Case Reports

Esophageal cancer associated with chronic mucocutaneous candidiasis. Could chronic candidiasis lead to esophageal cancer?

MAURÍCIO DOMINGUES-FERREIRA,* ANETE SEVCIOVIC GRUMACH,* ALBERTO JOSÉ DA SILVA DUARTE & DEWTON DE MORAES-VASCONCELOS*

*Primary Immunodeficiency Outpatient Unit, and †Laboratory of Medical Investigation in Dermatology and Immunodeficiencies, University of São Paulo School of Medicine, São Paulo, SP, Brazil

Chronic mucocutaneous candidiasis (CMC) is a rare disease associated with immunodeficiency and characterized by persistent and refractory infections of the skin, appendages and mucous membranes caused by members of the genus Candida. Several different disorders are classified under this common denominator, including chronic and recurrent mucocutaneous infections due to Candida spp., which are sometimes linked to autoimmune endocrinopathies. These fungal infections are usually confined to the mucocutaneous surface, with little propensity for systemic disease or septicemia. We describe a patient with CMC who had an esophageal candidiasis refractory to treatment for decades and who developed an epidermoid esophageal cancer. No risk factors such as familiar susceptibility, smoking, alcohol drinking, or living in an endemic area were verified. This case report suggests the participation of nitrosamine compounds produced by chronic Candida infections as a risk factor for esophageal cancer in a patient with autosomal-dominant chronic mucocutaneous candidiasis.

Keywords Chronic mucocutaneous candidiasis, esophageal cancer, Candida infection, nitrosamines, carcinogens, primary immunodeficiencies

Introduction

Chronic mucocutaneous candidiasis (CMC) refers to a heterogeneous group of rare disorders characterized by recurrent or persistent superficial infections of the skin, mucous membranes and nails caused by Candida spp., usually Candida albicans. The incidence may be familiar or sporadic. A specific subgroup of CMC patients who present autoimmune polyendocrinopathy associated with ectodermal dysplasia (APECED), showing an autosomal recessive inheritance. In this group, mutations in the AIRE gene (autoimmune regulator) have been identified [1]. An autosomal dominant form of CMC is associated with hypothyroidism, and a genetic defect has been suggested for chromosome 2p [2]. Genetic defects for other variants of CMC have not been reported. There have been three previous reports of the association of CMC with neoplasias, i.e., oral squamous carcinoma [3,4], thymoma [5] and recently, esophageal cancer [6,7]. A significant characteristic of these CMC cases is the fact that the patients presented with persistent and long established esophageal candidiasis and it has been proposed that this situation could
expose the esophageal mucus to carcinogens produced by the chronic infection.

The etiology of esophageal squamous cell carcinoma (ESCC) has been shown to be associated with genetic factors, as well as certain environmental stimuli, that damage DNA. It is recognized that smoking and alcohol consumption are major risk factors for esophageal cancer [8]. In small and specific endemic areas around the world, environmental exposure is the most important cause, probably due to dietary factors. In addition, some epidemiological studies suggest that nutritional deficiencies [9] and the ingestion of mycotoxins and nitrosamine compounds are other important factors related to the appearance of esophageal squamous cancer [10]. All these factors can induce or enhance DNA damage mediated by either oxidative stress or DNA-binding electrophiles, which in turn may initiate and/or promote carcinogenesis [11]. Few studies have tried to correlate the association of candidiasis and esophageal cancer [12,13]. The factors linking the development of neoplasia and CMC are unknown, but it is intriguing that one may find the presence of oral and esophageal cancer in patients with persistent oral and esophageal candidiasis. We describe a patient with CMC who had an esophageal candidiasis refractory to treatment for decades who developed an epidermoid esophageal cancer. As a result of this case, we present a hypothesis to explain this possible association.

Case report

A 43-year-old male patient, from a nonconsanguineous family, first presented oral candidiasis at two years of age. He developed onychomycosis and cutaneous lesions on the face and trunk, refractory to antifungal treatment associated with transfer factor. The skin and subsequent nail lesions eventually faded away, as was expected. Throughout his life several therapies were introduced to control the oral and esophageal candidiasis, without adequate control of the mucous lesions (Fig. 1). He was neither diabetic nor did he have other endocrinological diseases. He had two episodes of bronchopneumonia as a teenager and at 28 years of age, pulmonary tuberculosis was diagnosed, which was successfully treated without any relapse. During his follow-up, he complained of dysphagia and was submitted to an upper digestive endoscopy that showed a nodular lesion in the proximal region of the esophagus, diagnosed as an epidermoid carcinoma (Fig. 2). Due to the size of the tumor (Fig. 3) and its proximity to the large vessels (Fig. 4), the tumor could not be excised and the patient received radiotherapy and chemotherapy prior to the surgery. The patient was not alcoholic nor a tobacco smoker and had always lived in São Paulo metropolitan area, which is not an esophageal cancer endemic area. He was submitted to a second phase of chemotherapy, with partial response and died due to pulmonary metastases and pulmonary arrest. Familial antecedent of esophageal cancer was not reported but he had two sons both of whom had chronic mucocutaneous candidiasis.

Immunologic evaluation

When analyzing the patient’s laboratory follow-up studies, we noted a normal and stable number of lymphocytes and their subsets. His proliferative response via CD2 (PHA) and CD3 (OKT3) receptors and the T cell dependent stimulation of B lymphocytes (PWM) were normal. Moreover, his mononuclear cells responded adequately to Candida antigens despite his

Fig. 1 Photo of the patient showing cheilitis angularis and whitish plaques in the tongue secondary to Candida infection.

Fig. 2 Histopathological appearance of the squamous cell carcinoma of the esophagus.
evident susceptibility to persistent mucocutaneous Candida infections. His natural killer function as assessed by a Cr51 assay was also normal. Nevertheless, a significant immunological dysfunction was found with respect to the modulation of immune functions induced by his serum, such as suppression of mitogen and antigen induced lymphoproliferation, NK cytotoxic activity, and IL-2 secretion. On the other hand, there was an enhancement of IL-4 secretion and lymphocyte apoptosis (data presented elsewhere) [14].

Discussion

The main causes of esophageal cancer in Brazil are alcohol and smoking. Southern Brazil presents the highest incidence of esophageal cancer in the country and in Latin America and is associated with hot Mate tea drinking [15]. Our patient lived in a non-endemic area for esophageal cancer, did not present habitual alcoholic drinking or smoking and did not regularly consume hot Mate. So, he did not fit the profile of a typical patient prone to develop this type of cancer. The single outstanding feature that captured our attention, was the prolonged period that the patient presented oral and esophageal candidiasis, which was refractory to any treatment for decades.

Very recently two papers reported an association of esophageal cancer and CMC [6,7], but presented conditions different to ours. The Finnish report described one APECED patient with esophageal cancer, but this individual was also a regular smoker since his teen years and a high consumer of alcohol during his last years of life [6]. Rosa et al. [7] described three CMC patients with IgA deficiency (one not confirmed but who was a smoker). There was no information as to if they live in an endemic region for esophageal cancer. Association of IgA deficiency and neoplasias, mainly of the stomach and lymphoproliferative disorders have been described before [16,17]. Therefore the association of esophageal carcinoma without any other potentiating factors has never been described in familial CMC, making this the first report.

Another interesting point is that our patient presented an autosomal dominant form of CMC. There was no consanguinity and no other cases of CMC in his family prior to his own but both his sons presented CMC. Although endocrinopathy or autoimmunity were not found in this family, the severity of fungal infection was relevant. One of his sons died after a severe pulmonary infection (18 years of age) and the other one presented a complication of fungal infection (manuscript in preparation). These findings suggest a possible more severe immunologic disturbance in this family.

The absence of the usual predisposing factors and the specific clinical characteristics of CMC raised further questions as to whether chronic esophageal candidiasis leads to squamous cancer. Several studies
implicate *Candida* spp. infections in the development of oral cancer [18–20]. It seems likely that the continuous chronic inflammatory process due to persistent candidiasis in the esophagus contributed to the genesis of esophageal cancer. This kind of association is not epidemiologically relevant, but in the context of a rare disturbance with multiple distinct clinical facets, such as CMC, this association could be important.

Besides the immunologic disturbance involved in CMC, it is well established that nitrosamine compounds provoke esophageal cancer in rats [21,22]. Furthermore, some studies suggest that nitrosamine compounds in humans could trigger cancers of the stomach [23], nasopharynx [24], esophagus [25], mouth [26,27] and lung [28].

In relation to lung cancer the most important carcinogen-derived biomarkers currently being studied are those derived from lung carcinogens found in tobacco smoke, i.e., 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane and polynuclear aromatic hydrocarbons [28]. Some reports indicate that the participation of certain bacteria in the production of *N*-nitroso-*N*-methylbenzylamine (NBMA) through nitrite reductase and nitrate reductase in nitrosation catalysis [29,30] or by a direct chemical reaction between secondary amino compounds and nitrites. The latter is strongly pH dependent and does not proceed rapidly. Leach *et al.* demonstrated that the reaction mediated by bacteria is catalyzed by bacterial enzyme systems and proceeds much more rapidly at neutral pH than the spontaneous chemical reaction [31]. However, bacteria are not the only microorganisms implicated in NBMA synthesis; some studies have suggested that the high incidence of esophageal carcinoma in certain regions of Africa could be related to the action of the *Fusarium* spp. These fungi grow freely on maize, producing fumonisins, which reduce nitrites to nitrites and synthesize cancer-inducing nitrosamines. Nitrosamines are the presumed carcinogens in these cases. A traditional drink made of maize is a common beverage among males in some African countries with a high incidence of esophageal cancer [32,33]. Krogh *et al.* demonstrated the catalytic potential of *Candida* isolates recovered from leukoplakia lesions and from normal mucosa, for producing NBMA from the precursors *N*-benzyl-methylamine and nitrite [19]. They observed a different nitrosation potential for each *Candida* species isolated, ranked from 0 to 1.2 micrograms of NBMA/10⁶ cells. *C. albicans* strains showed the greatest nitrosation potential, whereas *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* were ranked lower. The yeasts with greater nitrosation potential were generally isolated from lesions with more advanced precancerous changes. This evidence provides support for the hypothesis that yeasts play a causal role in oral cancer by means of endogenous nitrosamine production [19]. Another interesting study by Hsia et al. [34] demonstrated the ability of *Candida albicans* to increase the nitrosative formation of the esophagus-specific carcinogen, benzylmethylnitrosamine (NBMA; *N*-nitroso-*N*-methylbenzylamine). In their study *C. albicans* was cultured at pH 6.8 with the precursors of NBMA, benzylmethylamine (BMA; *N*-methylbenzylamine) and NaNO₂. They observed a significant increase in the amount of NBMA formed in these cultures, compared to precursor-only controls. The amount of NBMA synthesized was directly related to the fungal cell number. It was suggested that cultured *Candida* released acidic metabolites that reduced the pH of the medium when only a low concentration of buffer was present. Spontaneous nitrosation of BMA was enhanced under these acidic conditions, although cell-mediated catalysis is another possibility. *Candida* spp. could catalyze the formation of NBMA by enzymes. They concluded that *C. albicans* infecting the esophageal epithelium could cause local formation of NBMA by both cell-mediated catalysis and by extracellular decrease in pH [34].

The careful evaluation of the singularity of our case suggest that the prolonged exposition to *Candida* due to immunologic disturbance and the production of NBMA by the fungus is probably related to the development of esophageal cancer in CMC patients. Therefore, this association is not probably a casual occurrence.

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**References**

6. Rautemaa R, Hietanen J, Niisalo S, Pirinen S, Perheentupa J. Oral and esophageal squamous cell carcinoma—a complication or component of autoimmune polyendocrinopathy-candidiasis-ecto-

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