures regarding the use of systemic medication include antimalarials, antibiotics or systemic corticosteroids.[11, 12] Since GGA is considered chronic form, the use of longterm systemic corticosteroids is inappropriate. Systemic doxycycline, pentoxifylline, dapsone or combination of rifampin, ofloxacin and minocycline can be used.[13] Biologic therapy can be used in refractory GA such as TNF-a inhibitors or JAK inhibitors.[14]

Physical modalities for GGA include phototherapy and lasers such as pulsed dye laser, CO2 laser, fractional laser and excimer laser.[1, 15]
We demonstrated cases with different types of GA including classic, interstitial and subcutaneous types. First two cases showed typical presentation of localized GA that manifests as firm erythematous annular plaques on extremities in middle age patients. Meanwhile, the latter case differs in terms of location of lesions that located on lower extremities with histology of subcutaneous pattern. The age of onset in the last patient was younger comparing to classic GA cases which compatible with the epidemiology of subcutaneous GA that favors younger age of onset. Our cases revealed no disease association. We prescribed very high to high potent topical corticosteroids for our patients and additionally used hydroxychloroquine for the first case. Treatment responses were satisfying and lesions were subsided with minimal residual hyperpigmentation.

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