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Oral and oesophageal squamous cell carcinoma — A complication or component of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, APS-I)

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Summary Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive disease exceptionally common in Finland. It is associated with a limited T lymphocyte defect, an autoimmune response to various tissues, particularly endocrine glands. Most patients have chronic oral candidosis, which has been suggested to be carcinogenic. In Finland 92 patients have been diagnosed with APECED and 66 of them are alive. Our aim was to study the possible association of APECED with oral and oesophageal carcinoma. We evaluated the medical histories of all 92 patients for morbidity, causes of death, and known risk factors for oral cancer. We invited all current patients for a clinical examination of their oral mucosa. Six of the 92 had developed oral or oesophageal squamous cell carcinoma (SCC) by the mean age of 37 (29–44 years) and four of them had died from it. The six represent 10% of the patients older than 25 years. Five of the six patients had long-lasting oral candidosis. Four of the six had

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smoked regularly for 15 years or more. One patient had been on immunosuppressive therapy for 6 years following kidney transplantation when SCC in her mouth occurred. The partial T cell defect of APECED seems to favour the growth of *Candida albicans* and predispose to chronic mucositis and SCC. Aggressive control of oral candidosis and close follow-up of oral mucosa is a necessity in patients with APECED.

Introduction

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), or autoimmune polyendocrine syndrome type I (APS-I),[1–3] is an autosomal recessive disease caused by mutations of the *AIRE* (autoimmune regulator) gene.[4–6] Its phenotype is widely variable regarding the components of the disease and age at onset.[1–3] The first components appear in most cases in the first decade of life but they may be delayed until adulthood. The disease occurs all over the world, but is rare except among Finns, Iranian Jews and Sardinians. In Finland 92 patients have been diagnosed with the disease since 1963 and 66 of them are currently alive.

Several endocrine glands and other organs may be destroyed or damaged by the patient's immune system. In approximate decreasing order of incidence these are parathyroid glands, adrenal cortex, ovaries, hair follicles, corneas, pancreatic bb-cells, gastric parietal cells, testes, skin melanocytes, liver parenchyma, thyroid gland, and pituitary somatotrophs. Ectodermal dystrophy may affect dental enamel, nails, and tympanic membranes. The most common component is oral candidosis which has been suggested to be carcinogenic.[1,2,7,8] Most patients can live a relatively normal life provided that their endocrine deficiencies are carefully substituted for.[1,2] The mean age of the Finnish patients currently is 31.8 years (2.8—60.5 years). The mean age at death has been 32.0 years (2.8—63 years) but a better understanding of the disease, a more close follow up and appropriate treatment appears to prolong life.

APECED is caused by mutations in the *AIRE* gene in chromosome 21q22.3.[8] The 545 amino acid Aire protein is a transactivator of gene transcription.[6,9,10] It appears to be involved in determination of thymic stromal organization and induction of self-tolerance.[11,12] At least 58 different mutations of *AIRE* have been described in patients with APECED.[5,9,13–15] Most of them are either missense mutations presumably preventing the necessary dimerization of Aire, or nonsense mutations leading to truncation of the protein. The internationally most common mutation, R257X, leads to loss of the C-terminal half of the protein. It covers almost 90% of the Finnish APECED genes.[4] The second most common mutation,[9] predominant in the USA,[13] and UK,[15] is a 13 nucleotide deletion. It is unclear whether the clinical picture of APECED depends on the type of the mutation. An exceptionally low prevalence of candidosis has been reported in Iranian Jewish patients,[16] who have a unique uniform missense mutation, which in contrast to the other mutations does not seem to prevent accumulation of the Aire protein into nuclear granules.[9]

From 1997 to 2001 the average annual incidence rate of primary cancer of the oral cavity was 1.4 for males and 0.7 for females per 100,000 population in the Finnish Cancer Registry.[17] On average, 185 new cases of primary cancer of the oral cavity (105 males, 80 females) and 219 new cases of primary cancer of the oesophagus (137 males, 82 females) were registered annually. The mean age at diagnosis for cancer of the oral cavity has been reported to be 62 years for males and 68 for females and for cancer of the oesophagus 68 and 72 years, respectively.[18] The most common morphological entity of these cancers is squamous cell carcinoma (SCC). We now report on a life-threatening association between APECED and oral and oesophageal SCC. Of our 58 patients over the age of 25, six have developed this malignancy and four have died from it. At the same time no other types of malignancies have been diagnosed in these patients.

Patients and methods

We reviewed the medical histories of all known 92 Finnish patients (45 males) with APECED for morbidity, causes of death, and known risk factors of oral cancer. The mean age of the Finnish patients today is 31.8 years (2.8—60.5 years). Of the patients 5 were under 10 years of age, 21 were 10—19 years old, 18 were 20—29 years, 22 were 30—39 years, 16 were 40—49 years and 10 were over 50 years. The histories were obtained from the Hospital for Children and Adolescents where most of the patients had been followed up even in adulthood by two of the authors (JP and SP); the Oral and Maxillofacial Unit of Helsinki University Central Hospital; and from other Finnish hospitals. We invited 62 of the patients, 15—62 years old, to a clinical check-up for oral mucosal lesions.

Results

The case histories of the six Finnish APECED patients who have developed oral or oesophageal squamous cell carcinoma are presented here.

Patient 1

This man, born in 1922, is the only patient we have not clinically examined and whom we diagnosed postmortem based on his history and his sister's clinically unequivocal APECED: hypoparathyroidism, diabetes mellitus, pernicious anaemia and candidosis. The patient had destructive nail candidosis by the age of 10 years and until his death, but no oral complaints suggesting an oral yeast infection were recorded. He developed alopecia by the age of 18 years which turned universal in some years. He was a regular smoker since his teen years, consuming a 20-pack of strong cigarettes daily until