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.
Discussion

Kuo et al first described CCP in 2 Taiwanese brothers in 1987. 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. 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. Although some authors have postulated a possible autosomal recessive mode of inheritance, 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 morphea 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. They are larger than adjacent keratinocytes and do not show cellular atypia. 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. 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. 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. However, Toker cells differ as they stain negatively for polyclonal...
Table 1. Characteristics of the 3 Singaporean Cases of CCP

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

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


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

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

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Table 2. Summary of 33 CCP Cases Reported in the Worldwide Literature (Cont’d)

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<tr>
<th>Author</th>
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<th>Sex</th>
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<th>Site</th>
<th>Lesion Count</th>
<th>Other Histologic Features</th>
<th>Mucin</th>
<th>Positive IHC Stains (Negative Stains in Parenthesis)</th>
<th>Follow-up</th>
<th>FHX</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>21</td>
<td>Lower abdomen, pubic</td>
<td>Few</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AE1/CEA/EMA (S100)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>F</td>
<td>4</td>
<td>Axilla, chest, abdomen, pubic</td>
<td>Numerous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AE1/3 CEA/EMA (S100)</td>
<td>Nil progression over 5 months</td>
<td>Nil</td>
</tr>
<tr>
<td>Gianotti, 2001</td>
<td>1/Italian</td>
<td>F</td>
<td>6</td>
<td>Chest, lower abdomen, pubic</td>
<td>NR</td>
<td>• Mild acanthosis</td>
<td>NR</td>
<td>AE1/CEA/EMA (S100)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mohanty, 2002</td>
<td>1/Indian</td>
<td>F</td>
<td>44 years</td>
<td>Chest, lumbar area, abdomen</td>
<td>6</td>
<td>• Mild hyperkeratosis • Mild acanthosis • Decreased basal pigmentation</td>
<td>−</td>
<td>AE1/3 CEA/EMA (S100)</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Benouni, 2007</td>
<td>3/Hispanic</td>
<td>M</td>
<td>8</td>
<td>Lower abdomen, pubic, axilla</td>
<td>50</td>
<td>• Decreased melanisation of lesional epidermis</td>
<td>−</td>
<td>CEA/CK7/HMW cytokeratin (S100, CD1a)</td>
<td>NR</td>
<td>First 2 patients are siblings</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>Axilla, abdomen, pubic, groin</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CEA/CK7/EMA (S100, CD1a)</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<th>Author</th>
<th>Ethnicity</th>
<th>Sex</th>
<th>Sex</th>
<th>Onset Age (Months)</th>
<th>Site</th>
<th>Lesion Count</th>
<th>Other Histologic Features</th>
<th>Mucin</th>
<th>Positive IHC Stains (Negative Stains in Parenthesis)</th>
<th>Follow-up</th>
<th>FHX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farley-Loftus**, 2008</td>
<td>Chinese</td>
<td>M</td>
<td>3</td>
<td>&gt;50</td>
<td>Abdomen, pubic</td>
<td>&gt;50</td>
<td>• Mild acanthosis &amp; papillomatosis</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>Nil</td>
</tr>
<tr>
<td>Yu††, 2009</td>
<td>Asian-American</td>
<td>F</td>
<td>8</td>
<td></td>
<td>Axilla, chest, pubic, genitalia, buttocks</td>
<td>Numerous</td>
<td>• Mild acanthosis</td>
<td>+</td>
<td>CK7 CAM5.2 CEA AE1/3 EMA GCDFP (S100, Her2, ER, PR, p53)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tseng‡‡, 2009</td>
<td>Taiwanese</td>
<td>F</td>
<td>12 (median)</td>
<td>Abdomen, pubic area, chest, axilla, groin, extremities</td>
<td>2–&gt;100</td>
<td>• Mild hyperkeratosis</td>
<td>3/3+</td>
<td>AE1 (5/5) CEA (2/2) EMA GCDFP (1/1) CAM5.2 (1/1)</td>
<td>Reduction in lesion count (10/11)</td>
<td>3 patients with affected siblings</td>
<td></td>
</tr>
<tr>
<td>Sim§§, 2011</td>
<td>Korean</td>
<td>F</td>
<td>2</td>
<td>NR</td>
<td>Chest, abdomen, pubic</td>
<td>NR</td>
<td>• Mild hyperkeratosis</td>
<td>NR</td>
<td>CK7 EMA CEA (S100, CD1a)</td>
<td>NR</td>
<td>Nil</td>
</tr>
<tr>
<td>Wysong</td>
<td></td>
<td></td>
<td>, 2012</td>
<td>Indian</td>
<td>F</td>
<td>9</td>
<td>Axilla, chest, pubic</td>
<td>NR</td>
<td>• Nil</td>
<td>–</td>
<td>AE1 CK7 CAM5.2 GCDFP (S100, ER, PR)</td>
</tr>
</tbody>
</table>

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CEA and mucin. 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; 64.3% showed a reduction in lesion count while 21.4% showed complete resolution.

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. More research is needed to elucidate the exact cell of origin.

REFERENCES


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