High Incidence of Head and Neck Squamous Cell Carcinoma in Patients With Fanconi Anemia

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Background: Fanconi anemia (FA) is a rare autosomal recessive disorder characterized by a high degree of genomic instability and predisposition to cancer development. Recent evidence suggests that the incidence of head and neck squamous cell carcinoma (HNSCC) may be increased in patients with FA.

Objective: To determine the cumulative incidence, tumor distribution, and outcome of HNSCC in patients with FA.

Design and Setting: We analyzed data from 754 subjects from the International Fanconi Anemia Registry, a prospectively collected database of patients with FA.

Main Outcome Measures: Cumulative incidence of HNSCC and 2-year overall, relapse-free and disease-specific survival.

Results: Of the 754 patients in the International Fanconi Anemia Registry, 19 (3%) had HNSCC. This is a significantly higher incidence of HNSCC compared with that observed in the general population (standardized incidence ratio, 500; 95% confidence interval, 300-781) (P<.001). The patients’ age ranged from 15 to 49 years (median, 31 years), and there was a 2:1 female predominance. Surgical treatment was well tolerated (n=17); however, radiation therapy and chemotherapy were associated with significant morbidity and mortality. Of the 19 patients, 10 (53%) developed locoregional recurrences within a median of 16 months from diagnosis. The median follow-up was 29 months. The 2-year disease-specific, overall, and relapse-free survival rates were 49%, 49%, and 42%, respectively. The cumulative incidence of relapse by the age of 40 years was 50%.

Conclusions: In patients with FA, there is a high incidence of aggressive HNSCC at a young age. Surgery remains the mainstay of treatment because patients with FA tolerate radiation therapy and chemotherapy poorly, with significant morbidity. An increased understanding of FA-associated malignancies is not only important in the clinical management of patients with FA but can also elucidate the role of chromosomal instability in the development of HNSCC in general.


Fanconi anemia (FA) is a rare autosomal recessive disorder characterized by short stature, various congenital malformations, progressive bone marrow failure at an early age, and cancer development.1,2 Fanconi anemia is characteristically defined by its cellular hypersensitivity to DNA cross-linking agents such as diepoxybutane and mitomycin.3 Based on the presence of mutations in one of the FA genes, FA can be divided into 8 complementation groups (A-G, including D1 and D2), with each group having in common the cellular hypersensitivity to cross-linking agents.4,5 Complementation groups A (65%), C (15%), and G (10%) account for most patients with this disorder reported to the International Fanconi Anemia Registry (IFAR). The severity of the phenotype is determined in part by the specific complementation group and more significantly by the type of genetic mutation.6 Because of these phenotypic differences among complementation groups, FA is a heterogeneous disorder; patients may be severely affected, with multiple congenital anomalies and severe aplastic anemia, or may have a mild phenotype, with no major malformations or hematologic abnormalities.7

The cancer susceptibility aspect of FA is associated with a defect in the ability to maintain the integrity of the genome, leading to a high degree of chromosomal instability.8,9 As such, FA belongs to a group of hereditary disorders called caretaker gene diseases, which also include ataxia-telangiectasia, nucleotide excision repair syndromes, Bloom syndrome, hereditary non-
polyposis colorectal cancer, and hereditary breast/ovarian cancer syndromes.10,11

An understanding of the relationship between genomic instability in patients with FA and cancer development has not been well elucidated secondary to the rare occurrence of FA in the general population and, thus, the small number of FA-associated neoplasms. Most studies evaluating neoplasms in patients with FA are based on case reports and literature reviews that are limited by small patient numbers, limited follow-up, and unconfirmed FA diagnoses. Although the most common and well-characterized malignancies are hematologic, several studies12,13 have suggested that FA is associated with an increased predisposition to nonhematologic (solid) tumors, particularly squamous cell carcinomas (SCCs) of the aerodigestive and anogenital tract. In this study, we reviewed 754 records of patients reported to the IFAR for the occurrence of head and neck SCC (HNSCC) and defined its cumulative incidence, clinical course, and outcome.

REGISTRY CHARACTERISTICS

The IFAR was established at The Rockefeller University in 1982 to collect clinical and genetic information from patients with FA. Registration into the IFAR typically occurs at diagnosis, and includes information on congenital and hematologic abnormalities and any history of neoplasm development. Comprehensive attempts to obtain follow-up data are made periodically.14 All reporting is voluntary and obtained with the consent of the patient or legal guardian. The diagnosis of FA is confirmed for each patient registered in the IFAR by the assessment of chromosomal breakage induced by diepoxybutane in the peripheral blood lymphocytes, as described in detail elsewhere.7

Malignancies occurring in this cohort of patients were identified by reviewing the clinical records of the 754 patients in the IFAR and supplemented by contacting all patients older than 20 years alive at last follow-up. In patients with HNSCC, a complete clinical history, including TNM stage, management, recurrence, and outcome, was ascertained. The pathologic features were confirmed by review of the surgical specimens by a reference pathologist (A.H.).

STATISTICAL ANALYSIS

This analysis focuses on the characteristics of HNSCC in patients with FA. The time to HNSCC was calculated as the time elapsed in years between the date of birth (ie, the date of FA onset) and the date of HNSCC diagnosis. The cumulative incidence of HNSCC was calculated by treating death as a competing cause of risk.15 The expected incidence of HNSCC in the general population was calculated using the Surveillance, Epidemiology, and End Results incidence rates of buccal and pharyngeal cancer.16 The observed and expected incidence rates were compared using an exact Poisson test.17 The standardized incidence ratio is calculated as the ratio of the observed/expected incidence rates. A normal approximation to the Poisson test statistic was used to obtain 95% confidence intervals. All patients with HNSCC underwent biopsy or surgery to confirm their cancer diagnosis. The end points of interest were overall, disease-specific, and relapse-free survival times. Overall survival time was calculated as the time elapsed in months between the date of biopsy or surgery and the date of death or of last follow-up. Disease-specific survival time was calculated as the time elapsed in months between the date of biopsy or surgery and the date of death due to disease or the last follow-up. Recurrence-free survival time was calculated as the time elapsed in months between the date of surgery and the date of disease recurrence. The Kaplan-Meier method was used to estimate the overall and the disease-specific survival times. The cumulative incidence of recurrence was calculated using a competing risk approach by considering death as a competing risk for time to recurrence.15 All computations were performed using SAS statistical software, version 8.0 (SAS Institute Inc, Cary, NC) and S-Plus 2000 software (MathSoft Inc, Seattle, Wash).

RESULTS

SUBJECT CHARACTERISTICS

Seven hundred fifty-four subjects with the diepoxybutane-confined diagnosis of FA were registered into the IFAR between 1982 and 2001 (Table 1). Of these subjects, 367 were females and 387 were males. Complementation groups were determined in 341 subjects, with 207 (61%) in group A, 78 (23%) in group C, 46 (13%) in group G, 8 (2%) in group F, and 2 (<1%) in group D2. In the remaining 413 patients, complementation groups were not determined. These patients were grouped together and referred to as nontyped. Of the 754 patients, 601 (80%) developed the onset of bone marrow failure; 219 patients underwent hematopoietic cell transplantation during the study. The overall survival of the patient population ranged from 1 month to 49 years (median, 24 years).

CUMULATIVE RISK OF HNSCC

Of the 754 patients registered in the IFAR, 19 cases (3%) of HNSCC were identified. The expected incidence rate based on the Surveillance, Epidemiology, and End Results buccal and pharyngeal cancer incidence was 0.038.
Thus, there is a significantly increased risk of HNSCC among patients with FA (standardized incidence ratio, 500; 95% confidence interval, 300-781) (P<.001). The median follow-up, based on the 735 patients without HNSCC, was 10.6 years. The cumulative incidence of developing HNSCC by the age of 40 years was 14% (Figure 1).

CHARACTERISTICS OF PATIENTS WITH HNSCC

There were 13 females and 6 males, ranging in age from 15 to 49 years (median, 31 years). Only 3 (16%) of the 19 patients had environmental risk factors, including alcohol or tobacco abuse. Five patients (26%) underwent hematopoietic cell transplantation before the development of the primary tumor. The FA complementation group was confirmed in 10 patients: 7 were in group A, 2 were in group C, and 1 was in group G. The information on the clinical presentation, stage, and treatment is presented in Table 2.

HNSCC TUMOR CHARACTERISTICS

The primary tumor site was the oral cavity in 13 patients (68%), the larynx in 2 (11%), the oropharynx in 2 (11%), the hypopharynx in 1 (5%), and unknown in 1 (5%). The most common subsite of oral cavity involvement was the tongue (n=6), followed by the alveolar ridge (n=2), the retromolar trigone (n=2), the floor of mouth (n=2), and the buccal mucosa (n=1). For TNM staging,18 7 patients (37%) had a stage I tumor and 12 (63%) had a stage IV tumor. Nine patients (47%) had clinically detectable ipsilateral nodal metastases, and 1 (5%) had distant metastases to the lungs at initial presentation.

SURGICAL MANAGEMENT

Seventeen patients (89%) underwent surgical resection of their primary HNSCC, with 10 simultaneously undergoing a total of 12 neck dissections (6 modified radical neck dissections, 4 selective neck dissections, and 2 radical neck dissections). Two patients did not undergo surgical treatment for their tumors; 1 died several days after the biopsy, and the other had widely metastatic disease at presentation. Of the 17 patients who underwent surgery, 5 (29%) underwent extensive reconstruction, including 1 jejunal free flap, 1 gastric pull-up, 2 fibular free flaps, and 1 bone graft. The remaining patients had primary closure of their defects. Four patients had a total of 6 postoperative complications, including 2 wound infections requiring hardware removal, 2 hematomas after fibular free flap reconstruction, and 1 aspiration pneumonia after supraglottic laryngectomy.

HISTOLOGIC CHARACTERISTICS

Surgical pathology reports and paraffin-embedded specimens were obtained from the treating institution, and confirmed SCC in all patients. In 13 patients, information concerning tumor differentiation was available: 4 were well differentiated, 6 were moderately differentiated, and 3 were poorly differentiated. The size of the primary tumor ranged from 1.0 to 4.7 cm (median, 1.8 cm). Margin status was available for 15 patients; 3 patients had microscopically positive margins, while 2 had margins of less than 1 mm. Information concerning depth of invasion, lymphovascular invasion, neural invasion, and extracapsular spread was not specified on most pathology reports and was not analyzed.

ADJUVANT THERAPY

A total of 8 patients underwent radiation therapy (XRT) at some time during treatment. Six patients underwent adjuvant XRT, 2 underwent palliative XRT for recurrence, and 1 underwent re-irradiation for recurrence. The XRT dosages ranged from 4000 rad (40 Gy) to 6100 rad (61 Gy), with fields to the neck and primary sites in all patients. Chemotherapy (CTx) was rarely undertaken in patients with FA because of the known deleterious effects of myelosuppression in patients with a baseline bone marrow disorder. Three patients underwent CTx during their treatment course: 1 patient underwent adjuvant concurrent chemoradiation, 1 underwent CTx as the primary treatment, and 1 was treated with a combination of methotrexate and XRT for recurrent disease.

All 6 patients who underwent adjuvant XRT had associated complications, which were dose limiting in 3 patients. Early XRT-associated complications included thrombocytopenia (n=2), anemia (n=2), myelosuppression (n=2), and skin breakdown with ulcer formation (n=1), while late complications included tracheal (n=1) and esophageal (n=1) stenosis. Two patients died of severe myelosuppressive complications shortly after termination of XRT.

SECOND PRIMARY TUMORS

Patients with FA have a tendency to develop multiple malignancies. Overall, 12 (63%) of the 19 patients with HNSCC developed multiple malignancies, with 5 developing more than 2 primary malignancies. Of these patients, 9 developed a second primary SCC, including anal SCC (n=2), cervical SCC (n=2), vulvar SCC (n=2), a second head and neck primary tumor (n=2), and cutaneous SCC (n=1). One patient developed a total of 4 malignancies (myelodysplastic syndrome, breast carcinoma, HNSCC, and anal SCC) before the age of 40 years.
and was not diagnosed as having FA until after her third malignancy, when she was found to have anemia during her preoperative workup.

OUTCOMES

Follow-up and outcome information was available for all 19 patients. Fourteen (74%) of the patients died during the study period. Eleven (58%) died as a consequence of HNSCC. The median follow-up, based on the 5 patients who were alive at last follow-up, was 29 months. Of the 5 patients alive at last follow-up, 4 were alive without disease. Ten (53%) of the patients had recurrence of their tumor, with a median disease-free interval of 16 months; 7 patients experienced a local recurrence, 6 had a neck recurrence, and 1 had distant metastases. The
The ability of a cell to maintain genomic integrity under normal circumstances, and the failure of this mechanism during cancer development, is not well understood. Investigations of genetic alterations in patients with other malignancies have implicated chromosomal instability as a major pathway for genetic progression of malignancy, and were reported in several sites, including the lung, breast, and cervix. Similarly, HNSCC exhibits a significant degree of structural and numerical chromosomal alterations compared with other solid tumors of epithelial origin. Genetic progression models and data on premalignant lesions have demonstrated that chromosomal loss occurs early during HNSCC progression, accompanied by a high incidence of structural and numerical chromosomal aberrations. A recent investigation has shown that ongoing chromosomal instability is a significant and consistent feature of HNSCC. However, to our knowledge, no human model of chromosomal instability associated with HNSCC has been described.

The propensity for patients with FA to develop cancer is well documented. Kaplan et al suggested that there are 2 major defects that play a role in the development of malignancies in patients with FA: defective chromosomal stability and immunodeficiencies. Chromosomal studies in patients with FA have shown an increased spontaneous instability, especially in lymphocytes. Aberrations, such as breaks, fragments, and dicentric centromeres, have been described. The tendency to malignant transformation can also be seen in the increased susceptibility of fibroblast culture from patients with FA to transformation by an oncogenic simian virus (simian virus 40). Todaro et al showed that this tendency was 10 times higher than in normal fibroblasts.

The best-described malignancies associated with FA are hematologic in origin. Several reports have also suggested that patients with FA are predisposed to solid tumors, particularly HNSCC and SCC of the anogenital region. Lustig et al reviewed the literature and identified 17 cases of HNSCC associated with FA. In their report, they concluded that these carcinomas occurred in young patients (<30 years), were equally common in females as in males, and originated from the tongue (n=9), gingiva (n=3), pyriform sinus (n=1), postcricoid region (n=1), and the upper third of the esophagus (n=1). Other case reports and literature reviews have supported these findings. In this study, we analyzed 754 subjects with FA to determine the cumulative incidence of developing HNSCC. The data presented in this study show a significantly increased risk of HNSCC in patients with FA compared with the expected incidence rate based on the Surveillance, Epidemiology, and End Results buccal and pharyngeal cancer incidence. By the age of 40 years, the cumulative incidence of developing HNSCC approaches 14%. Not only are patients with FA strongly predisposed to the development of HNSCC but they also have an earlier onset of HNSCC (median age of onset, 31 years) compared with the general population (median age of onset, 45 years). Patients with phenotypically mild FA who have no bone marrow failure or leukemia development and who survive into the third decade of life are at a significant risk of developing HNSCC. In addition, the life expectancies of more severely affected patients with FA increase with improvements in hematopoietic cell transplantation, the number of patients developing HNSCC will most likely increase as well.

Overall, 13 (68%) of the 19 HNSCCs identified were in the oral cavity, particularly the tongue (6 patients [32%]). This finding is similar to the findings in the review by Lustig et al, who found a 52% incidence of tongue carcinoma. The affinity of FA-associated SCC to the oral cavity and especially to the tongue is striking because the incidence of tongue carcinoma in the normal population is only 10% to 20%. The development of multiple primary malignancies, particularly SCC, is another common finding in patients with FA. The reason for the strong propensity for patients with FA to develop multiple oral cavity SCCs and secondary SCCs of the mucous membranes is unclear. Kennedy and Hart noted that patients with FA have a marked affinity for carcinomas of the mucous membranes of the anogenital and oral areas. In their review, they found that 5 (36%) of 14 patients developed carcinoma in more than 1 mucosal site.

An interesting hypothesis for predisposition to multiple SCCs is the possible increased susceptibility of the oral cavity and genital region to local predisposing factors, including environmental toxins and viruses. The virus association is interesting because the mucous membranes are a common route for oncogenic viral infections, especially the human papillomavirus and the herpesvi-
In addition, the immunosuppression associated with persistent bone marrow failure and the underlying genetic instability in these patients may predispose these patients to viral infections. In this study, 2 of our patients with HNSCC had pathologic evidence of intraoral human papillomavirus infections, which has been shown to predispose to SCC development in the head and neck and anogenital regions. Also, 9 (56%) of the 16 patients with FA who developed SCC of the cervix, vulva, and anus showed evidence of human papillomavirus–associated condylomas before developing SCC (D.I.K., A.D.A., J.S., A.G.H., A.G., and B.S., unpublished data, 2001). However, whether human papillomavirus infection or other causative factors play a role in oncogenesis in these patients is not yet known, and requires further elucidation.

Most patients with FA in our series developed aggressive head and neck tumors with bone invasion and regional metastases at presentation. Even in the patients with early-stage disease, there was a tendency to develop field cancerization of the oral cavity, necessitating multiple excisions and eventual radical resections to remove uncontrolled recurrence. Of the 19 patients in this series, 10 (53%) developed recurrences at a median interval of only 16 months. This aggressive type of tumor behavior negatively affected survival outcome in these patients, with 2-year disease-specific and relapse-free survival rates of only 49% and 42%, respectively. Compared with other studies evaluating outcomes for patients with oral cavity SCC younger than 35 years, the outcome for those with FA-associated HNSCC is worse. In a recent study of patients younger than 35 years with oral cavity carcinoma, the 5-year survival was 57.3%. Another study analyzing 12 patients younger than 35 years showed a 2-year survival of 57%. The underlying genomic instability in patients with FA may increase the likelihood of developing mutations that select for a more aggressive phenotype or allow for the development of an early recurrence.

The treatment for those with FA-associated HNSCC was similar to that for the normal population, with surgery being the primary therapeutic approach. The main preoperative problem in patients with FA is the bone marrow failure that is associated with the disorder, requiring preoperative consultation with a hematologist and the possibility of blood and platelet transfusion before surgery. A further concern for the surgeon is the development of postoperative complications, including wound infection and hematoma. In this study of FA-associated HNSCC, there were postoperative complications in 5 (26%) of the 19 patients, but, in general, most patients with FA tolerated surgery well, with minimal long-term morbidity.

With the increased susceptibility of patients with FA to mutagenic stimuli, the adjuvant management of HNSCC becomes more complicated. The defective DNA repair mechanisms in these patients make nontumor tissues more susceptible to the short-term and delayed tissue effects of XRT. This increased susceptibility can present a problem in determining and delivering a curative surgical dose of XRT without causing significant damage to normal tissues. Standard doses of adjuvant XRT are, therefore, reduced in most cases. The use of conventional CTx protocols, which include the cross-linking agent cisplatin (a compound especially damaging to FA cells), can cause severe systemic complications, including irreversible aplastic anemia and catastrophic organ damage. However, there has been controversy over whether patients with FA can tolerate XRT and/or CTx. In a literature review by Lustig et al., they concluded that in the 5 patients who were treated for HNSCC by XRT as primary or adjuvant therapy, all of them tolerated it without difficulty. In contrast to this conclusion, external beam XRT and CTx were not well tolerated by the patients with FA in our study. All 6 patients who underwent adjuvant XRT had XRT-induced complications, with 3 having severe systemic complications necessitating termination of therapy. Two patients had severe XRT-induced myelosuppression and died shortly after the termination of therapy. Therefore, adjuvant XRT and CTx must be used with care in patients with FA to avoid systemic complications, and they are not advised as primary treatment. The inability to use multimodal therapy without local and systemic complications makes management of HNSCC in patients with FA difficult and may impact recurrence rates and survival.

Because of the complex nature of the treatment for FA-associated HNSCC, careful screening of the head and neck in patients with FA is essential to discover oral cavity lesions at an early stage. Based on the age distribution in this study, biannual screening of the oral cavity and oropharynx should start between the ages of 15 and 20 years. However, in patients with FA with a history of leukoplakia or recurrent oral lesions, head and neck examinations are recommended every 6 to 8 weeks. Early identification of HNSCC and, thus, early therapeutic interventions may be translated into improved survival, or at least may reduce the necessity for more aggressive surgical approaches.

Although the large number of patients and the long follow-up make the IFAR database unique in analyzing the incidence and the cumulative probability of developing HNSCC in patients with FA, there are potential limitations. One problem is the possibility of selective reporting. Another is that there was no prospectively defined study design; reporting of malignancy development was determined by the participating physicians even after the subjects were registered into the database. A third consideration is the completeness and accuracy of data reporting; no audits of reporting centers were performed. However, by using this database, we have been able to estimate the frequency of HNSCC in a rare population of patients with a known genetic disease characterized by chromosomal instability.

CONCLUSIONS

To our knowledge, this registry-based study represents the largest reported series of HNSCCs associated with FA. Patients with FA have an increased incidence of aggressive HNSCC that frequently develops at an early age and has a poor prognosis. Primary surgery remains the mainstay for treatment; XRT and CTx are not well tolerated by patients with FA because of severe systemic compli-
cations. Careful screening of the head and neck in patients with FA is essential to discover oral cavity lesions at an early stage. There is also a tendency for the development of multiple SCCs of the mucous membranes of the aerodigestive and anogenital tracts. The strong predisposition to SCC makes FA an excellent model to study the role of chromosomal instability in the development of SCC.

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