A Case Report of Clear Cell Papulosis and a Review of the Literature

Dear Editor,

Clear cell papulosis (CCP) is a rare dermatosis seen predominantly in infants of Asian background. It presents with hypopigmented and minimally palpable, flat-topped papules, sited over the lower abdominal or pubic regions, or along the milk lines.

We present a series of 3 local patients with CCP, highlighting their clinicopathologic characteristics and review the existing literature of published cases. Two cases of this series have been previously published.[1,2]

Case 1

A healthy 16-month-old Chinese female presented in 2003 with 2 hypopigmented macules and 1 flat-topped papule in the pubic region, ranging from 3 mm to 9 mm in diameter. These were not preceded by trauma or inflammation. The lesions were asymptomatic. The rest of her skin examination was normal. There was no family history of similar lesions.

Histopathologic examination showed proliferation of clear cells, with round to oval nuclei and abundant cytoplasm, arranged either in clusters or singly along the basal and suprabasal epidermis. There was also mild epidermal acanthosis, and reduced melanin pigmentation.

The cytoplasm of these cells stained positively with mucicarmine, periodic-acid Schiff (PAS) and alcian blue. Immunohistochemical profile of these cells was: +CEA, +EMA, +AE1/3, +CK7, +CAM5.2, –GCDFP, –CK20, –S100.

At 1-year follow-up, the patient's lesions remained unchanged.

Case 2

An 18-month-old Chinese male presented in 2005 with multiple asymptomatic, slightly elevated and hypopigmented papules for 3 months. These were seen at the lateral aspects of his lower abdomen and groin. There were also lesions on an area adjacent to the right nipple. Individual lesions were 1 mm to 3 mm in size. There was no family history of similar lesions.

Histopathologic findings were consistent with clear cell papulosis, showing round to oval clear cells with abundant clear cytoplasm located in clusters or singly amongst basal keratinocytes. These cells were larger than adjacent keratinocytes and stained positively with PAS. Immunohistochemistry was positive for CEA and AE1, but negative for S100.

The patient defaulted on follow-up.

Case 3

A 3-year-old Chinese male presented in 2015 with asymptomatic, hypopigmented macules since 7 months' age. They first appeared on his penile shaft and progressively spread to the suprapubis (Fig. 1), abdomen and axilla. There was no family history of similar lesions.

Histopathologic findings confirmed CCP, with increased numbers of large clear cells in the basal epidermis. These cells had larger, more vesicular nuclei and abundant clear cytoplasm (Fig. 2) which stained positively for PAS. Staining with CK7 was positive, highlighting similar cells in the suprabasal epidermis and "tadpole-tail" like projections of some cells (Fig. 3).

The lesions remained unchanged over a 3-month period of follow-up and the patient will continue to be seen annually.

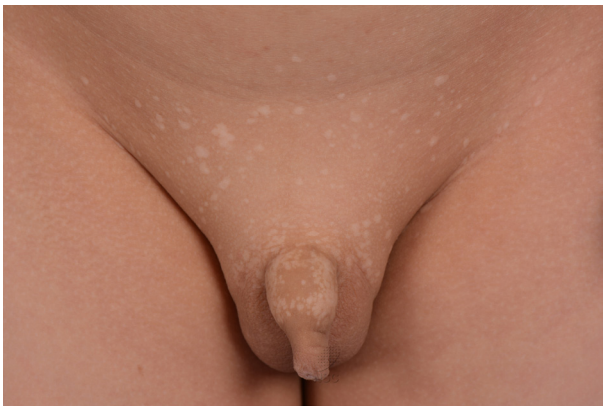

Fig. 1. Hypopigmented macules and barely palpable papules over the penile shaft and suprapubis.

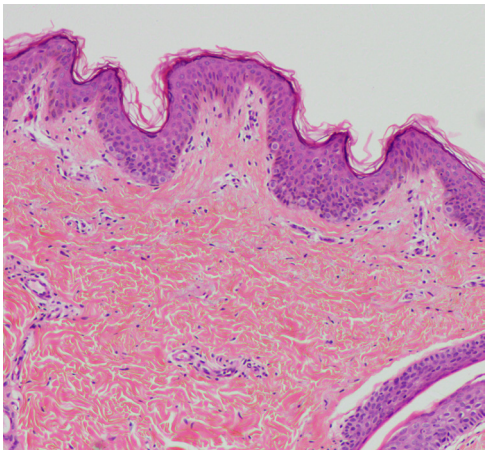

Fig. 2. Proliferation of clear cells in the basal epidermis, larger than adjacent keratinocytes (H&E, 100x).

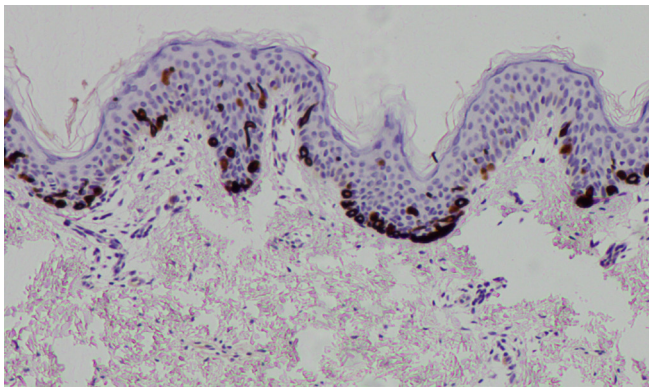

Fig. 3. Positive staining with CK7. Scattered clear cells in the suprabasal epidermis are more evidently seen. A "tadpole tail"-like projection is present in some cells (100x).

Discussion

Kuo et al first described CCP in 2 Taiwanese brothers in 1987.[3] To date, only 35 cases have been reported in the literature. We describe our 3 local cases (2 were previously published) and compare their clinical and histopathologic features (Table 1).

All 3 cases presented with typical hypopigmented, barely palpable papules and macules in the characteristic anatomical distribution of the pubic, inguinal or lower abdominal regions. The lesions were asymptomatic and non-progressive. Demographically, all patients were of Chinese ethnicity and the onset was in infancy. Family history was non-contributory in all cases. Histopathologic features were consistent in all 3 cases, showing characteristic larger cells with abundant clear cytoplasm in the basal epidermis. These clear cells stained positively for mucin, as well as CK7, CEA and AE1/3. S100 immunohistochemistry was negative in all cases.

Our 3 cases are similar to other reports (Table 2) in terms of clinical, demographic and histopathologic features. Individual lesions are small and there have been no reports of lesions greater than 1 cm; the number of lesions can vary from 3 to over 100. Lesions have a predilection for the abdomen, particularly the lower half (81%, 29/36 cases) and the pubic area (56%, 20/36 cases). Other common sites include the chest (42%, 15/36 cases) and axilla (33%, 12/36 cases). Lesions have been observed to follow the milk line.[4] The back, buttocks and extremities are seldom involved.[5,6]

Epidemiologically, only 6 out of 36 cases were of non-Asian ethnicity. The overall mean age of onset is 13.9 months (range, 0 to 71 months); however, 1 case of CCP occurring in adulthood has been reported.[7] Although some authors have postulated a possible autosomal recessive mode of inheritance,[5] contributory family history is only observed in a quarter of patients (9/36 cases).

The distinctive clinical characteristics of CCP enable it to be distinguished from other paediatric hypopigmented dermatoses. Differential diagnoses with potential therapeutic or prognostic differences include plane warts, tinea versicolor-like lesions of epidermodysplasia verruciformis, guttate morphoea and lichen sclerosus.

Histopathological findings can readily differentiate between CCP and the aforementioned clinical differentials based on the histologic hallmark of a proliferation of larger clear cells within the basal epidermis. These cells exist singly or in small clusters, and can be found within the spinous or granular layers, albeit in smaller numbers.[3] They are larger than adjacent keratinocytes and do not show cellular atypia.[5] Majority of these cells show positive staining for mucin (82.6%, 19/23 cases). A cytoplasmic “tadpole-tail”-like process that is directed superficially has been described.[3] Other minor co-existing features include mild acanthosis, mild hyperkeratosis and decreased basal melanin.

Multiple immunohistochemical stains have been used to detect the cells of CCP. [3-14] The most commonly used stains include AE 1/3 (21/21 cases positive), CEA (21/21) and EMA (18/18). Negative staining with S100 (17/17) is also consistently observed. Other less commonly used stains include CK7 (8/8), GCDFP (6/7) and CAM5.2 (5/5).

Pathogenetically, Toker cells have been postulated to be the cell of origin in CCP, given their similar anatomical distribution (“milk line” configuration) and histological features. They also share similar immunohistochemical profiles, with both staining positively for EMA, CK7 and other low-molecular-weight cytokeratins.[15] However, Toker cells differ as they stain negatively for polyclonal

Table 1. Characteristics of the 3 Singaporean Cases of CCP

	Age at Presentation (Months)	Race	Sex	Age of Onset (months)	Site of Involvement	No. of Lesions	Diameter of Lesions	FHX	Mucin Staining	Positive IHC	Negative IHC
Case 1*	16	Chinese	F	NR	Pubic	3	3 mm to 9 mm	Nil	Positive for mucicarmine, alcian blue, PAS	AE1/3 CEA EMA CAM5.2 CK7	S100 CK20 GCDFP
Case 2†	18	Chinese	M	15	Groin, lower abdomen, chest	Multiple	1 mm to 3 mm	NR	Positive for PAS	AE1 CEA	S100
Case 3	36	Chinese	M	7	Pubic, genitals, abdomen axilla	Multiple	NR	Nil	Positive for PAS	CK7	

CAM5.2: Cell adhesion molecule 5.2; CEA: Carcinoembryonic antigen; CK7: Cytokeratin-7; CK20: Cytokeratin-20; EMA: Epithelial membrane antigen; F: Female; FHX: Family history; GCDFP: Gross cystic fluid disease protein; IHC: Immunohistochemistry; M: Male; NR: Not reported; PAS: Periodic acid-Schiff

*Kumarasinghe SP, Chin GY, Kumarasinghe MP. Clear cell papulosis of the skin: a case report from Singapore. Arch Pathol Lab Med 2004;128:e149-52.

†Chong WS, Ong BH, Kumarasinghe SP. Hypopigmented papules in an Asian boy. Pediatr Dermatol 2005;22:268-9.

Table 2. Summary of 33 CCP Cases Reported in the Worldwide Literature

Author	No. of Cases/ Ethnicity	Sex	Onset Age (Months)	Site	Lesion Count	Other Histologic Features	Mucin	Positive IHC Stains (Negative Stains in Parenthesis)	Follow-up	FHX
Kuo*, 1987	2/Taiwanese	M	Birth	Shoulders, chest, abdomen, pubic	15	• Moderate hyperkeratosis • Moderate acanthosis • Decreased basal pigmentation • Slight disorganisation of keratinocytes	+	AE1/AE3 CEA EMA (S100)	NR	Patients were brothers
		M	7	Chest, abdomen	5					
Kuo†, 1995	3/Taiwanese	M	12	Lower abdomen	5	• Mild hyperkeratosis • Moderate acanthosis • Decreased basal pigmentation • Slight disorganisation of keratinocytes	+	AE1 CEA EMA GCDFP	NR	Nil
		M	24	Lower abdomen, inguinal area	>100					
		F	NR	Lower abdomen, chest	20					
Kim‡, 1997	1/Korean	F	10	Lumbar area, buttocks	Numerous	• Mild hyperkeratosis • Mild acanthosis • Decreased basal pigmentation	+	AE1 CEA EMA IKH4 CAM5.2 (S100)	NR	Nil
Lee§, 1998	4/Taiwanese	F	24	Axilla, chest, abdomen, pubic, groin	100	• Mild acanthosis • Decreased melanisation of epidermis, but normal number of basal melanocytes	+	AE1/AE3 CEA EMA (S100)	NR	First 2 patients are sisters
		F	20	Pubic	Few					

CAM5.2: Cell adhesion molecule 5.2; CEA: Carcinoembryonic antigen; CK7: Cytokeratin-7; CK20: Cytokeratin-20; EMA: Epithelial membrane antigen; ER: Estrogen receptor; FHX: Family history; GCDFP: Gross cystic fluid disease protein; Her2: Human epidermal growth factor receptor-2; IHC: Immunohistochemistry; NR: Not reported; PR: Progesterone receptor

*Kuo TT, Chan HL, Hsueh S. Clear cell papulosis of the skin. A new entity with histogenetic implications for cutaneous Paget's disease. Am J Surg Pathol 1987;11:827-34.

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§Lee JY, Chao SC. Clear cell papulosis of the skin. Br J Dermatol 1998;138:678-83.

‖Gianotti R, Cambiaghi S, Locatelli A, Gelmetti C. Clear cell papulosis (pagetoid papulosis) in a non-Asian patient. Dermatology 2001;203:260-1.

¶Mohanty SK, Arora R, Kakkar N, Kumar B. Clear cell papulosis of the skin. Ann Diagn Pathol 2002;6:385-8.

#Benouni S, Kos L, Ruggeri SY, North PE, Drolet BA. Clear cell papulosis in Hispanic siblings. Arch Dermatol 2007;143:358-60.

**Farley-Loftus R, Bossenbroek NM, Rosenman K, Schaffer JV. Clear cell papulosis. Dermatol Online J 2008;14:19.

††Yu Y, Sukhatme S, Loo DS. Clear cell papulosis: a connection of clear cells to toker cells or paget disease. Arch Dermatol 2009;145:1066-8.

‡‡Tseng FW, Kuo TT, Lu PH, Chan HL, Chan MJ, Hui RC. Long-term follow-up study of clear cell papulosis. J Am Acad Dermatol 2009;63:266-73.

§§Sim JH, Do JE, Kim YC. Clear cell papulosis of the skin: acquired hypomelanosis. Arch Dermatol 2011;147:128-9.

‖‖Wysong A, Sundram U, Benjamin L. Clear-cell papulosis: a rare entity that may be misconstrued pathologically as normal skin. Pediatr Dermatol 2012;29:195-8.

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		M	21	Lower abdomen, pubic	Few					
		F	4	Axilla, chest, abdomen, pubic	Numerous					
Gianotti‖, 2001	1/Italian	F	6	Chest, lower abdomen, pubic	NR	• Mild acanthosis	NR	AE1 CEA EMA (S100)	NR	NR
Mohanty¶, 2002	1/Indian	F	44 years	Chest, lumbar area, abdomen	6	• Mild hyperkeratosis • Mild acanthosis • Decreased basal pigmentation	–	AE1/3 CEA EMA (S100)	Nil progression over 5 months	Nil
Benouni# 2007	3/Hispanic	M	8	Lower abdomen, pubic, axilla	50	• Decreased melanisation of lesional epidermis	–	CEA CK7 HMW cytokeratin (S100, CD1a)	NR	First 2 patients are siblings
		F	71	Chest, abdomen, pubic	NR					
		M	23	Axilla, abdomen, pubic, groin	NR	• Nil	+	CEA CK7 EMA (S100, CD1a)		

CAM5.2: Cell adhesion molecule 5.2; CEA: Carcinoembryonic antigen; CK7: Cytokeratin-7; CK20: Cytokeratin-20; EMA: Epithelial membrane antigen; ER: Estrogen receptor; FHX: Family history; GCDFP: Gross cystic fluid disease protein; Her2: Human epidermal growth factor receptor-2; IHC: Immunohistochemistry; NR: Not reported; PR: Progesterone receptor

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Farley-Loftus[**], 2008	1/Chinese	M	3	Abdomen, pubic	>50	• Mild acanthosis & papillomatosis	+	NR	NR	Nil
Yu[††], 2009	1/Asian-American	F	8	Axilla, chest, pubic, genitalia, buttocks	Numerous	• Mild acanthosis	+	CK7 CAM5.2 CEA AE1/3 EMA GCDFP (S100, Her2, ER, PR, p53)	NR	NR
Tseng[‡‡], 2009	14/Taiwanese	10F 4M	12 (median)	Abdomen, pubic area, chest, axilla, groin, extremities	2 – >100	• Mild hyperkeratosis • Mild to moderate acanthosis • Decreased basal pigmentation	3/3 +	AE1 (5/5) CEA (2/2) EMA (2/2) GCDFP (1/1) CAM5.2 (1/1)	Reduction in lesion count (10/11) Increase in lesion size (1/11)	3 patients with affected siblings
Sim[§§], 2011	1/Korean	F	2	Chest, abdomen, pubic	NR	• Mild hyperkeratosis • Mild acanthosis • Decreased melanisation of epidermis, but normal number of basal melanocytes	NR	CK7 EMA CEA (S100, CD1a)	NR	Nil
Wysong[‖‖], 2012	1/Indian	F	9	Axilla, chest, pubic	NR	• Nil	–	AE1 CK7 CAM5.2 GCDFP (S100, ER, PR)	NR	NR

CAM5.2: Cell adhesion molecule 5.2; CEA: Carcinoembryonic antigen; CK7: Cytokeratin-7; CK20: Cytokeratin-20; EMA: Epithelial membrane antigen; ER: Estrogen receptor; FHX: Family history; GCDFP: Gross cystic fluid disease protein; Her2: Human epidermal growth factor receptor-2; IHC: Immunohistochemistry; NR: Not reported; PR: Progesterone receptor

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CEA and mucin.[8,15] Of importance, Toker cells have been implicated as the precursors of Paget's disease. However, Tseng et al demonstrated that none progressed to Paget's disease in their cohort of 19 CCP patients. These patients were followed-up over a median of 11.5 years;[5] 64.3% showed a reduction in lesion count while 21.4% showed complete resolution.[5]

Conclusion

CCP is a rare but distinctive infantile dermatosis with characteristic clinical and histologic findings. Lesions are asymptomatic and longitudinal follow-up of cases has demonstrated a benign course. Hence, no treatment is necessary.[5] More research is needed to elucidate the exact cell of origin.

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