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Chronic mucocutaneous candidiasis and oesophageal cancer

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Chronic mucocutaneous candidiasis (CMC) is often accompanied by endocrine or inflammatory disorders. The association of CMC with squamous cell carcinoma of the oral cavity or oesophagus have been described in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). We describe three cases of CMC and oesophageal cancer without the APECED syndrome. The first case refers to a 41-year-old man with *Candida* paronychia and oral infection and selective IgA deficiency since childhood, who later developed an oesophageal cancer. The second case is a 30-year-old man who presented CMC features at the age of 2 together with selective IgA deficiency. Later on he was diagnosed with an oesophageal squamous cell carcinoma. His mother, the third case reported, had oral thrush since childhood and at the age of 29 she presented with an oesophageal squamous cell carcinoma. The three patients reported died due to oesophageal cancer. This is the first case report describing the development of oesophageal cancer in patients with CMC without the APECED syndrome. Patients with CMC need close follow-up with good oral hygiene and aggressive treatment of oral and oesophageal candidiasis. Routine endoscopic screening for patients with CMC that develop symptoms of oesophageal candidiasis and for patients with CMC with a family history of oesophageal cancer is suggested. Avoidance of additional risk factors for oral and oesophageal cancer like cigarette smoking and excessive alcohol consumption are also warranted.

Keywords chronic mucocutaneous candidiasis, cancer, esophageal neoplasms, Candida, autoimmune polyendocrinopathy, antifungal agents

Introduction

Chronic mucocutaneous candidiasis (CMC) is a syndrome characterized by persistent or recurrent infections caused by *Candida* species involving the skin, nails and mucous membranes. Most cases of CMC are sporadic [1], secondary to other medical conditions, such as HIV infection, steroid administration, use of dentures or iron deficiency. Primary CMC has been reported to have a genetic basis (familial CMC), either autosomal dominant [2] or recessive [3]. CMC is often accompanied by endocrine or inflammatory disorders [1] with their associated morbidities. The association of CMC with squamous cell carcinoma of the oral cavity or oesophagus have been described in only three reports [4–6]. Two of these cases were included in a series of Finnish patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Here we report that 3 patients with CMC without features of the APECED syndrome developed oesophageal cancer. The literature regarding this subject is reviewed and suggestions for patients' surveillance are presented.

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Case reports

Case 1

This 41-year-old Caucasian man first developed documented *Candida* paronychia and oral infection at the age of 2. He was also diagnosed with selective IgA deficiency, and there were no organ-specific autoantibodies. Throughout childhood and teenage years he continued to have repeated infection of his mouth and nails, manifested as chronic paronychia, superficial white onychomycosis and damaged nail plates. Later he developed a seborrhoeic eruption on his trunk attributed to *Candida* species. He was treated successfully until late 2002 with fluconazole but several oral swabs obtained in 2003 revealed fluconazole-resistant isolate of *Candida albicans* (MIC of 8 mg/l). The isolate tested susceptible to itraconazole (MIC of 0.125 mg/l), but this drug was not tolerated by the patient. Skin scrapings in 2003 showed *Trichophyton rubrum*. The patient had a subtle disturbance of pneumococcal antibody production in that the dominant response was of the IgG_1 subclass rather than the IgG_2 subclass response as expected in adults. In the summer of 2004 he was admitted to the hospital where multiple endoscopies showed a mass in the fundus of the stomach, which was thought to be a *Candida* bezoar. A severe stricture of 3 cm was seen in the gastro-oesophageal junction. Multiple biopsies showed the presence of a fungal mass, without evidence of malignancy. *C. albicans* was recovered from culture but susceptibility testing was not performed. The patient was given amphotericin B desoxycholate and high dose omeprazole. He was discharged on standard dose of voriconazole but a probable drug interaction with omeprazole via CYP2C19 led to neutropenia and reduced left ventricular function requiring hospital admission. He recovered from this and in April 2005 was admitted again to the hospital because of very little food intake and considerable weight loss. Investigations showed a very large mass at the lower end of his oesophagus and upper part of his stomach extending to his liver. A percutaneous endoscopically-guided gastrostomy (PEG) tube was inserted, and multiple biopsies of the oesophagus were negative for malignancy. As *Candida* infection persisted on his tongue despite a therapeutic voriconazole level, 5-flucytosine was added. However, the patient was unable to tolerate it due to nausea. Several oesophageal dilatations were performed to lessen dysphagia, with little success. He was admitted to the hospital in May 2005 for IV caspofungin, with some improvement. He was again admitted to hospital in December 2005 feeling feverish and generally unwell. Multiple blood cultures came positive to *Streptococcus milleri*, and pus surgically drained from a brain abscess also revealed these organisms. A swab from the tongue taken in March 2006 revealed *Candida glabrata* with a high MIC to fluconazole (>64 mg/l), itraconazole (>8 mg/l), and voriconazole (4 mg/l). Two years after the first suspicion of malignancy in 2006, the patient died and the autopsy showed the presence of a well differentiated squamous cell carcinoma of the distal oesophagus invading the surrounding soft tissue. *C. glabrata* was isolated from the tumour, which measured around 8×8 cm with a small area of perforation and necrosis of the surrounding mediastinal soft tissue. His three sisters and parents were unaffected.

Case 2

This 30-year-old man of mixed ancestry (black and Caucasian), first presented horny growths on the scalp at the age of 2 which gradually extended to become more impressive, with associated moderate hair loss. There was inflammation of the nail folds of the right index and left middle fingers, with associated dystrophy of the fingers. There was also hypertrophic candidiasis of the lips and tongue. *C. albicans* was isolated from nail clippings and from the mouth and fungal elements were seen on microscopy of scrapings from the scalp although *Candida* was not isolated. He had selective IgA deficiency. At the age of 14 he developed dysphagia and numerous tiny perifollicular de-pigmented macules, a rather odd pattern of vitiligo. At the age of 18 he was diagnosed with iron deficiency anaemia. The dystrophy of the fingers and nail folds inflammation persisted throughout adulthood (Fig. 1), and he was treated with intermittent courses of ketoconazole and itraconazole, in addition to nystatin pastilles. In 1995 *C. albicans* was again recovered from patients' mouth – the isolate was fully susceptible to fluconazole, itraconazole and amphotericin B but resistant to flucytosine. Genetic tests were performed and ruled out the presence of APECED. In February 2006 the patient was put on continuous fluconazole treatment (200 mg daily). In the same year at the age of 28 he was diagnosed with a moderately differentiated squamous cell carcinoma of the oesophagus (Fig. 2) which was treated with neoadjuvant chemotherapy and surgery. One year later the disease recurred and the patient received second-line chemotherapy. Anti-fungal therapy was changed to voriconazole (200 mg twice daily) in October 2006, without success. The patient died in late 2006. His family history was notable for recurrent fungal infections and oesophageal cancer in his mother (described

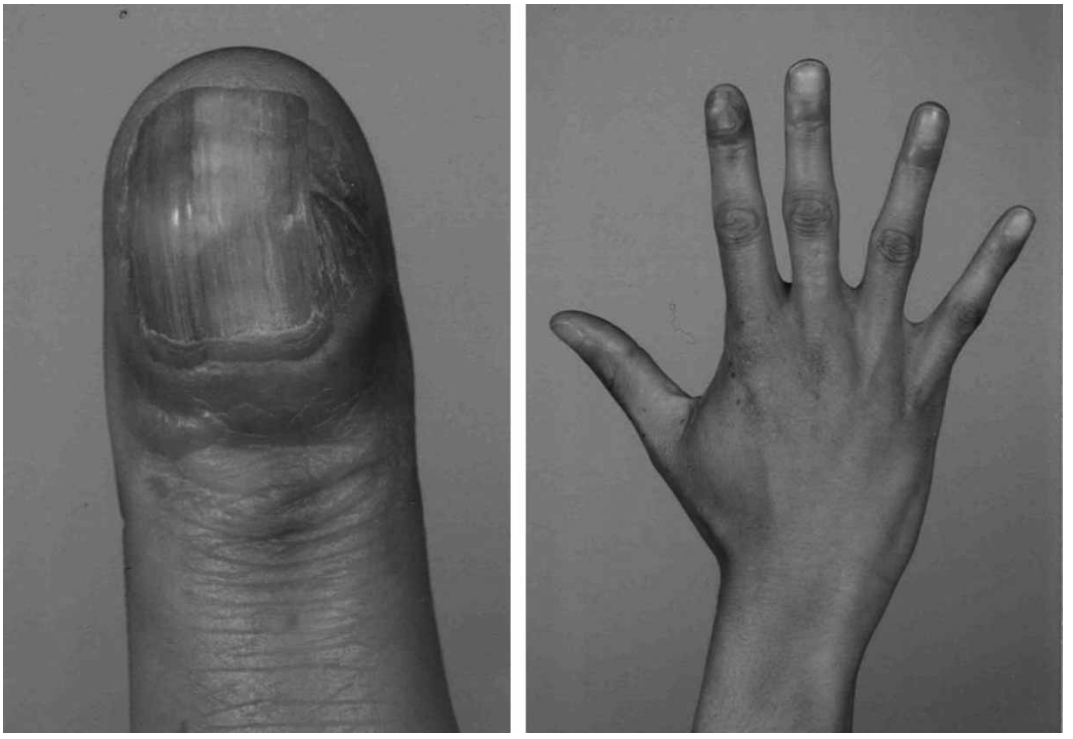

Fig. 1 Dystrophy of the fingers and nail fold inflammation (Case 2).

as Case 3, below). His sister had a few slightly horny excrescences on the scalp and similar but less marked changes in the mouth and on the lips. She also has recurrent oral candidiasis without symptoms of oesophageal candidiasis, and without vaginal candidiasis. One of his two daughters (now aged 6 years) also had oral candidiasis, with some recurrent mild eruptions on her face (possible impetigo) and lower lid styes. The other daughter, now aged 16 months appears to be disease free, apart also from mild facial eruptions, possibly impetigo. Genetic tests were performed and ruled out the presence of AIRE mutations R257X & 964del13 in the family.

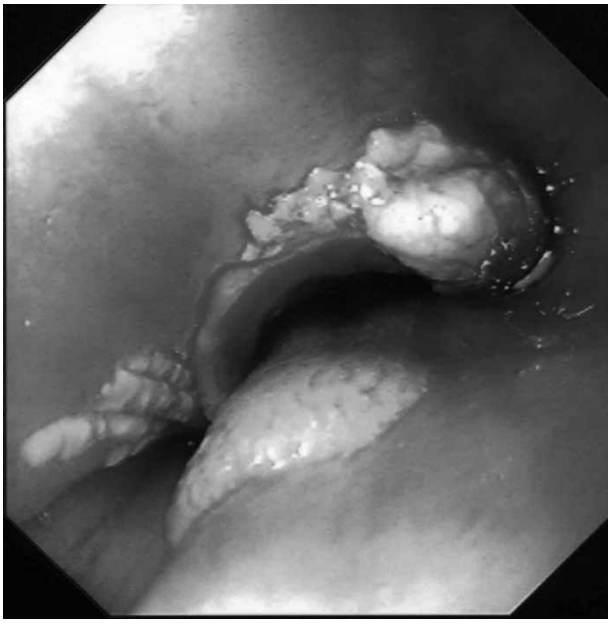

Fig. 2 Moderately differentiated squamous cell carcinoma of the oesophagus (Case 2).

Case 3

This lady (the mother of patient presented as Case 2) suffered from oral thrush since early childhood. She gave a history of growths on the scalp as a child (less severe than in Case 2), and required occasional treatments for vaginal candidiasis. She also had marked periodontal disease, and smoked about 10 cigarettes daily. At the age of 29 she presented with weight loss and progressive dysphagia. Upper gastrointestinal endoscopy showed a granular tumour involving the middle third of the oesophagus. Biopsy confirmed the presence of a well differentiated squamous cell carcinoma of the oesophagus, and the tumour was found to invade the left main bronchus. The patient received palliative radiotherapy and died soon after the diagnosis of cancer was made in 1987. Unfortunately

neither *Candida* species involved in her disease nor their susceptibility to antifungal drugs was known.

Discussion

We describe three cases of CMC without endocrinopathy accompanied by the development of squamous cell oesophageal carcinoma at a young age. Two of the patients had confirmed selective IgA deficiency and one of them had vitiligo. As illustrated in this paper, patients with CMC usually have persistent or recurrent infections of the skin, nails and mucous membranes caused by *Candida* species (generally *Candida albicans*) and rarely develop candidaemia or other forms of invasive candidiasis [7]. They can present one of several clinical syndromes, as follows.

CMC syndromes

Chronic oral candidiasis. These patients usually suffer from recurrent candidiasis of the tongue and oral mucosa, without oesophageal, skin or nails involvement [7]. This is sometimes accompanied by iron deficiency [3]. Chronic oral candidiasis is very common in patients infected with the HIV, where it can present as pseudomembranous, erythematous or hyperplastic candidiasis or as angular cheilitis [8]. Dentures may also be a cause of oral candidiasis, possibly due to reduced bathing of oral membranes with saliva [9]. Inhaled glucocorticoids may suppress mucosal immunity, being described as a potential cause of chronic oral candidiasis [8].

Familial chronic mucocutaneous candidiasis. There are two recognized forms of this disease: autosomal recessive and autosomal dominant. The most striking clinical feature of the autosomal recessive disorder is chronic oral candidiasis. The nails are usually affected and cutaneous candidiasis is less frequent. There is no evidence of any endocrine disorder associated with this syndrome [9]. Most patients manifest symptoms early in life, usually by the age of 2. In a series of 22 patients with familial CMC, there were 7 pedigrees with siblings affected and, in 3 of them consanguinity was established [3]. Both sexes were equally involved and the parents and children of affected individuals were all clinically normal. The autosomal dominant form of the disease was described by several authors [2,10–13]. In the series of Sams *et al*. [2] and Jorizzo *et al*. [10], 9 persons in 3 generations were affected. There were dermatophytosis, alopecia, loss of teeth, and recurrent viral infections in some of the cases. Three out of 8 affected patients had total cutaneous anergy. *Candida* intracranial mycotic aneurysm has also been described in a CMC patient with refractory candidiasis of the mouth and nails [12]. This patient had a family history of chronic mycotic infections of the skin, hair, nails, and mouth. In another family, none of the 4 patients with CMC had clinical evidence of endocrinopathy, however, laboratory studies of the proband showed a positive result for thyroid microsomal and antiparietal cell antibodies, as well as iron deficiency anaemia [13].

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). APECED or autoimmune polyendocrine syndrome type I (APS-I), is an autosomal recessive disorder. The gene for APECED, designated AIRE (autoimmune regulator), is located in chromosome 21q22.3 [14,15]. It encodes a protein that is a transactivator of gene transcription, involved in determination of thymic stromal organization and induction of self-tolerance [16]. The disease is rare except among Finns, Iranian Jews and Sardinians [5]. The phenotype of the disease varies according to the age at onset [17]. Usually it appears in the first decade of life but may also not start until adulthood. The disease can damage or even destroy endocrine glands and other organs. The most affected organs are parathyroid glands, followed by adrenal cortex, ovaries, hair follicles (alopecia), cornea (keratopathy), pancreatic beta-cells (insulin-dependent diabetes mellitus), gastric parietal cells, gonads, skin, melanocytes (vitiligo), liver (autoimmune hepatitis), thyroid gland (hypothyroidism) and pituitary somatotrophs [5].

The first manifestations of this disorder are usually recurrent oral candidiasis, which is believed to be carcinogenic [18], and diaper rash caused by cutaneous candidiasis. The lesions may spread and involve the scalp, extremities, nails and other skin sites [7]. In a series of 68 patients from 54 families with CMC, 47% of the patients had 4 or 5 associated disorders and 60% had 2 or more endocrinopathies [17]. In some patients, adrenal failure and hypothyroidism developed only in the 4th and 5th decades. Therefore, annual evaluations of endocrine function are recommended for patients with CMC. More frequent evaluations are suggested for those patients with endocrinopathy already diagnosed or for those whose siblings have APECED [7]. Patients who are monitored for endocrinopathies and whose candidiasis and infectious complications are treated are expected to have a good life expectancy and a reasonable quality of life [7].

CMC with thyroid disease. In this disorder, a combination of CMC (fungal infections of the skin, nails, and mucous membranes) and thyroid disease segregate as

an autosomal dominant trait with reduced penetrance [1]. It is distinguished from APECED by the mode of inheritance and lack of associated multiple endocrinopathy.

Chronic localized candidiasis. In this form of CMC, the cutaneous lesions present as thick, tightly adherent crusts on the scalp and face (*Candida* granulomas). Most patients also have oral candidiasis presenting during early childhood and both sexes are equally affected. There is no known genetic basis for this form of candidiasis [7].

Chronic mucocutaneous candidiasis with thymoma. This form of disease should be suspected when adults develop mucous membrane and cutaneous candidiasis. The youngest reported case is age 35 years [19]. There is no endocrinopathy, but there may be diseases associated with the thymoma such as aplastic anaemia, myasthenia gravis or hypogammaglobulinemia. Both malignant and benign thymomas have been reported. Removal of the thymic tumour usually is not accompanied by resolution of candidiasis [19].

Candidiasis with chronic keratitis. This seems to be an autosomal dominant disease [7]. Keratopathy was found in 24 of the 68 patients with CMC reported in a case series [17]. An association among alopecia, chronic candidiasis and keratopathy was also described in 2 Turkish siblings; their parents were normal and there was no family history of a similar disorder [7].

Candidiasis with the hyper-immunoglobulin E (IgE) syndrome (HIES). HIES are primary immunodeficiencies characterized by a clinical triad of recurrent staphylococcal abscesses, recurrent cystic pneumonia, and serum IgE levels of >2000 IU/ml [20]. The syndrome is transmitted as a single locus autosomal dominant trait with variable expressivity. Patients with HIES usually have impaired cell-mediated immune responses [21]. A review of 30 patients with HIES showed that 83% also had chronic candidiasis of the mucous membranes and nails [22].

Association between CMC and malignancy

We describe in this series that 3 patients with CMC eventually developed oesophageal cancer and no patient was diagnosed with APECED. Two of these cases were marked by an important family connection, affecting both mother and son. APECED has been associated with oral or oesophageal cancer in a series of Finnish patients with the disease [5,6]. Of 58 patients who were homozygotes or heterozygotes for the mutation R257X, 5 developed oral and 1 developed oesophageal squamous cell carcinoma. Cigarette smoking and high alcohol intake were described for 4 and 3 patients, respectively, which are known aetiologic factors for the development of squamous cell tumours of the mouth and oesophagus. However, in all 6 patients the malignancies appeared between the ages 29 and 44, while most people without APECED who develop oesophageal and oral cancer are over 60 years old [23]. Five of the 6 malignancies were aggressive and showed a poor response to treatment so the existence of a genetic predisposition linking APECED to squamous cell cancer has been suggested, although not proven. The authors concluded that the malignant neoplasms were presumably induced by chronic candidiasis [6]. In another case repost, two patients with CMC were found to have oral cancer in the 4th decade of life [4]. The natural history of these tumours was more aggressive than the usual, with a clear metastatic potential in one case and the presence of three separate oral tumours in the other case. The authors suggested that a state of altered immunity known to occur in CMC could be the cause for the development of oral cancers. However, this suggestion was only speculative. In our first patient the tumour was less aggressive than is typical and indeed could not be confirmed histologically until death 2 years after presentation. In the second case the cancer was much more aggressive despite active intervention. Case 3 already presented with advanced stage malignant disease and received palliative care only.

IgA deficiency was confirmed in 2 of our patients (patient 3 was not tested). IgA is the principal class of antibody in secretions, including saliva, tears, milk, and respiratory and intestinal secretions. Selective IgA deficiency is the most common form of antibody deficiency. Usually, patients with isolated IgA deficiency do not suffer from any particular disease. When disease is present, however, it takes the form of sinopulmonary infections, a sprue-like syndrome, or autoimmune disorders [24]. In the absence of IgA, certain organ systems (mainly the gastrointestinal and lymphoid tissues) may be at increased risk for malignant transformation [25]. IgA deficiency has been associated with CMC [26]. It has also been associated with the development of solid tumours like gastric adenocarcinoma [27–30], cervical carcinoma [31], colorectal adenocarcinoma [32,33], squamous cell carcinoma of the skin [34] and lung carcinoma [35,36]. It was suggested that the association of IgA deficiency and gastric carcinoma may be related to the inability of IgA molecules to fix complement [24]. There are no

reports on the association of oesophageal cancer and IgA deficiency in the literature. However, as it was already shown that local and systemic immune responses may influence the natural history of oesophageal squamous dysplasia [37], with progression to cancer, further studies looking at the possible association of IgA deficiency and oesophageal cancer seems worthy.

In a rat model of oral mucosal candidiasis combined with a model of oral mucosal carcinogenesis, *Candida albicans* directly promoted the development of neoplasia in oral epithelium that had been primed with a carcinogenic stimulus, suggesting direct participation of *C. albicans* in neoplastic transformation in humans [38]. Strains of these yeasts from human oral precancerous lesions showed a high potential to form N-nitrosobenzylmethylamine (NBMA) from the precursors N-benzylmethylamine and nitrite, maybe playing a causal role in the development of oral cancer [39]. An *in vitro* study showed that *C. albicans* strains have a marked capacity to produce toxic and carcinogenic acetaldehyde from ethanol in saliva samples, what may be an important aetiologic factor for the development of oral cancer associated with ethanol consumption [40]. There is also description of chronic hyperplastic candidosis (or candidal leukoplakia) of the oral mucosa associated with epithelial dysplasia and potential for the development of squamous cell carcinoma at the lesional site [41–43]. All these factors together may suggest that chronic infection by *Candida* species, especially *C. albicans*, may be a contributing factor to the development of oral cancer in patients with CMC. The same could be true for oesophageal cancer, considering that all 3 patients we describe had evidence of long term oesophageal candidiasis.

Conclusions

This is the first case report describing the development of oesophageal cancer in patients with CMC without the APECED syndrome. Besides the carcinogenic potential of *Candida* species, one could speculate that a genetic defect responsible for the altered T-cell function in patients with CMC could be an important factor in the development of squamous cell cancer, as suggested by Rautemaa *et al*. [5].

According to the large Finnish experience [5], patients with CMC need close follow-up with good oral hygiene and aggressive treatment of oral and oesophageal candidiasis. Secondary long term prophylaxis with antifungal drugs seems justified in CMC patients suffering from chronic *Candida* infections, and erosive oesophageal lesions lasting more than 2 weeks should be biopsied to exclude malignancy. Based on the 3 cases described in this case report, we would also suggest routine endoscopic screening for patients with CMC that develop symptoms of oesophageal candidiasis and for patients with CMC with a family history of oesophageal cancer, as the sister and daughters of the second patient described above. Unfortunately, as biopsies might be falsely negative for malignancy, the best screening strategy for these patients remains to be elucidated. Avoidance of additional risk factors for oral and oesophageal cancer like cigarette smoking and excessive alcohol consumption are also warranted.

Conflicts of interest

None to declare.

Authorship contributions

DDR, ACP and DWD conceived of the study, participated in its design and coordination, and drafted and approved the final manuscript.

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