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# Endoscopic findings and esophageal cancer incidence among Fanconi Anemia patients participating in an endoscopic surveillance program

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ABSTRACT

*Background and aims:* The primary clinical characteristics of Fanconi Anemia (FA) include typical physical features, progressive bone marrow failure, and an increased incidence of neoplasms, including esophageal carcinoma. Currently, there are no data regarding endoscopic findings or the interval time to malignancy in these patients. Data about the contribution of Human Papilloma Virus (HPV) to esophageal carcinoma is conflicting. Our objective is to document the upper gastrointestinal (GI) findings at baseline, document cancer incidence, and evaluate the role of HPV among these cancers.
*Methods:* We reviewed endoscopic and clinical data of FA subjects who participated in active surveillance before cancer diagnosis. Incident esophageal cancers were stained for HPV $^{p16}$ protein.
*Results:* Eight FA patients were included (men 62.5%; median age at first endoscopy 20 years, median endoscopies number: 5.5). At baseline, 8/8 had endoscopic evidence for reflux esophagitis. In 3/8 the reflux esophagitis was mild and in 5/8 it was moderate or severe. During the follow up time (median time 4.5 years 2/8 developed Barrett's esophagus and 2/8 patients had incident esophageal squamous cell carcinoma during follow up, at intervals of eight and eighteen months from the previous upper endoscopy. Both cancers stained negative for HPV $^{P16}$.
*Conclusions:* FA subjects have both an extremely high risk for esophageal cancer within short intervals and a very high prevalence of reflux esophagitis with various severities. Active surveillance programs in specialized centers including annual upper endoscopies should be considered in these patients.


## 1. Introduction

Fanconi Anemia (FA) is a rare autosomal recessive disease, characterized by specific congenital anomalies, bone marrow failure, and an increased risk of developing malignant tumors [1–3]. The physical anomalies involve the skeletal system, the gonads, the urinary tract, and the gastrointestinal tract. Bone marrow failure is usually progressive, with cumulative incidence of 80–90% by the fifth decade [1–3].

Up-to-date, 22 FA associated genes have been identified and their product proteins are involved in DNA damage detection and repair [1,4–9].

In certain ethnic groups, a founder mutation has been described, including the *FANCC* and *FANCD*1 mutations in Ashkenazi Jews and *FANCA* in other Israeli population [1]. The estimated FA mutation carrier in Israel is 1 in 93 [1].

It is well established that FA patients are prone to develop hematological and solid malignancies, mainly acute myeloid leukemia and squamous cell carcinoma (SCC) of the head and neck, skin and genitalia [1–3,10].

The incidence risk for esophageal SCC among FA patients has been estimated in the range of 1200–6200 in the most recent report [10–13]. And yet, data regarding the endoscopic findings in this

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population are lacking. Furthermore, there are no clear guidelines for surveillance of esophageal carcinoma in these patients [1–3,14].

The high risk cancer clinic in the Department of Gastroenterology at the Rabin Medical Center is a tertiary referral center for the largest health maintenance organization in Israel. As such, patients diagnosed with FA are referred to our clinic to formulate a malignancy surveillance plan. Our objectives is to document the upper gastrointestinal (GI) findings at baseline, document the interval time to cancer and evaluate the presence of human papilloma virus (HPV) among these cancers, since HPV infection has been associated with increased risk of esophageal cancer in non-FA patients [15,16] and FA patients also appear to be more prone to HPV infection [17].

HPV $p16^{INK44a}$ expression measured by immunostaining has been suggested as a surrogate for transcriptionally active HPV 16 [18]. Although the current gold standard used in HPV research includes PCR-based assays designed to detect either HPV DNA or RNA, the specificity of the of the Dako staining (detailed in the Methods) is estimated as 93% [18].

By integrating into the host genome, HPV oncogenes E6 and E7 drive the genomic instability to promote DNA damage and gene mutations which may contribute to carcinogenesis in FA patients [19].

## 2. Methods

### 2.1. Study design

Between January 2007 and December 2015 eight patients with a diagnosis of FA, based on chromosomal breakage testing and gene sequencing, were referred to our high risk cancer clinic. All of them participated in an esophageal cancer surveillance program which included an annual upper endoscopy, starting upon referral to the high risk cancer clinic. An earlier repeat endoscopy is performed if the patients present with suggestive symptoms or when the endoscopists thought that the endoscopic findings require an earlier follow-up.

The primary endpoints were defined as any endoscopic abnormalities found in these patients and the interval time from last endoscopy to esophageal malignancy diagnosis. Medical records as well as all endoscopy records and histological results were reviewed by the authors. All slides were reviewed by a single expert GI pathologist at the Rabin Medical Center.

### 2.2. Endoscopic procedures and diagnosis of gastroesophageal reflux disease

All of the upper endoscopies were performed by two expert endoscopists (Z.L, O.B.B), who each perform more than 2500 endoscopies each year. All endoscopic procedures were performed under conscious sedation using intravenous midazolam and fentanyl. Reflux esophagitis was graded using the Los Angeles (LA) classification [20]. Endoscopic procedures were done using white light endoscopy, and since May 2015 with high-definition white light endoscopy. Suspicious mucosal lesions were biopsied. Random esophageal biopsies were not performed. In case of suspected Barrett's esophagus, biopsies were obtained from the gastroesophageal junction according to the Seattle protocol [21].

### 2.3. Detection of HPV infection

We used formalin fixed and paraffin embedded material from esophageal squamous cell carcinomas (n = 2). For p16 immunohistochemistry, we used a Pharmingen immuno-histochemistry monoclonal mouse antibody (BD Biosciences, CA) at 1:50 automatic dilution for 30 min at room temperature, followed by an addition of secondary Dako EnVision™ biotinylated horseradish peroxidase-conjugated mouse antibody (K4001) for 30 min at room temperature without dilution, then stained with ultra-marque diaminobenzidine reagent two to four minutes (Dako, CA; K3468) Immunostaining was evaluated by the study pathologist (S.M). Immunostaining in more than 50% (subjective assessment) of the tumor cells was considered positive [22].

This study was approved by the by Rabin Medical Center Institutional review board.

## 3. Results

Eight FA subjects, from different ethnic backgrounds, were asked to come to the high risk cancer clinic, and all of them participated in the active GI surveillance program. Seven out of the eight subjects had a verified germline mutation, five were Jews and three were Arabs. Four subjects underwent allogeneic hematopoietic stem cell transplantations at an average age of 8.5 years due to severe pancytopenia. Characteristics of the study population are presented in Table 1.

### 3.1. Initial upper GI findings

All patients underwent at least one upper endoscopy. The median age at the first endoscopy was 20 years (range 10–39 years) and the median number of endoscopies per patient was 5.5 (range 4–14). Five patients were symptomatic, one had a history of esophageal atresia, and two had symptoms of reflux disease. Three patients were asymptomatic at the first endoscopy (Table 2).

All eight patients had significant endoscopic findings: Three had evidence of severe reflux esophagitis (LA classification grade C or D), two had moderate esophagitis (LA grade B) and three had mild esophagitis (LA grade A) (Table 2). There were no adverse events related the anesthesia or endoscopic procedures.

### 3.2. Esophageal complications on follow-up

Two patients eventually developed Barrett's esophagus (both cases were short segment) and one had reflux related esophageal stricture. Eventually, two of the patients developed esophageal squamous cell carcinoma during follow-up, with an interval of eight and eighteen months from the previous upper endoscopy. These two patients with SCC were not the same patients who had Barrett's esophagus.

Both cancers were negative for HPV p16 stain from the tumors' tissue.

#### 3.2.1. Patient #1

This patient had an esophageal atresia as part of a VACTERL association (standing for: Vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal and radial anomalies limb defects). She had undergone esophageal atresia repair at infancy. Later on, she developed severe symptomatic reflux esophagitis documented by endoscopy and also by esophageal PH-monitoring, with a Demeester score of 223 [23]. An esophageal manometry study demonstrated a dilated, non-contractile esophagus, with ineffective peristaltic contractions. She complained of progressive dysphagia and eventually was diagnosed at age 35 with esophageal SCC, eight months after the previous endoscopy. She was treated surgically and eventually died of complications related to tumor progression within a year.

#### 3.2.2. Patient #2

This patient was diagnosed with SCC of the tongue at age 32 that was treated surgically and with breast cancer at age 39 that was

**Table 1**
Patients' characteristics. FA—Fanconi anemia. HSCT—Hematopoietic stem cell transplantation. N/A—not applicable.

| | Patient #1 | Patient #2 | Patient #3 | Patient #4 | Patient #5 | Patient #6 | Patient #7 | Patient #8 |
|---|---|---|---|---|---|---|---|---|
| Gender | Female | Female | Male | Male | Male | Male | Male | Female |
| Ethnicity | Jew | Jew | Arab | Jew | Arab | Jew | Arab | Jew |
| Gene mutation | Mutation not found | FANCC: IVS4 + 4 A > T (c.456 + 4 A > T); one unknown mutation | FANCA: c.4292-2 A > C (IVS43-2 A > C) homozygote | FANCA: exon 31–36 del; 4275delT | FANCA: 58 kb incl. ex. 6–31; FANCA del 523–3066 | FANCA: c.2574C > G (p. Ser858Arg) homozyote | FANCG: c.IVS4 + 3 A > G: | FANCA: c.4292-2 A > C (IVS43-2 A > C) homozygote |
| HSCT age (years) | N/A | N/A | 6 | 9 | N/A | N/A | 9 | 10 |
| HSCT cause | N/A | N/A | Aplastic anemia | Aplastic anemia | N/A | N/A | Aplastic anemia | Aplastic anemia |
| HSCT type | N/A | N/A | Allogeneic-sibling | Allogeneic-sibling | N/A | N/A | Allogeneic-sibling | Allogeneic-sibling |
| Stature | Normal | Normal | Short | Short | Short | Short | Short | Short |
| VACTERL-H anomaly | Yes (esophageal atresia) | No | No | No | No | No | No | No |
| Other FA features and congenital anomalies | None | None | Abnormal facial features | Abnormal facial features | Abnormal facial features | Abnormal facial features, Bronchial hypoplasia | Abnormal facial features, Microcephaly | None |
| Age of FA diagnosis (years) | 6 | 19 | 5 | 6 | 10 | 11 | 7 | 6 |
| Age at end of study/death (years) | 36 | 48 | 24 | 25 | 32 | 30 | 24 | 28 |
| Survival | Deceased | Deceased | | | | | | Deceased |
| Cause of death | Esophageal cancer | Lung and base of tongue cancer | | | | | | Base of tongue cancer |

**Table 2**
Patients' symptoms and endoscopic findings. GERD—gastro-esopphageal reflux disease. LA—Los Angeles esophagitis classification. N/A—not applicable. SCC—squamous cell carcinoma. HPV—human papilloma virus.

| | Patient #1 | Patient #2 | Patient #3 | Patient #4 | Patient #5 | Patient #6 | Patient #7 | Patient #8 |
|---|---|---|---|---|---|---|---|---|
| GI symptoms | Chronic dysphagia, GERD | GERD | GERD | GERD | GERD | None | None | None |
| Age at gastrointestinal symptoms | Infancy | Adulthood | adolescence | adolescence | adolescence | N/A | N/A | N/A |
| Age at first endoscopy (years) | 10 | 39 | 19 | 19 | 24 | 23 | 18 | 21 |
| Number of endoscopies performed during surveillance | 14 | 10 | 5 | 6 | 5 | 6 | 4 | 5 |
| Endoscopic findings (age,years) | Reflux esophagitis LA grade C (25–35) | Reflux esophagitis LA grade C (39) | Reflux esophagitis LA grade C (19) | Reflux esophagitis LA grade B (19) | Reflux esophagitis LA grade B (24) | Reflux esophagitis LA grade A (23) | Reflux esophagitis LA grade A (18) | Reflux esophagitis LA grade A (21) |
| GERD related esophageal complications | N/A | Peptic stricture | Barrett's esophagus (C0M1according to Prague classification) | Barrett's esophagus (C0M2 according to Prague classification) | N/A | N/A | N/A | N/A |
| HPV P16 tumor immunohis-tochimestry staining | negative | negative | N/A | N/A | N/A | N/A | N/A | N/A |
| Malignancies (age,years) | Esophageal SCC (35) eight months after previous endoscopy | 1.Tongue SCC (32) 2.Breast carcinoma (39) 3.Esophageal SCC (47) eighteen months after previous endoscopy 4. Lung and base of tongue SCC (48) | N/A | N/A | N/A | N/A | N/A | N/A |

treated surgically as well. Recurrent upper endoscopies revealed severe reflux esophagitis with a non-obstructing peptic stricture at the gastro-esophageal junction. Eventually mid esophagus SCC was diagnosed on an upper endoscopy, 18 months after her last EGD, and was treated by surgical resection (T2N0). Unfortunately, several months following the esophageal operation she was diagnosed with SCC of both the hypopharynx and the lung. She eventually died at age 48.

## 4. Discussion

In this study we provide data regarding the endoscopic findings preceding a diagnosis of esophageal carcinoma and the interval between endoscopy and diagnosis in a cohort of FA patients. We have showed that esophageal cancer developed within an extremely short interval from the previous endoscopy. We also provide solid evidence for an extremely high prevalence of reflux esophagitis among these patients, including severe and complicated disease (such as Barret's esophagus and peptic stricture). Finally, we note that two of our patients with esophageal cancer were HPV negative in the tumor tissue.

The highly increased standardized incidence rate (SIR) for esophageal SCC among FA patients is well documented, and has been estimated in the range 1200–6200 in the most recent report [10–13]. In this cohort, since only 2 patients were diagnosed with esophageal cancer, the SIR could not be reliably determined. It should be taken into account that our study includes only 8 patients, and hence, we could not refer to ethnicity (Jews/Arabs and Ashkenazi/Sephardic Jews). Moreover, our cohort may also be biased by active surveillance since theoretically, competing event (e.g. squamous cell carcinoma of the head and neck) may mask the presence of early esophageal cancer in the same patient.

Furthermore, a selection bias might also play a role, since the more symptomatic patients were possibly more likely to participate in the surveillance program.

Until now, there has been no available literature concerning the prevalence of esophageal reflux disease among FA subjects. The VACTERL association, described in association with FA, may increase the risk of gastroesophageal reflux disease (GERD), as occurred in Patient #1 [24].

Actually, Barrett's esophagus was described in 6.6% of patients with repaired esophageal atresia (at a median age of 31.6 years) [25]. Reflux disease has been associated with increased oxidative damage to the esophageal mucosa and is involved in carcinogenesis [26]. This association, along with the susceptibly of FA patients to oxidative stress and DNA damage, might suggest that GERD plays a role in the pathogenesis of carcinoma in our patients [26,27]. A significant proportion of the study population showed evidence of complicated esophageal reflux disease, including Barrett's esophagus and peptic stricture. All patients had evidence of esophagitis on endoscopy even in asymptomatic patients, emphasizing the role of reflux disease in our patients and raising questions regarding the role of screening endoscopy and intensive anti-reflux treatment, such as proton pump inhibitors, in lowering the risk of esophageal malignancy in FA patients.

Oral antioxidants might play a role in dealing with the oxidative stress in FA patients [28], but no clear clinical benefit of these agents has been proved. Furthermore, high doses of antioxidants vitamins, such as Vitamin A and Vitamin C, might have a deleterious effect in FA patients [29].

Interestingly, although Hematopoietic Stem Cell Transplantation (HSCT) is considered as a risk factor for malignancy [3], neither of our two patients with esophageal carcinoma underwent HSCT.

Current published data regarding FA patients suggest that an annual esophageal endoscopy screening may be considered, but do not specify a recommended age of onset or screening intervals [1]. The updated Gene Reviews suggest performing an upper endoscopy only for individuals with dysphagia or odynophagia [2]. Others suggest upper gastrointestinal screening endoscopy at the age of 15, or 2–3 years after HSCT [3]. Our data show evidence of reflux esophagitis in patients at age 18, suggesting that endoscopy screening should be initiated at adolescence. The fact that two out of our eight subjects were diagnosed with cancer at eight and eighteen month intervals, suggests that the interval time for endoscopy should be relatively short. The surveillance of patients with tylosis, another rare genetic disorder characterized by hyperkeratosis of the palms and extremely high risk of esophageal squamous cell cancer, includes annual gastroscopy with biopsy of any suspicious lesion and quadratic random biopsies (four biopsies equally spaced apart at any particular level) from the upper, middle and lower esophagus to identify dysplasia [30]. Yet, at our center, we recommend performing upper endoscopy in FA patients at no longer than twelve months interval using white light high definition endoscopy. Random esophageal biopsies or esophageal chromoendoscopy are not routinely used in our center in the surveillance of FA patients, and their role is yet to be determined.

Surveillance interval should be individualized and take into account also the risks of sedation and the inherent risks of invasive procedure for each patient. Un-sedated trans-nasal upper endoscopy is another screening alternative that could be in considered in this population [31].

We further suggest that FA patients should be evaluated by esophageal manometry and 24 h PH-monitoring and should be treated with an intensive regime of proton pump inhibitor, with proof of acid suppression. Whether these interventions will lower the risk of future malignancy development remains to be seen.

Although our two patients with esophageal cancer stained negative for HPV, early HPV vaccination is strongly recommended at an early age to prevent HPV infection in FA patients [32].

In our study, two patients were diagnosed with cancer during surveillance although they were symptomatic for a long time prior to diagnosis and had previous negative endoscopies. In the first case, the patient died of screen-detected cancer and in the second case, the patient survived the screen-detected cancer and eventually died of other cancer. Hence, we cannot conclude that surveillance endoscopies improved survival in our cohort.

The strength of our study is found in the prospective design, which provides evidence for the endoscopic findings at baseline (without cancer) and clear evidence for the interval time for cancer not evident in the previous endoscopy.

The limitation of the study is the small sample size, and the possible referral bias of symptomatic patients.

In conclusion, in this small cohort of FA patients who participated in an active surveillance program, our evidence shows an extremely high risk for esophageal cancer within short intervals and an extremely high prevalence for reflux esophagitis with various severities. Active surveillance programs in specialized centers including annual upper endoscopies should be considered in these patients.

## Conflict of interest

None declared.

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