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Clinical Vignette: Early-Onset Head and Neck Cancer: Beware of Fanconi Anaemia!

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Introduction

Our department recently received a letter of referral from an otolaryngologist concerning a 31-year-old Caucasian male with inoperable (T4N2c) squamous cell cancer of the base of his tongue. According to this letter, a brother of the patient had died from early-onset cancer of the soft palate a few years ago. The patient and his two healthy siblings were referred with the question whether or not a hereditary cancer-predisposing disorder was present in this family. The letter also mentioned the fact that the patient would receive an experimental combination of radiation treatment and chemotherapy.

Without knowing any further clinical details, the possibility of Fanconi anaemia (FA) [1] crossed our minds. Oral cancer is a very rare diagnosis in young individuals from the Dutch general population, with incidence rates per 100,000 person-years being smaller than 0.5 for cancer of the palate or tongue in the 30-34-year age group [2]. Fanconi anaemia, an autosomal recessive disorder, is associated with early-onset head and neck cancer and a range of other neoplasms [3-5]. The fact that no congenital anomalies had been mentioned in the referral letter did not exclude the possibility of FA, because either the otolaryngologist might not have realized their importance with respect to a genetic diagnosis, or they simply had not been present as would be expected in up to one-third of FA patients [6]. We were concerned about the scheduled treatment because of the strongly increased risk of complications after therapy with mutagenic agents (chemical or radiation) in FA patients [3, 7-10]. Immediately but unsuccessfully, we tried to contact the referring physician by telephone. An urgent letter was therefore sent to this physician, mentioning the fact that FA was at least a theoretical possibility in this patient (who we had not seen yet) and might severely complicate his treatment. An offer to quickly test the patient's lymphocytes for signs of FA (increased chromosomal breakage and structural rearrangements after culture with the DNA cross-linking agent mitomycin C) was included. We also contacted the family physician who informed us that the patient had declined further treatment and had already died around the time we received the letter of referral. Upon explaining the reason for our inquiry, we were surprised to learn that the deceased brother of the patient had indeed been diagnosed with FA as a child! The old medical files of both brothers were retrieved.

The brother of the referred patient had been diagnosed with Fanconi anaemia in his late teens on the basis of pancytopenia, increased HbF, short stature (<P3, skeletal age several years behind

calendar age), horse-shoe kidney, axillary and inguinal hyperpigmentation, a few café-au-lait spots on the skin and increased chromosomal breakage typical for FA. He was diagnosed with squamous cell cancer of the soft palate at the age of 31 and died at the age of 34 (no details on treatment are available). His younger brother (the referred patient) had been diagnosed as a teen with short stature (<P3, skeletal age several years behind calendar age), persistent mild leukopenia and thrombopenia and a severe congenital sub-pelvic stenosis of one of his kidneys. Although the patient had not been tested for chromosomal breakage, it is fair to assume that he had FA as well. For reasons unknown to us, the referring otolaryngologist had not been aware of the diagnosis of FA in this family or had not realised its association with head and neck cancer.

The parents and their two healthy adult children (i.e. sibs of the deceased patients) were seen at our familial cancer clinic. At their own request, the children were tested for chromosomal breakage and rearrangements, with normal results. The parents as well as their children expressed sincere amazement after learning about the diagnosis of FA in their family and its association with head and neck cancer and other neoplasms. The parents could not recollect having ever heard about this disorder before, although we assume that the paediatricians have discussed it with them many years ago. No follow-up aimed at early detection of cancer had apparently been performed in their adult sons with FA. Current FA guidelines do advise such surveillance [5, 11] and include gynaecological examination and Pap smears, annual rectal examination, and frequent dental and oropharyngeal examinations. Annual oesophageal endoscopy has also been recommended. We cannot help feeling that if medical (oncological) surveillance had been more aggressively pursued after childhood in these two brothers with Fanconi anaemia, their early deaths might have been prevented. This case also makes one wonder which proportion of FA patients that reach adulthood and are lost to paediatric follow-up, are actually under recommended oncological surveillance. We would like to conclude this paper on a more positive note. This clinical history illustrates the increasing trend we observe among clinicians from disciplines that did not traditionally refer many patients for (onco)genetic analysis, to recognise early-onset cancer as an important warning sign of inherited cancer predisposition and to consult a family cancer clinic in those cases. An overview of referral guidelines for cancer genetics consultations has recently been published [12]. To those we would like to add that in the case of early-onset head and neck cancer, the possibility of Fanconi anaemia, and therefore referral, should always be very seriously considered.

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