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Case Report

Head and Neck Carcinoma in Fanconi's Anaemia—Report of a Case and Review of the Literature

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Fanconi's anaemia (FA) is a rare autosomal recessive syndrome characterised by progressive lethal pancytopenia, skeletal abnormalities, hyperpigmentation and increased chromosomal aberrations. A high incidence of leukaemia and hepatocellular and squamous cell carcinomas (SCC) have been reported in FA patients. A rare case of SCC of the dorsum of the tongue in a FA patient is presented. A review of the reported cases of head and neck carcinoma in FA patients shows a different male: female ratio than previously reported, and a high incidence of carcinoma of the tongue.

Keywords: Fanconi's anaemia, head and neck carcinoma

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INTRODUCTION

FANCONI'S ANAEMIA (FA) is a rare autosomal recessive syndrome first described in 1927 as a progressive lethal anaemia and brown pigmentation of the skin. Subsequently, this term was extended to a syndrome that included pancytopenia with hypoplastic bone marrow, skeletal, renal and ophthalmological deformities, and chromosomal aberration [1, 2]. The outcome is always fatal, most patients dying from pancytopenia-related sepsis [3]. An increasing number of reports connect FA with a high incidence of squamous cell carcinoma (SCC) of the mucous membranes, hepatocellular carcinomas, and leukaemia [4].

The first case of head and neck carcinoma (HNC) in a FA patient was reported by Esparza and Thompson in 1966 [3], and since then another 16 cases have been described [4–6].

This paper is a review of all reported cases of FA with HNC, including a new case of FA with SCC of the dorsum of the tongue. Carcinoma of the dorsum of the tongue is a rare entity [7], and to the best of our knowledge this is the first report of its association with FA.

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CASE REPORT

A 32-year-old Caucasian woman was referred to our unit in 1990 with a tongue lesion of 2 years' duration diagnosed as mycotic and treated accordingly with nystatin. Diagnosed with FA in 1972, she has been treated since then with 10 mg/day prednisone and intermittent blood transfusion. On admission, she presented with typical signs of FA, including small stature (152 cm), dry brown-grey pigmentation, mild diabetes mellitus, and advanced chronic periodontitis. A previous genetic survey had shown chromosomal aberrations (hyperploid, hypoploid and normoploid cells with multiple chromosomal breaks). The haematological tests revealed an advanced stage of pancytopenia (1.5×10^9/l, Hb 8.6 g/dl, and platelets 13×10^9/l).

Poor hygiene, missing teeth, multiple caries, and advanced periodontal disease were found. The oral mucosa was erythematous with white patches on both angles of the mouth, and the tongue was covered with a thick layer of Candida. A well-circumscribed exophytic lesion of 3 cm diameter was seen on the anterior third of the right side. There was no cervical adenopathy.

An incisional biopsy under local anaesthetic revealed a well-differentiated SCC. Considering the poor systemic condition and the advanced stage of FA, a partial glossectomy with primary closure was performed under general anaesthesia. Intra-operative bleeding was controlled by whole blood and platelet transfusion as well as resection with CO_2 laser (20 W continuous mode). The patient recovered, and the surgical wound healed in spite of her poor physical condition and a severe Klebsiella and Pseudomonas sepsis, which developed postoperatively.

Table 1. The age distribution of cancer in FA patients

	No.	Average Age
Children	4	12.0±1.2
Adults	12	26.8±6.4
Total	16	23.1±8.5

The age of one of the study patients was unknown (8).

Table 2. Distribution by site of SCC in FA patients

Head and neck		Intraoral		Tongue	
Intraoral	12	Tongue	9	Lateral	4
Nasopharynx	4	Mucosa	1	Dorsum	1
Oesophagus	1	Gingiva	3	Base	2
				Unknown	2
Total	17		13		9

Two months later she was again hospitalised because of a rapidly growing right submandibular mass diagnosed by a fine-needle biopsy as a poor-to-moderately differentiated SCC. Radiotherapy of the neck was performed on a day-care basis, as advancing pancytopenia (WBC 1.1×10^9/l, RBC $2.48 \times 10^6/mm^3$, Hb 8.8 g/dl, and platelets $10/l \times 10^9$) ruled out chemotherapy or radical surgery.

One month later she was admitted with severe bleeding from the oropharynx, oral mucosa, and gingiva due to radiation mucositis. She was treated with a cold solution of tranexamic acid and thorough oral hygiene. Prophylactic mezlocyllin and gentamicin and supportive intravenous (i.v.) hyperalimentation and blood transfusion were given. At this stage the blood count dropped to 5.7 g/dl Hb, 0.2×10^9/l WBC and 7×10^9/l platelets. Gradually the symptoms disappeared, and her physical state improved. The metastatic growth disappeared, although she had received only 3.2 Gy. She died 6 months later from sepsis.

Table 3. Sex distribution of FA cancer patients

	Head and neck		Intraoral		Tongue	
	No.	%	No.	%	No.	%
F	10	58.8	7	53.8	4	44.4
M	7	41.2	6	46.2	5	55.6
Total	17	100	13	100	9	100

DISCUSSION

We reviewed 16 cases of HNC in FA patients reported in the literature, in addition to our own case.

FA is a rare familial autosomal recessive condition [2], and 5 of the 17 patients had additional family members with FA [1, 3, 4, 5, 8]. The average age of onset of FA is 4–7 years. Males are affected twice as often as females [4]. Bone marrow failure develops gradually up to the second or third decade, and the majority of patients die of sepsis within 5 years of becoming anaemic [2]. A pre-anaemic phase has recently been recognised, and a less severe or incomplete form has been observed [9]. Patients in this latter group tend to develop malignancies more frequently than others.

The propensity of FA patients to develop secondary malignancies such as carcinoma and leukaemia is well documented. Kaplan *et al.* [4] suggested that there are two major defects that play a role in the development of malignancies in FA patients: defective DNA repair and immunodeficiencies. Chromosomal studies in FA have shown an increased spontaneous instability, particularly in lymphocytes. Aberrations such as breaks, fragments, endoduplication and discentric centromeres have been described [1]. Investigators have found increased chromosomal instabilities to such mutagens as mitomycin C, cyclophosphamide, diepoxybutane, and long wave-length ultraviolet light [10, 11]. None of the reviewed FA patients was reported to have normal chromosomes. Of the 8 patients with HNC in FA who underwent chromosomal studies, all had abnormalities. Abberations seen in FA patients appeared to be similar to those seen following radiation injuries or viral infection [1]. DNA function is impaired, as manifested by a breakdown in the repair of chromosomal cross-linking induced by polyfunctional alkylating agents [12].

Table 4. The distribution of SCC in reported FA patients by site, age, and sex

	Total		Adults		Children	
	Female	Male	Female	Male	Female	Male
Head and neck						
No.	10	7	9	4	1	3
Ave. age	24.9±7.4	20.1±9.4	26.4±6.0	26.0±6.4	11	12.3±1
Ratio F:M	1.44		2.25		0.33	
Intraoral						
No.	7	6	6	3	1	3
Ave. age	22.1±6.2	19.2±1	22.4±3.3	29.5±8.5	11	12.3±1
Ratio F:M	1.16		2.00		0.33	
Tongue						
No.	4	5	3	3	1	2
Ave. age	23.0±8.2	20.5±10.8	27.0±5.0	29.5±8.5	11.5±0.5	
Ratio F:M	0.80		1.00		0.50	

Table 5. Clinical and histological characteristics of carcinomas in FA patients

Ref. no.	Site	Grade	TNM	Clinical presentation
1	Rt. pyriform sinus	Moderately differentiated	$T_4N_0M_0$	3 × 4 cm, fungating lesion
4	Lt. lat. tongue	Moderately differentiated	$T_1N_0M_0$	1.5 cm diam, erythematous lesion indurated margins
6	Rt. lat. tongue	Poorly differentiated	$T_1N_0M_0$	7 × 3 mm, oval superficial ulceration
15	Lt. lat. tongue	—	$T_1N_0M_0$	1 × 2 cm, raised lesion, indurated margins
20	Lt. gingiva and mandible	Well differentiated	—	Huge radiolucent lesion tooth 44–36, exophytic purulent lesion area 36
2	Posterior cricoid	—	$T_1N_1M_0$	Ulcerative lesion
23	Tongue	Well differentiated	$T_4N_1M_0$	7 × 7 × 3 cm, white necrotic fungating lesion
9	Oral mucosa	Well differentiated	$T_3N_0M_0$	3 × 4 ulcerative lesion, white necrotic areas
24	Pyriform sinus	Moderately differentiated	—	Ulcerative lesion
*	Dorsum of tongue	Well differentiated	$T_2N_0M_0$	3 cm diam, round exophytic lesion

*Our case.

Table 6. Reported treatment modalities and outcome in FA cancer patients

Case no.	Site	Main treatment modality	Adjuvant therapy	Outcome at reported time
1	Pyriform sinus	Pharyngoesophagectomy and rt. radical neck dissection and reconstruction with free jejunal graft	—	Alive
3	Oesophagus	Resection, reconstruction with transverse colon	Co60 therapy before surgery	Died after surgery
4	Tongue	Partial glossectomy and suprahyoid neck dissection	—	Alive after 18 months
6	Tongue	Partial glossectomy	—	Alive
2	Post cricoid	Pharyngolaryngectomy, rt. radical neck dissection and reconstruction with free jejunal graft	Radiation therapy, 3250 rads	Died 1 year after surgery due to metastasis
15	Tongue	Partial glossectomy	—	Alive
25	Tongue and gingiva	Cryosurgery	—	Died of sepsis
20	Gingiva	Radiation therapy, 6800 rad	Bleomycin	Died of sepsis
22	Tongue	Partial glossectomy	Radiation therapy	Alive after 1 year
23	Tongue	—	Cis retinoic acid and 5-fluorouracil	Died after 3 months
9	Oral mucosa	Cryosurgery	Radiation therapy, 5600 rads	Died after 1 year
24	Pyriform sinus	Chemotherapy—pepleomycin	—	Died of haemorrhage
*	Tongue	Partial glossectomy, CO_2 laser	Radiation therapy, 3200 rads	Died of sepsis

*Our case.

Other parameters related to impaired DNA repair are decreased hexokinase and ATP levels in lymphocytes.

The tendency to malignant transformation can also be seen in the increased susceptibility of fibroblast culture from FA patients to transformation by oncogenic simian virus (SV-40) [13, 14]. Todaro *et al.* [14] showed that this tendency was ten times higher than in normal fibroblasts.

FA patients are genetically prone to the development of leukaemia, hepatocellular carcinoma and SCC of the mucous membranes. Reed *et al.* [1] found that patients who develop SCC were an average of 17 years older than those who develop leukaemia (average 14 years old). Kennedy and Hart [15] showed that those patients with relatively mild bone marrow problems in the pre-anaemic phase who are able to survive up to the third and fourth decade are at risk of developing SCC. Okuyama and Mishima [16] found that the average age when

*Table 7. Time lapse between the age of diagnosis of FA and the age of diagnosis of SCC in 13 reported patients**

	No.	Average time lapse (year)
Adults	9	12.8±5.5
Children	4	5.0±2.1
Total	13	10.5±6.0

*See refs [8, 13, 24].

these tumours developed was 23+6.9 years. In the present review of head and neck SCC among FA patients, two distinct age-groups were distinguished (Table 1): a children's group averaging 12 years of age, and a young adult's group averaging 26.8 years of age. Both of these groups are much younger than the average HNC carcinoma patients in the general population (45 years of age) [17].

Kennedy and Hart [15] pointed out that SCC has a marked affinity for the mucous membranes of the anogenital and oral areas. In his review he found that of 14 cases—5 where carcinoma involved more than one mucosal site (e.g. anus +vulva, tongue+gingiva)—9 were intraoral, 2 were in the oesophagus, 2 in the anal mucosa and 6 in the genital mucosa. Only the carcinomas of the head and neck area were included in this review. Of a total of 17 cases found in the literature, 9 were on the tongue, 3 on the gingiva, 2 on the piryform sinus, 1 on the cheek mucosa, 1 post cricoid and 1 on the upper third of the oesophagus (Table 2). The affinity of SCC to the oral cavity, and especially to the tongue (9 of 17), is especially striking. According to MacCombe *et al.* [18], 16.5% of all oral carcinomas in the average population are carcinoma of the tongue; a more recent review of Van den Waal and Pindborg [17] showed an incidence of only 10.2%. In FA patients the incidence of tongue cancer was as high as 69%. A similarly high incidence of carcinomatous transformation occurs in some other genetic diseases, such as xeroderma pigmentosum, Bloom's syndrome, and ataxia telangiectasia [15].

An interesting question is whether the tendency to develop malignancy in FA results only from the genetic disorder (chromosomal breakage and deficient repair) or is due to increased susceptibility to local predisposing factors. Swift and Hirschhorn [19] found a connection between viral infection and relapse of the FA. In the present review 3 cases of intraoral herpes simplex infection were found, all of them in patients who developed carcinoma of the tongue. A high correlation between advanced chronic periodontitis and FA, previously noted [6, 21], was confirmed in this review (4 of the 17 patients). Whether herpetic infections, advanced periodontitis or monilia are local precipitating factors for malignancy or a superimposed disease on a debilitated patient is not yet known.

While the male : female ratio of patients in FA is 2 : 1, Reed *et al.* [1] found that this ratio was reversed among FA patients who developed SCC. Kennedy and Hart [15] found a similar ratio. However, the findings with HNC are quite different. 10 of the 17 cases were women—58.8%, while in the subgroup of carcinoma of the tongue only 4 out of 9 were women—44% (Table 3). Table 4 presents an analysis of the distribution of carcinoma by sex, age, and location. Among all 17 patients, more men tended to develop carcinoma of the tongue, and they were younger than their female counterparts (column 1). Among the young adult patients, more men developed tongue cancer, the female:male ratio was smaller, and the age difference between the sexes was less than in the whole group. In the children's group, there was a clear propensity for carcinoma of the tongue, especially among boys. The information on the clinical presentation of the carcinomas and their clinical and histological grading is presented in Tables 5 and 6.

The treatment for carcinoma was similar to that for the normal population, surgery being preferred by most of the clinicians. As the main problem in FA patients is impairment of haematological and coagulation functions, platelets and blood transfusions were usually given prior to surgery. In three cases a special surgical technique was used to minimise bleeding: cryosurgery in two [9, 25] and CO_2 laser in a third. Chemotherapy was rejected by most of the physicians because of its deleterious effects on an already hypoplastic bone marrow. Some clinicians feared to advise radiotherapy [20] because of its potentially carcinogenic effect on patients with an abnormal DNA function, maintaining that the risk of tissue damage is much higher than in normal patients because of the defective repair mechanism in wound healing [4]. Nevertheless, 5 patients were treated by radiotherapy as a primary or adjuvant therapy, and all of them, including our own, supported it satisfactorily [10, 21].

Another important issue is the development of carcinoma in those FA patients treated by bone marrow transplantation (BMT), reported in the literature in only 2 cases [21, 22]. Allogenic BMT is used as a treatment for haematologic malignancies and other non-malignant haematologic disorders. The conventional conditioning regime in FA patients includes cyclophosphamide (20 mg/kg) and thoracoabdominal radiation (5 Gy) prior to transplantation. Cyclosporine A is given to prevent graft versus host disease. Only 1 of 40 BMT-treated FA patients developed carcinoma, 6 years after the transplant. The incidence (2.5%) and the time lapse (6 years) is similar to that of patients treated for acute aplastic anaemia (which was the control group in the case reported above). It is not clear whether the malignancy was caused by the basic FA genetic disorder or was a side effect of the BMT therapy. In any case it seems that BMT does not decrease the incidence of carcinoma.

In the paediatric cases (up to 14 years of age) [4, 9, 22, 23], it appears that the earlier the haematologic symptoms of FA appeared, the earlier the carcinoma developed; the time lapse between the appearance of the FA symptoms and the development of the malignancy averaged 5 years. In comparison, in the adult group, with delayed appearance of the haematological symptoms, the time lapse averaged 12.8 years (Table 7). If impaired genetic factors cause an early appearance of the FA syndrome, the same factor may cause the early appearance of malignancies. Thus, there are two distinct groups of patients: (1) severe genetic disturbances > early FA symptoms > early malignancies, and (2) mild disturbances > delayed FA symptoms > late malignancies. Whether the causative trigger or mechanism for developing malignancies is the same as for the development of FA symptoms is a question that needs further research.

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