Case Report

Generalized Granuloma Annulare Presenting with Lesions Resembling Eruptive Xanthoma

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Generalized granuloma annulare (GGA) and eruptive xanthoma are dermatological diseases that occasionally share some clinical and histological similarities. Associated underlying medical conditions and clinical course are essential guides to the proper diagnosis. The authors reported a case of disseminated yellowish-red papules in a 24-year-old female with high levels of serum fasting blood sugar, triglycerides, and cholesterol. The provisional diagnosis was eruptive xanthoma but histopathology and immunoperoxidase study revealed granuloma annulare. The remission of the skin lesions soon after control of dyslipidemia and diabetes mellitus is not typical for the usual GGA, which has a chronic relapsing course and a poor response to treatment. Further studies are required to differentiate these two entities when they come into the clinicopathological mimicry.

Keywords: *Granuloma annulare, Eruptive xanthoma*

J Med Assoc Thai 2013; 96 (1): 117-20
Full text. e-Journal: *http://jmat.mat.or.th*

Granuloma annulare (GA) is a relatively common dermatosis of unknown etiology with self-limited clinical course. Generalized granuloma annulare (GGA) is an uncommon subtype of GA which occurs in 15% of GA patients. It is characterized by numerous small skin-colored to pink papules in a symmetric distribution on the trunk and extremities with typical annular distribution[1]. There have been reports of a higher frequency of diabetes and serum lipid abnormalities as compared to the other forms of GA[2-5]. Eruptive xanthoma (EX) is a type of dermatosis due to excessive lipid deposits in the skin, which is characterized by small yellowish cutaneous papules with an erythematous halo. The lesions tend to arise abruptly in crops on the extensor surface of arms, legs, and buttocks, and can be generalized distribution[6]. EX has been known to associate with either familial hypertriglyceridemia or secondary hypertriglyceridemia as well as diabetes mellitus, alcohol ingestion, obesity, chronic renal failure, nephrotic syndrome, pancreatitis, hypothyroidism, biliary cirrhosis and medications (estrogens, corticosteroids, miconazole, isotretinoin, and etretinate)[7]. Histopathological study should lead to the definite diagnosis of these two conditions, however; there have been a few previous reports of eruptive xanthoma with granuloma annulare-like microscopic appearance[8,9]. The authors described a case of GGA proved by histopathological finding with the clinical features that mimic EX.

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Case Report

A 24-year-old Thai female, with no previous medical history, presented with a sudden onset of multiple asymptomatic yellowish red papules on the extremities for five days. Her father had a history of well-controlled dyslipidemia and diabetes mellitus (DM). The patient was initially treated with potent topical corticosteroids, with no improvement. Dermatological examination revealed bilateral discrete yellowish-red papules on the dorsum of both hands and around the elbows and knees with a few lesions showing central umbilications (Fig. 1A, B). The papules were scattered without annular distribution. The eruption was not found on the trunk, the head and neck region, or the mucous membrane. The clinical differential diagnoses included eruptive xanthoma, granuloma annulare, papulonecrotic tuberculid, and insect bite reaction. Laboratory investigations showed serum fasting blood sugar of 381 mg/dl, serum triglycerides of 1,883 mg/dl, and total serum

cholesterol of 348 mg/dl. Urine sugar was positive and the amylase level was not elevated. Complete blood count and chest X-ray were normal. The renal and liver functions were also unremarkable.

A punch biopsy was obtained from a papule on the right elbow for histopathological examination. The specimen showed normal epidermis and stratum corneum. The underlying dermis appeared hypercellular with interstitial infiltration composedly of histiocytes and lymphocytes in the superficial reticular dermis forming vague palisaded granuloma. The histiocytic infiltration showed bland-looking appearance without any foamy cytoplasm. Multinucleated giant cells, well-formed granulomas, and necrobiosis as well as eosinophils were absent. Alcian-blue pH 2.5 highlighted increased mucin in the central area of the granuloma and the infiltrating histiocytes stained positive for CD68 (Fig. 2A-D). Therefore, a diagnosis of GGA was made.

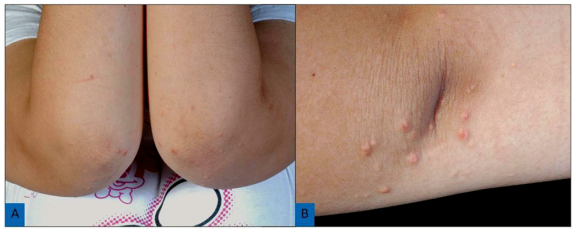

Fig. 1 A) Multiple painless yellowish red papules around the elbows. B) Few umbilicated papular lesions in a close-up view.

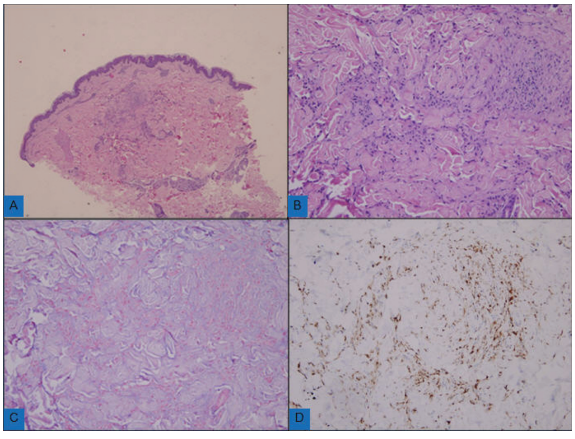

Fig. 2 A) Nodular infiltration in superficial dermis (H&E staining, 40x). B) Histiocytic infiltration is noted between collagen bundles forming interstitial pattern with vague palisaded granuloma formation (H&E staining, 200x). C) Alcian-blue pH2.5 highlighted increased mucin in the center of the granuloma. D) Positivity of the bland histiocytes for CD68.

The patient was referred to the endocrinologist for the management of dyslipidemia and type 2 DM. Her fasting serum lipid and glycemic level improved dramatically and returned towards near-normal levels after the combination therapy of dietary control, gemfibrozil, and metformin. All skin eruption subsided within a few months of treatment. During the follow-up period of 18 months, there were no recurrent lesions afterwards.

Discussion

GA is a chronic, benign inflammatory skin disease of unknown etiology and its pathogenesis has not been well-established. GA classically presents as arciform to annular skin-colored plaques that are commonly located on the extremities of young people. As a clinical subtype of GA, GGA has been reported to have numerous discrete papules and plaques in a symmetric distribution on the trunk and extremities with typical annular distribution[1,10]. GGA can be differentiated from the classical GA by a later age of onset, a wide distribution of lesions, a chronic course with a low tendency to spontaneous resolution and a poor therapeutic response. GGA has been reported to have a higher frequency of diabetes and serum lipid abnormalities as compared to the other forms of GA[2-4]. Clinical associations between GGA and malignancies, thyroid diseases, hepatitis C virus, HIV infection and other viral infections have also been reported, but a causative relationship has not been formally established[2,3,5].

Clinically, GGA has been previously reported as predominantly annular lesions in 67% of cases and nonannular lesions in 33% with no significant difference in age at onset of patients with annular and those with non-annular lesions. The eruption typically consisted of symmetrically scattered papules favoring the area of arms, chest, thighs, and abdomen[2,5]. Our patient presented with disseminated yellowish-red papules over both arms without annular lesions and no truncal involvement which is rarely reported[11,13]. Association of GGA with DM and dyslipidemia has been observed in a small number of clinical studies and case reports[2,11,12,14]. Therefore, in our patient, the combination of the yellowish-red papular eruption with high serum blood sugar and serum lipid levels could mislead to the diagnosis of eruptive xanthoma, which is more correlated with the diabetic lipemia[15-17].

Pathologically, GGA with predominantly non-annular lesions shows an interstitial infiltrate of histiocytes and a sparse perivascular infiltrate of lymphocytes with or without palisading pattern and rarely presence of collagen degeneration and mucin deposits[2,5,12-14]. According to the previous literature[8,9], GA has been reported to have some histopathologic similarities with EX in superficial dermal location, interstitial and perivascular infiltrate of lymphohistiocytes, deposits of mucin, and disruption of reticular dermis that are all documented in our case. However, there are some features of epithelioid histiocytes without foamy cytoplasm, positive mucin staining in the center of the infiltrate and no extracellular lipid deposit, which help to distinguish the presented case from EX.

Although clinical-dermatological response to the treatment of underlying medical condition would be unlikely if the patient had GGA since it has been known to have a longstanding course with a poor therapeutic response. The rapid resolution of the skin lesions in the presented case might be considered coincidental in GA, which spontaneous resolution is well recognized[18], or an improvement influenced by the treatment.

In summary, the authors reported a case of GGA in a diabetic patient with dyslipidemia that demonstrated clinicopathological similarities with EX. Therefore, high index of suspicion are required for both clinicians and pathologists to be aware of the mimicry of these two conditions.

Potential conflicts of interest

None.

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รายงานผู้ป่วย generalized granuloma annulare ที่มีลักษณะผื่นผิวหนังคล้าย eruptive xanthoma

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Generalized granuloma annulare (GGA) และ eruptive xanthoma (EX) เป็นภาวะทางผิวหนังที่อาจตรวจพบอาการแสดงทางผิวหนังและพยาธิสภาพของผื่นที่คล้ายคลึงกันได้ ดังนั้นจึงมีความจำเป็นต้องอาศัยประวัติโรคประจำตัวของผู้ป่วยที่มีความสัมพันธ์กับภาวะดังกล่าวข้างต้นร่วมกับการดำเนินโรคที่มีความจำเพาะแตกต่างกันของโรคทั้งสองชนิดเพื่อนำไปสู่การวินิจฉัยที่แม่นยำและถูกต้องยิ่งขึ้น คณะผู้นิพนธ์ได้รายงานผู้ป่วยหญิงไทยอายุ 24 ปี ที่มีผื่นที่ผิวหนังเป็นตุ่มสีเหลืองแดงจำนวนหลายตุ่มกระจายอยู่บริเวณแขนทั้งสองข้าง ร่วมกับการตรวจพบภาวะน้ำตาลในเลือดและระดับไขมันชนิดคลอเรสเตอรอลและไตรกลีเซอไรด์สูงเกินเกณฑ์ปกติ โดยผู้ป่วยได้รับการวินิจฉัยเบื้องต้นเป็น EX แต่ผลการตรวจทางพยาธิวิทยาของชิ้นเนื้อจากรอยโรคร่วมกับการย้อมพิเศษเข้าได้กับ granuloma annulare จึงนำไปสู่การวินิจฉัยโรค GGA สำหรับผู้ป่วยรายนี้ผื่นยุบลงในระยะเวลาอันสั้นตามหลังการรักษาโรคเบาหวาน และภาวะไขมันในเลือดสูงพบได้ไม่บ่อยนักสำหรับ GGA ที่โดยทั่วไปมักจะมีการดำเนินโรคที่ยาวนานและไม่ค่อยตอบสนองต่อการรักษา ดังนั้นในอนาคตจึงควรมีการศึกษาเพิ่มเติมเกี่ยวกับอาการแสดง การดำเนินโรค รวมทั้งการตรวจพบทางพยาธิวิทยาเพื่อเป็นแนวทางในการวินิจฉัยแยกภาวะทั้งสองออกจากกัน
