Clear cell acanthoma (CCA)-like lesions of the nipple/areola: A clinicopathological study of 12 cases supporting a nonneoplastic eczematous disease

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Background: Clear cell acanthoma (CCA) of the nipple/areola has been reported. The CCA-like histology more likely represents a feature of eczematous dermatitis of the nipple/areola.

Objective: We reviewed cases of CCA-like lesions of the nipple/areola and compared them with classic CCA to clarify their relationship.

Methods: The clinicopathological features of 12 cases of CCA-like lesions of the nipple/areola were compared with classic CCA. The literature on this condition was reviewed, and the results of various treatments were analyzed.

Results: CCA-like lesions of the nipple/areola were clinically different from those of classic CCA. Although they shared the glycogen-rich clear epidermal cells with neutrophilic exocytosis, dermal eosinophils appeared to be a distinctive feature. The anatomic site and association with atopic dermatitis suggested that CCA-like lesions of nipple/areola might represent a manifestation of atopic eczema involving nipple/areola. Topical steroids could be effective.

Limitations: This was a retrospective study with limited cases.

Conclusions: Although CCA-like lesions of the nipple/areola shared histopathological features with classic CCA, their clinical changes were consistent with dermatitis. We propose to name this condition CCA-like eczematous dermatitis of the nipple/areola. (J Am Acad Dermatol 2019;80:749-55.)

Key words: areola; breast; clear cell acanthoma; dermoscope; eczema; nipple.

Clear cell acanthoma (CCA) was originally reported by Degos and Civatte[1] as a benign epidermal tumor characterized by glycogen-rich clear cells with neutrophilic exocytosis. The tumor usually presents as an erythematous nodule with a moist surface and is surrounded by a collarette of scales occurring in late middle-aged individuals. The lesions have a predilection for legs. Kim et al[2] first described a case of CCA presenting as nipple eczema in 1999. Thereafter, 6 similar cases were reported.[3-5] Although those cases shared a histologic appearance with CCA, their clinical manifestations were different. The nonneoplastic inflammatory nature of those lesions has been raised.[4,5] We studied

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and analyzed our collected similar cases and compared them with the cases reported in the literature as CCA of the nipple/areola to establish that they were nonneoplastic inflammatory diseases.

METHODS

The clinicopathological features of 12 cases of CCA-like lesions of the nipple/areola that were collected from May 2005 to February 2015 at Chang Gung Memorial Hospital in Taiwan were studied. Those cases were retrieved from our institutional files under the diagnosis of CCA or CCA-like dermatitis of the nipple/areola. Dermoscopic examinations were performed on 3 cases. In addition to hematoxylin and eosin–stained slides, periodic acid–Schiff stain with and without diastase digestion was performed on all cases to detect any cytoplasmic glycogen in the lesional clear epidermal cells. All previously reported cases were reviewed and compared with our cases.

CAPSULE SUMMARY

- Clear cell acanthoma–like lesions of the nipple/areola have been reported without clarification of their nature and treatment modality.
- The clinical appearance along with tissue eosinophilia and steroid responsiveness supported that they were not true clear cell acanthoma.
- The histologic appearance could be a pitfall for dermatopathologists unaware of this condition.

RESULTS

The clinical features of 12 cases are summarized in Table I. Ten patients were female, and 2 were male. Their ages ranged from 13 to 69 years, with a median age of 19 years. The disease duration ranged from 1 to 24 months, with a median duration of 4 months. Six patients had bilateral involvements of the nipple/areola (Fig 1, *A*). One patient had involvement of only the right nipple/areola (Fig 1, *B* and *C*). The other 5 patients only had unilateral involvement of the areola. Clinically, the involved nipple and/or areola showed erythematous, brown, or pigmented plaques with or without an

Table I. Features of patients with clear cell acanthoma–like lesions of the nipple/areola

Patient	Age, y/sex	Location	Duration	Atopic dermatitis	Histopathology: Eosinophilic exocytosis	Histopathology: Dermal eosinophils	Treatment	Follow-up duration	Outcome
1	17/M	Bilateral mainly areola	2 y	–	Absent	Moderate	(1) 0.1% Mometasone cream; (2) cryotherapy; (3) Er:YAG laser; (4) ILSI	4 y 5 mo	Little improvement to treatment, spontaneous resolution 6 mo later
2	17/F	Bilateral diffuse nipple and areola	3 mo	+	Focal	Brisk	0.1% Mometasone furoate cream	6 y	Good response, complete remission
3	13/F	Bilateral mainly areola	2 y	+	Focal	Moderate	0.1% Mometasone furoate cream	8 y 5 mo	Good response, complete remission
4	20/F	Bilateral mainly areola	1 mo	–	Absent	Brisk	(1) 0.1% Betamethasone valerate cream; (2) 0.05% fluocinonide cream	10 mo	Good response, but recurred if treatment stopped
5	15/F	Right diffuse nipple and areola	5 mo	–	Prominent	Brisk	(1) 0.1% Betamethasone valerate cream; (2) ILSI	10 mo	Good response, no recurrence
6	19/F	Right mainly areola	1 y	+	Absent	Mild	0.1% Betamethasone valerate ointment	5 mo	Good response, but recurred if treatment stopped
7	28/F	Left mainly areola	2 y	–	Absent	Mild	0.1% Betamethasone valerate cream	3 mo	Moderate improvement
8	20/F	Bilateral diffuse nipple and areola	1 y	–	Absent	Mild	Betamethasone + gentamicin cream	1 mo	Moderate improvement
9	35/F	Right mainly areola	1 mo	–	Focal	Brisk	–	2 wk	?
10	47/F	Left mainly areola	2 mo	–	Focal	Moderate	–	2 wk	?
11	19/M	Bilateral diffuse nipple and areola	3 mo	–	Absent	Brisk	Clobetasol propionate ointment	2 wk	Moderate improvement
12	69/F	Right mainly areola	1 mo	–	Prominent	Brisk	Betamethasone + gentamicin 0.1% cream	3 mo	?

All patients were from Taiwan and all lesions were pruritic.
Er:YAG, Erbium:yttrium-aluminium-garnet; *F*, female; *ILSI*, intralesional steroid injection; *M*, male; ?, unknown.

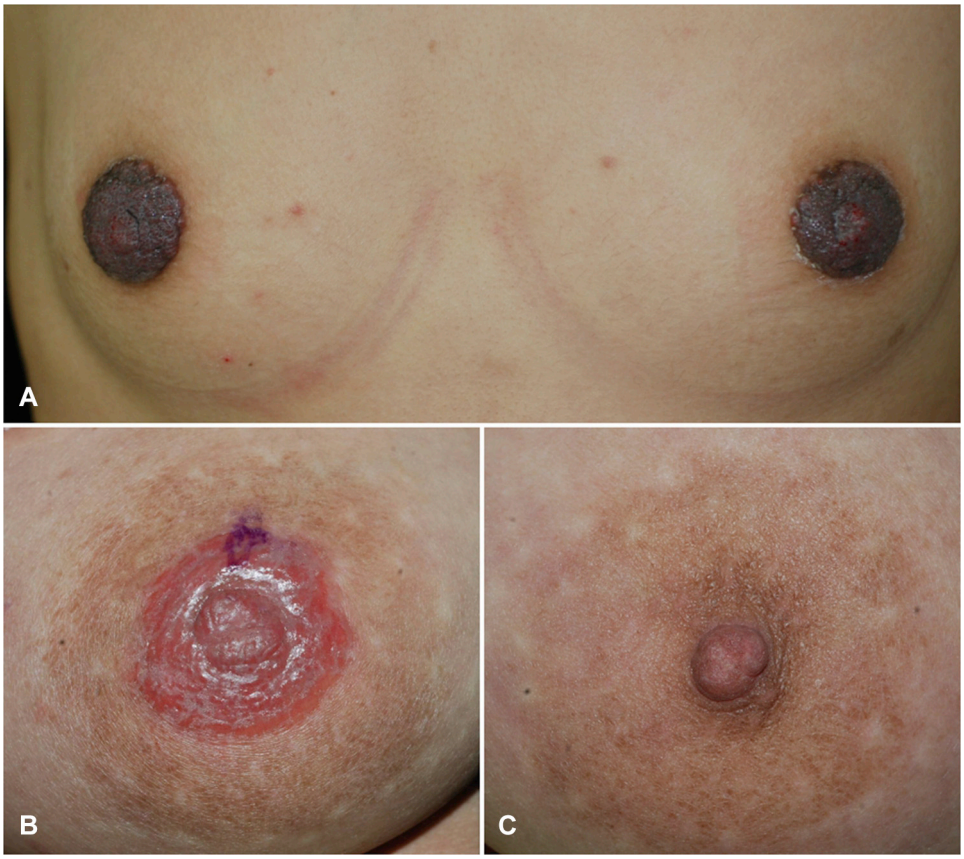

Fig 1. Clear cell acanthoma–like lesions of the nipple/areola. **A**, Bilateral involvement of the nipple and areola (case 2). **B**, Unilateral involvement of the right nipple and areola (case 5). **C**, The uninvolved left nipple and areola (case 5).

oozing surface (Fig 2). Three patients had a history of atopic dermatitis. Topical steroid preparations of various potencies were applied and 5 patients showed remarkable improvements with decreased discharge and pruritus. Three patients had a moderate response. Two patients experienced recurrence after cessation of the treatment. Three patients were lost to follow-up. The dermoscopic findings performed on 3 cases were different from what have been described for CCA.[6] Our cases showed evenly distributed dotted or glomeruloid vessels without linear or reticular arrays observed in CCA (Fig 3). All biopsy specimens showed CCA-like changes (Fig 4) with abundant cytoplasmic glycogen, as demonstrated by a periodic acid–Schiff stain with and without diastase digestion (Fig 5). Except for 2 cases, neutrophilic exocytosis was observed (Fig 6, *A*). A variable number of eosinophils was observed in the dermis in all cases (Fig 6, *C*, and Table I), and 6 cases also showed exocytosis of eosinophils (Fig 6, *B*, and Table I). Biopsy specimens were taken from lesional skin. The boundary between the lesions and the adjacent noninvolved skin was not available for examination.

DISCUSSION

Seven previously reported cases of CCA of the nipple/areola are summarized in Table II, and they were compared to the 12 current cases in Table III. Except for an Italian man[4] and 2 Brazilian women,[5] all of the other subjects were Asian. This condition appears to be more prevalent in Asia. Some patients were noted to have atopic dermatitis, which might be contributory to a higher prevalence of the CCA-like lesions of the nipple/areola for Asians,[7] as atopic dermatitis incidence is lower in Western countries.[7] This disease was mainly observed in younger female individuals; however, it was also observed in male patients. The lesions occurred on the areola with frequent simultaneous involvement of the nipple. One Korean case had only nipple disease, and another Korean case had involvement of only the areola. Half of the current cases had bilateral involvement of the nipple and areola, whereas all

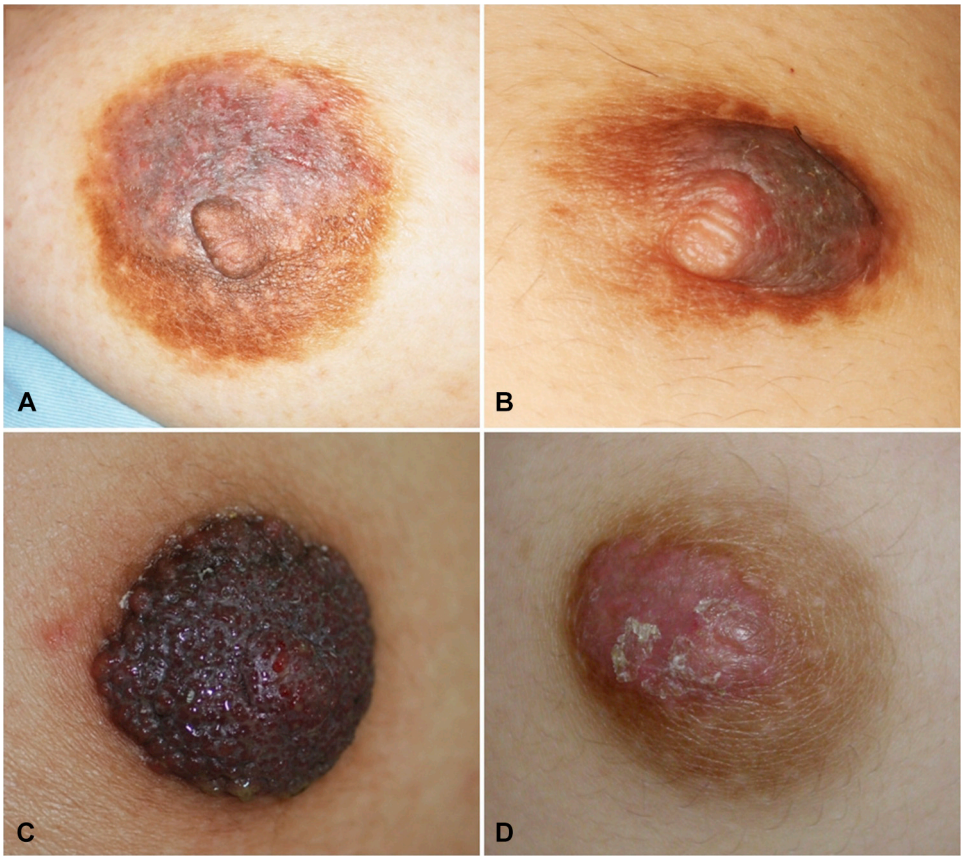

Fig 2. Clear cell acanthoma–like lesions of the nipple/areola. The clinical appearances of the involvement of the areola (**A** and **B**) and involvement of both the nipple and areola (**C** and **D**). The lesions were erythematous, brown, or darkly pigmented mulberry-like plaques with a slightly scaly and moist surface.

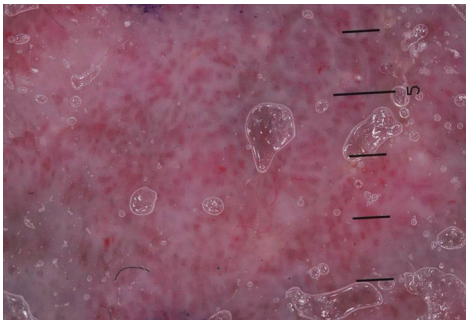

Fig 3. Clear cell acanthoma (CCA)-like lesions of the nipple/areola. Dermoscopic examination of the case 5 lesion showed evenly distributed dotlike vessels, which were different from the reticular and linear patterns observed in CCA.

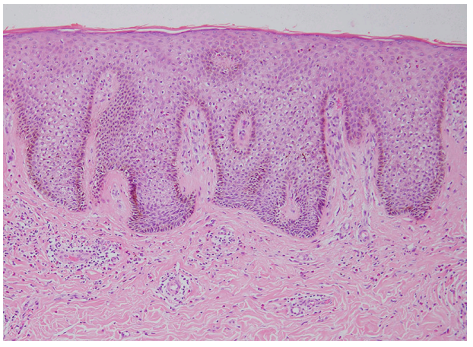

Fig 4. Clear cell acanthoma–like lesions of the nipple/areola. Photomicrograph of the case 6 areolar lesion showed marked acanthosis composed of clear epidermal cells with exocytosis and perivascular lymphocytic infiltrates with many scattered eosinophils in the dermis.

previously reported cases had only unilateral disease. All of the patients except 1 previously reported case presented with pruritus. Clinically, the lesions were eczematous in appearance and were only found to show CCA-like changes with glycogen-rich clear cells and neutrophilic exocytosis upon histopathological study. Veiga et al[5] noted dermal eosinophilic infiltration in both of their cases. We

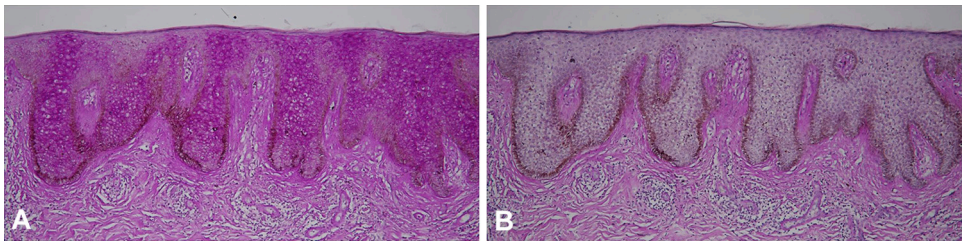

Fig 5. Clear cell acanthoma–like lesions of the nipple/areola. The clear epidermal cells contained abundant cytoplasmic glycogen, as detected by a periodic acid–Schiff stain without (**A**) and with (**B**) diastase digestion.

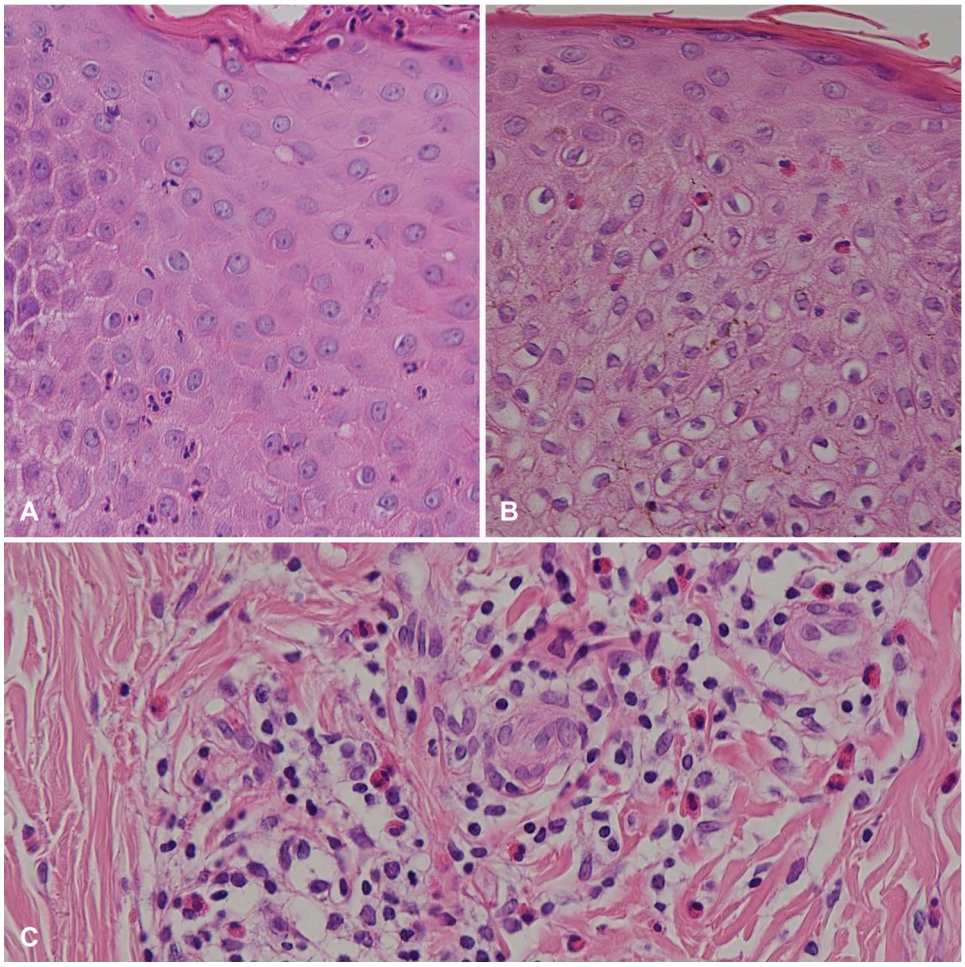

Fig 6. Clear cell acanthoma–like lesions of the nipple/areola. Higher magnification showed neutrophilic exocytosis (**A**), eosinophilic exocytosis (**B**), and perivascular lymphocytic infiltrates with many eosinophils in the dermis (**C**).

found eosinophils as a prominent component of the dermal inflammatory infiltrate in all current cases and eosinophilic exocytosis in half of them. Eosinophils are not a typically found in the dermal inflammatory infiltrate in CCA, except in 1 of the 37 CCA cases that was reported by Brownstein et al.[8] Peters et al[9] described eosinophilic exocytosis in 78% of their areola specimens with spongiotic dermatitis and speculated that the structural difference of the nipple and areola could be the factor to induce eosinophilic infiltration in cellular immune response, which might explain the predominant eosinophilic infiltration of CCA-like lesions of the nipple/areola observed. The clinical appearance,

Table II. Reported cases of clear cell acanthoma of the nipple/areola

Patient	Age, y/sex	Race	Location	Duration	Atopic dermatitis	Inflammatory infiltrate	Treatment	Outcome	References
1	23/F	Korean	Left nipple*	3 mo	+	Not reported	Systemic and topical steroid for 2 wk	No improvement	2
2	37/F	Korean	Right nipple/areola	1 y	−	Not reported	Cryotherapy	−	3
3	13/F	Korean	Left nipple/areola	2-3 mo	+	Neutrophilic exocytosis	Cryotherapy	−	3
4	14/F	Korean	Right areola	8 mo	−	Not reported	Excision	−	3
5	26/M	Italian	Nipple/areola	4 mo	+	Neutrophilic exocytosis and dermal lymphohistiocytic infiltrate	Topical steroids	Minimal improvement	4
6	25/F	Brazilian	Left nipple/areola	1 y	−	Eosinophilic exocytosis	2% Boric acid wet dressings, oral nimesulide, oral and topical antibiotics, topical steroids, and tacrolimus ointment	Not effective	5
7	18/F	Brazilian	Left nipple/areola	4 mo	−	Neutrophilic exocytosis and dermal eosinophilic infiltrate	0.05% Clobetasol cream	Cleared within weeks	5

F, Female; *M*, male.
*Clinical picture also shows prominent areolar involvement.

Table III. Comparison with previously reported cases

	Reported cases (n = 7)	Current series (n = 12)
Female/male ratio	6:1 (1/7)	5:1 (2/12)
Mean age at diagnosis	22.2 y	18.4 y
Pruritic symptom	85.7% (6/7)	100% (12/12)
Bilateral involvement	0% (0/7)	50.0% (6/12)
Atopic dermatitis	42.8% (3/7)	25.0% (3/12)

frequent association with atopic dermatitis, presence of eosinophils in the lesions, and response to steroid treatment in some cases all favored a nonneoplastic eczematous disease, which was further supported by different dermoscopic findings.[6] A polypoid CCA on the right nipple that was reported by Park et al[7] appeared to be different, which could be a real CCA occurring on the nipple. It is not clear why eczematous disease of the nipple/areola would cause histopathological CCA-like changes.

CCA was originally regarded as a benign epidermal epithelial neoplasm.[1,8] However, the neoplastic nature has been challenged by the observation of CCA-like changes occurring in psoriasis,[10] in skin grafts,[11] and incidentally in seborrheic keratosis.[12] The evidence thus suggests that the observed CCA-like changes were a nonneoplastic inflammatory reaction. Our observations of the CCA-like changes that occurred on the nipple/areola also support the connotation of a nonneoplastic inflammatory disease. We propose to call this condition CCA-like eczematous dermatitis of the nipple/areola. The causes of the CCA-like changes that occur in eczema of the nipple and areola remain to be investigated. It is important for dermatopathologists to be aware of this entity to avoid unnecessary surgical procedures.

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