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CASE REPORT

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Squamous cell carcinoma of the tongue in a patient with Fanconi's anemia: a case report and review of the literature

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Abstract Fanconi's anemia (FA) is an autosomal recessive disorder characterized by constitutional aplastic anemia and congenital abnormalities. Patients with this disorder are prone to develop leukemia. Besides the risk of squamous cell carcinoma (SCC), development especially in the head and neck region is also increased. Up to now 40 patients with FA have been reported to develop SCC, and in 14 of them the tongue was the primary site. All of the reported SCC in FA patients originated in mucosal and mucocutaneous sites, especially oral (*n*=25) and anogenital sites (*n*=8) and the esophagus (*n*=6), with the exception of two patients with multiple cutaneous involvement. We report a new case of SCC of the tongue in a patient with FA and review the previous SCC cases.

Keywords Fanconi's anemia · Squamous cell carcinoma · Tongue

Introduction

Fanconi's anemia (FA) is a rare autosomal recessive disorder characterized by constitutional aplastic anemia and congenital abnormalities, such as microcephaly, absence of the radii and the thumb, short stature, and malformations of the heart and the kidney [1, 2]. Patients with this disorder are prone to develop hematological malignancies, namely, leukemia and squamous cell carcinoma (SCC), especially of the head and neck and anogenital region [3]. Up to now 40 cases of SCC in association with FA have been reported in the literature [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38]. Fourteen of these cases were the SCC involving the tongue [3, 4, 9, 11, 16, 21, 25, 26, 28, 29, 32, 33, 38]. We would like to report another case and review the previous SCC cases.

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Case report

A 29-year-old female was admitted to the emergency service with neutropenic fever and thrombocytopenia. Nine months previously, she had undergone partial glossectomy and right radical neck dissection, and the diagnosis was nonkeratinized SCC of the tongue. She had been receiving radiotherapy for 1.5 months because of local recurrence. On physical examination, her performance status was poor, she was physically retarded (short stature and microcephalic), and had a deformed right thumb, generalized hyperpigmentation of the skin and petechia, and ecchymosis on the extremities. Her blood pressure was 90/60 mmHg, pulse 128 bpm, and she had a fever of 38.5°C. She had severe mucositis interrupting her oral feeding. Inspiratory rales on the right hemithorax and 3/6 systolic murmur at the apex were heard. Bilateral pretibial edema was palpated. She had an external urogenital abnormality. She was the third offspring of a marriage between first cousins and one of her sisters died because of abnormal bleeding when she was 8 years old. She had been under the care of pediatric hematology and cardiology departments since the age of 8 and had been diagnosed with FA and patent ductus arteriosus (PDA). Hematological findings included a hemoglobin count of 10.6 g/dl, a platelet count of 9000/mm^3, and a leukocyte count of 700/mm^3. Computed tomography of the chest revealed minimal right pleural effusion, bilateral consolidation, and multiple bilateral pulmonary nodules, the largest 2×1 cm in diameter. Abdominopelvic ultrasonography was normal. Echocardiography revealed systolic dysfunction with an ejection fraction of 49%. Despite all supportive efforts, including hematological growth factors, antibiotics, feeding tubes, transfusions, and fluid and electrolyte imbalance corrections, the patient deteriorated progressively and died of septic shock after 5 days of follow-up.

Discussion

In 1927 Fanconi described two brothers with progressive lethal anemia and congenital malformations [1]. FA is a genetically determined disorder characterized by progressive pancytopenia, growth retardation, congenital abnormalities, and frequent chromosomal breaks in fibroblast-lymphocyte cultures [2]. Typical FA patients usually die due to the bone marrow failure or leukemia

Table 1 Summary of the reported FA cases with SCC. *CA* chromosomal abnormalities, *AND* androgen use for treatment of FA, *RT* radiotherapy, *PG* partial glossectomy, *SND* suprahyoid neck dissection, *LR* local recurrence, *H* skin hyperpigmentation, *R* renal anomaly, *S* skeletal anomaly (short stature, absence of radius, thumb, microcephaly, etc.), *U* urogenital anomaly, *E* ear problems as hearing loss, *C* cardiac abnormalities, *I* dull intelligence, *DWED* died with evidence of disease, *NED* no evidence of disease, *ABMT* allogeneic bone marrow transplantation, *HPV* human papillomavirus, *NS* not stated

Case No.	Year	Age of SCC (FA)	Sex	Site	Author	CA	AND	Clinical manifestation	Treatment of SCC	Result	Follow-up period	Comment
1	1966	26	F	Esophagus	Esparza and Thompson [7]			NS	RT, surgery	Exitus (pneumonia)	NS	NS
2	1966	31 (30)	F	Anal margin and vulva (CIS)	Swift et al. [2]	+	+	E+H+I	Surgery	Exitus (Staph. pneumonia)	2 years after CA diagnosis	Sibling FA+SCC (case 4), grandfather died of tongue SCC
3	1970	21	F	Gingiva	McDonough [8]	+		R+E+S	Surgery	NS	NS	NS
4	1971	38 (36)	F	Anal margin and vulva (CIS)	Swift et al. [6]	+		E+S+H+late menarche	Surgery	NS	NS	Sibling FA+SCC (case 2), grandfather died of tongue SCC
5	1971	21	F	Gingiva	Swift et al. [6]	+		R+E+S	NS	NS	NS	NS
6	1973	38 (14)	M	Tongue	Guy and Auslander [4]	+	+	R+U+S	NS	NS	NS	Diabetic retinopathy+ hepatoma, brother FA
7	1975	21(7)	M	Gingiva and tongue	Sarna et al. [9]	+	+	Mild H	Cryosurgery	Exitus-gr (–) sepsis	(NED-at autopsy)	Sibling hepatoma+ leukemia
8	1978	26	F	Skin (multiple sites)	Puligandla and Schumacher [10]	+		S	NS	NS	NS	Recurrent infection, gum bleeding
9	1980	30 (15)	F	Tongue	Schofield and Worth [11]		+	NS	PG	NS	NS	Squamous metaplasia of bladder mucosa, dental caries, periodontitis
10	1980	19 (61/2)	F	Oral cavity	Vaitiekaitis and Grau [12]		+	R+S+H	Surgery, RT, bleo. (LR)	DWED (vulvar abscess)	Died 2.5 months after CA diagnosis	Steroid-induced DM, periodontitis, dental caries
11	1980	26	F	Esophagus	Aho et al. [13]			NS	NS	NS	NS	NS
12	1980	28	F	Vulva, vagina, and cervix	King and Arnold [14]		NS	NS	NS	NS	NS	
13	1981	24 (9)	F	Vulva	Ortonne et al. [15]	+	+	R+S+H	Surgery (LR two times)	NED	12 months	Brother skeletal deformity, died at age 15
14	1981	38	M	Tongue	Swift [16]			NS	NS	NS	NS	NS
15	1982	20 (14)	F	Vulva and tongue	Kennedy and Hart [3]	+		S+H	Surgery	NED	6 months, alive	Juvenile onset DM
16	1982	25 (7)	F	Multiple cutaneous SCC	Hersey et al. [17]			NS	Surgery	DWED	12 months	Bowen's disease and warts, NK activity defects
17	1983	25 (8)	M	Pyriform sinus and hypopharynx	Reed et al [18]		+	None	Surgery	NED	8 months, alive	2 siblings FA

Table 1 (continued)

Case No.	Year	Age of SCC (FA)	Sex	Site	Author	CA	AND	Clinical manifestation	Treatment of SCC	Result	Follow-up period	Comment
18, 19	1984	22 (9), 22 (8)	FF	Multicentric genital tract	Wilkinson et al. [19]			None, S+H	Surgery+RT, surgery	DWED, NED	3 months, 12 months. alive	Genital human papilloma virus infection
20	1984			Esophagus	Gutierrez et al. [20]			NS	NS	NS	NS	NS
21	1985	13 (8)	F	Tongue	Kaplan et al. [21]	+	+	NS	PG, SND	NED	18 months, alive	T1N0M0 sister, FA carrier
22	1986	14	M	Oral cavity	Kozhevnikovet al. [22]			NS	NS	NS	NS	NS
23	1988			Esophagus	Gendal et al. [23]			NS	NS	NS	NS	NS
24	1989	39	F	Oral cavity	Fukuoka et al. [24]	+		H+S+U+C	Pepleomycin+CS	DWED	NS	Died due to massive hemorrhage
25	1990	29 (14)	F	Tongue base and left tonsillar fossa	Bradford et al. [25]			NS	Cisplatin-FU+RT+surgery (LR)	DWED pneumonia	6 months after CA diagnosis	T4N0M0 ABMT (age 20), HPV (+), smoking (+), alcohol (+)
26	1990	11 (5)	M	Tongue	Murayama et al. [26]			S	Cis-retinoic acid+FU	DWED	3 months	ABMT (age 8)
27	1991	29 (18)	F	Post-cricoid	Snow et al. [27]		+	S+H	Surgery+RT (recurrence)	DWED	1 year after CA	NS
28	1991	12 (6)	M	Tongue	Socie et al. [28]			NS	NS	NS	NS	ABMT (age 6)
29	1991	31 (12)	F	Esophagus	Linares et al. [5]		+		None	DWED	2 weeks	Hepatoma, oxymetholone use for 10 years
30	1992	30	F	Tongue	Flowers et al [29]	+		H+S	NS	DWED	NS	ABMT (age 20)
31	1992	24	F	Tongue	Flowers et al. [29]	+		H+S	NS	NS	NS	ABMT (age 14)
32	1993	51 (31)	F	Anal margin/canal	Lebbe et al. [30]	+	+	H+S	Incomplete excision+topical FU	LR, excision	14 months	Vulvoanal Bowen's disease, HPV (–)
33	1994	36	F	Esophagus	Soravia and Spiliopoulos [31]			NS	Surgery	NS	NS	NS
34	1995	32 (14)	F	Tongue	Lustig et al. [32]			NS	Surgery+RT	Exitus (sepsis)	3 months after CA	NS
35	1995			Tongue	Somers et al. [33]			NS	NS	NS	NS	HPV (–)
36	1996	44	F	Oral	Koo et al. [34]			NS	Cis-retinoic acid	Recurrence in 6 months	NS	NS
37	1997	18 (8)	F	Buccal mucosa	Millen et al. [35]			NS	Surgery, RT (LR)	DWED	3 months	ABMT (age 9)
38	1997	26 (6)	M	Gingiva	Altay et al. [36]			NS	NS	NED	1 year, alive	NS
39	1998	30	M	Supraglottic larynx	Doerr et al. [37]			NS	Surgery	NS	NS	T2N2aM0, smoking (+), alcohol (+)
40	2000	24 (5)	F	Tongue	Jansisyanont et al. [38]			S+H	Surgery	NED	6 months, alive	ABMT (age 9) cervix atypia
41	2001	29 (8)	F	Tongue	Presented case			H+S+U+E+C	Surgery+RT	DWED	9 months	

within the first decades of life and most of them die within 5 years of diagnosis of anemia [3]. Patients with FA are also at greater risk for developing solid tumors. The incidence of hepatocellular carcinoma has also been reported to be increased in patients with FA treated with anabolic steroids [4, 5]. Since diffuse hyperplasia, hyperplastic nodules, and hepatocellular carcinoma have also been demonstrated in patients treated with anabolic steroids for other reasons, it seems that the contributing causal effect of FA is unclear. Malignant transformation in the mucosa and mucocutaneous sites, especially urogenital and oral squamous cell carcinomas, have been reported in FA patients. Since SCC of these sites is very rare in patients of this age, it seems logical to conclude that FA predisposes to these malignancies [6]. SCC is most often seen in FA patients with mild bone marrow dysfunction. This is because these patients are the ones who survive for several decades, long enough for cancer development. The median age of diagnosis of 41 patients with SCC in FA was 26 years (range: 11–51) [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38] (Table 1). SCC in FA is approximately three times more common in females than males. There has been a high prevalence in siblings and a high rate of consanguinity in parents of patients with FA. All of the reported SCC in FA patients originated in mucosal and mucocutaneous sites, especially oral (n=25) and anogenital sites (n=8) and the esophagus (n=6), with the exception of two patients with multiple cutaneous involvement [10, 17]. In two siblings SCC of both anus and vulva [2, 6] and in one case SCC of both vulva and tongue [3] was reported. SCC in and around healing teeth sockets has been reported [8, 9, 16]. Among the cases of SCC in the head and neck region, the tongue is the commonest site involved and our case is the 14th to be reported. Guy et al. reported a patient with SCC of the tongue associated with hepatocellular carcinoma (HCC) [4] and Linares et al. reported a patient with SCC of the esophagus and HCC [5]. Both cases had a history of androgen use for the treatment of FA. Seven of the reported cases had SCC of the head and neck 3–10 years (median: 9 years) after allogeneic bone marrow transplantation (ABMT) for the treatment of FA. Increased incidence of some malignant tumors has been reported in patients undergoing bone marrow transplantation. Witherspoon et al. [39] reported a retrospective analysis of 2246 patients transplanted for aplastic anemia and leukemia and found 1.6% secondary tumors. Although most of the secondary tumors were non-Hodgkin lymphomas (16 of 35), the incidence of SCC (tongue, oral cavity, and vulva) was also reported to be increased [39]. Acute graft-versus-host disease (GVHD) treated with antithymocyte globulin, monoclonal anti-CD3, or conditioning with total body irradiation (TBI) is thought to be the risk factor for the development of secondary tumors. Besides genetic predisposition, immunosuppressive therapy can lead to increased incidence of secondary malignancies in FA transplant recipients [35, 40]. It is interesting that ABMT does not prevent development of secondary malignancy, and prolonged immunosuppression could probably be an additional risk factor. Moreover, by curing aplastic anemia, bone marrow transplantation paradoxically increases the incidence of secondary tumors since patients with FA live long enough to develop solid tumors related to immunosuppression and accompanying genetic predisposition [41].

Most FA patients including ours died due to sepsis in an immunocompromised state lasting 2.5–24 months; thus, highly aggressive chemotherapy is controversial. Since SCC in these patients is usually biologically more aggressive, adjuvant treatment should normally be considered; however, use of radiotherapy and chemotherapy is controversial because they may be hazardous in these patients due to low tolerance since DNA repair is defective. Use of alkylating agents that cross-link DNA can especially be very toxic [21, 30].

Increased susceptibility to viral transformation, susceptibility to mutagens, possible immune system defects, and especially chromosomal instability and defective DNA repair have been demonstrated to play a role in the development of neoplasia in FA. Through illumination of the mechanism(s) of SCC development in patients with FA, it will be possible to gain new insights into our understanding of carcinogenesis since most of these patients have no predisposing factors for the development of SCC such as advanced age, alcoholism, tobacco use, and poor nutrition.

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