Concise case report

Autosomal dominant chronic mucocutaneous candidiasis and hypothyroidism, complicated by oesophageal carcinoma

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**Summary**

We report describe three generations of a family with autosomal dominant chronic mucocutaneous candidiasis (CMCC) associated with primary hypothyroidism and squamous cell carcinoma of the oesophagus in the index case. We report this family to increase awareness of this rare, autosomal dominant variant of CMCC associated with hypothyroidism and wish to highlight the risk of developing oesophageal squamous cell carcinoma at a young age as a fatal complication of CMCC.

**Introductory paragraph**
CMCC is characterized by chronic infection of skin, nails and mucous membranes with candida, refractory to conventional topical therapy and usually presents in early childhood. CMCC with endocrine disease is most commonly attributed to the autoimmune polyglandular syndrome (APS) Type I, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), which has an autosomal recessive pattern of inheritance. More recently a distinct variant of CMCC has been described, which has an autosomal dominant pattern of inheritance and is associated with primary hypothyroidism. (Reference 5 – but it will have to become 1 and the others be renumbered – sorry) There have only been a few reports of patients with CMCC complicated by oral and oropharyngeal squamous cell carcinoma at a young age. (Appropriately numbered references)

Report

Patient 1 was a man, who developed candidiasis at the age of 4 years affecting the nails, oropharynx, and oesophagus. From the age of 38 years he was treated with long-term oral ketoconazole, which controlled his oral candidiasis. At the age of 32 years he was diagnosed with primary hypothyroidism. At the age of 42 years he was diagnosed with a well differentiated squamous cell carcinoma of the oesophagus, from which he died five months later. He had been a smoker for 23 pack-years. His parents and 9 siblings did not have CMCC or associated endocrinopathies. He had three children, of which his daughter, Patient 2, and younger son, Patient 3, have CMCC.
Patient 2 developed persistent oral candidiasis at 6 months of age and subsequently developed vaginal and oesophageal involvement. From the age of 13 years she has had recurrent candidal infection of the finger nails requiring repeated nail avulsions. From the age of 28 years intermittent treatment with oral fluconazole has helped her candidiasis. So far, patient 2 has no evidence of hypothyroidism or other endocrinopathies. She has two children aged 15 and three years, neither of whom have CMCC or associated diseases.

Patient 3 (Fig.1) developed persistent oral candidiasis at the age of three years, initially treated with oral ketoconazole. From the age of 23 years he has been treated with long-term itraconazole, which improved his oropharyngeal candidiasis and topical miconazole gel for angular cheilitis. At the age of five years he was diagnosed with primary hypothyroidism. Patient 3’s three year old son has recently been diagnosed with oral candidiasis, which is kept under control with amphotericin lozenges and miconazole gel. His thyroid function tests are normal. Patients 2 and 3 tested negative for the two commonest APECED associated autoimmune regulator gene (AIRE) mutations. Apart from primary hypothyroidism affecting the father and son (Patients 1 and 3), there are no endocrinopathies, organ specific autoimmune diseases or antibodies and no immunodeficiency syndromes in the reported family. The family tree (Fig. 2) illustrates the autosomal dominant mode of inheritance of CMCC in the this reported family.

Familial forms of CMCC can be inherited with or without endocrinopathies in either an autosomal recessive or dominant pattern (Table 1). APECED is inherited in an autosomal recessive manner due to mutations in the AIRE gene located on chromosome 21q22.3 (OMIM 240300). The two commonest mutations in this gene are c.769C>T that creates a nonsense mutation in exon 6 (p.R257X) and c.964del13 which is a 13bp deletion in exon 8. These two mutations are responsible
for 80% of AIRE mutations\textsuperscript{4} and both were negative in the reported family.\textsuperscript{4} APECED is mainly associated with autoimmune hypoparathyroidism and adrenocortical insufficiency.\textsuperscript{2,3,4}

The reported family’s presentation is in keeping with the autosomal dominant CMCC syndrome associated with primary hypothyroidism,\textsuperscript{5} originally described by Coleman and Hay.\textsuperscript{5} The gene defect for this syndrome has recently been mapped to chromosome 2p – OMIM 606415.\textsuperscript{6} Although a rare variant of CMCC, it is important to recognize these families in view of the autosomal dominant inheritance pattern with an attendant greater genetic risk and the need to remain alert for the development of hypothyroidism, the diagnosis of which might otherwise be delayed. Routine monitoring of thyroid function from an early age has therefore been recommended in this patient group.\textsuperscript{5}

There is very limited literature on patients with CMCC who developed SCC of the oral or oesophageal mucosa at a young age.\textsuperscript{7,8} In a recent study of 92 Finnish patients with APECED, 10% (n=6) of cases aged over 25 years developed SCC of the oral (n=5) or oesophageal (n=1) mucosa. This was fatal in 4 of these patients between the ages of 29 to 44 years.\textsuperscript{9} The CMCC was felt to be contributory to the development of the SCC in addition to other risk factors including smoking, alcohol and immunosuppression.\textsuperscript{8,9}

Our index case, who had longstanding oropharyngeal and oesophageal candidiasis and was a smoker, developed a fatal SCC of the oesophagus at the age of 42 years, with a fatal outcome. He exemplifies the importance of being vigilant for early onset squamous cell carcinoma of the upper gastrointestinal tract mucosa in patients with CMCC. In addition to optimal control and regular monitoring of the mucosal candidiasis, we recommend early counselling on the avoidance of other
extrinsic risk factors for oral and oesophageal SCC including smoking and excessive alcohol intake.
Legends

Figure 1 Tongue of Patient 3, with white plaques and fissures secondary to chronic candidal infection

Figure 2 Family tree demonstrating an autosomal dominant inheritance pattern

Table 1 Modes of inheritance and gene defects for CMCC with and without endocrinopathy
References


9 Rautemaa R, Hietanen J, Niissalo S et al. Oral and oesophageal squamous cell carcinoma – A complication or component of autoimmune polyendocrinopathy-
candidiasis-ectodermal dystrophy (APECED, APS-1). *Oral Oncology* 2007;43:607-
<table>
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<th>Inheritance pattern</th>
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Figure 2

- Patient 1: primary hypothyroidism (patients 1 and 3)
- Mucocutaneous candidiasis

Symbol X: primary hypothyroidism (patients 1 and 3)