Clear Cell Papulosis of the Skin

A Case Report From Singapore

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• Clear cell papulosis of the skin is a rare condition; to our knowledge only 12 cases have been reported. Here, we report for the first time a case of clear cell papulosis with cytokeratin 7 expression and provide a comprehensive literature review. A 16-month-old girl presented with 3 hypopigmented lesions in the pubic region that were 3 to 9 mm in diameter; 1 lesion was papular, and the other 2 were macular. A skin biopsy revealed acanthosis with a proliferation of clear cells along the basal and suprabasal layers of the epidermis occurring in small clusters and singly. The cells had round to oval regular nuclei with abundant to moderate lightly eosinophilic to clear cytoplasm and intracytoplasmic mucin. Immunostaining produced positive results for carcinoembryonic antigen, AE1/3, epithelial membrane antigen, cell adhesion molecule 5.2, and cytokeratin 7 and negative results for gross cystic fluid disease protein, S100, and HMB-45. Clear cells of clear cell papulosis are mucin-positive and S100-negative glandular-secretory epithelial cells with histogenetic features of Toker cells of nipple and Paget cells. Immunohistochemical features support an eccrine secretory cell origin because the clear cells are consistently and strongly positive for carcinoembryonic antigen, positive for cell adhesion molecule 5.2, and negative or rarely positive for gross cystic fluid disease protein.

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Clear cell papulosis (CCP) of the skin is a rare condition, which has been reported mostly among Taiwanese children. To our knowledge, only 12 cases have been reported.[1–7] Clinically, the lesions are hypopigmented or depigmented macules and papules appearing on the pubic region and the milk line distribution in small children without evidence of pityriasis versicolor infection, preceding inflammation, or vitiligo.

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REPORT OF A CASE

A 16-month-old girl was brought by her parents to the National Skin Centre because of whitish spots in her pubic region. There was no preceding history of trauma or inflammation and no pruritus. Examination of this healthy, active baby revealed 2 hypopigmented macules and 1 hypopigmented flat-topped papule in the pubic region (2 on one side and 1 on the other side) that were 3 to 9 mm in diameter. There was no sensory impairment. These lesions were somewhat symmetrically distributed (Figure 1). There were no neurologic, ocular, cardiac, auditory, or skeletal abnormalities. Pigmentation of the rest of the skin was normal. There were no ''café-au-lait'' macules. The parents were both Singaporeans of Chinese descent, and they were not related to any individuals from Taiwan. There was no parental consanguinity or family history of similar lesions.

A clinical diagnosis of clear cell papulosis of the skin was made. Scrapings from these lesions were examined to exclude pityriasis versicolor. There were no fungal elements suggestive of *Malassezia furfur* infection.

At the time of the short follow-up examination 1 year after the original diagnosis, the lesions had not changed significantly.

A skin biopsy was performed from a lesion on the pubic area and the tissue was fixed in 10% formalin. Sections were stained with hematoxylin-eosin and the histochemical stains Alcian blue, Masson Fontana, periodic acid–Shiff, and mucicarmine. Cells were also immunostained for polyclonal carcinoembryonic antigen (CEA; A0115, Dako Corporation, Carpinteria, Calif), AE1/3 (M3515, clones AE1 and AE3, Dako), cell adhesion molecule 5.2 (CAM 5.2; BD349205, Becton Dickinson, Sparks, Md), cytokeratin (CK) 7 (M7018, clone OV-TL12/30, Dako), CK20 (M7019, clone Ks20.8, Dako), epithelial membrane antigen (EMA; M0613, clone E29, Dako), S100 (Z0311, Dako), HMB-45 (M0634, Dako), and gross cystic fluid disease protein (GCDFP; MS 1170-S1, clone 23A3, NeoMarkers, Fremont, Calif).

PATHOLOGIC FINDINGS

Hematoxylin-eosin–stained sections revealed mild acanthosis of the epidermis. Rete ridges were expanded. A proliferation of clear cells was noted along the basal and suprabasal layers of the epidermis; the cells occurred in small clusters or singly. The number of cells diminished toward the surface. The cells had round to oval regular nuclei with abundant to moderate lightly eosinophilic to clear cytoplasm (Figure 2). There were several cells with larger nuclei (slightly larger than those of keratinocytes and approximately twice the size of those of melanocytes). Generally, nuclear chromatin was paler than that of keratinocytes and melanocytes. No pleomorphism or mitoses were seen. Nucleoli were not prominent. The clear cells

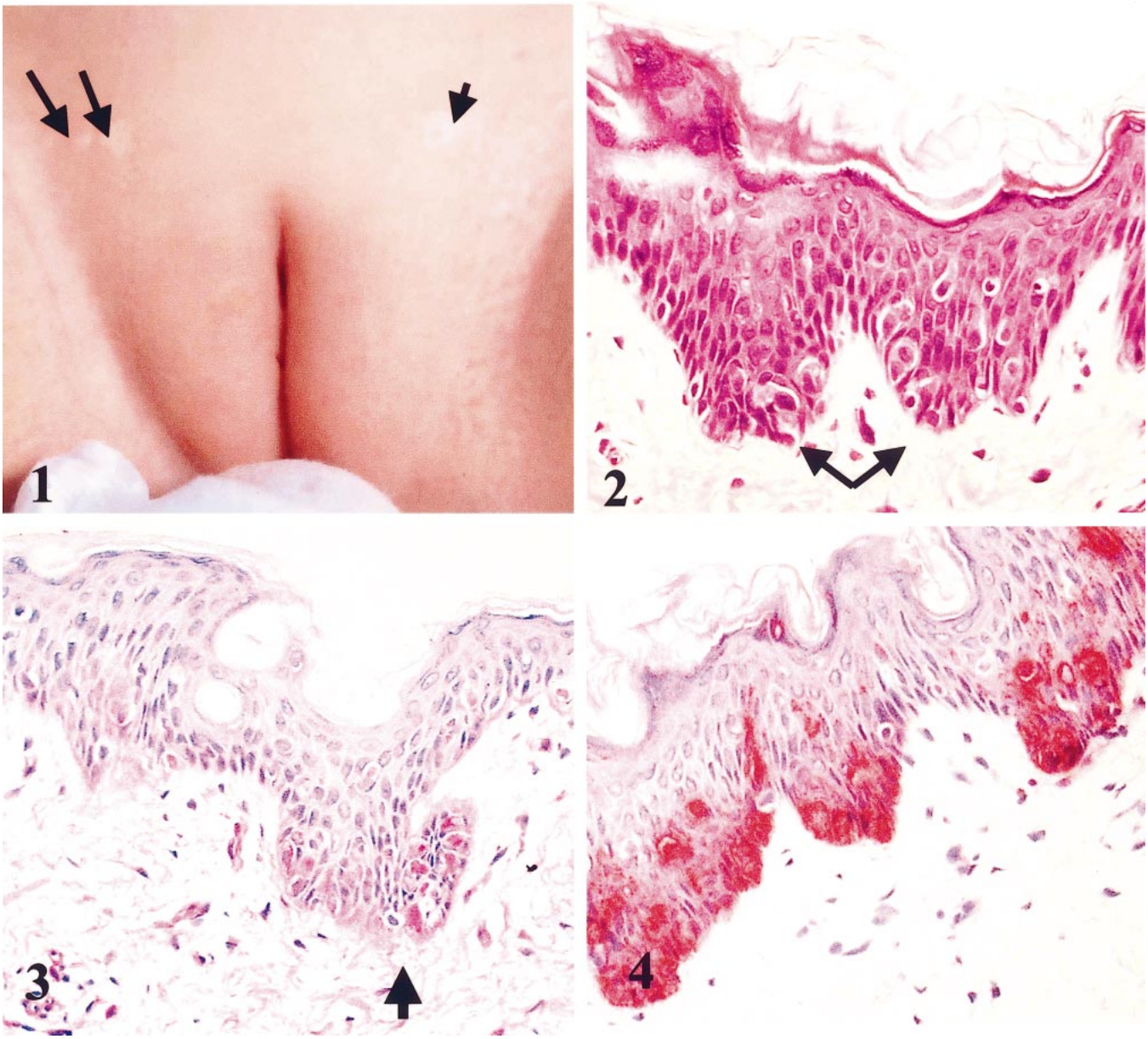

Figure 1. *Two hypopigmented macules and a flat-topped papule in the pubic region (2 on the patient's right side, long arrows; 1 on the left side, short arrow) 3 to 9 mm in diameter.*

Figure 2. *Clear cells located among the basal and suprabasal cells of the epidermis (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Dark pink to red intracytoplasmic mucin within the clear cells (mucicarmine, original magnification ×200).*

Figure 4. *Immunohistochemical staining produced a very strong cytoplasmic positive reaction in the clear cells, highlighting a larger number of cells compared with that seen in sections stained with hematoxylin-eosin and mucicarmine (carcinoembryonic antigen, original magnification ×200).*

were not pigmented. Melanin pigmentation was significantly reduced in the area of clear cell proliferation compared with the normal areas (confirmed by Masson Fontana stains). The dermis was unremarkable.

Histochemical and Immunohistochemical Stains

Mucicarmine, periodic acid–Schiff, and Alcian blue stains produced positive reactions in the cytoplasm of abnormal cells (Figure 3). Masson Fontana stain revealed a significant decrease of melanin in the areas of the epidermis occupied by clear cells.

Immunohistochemical Stains

Carcinoembryonic antigen immunostain produced a strong positive reaction (Figure 4) that highlighted many more abnormal cells in addition to those that had clear cytoplasm as revealed by light microscopy. The cells were also positive for EMA, AE1/3, CK7, and CAM 5.2 but were negative for GCDFP, S100, and CK20. In contrast, S100 stain decorated melanocytes and their dendritic processes, but the clear and abnormal cells were negative. Another notable feature was the reduction or replacement of basal melanocytes in the areas of abnormal cell prolifer-

Table 1. Clinical Features of Present and Reported Cases of Clear Cell Papulosis

Authors	No. of Cases	Origin/Ethnicity	Average age, y	Sex	Lesions			
					Location	No.	Size, mm	Appearance
Kuo et al,[1,7] 1987, 1995	5	Taiwanese (Chinese)	2.2	M = 4 F = 1	Lower abdomen, chest, groin	Multiple	2–10	Whitish papules
Kim et al,[3] 1997	1	South Korean	1	M	Lumbar area, scrotum, buttocks	. . .	2–3	Smooth, whitish, flat papules
Lee and Chao,[5] 1998	4	Taiwanese (Chinese)	2.4	M = 3 F = 1	Abdomen, pubic area, axillary, chest, upper thighs	Multiple	1–10	Hypopigmented, flat papules
Gianotti et al,[4] 2001	1	Italian	3	F	Pubic, lower abdomen	Multiple	Few	Palpable, hypopigmented
Mohanty et al,[2] 2002	1	Indian	46	F	Anterior abdomen, lumbar region, upper chest	Single	8–10	White, smooth papular eruption
Present case	1	Singapore (Chinese)	1.3	F	Pubic area	Multiple	3–9	Hypopigmented, 2 macules, 1 flat papule

Table 2. Histochemical and Immunohistochemical Profiles of Present and Reported Cases of Clear Cell Papulosis

Authors	No. of Cases	Reactions*							
		Mucin	CEA	S100	EMA	AE1/3	GCDFP	CAM 5.2	CK7
Kuo et al,[1,7] 1987, 1995	5	+	+	NM	+	+	+ (a small number)	NM	NM
Kim et al,[3,6] 1997, 2002	1	+	+	−	+	+	NM	+	NM
Lee and Chao,[5] 1998	4	+	++	−	+/++	++/+++	NM	NM	NM
Gianotti et al,[4] 2001	1	NM	++	−	+	+++	NM	NM	NM
Mohanty et al,[2] 2002	1	−	+	−	+	+	NM	NM	NM
Present case	1	+	+++	−	++	++	−	+	++

* − indicates negative; +, positive; NM, not mentioned; CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; GCDFP, gross cystic fluid disease protein; CAM, cell adhesian molecule; and CK, cytokeratin.

ation highlighted by S100 and HMB-45 immunostains. Of all positive immunostains, CEA was the strongest.

COMMENT

Clinical significance, biological behavior, and even the exact histogenesis of clear cell papulosis is uncertain, although new information is emerging, with more cases being reported from Southeast and Southern Asia and Europe.[1–7]

Table 1 contains a list of the clinical features of previously reported cases and the present case.

The most common age group affected is children 1 to 4 years of age; the most common sites affected are the pubic region, lower abdomen, and anterior trunk. Sometimes the lesions vaguely follow the milk line anteriorly. The most common clinical appearance is flat, hypopigmented small papules, each several millimeters in diameter. Most lesions occur in groups. No long-term follow-up reports are available to determine the biological nature of these lesions. The natural history of these lesions is not known, that is, whether these lesions will eventually evolve into extramammary Paget disease (EMP) or whether the cells will die and the lesions will eventually disappear. At the short follow-up examination conducted 1 year after the original diagnosis, the lesions had not changed significantly. Most reported cases of CCP have many hypopigmented macules and papules, but reported EMP cases have not included multiple lesions. It is unlikely that all these lesions would evolve into EMP.

CCP is a rare cause of macular hypopigmentation or depigemtation. The exact reason for the pigmentary change is not known, although a reduction of melanin pigmentation was demonstrated in the present case and a few others.[5,7] Similar depigmentation has been reported in some cases of EMP.[8,9] A functional defect in melanogenesis or melanin distribution is more likely than loss of pigmentation due to a physical reduction of melanocytes. If there is no inhibitory effect and no functional problem, the pigment should migrate from the normal skin to the hypopigmented skin; these papules and macules are surrounded by normally functioning melanocytes in the surrounding skin. A similar theory has been proposed for depigmented macules seen in cases of EMP.[8]

The most common microscopic features reported in CCP cases are acanthosis of the epidermis, hypopigmentation, and the presence of clear cells basally and suprabasally. The clear cells are larger than the keratinocytes and contain abundant clear vacuolated cytoplasm and pale nuclei. The features were present in the present case. We also noted very focal clustering or grouping of the clear cells, a feature reported by Kuo and others.[7] Nuclear grooving has been reported in some cases[5,7] but was not obvious in the present case.

Comparing the staining characteristics of previous cases (Table 2), consistent positive results have been reported for mucin and for CEA and AE1/3. Others have reported positive results for CAM 5.2, IKH-4, EMA, and GCDFP. We have demonstrated for the first time positive staining of clear cells of CCP for CK7. Paget cells and Toker cells of the nipple are also positive for CK7 with a high degree of sensitivity.[10] Epidermal keratinocytes are clearly negative for CK7.

Kuo et al[7] reported focal positive results for GCDFP, although the cells in the present case did not stain in spite of repeated attempts to exclude false-negative results. Salivary tissue used as a positive control produced a convincingly marked positive reaction in the acinar cells. Analyzing the other reports carefully, we failed to find positive results for GCDFP. Kuo et al stated that only a smaller number of clear cells were stained with GCDFP.

GCDFP produces positive results in cells of Paget disease and is a consistent marker for apocrine cells. However, it produces negative results in some cases of Paget disease, particularly those without an associated underlying malignancy.[11] GCDFP staining is negative or only infrequently positive in eccrine tumors[12] but positive in salivary acinar structures and sweat glands.[13] Although GCDFP appears to be highly specific, its sensitivity is reported to vary from 50% to 74%.[13] The clear cells of CCP in the present case were strongly positive for CEA but were negative for GCDFP. Eccrine glands are more strongly positive for CEA than are apocrine cells. Conversely, apocrine cells stain more strongly with GCDFP. Toker cells of the nipple have a very low prevalence of positive staining for GCDFP.[10]

Strong and consistent positive staining of clear cells of CCP for CEA and negative or weak staining for GCDFP suggest that the cells are unlikely to be of apocrine secretory cell origin, a view shared by Kim et al,[6] who also used an array of stains in an attempt to understand the histogenesis of these cells.

CCP should be differentiated from premalignant or malignant lesions such as Paget disease or EMP, pagetoid squamous carcinoma, pagetoid melanoma, sebaceous carcinoma, and pagetoid dyskeratosis. Glycogenated squamous cells of the epidermis also may appear clear.

Extramammary Paget disease, pagetoid squamous carcinoma, and pagetoid melanoma may show the typical pagetoid arrangement of cells within the epidermis, similar to that in CCP cells. However, all those entities have malignant cytologic features, whereas clear cells of CCP are remarkably bland. Sebaceous carcinomas contain clear cells, but these cells differ from those of CCP because they also have malignant features.

Toker cells (predominantly present in the nipple skin) are strikingly similar in morphology to clear cells of CCP, but they are not known to contain intracytoplasmic mucin. In all but one of the cases reported so far (Table 2), clear cells of CCP have intracytoplasmic mucin. These cells share positive mucin results and strong CEA expression with Paget cells and light microscopic appearance and negative GCDFP results with Toker cells. They share positive CK7, EMA, CAM 5.2, and AE1/3 results with both cell types.

There seems to be a phenotypic and immunohistochemical relationship between the clear cells and both Toker cells and Paget cells, although these 2 types of cells are at the extreme ends of a biological continuum. Toker cells occur in the normal nipple epidermis, whereas Paget cells are either malignant or premalignant. The question arises as to whether clear cells of CCP are a link between these 2 extreme cell types.

Clear cells of CCP are mucin-positive, S100-negative glandular-secretory epithelial cells that share histogenetic features with Toker cells and Paget cells. The histogenesis is less likely to be of apocrine origin. The histogenesis and the biological significance of CCP has not yet been determined. Although these cells share similarities with both Toker cells and Paget cells, they may be a unique cell type. There is no necessity to lump them into either of these 2 types of cells despite the observed similarities.

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