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【 CASE REPORT 】

Three Cases of Esophageal Cancer Related to Fanconi Anemia

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Abstract:
The risk of carcinogenesis increases after 20 years old in patients with Fanconi anemia (FA). We herein report three rare cases of FA combined with esophageal cancer in women; all patients were diagnosed with FA in early childhood. Patients 1 and 2 were diagnosed with advanced and superficial esophageal cancer, respectively, at 21 and 30 years old, respectively. Patient 3 was diagnosed with superficial esophageal cancer, underwent curative surgery at 26 years old, and survived for over 5 years without recurrence. Therefore, establishing a protocol for the early detection of esophageal cancer in FA patients over 20 years old is important.

Key words: Fanconi anemia, esophageal cancer, treatment, screening

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Introduction

Dr. Guido Fanconi first reported sibling cases of familial anemia and physical malformation in 1927, and the disease concept was later named Fanconi anemia (FA) (1). Subsequently, he developed the diagnostic criteria for FA, consisting of 1) pancytopenia, 2) skin pigmentation, 3) congenital deformities, 4) short stature, 5) gonadal dysfunction, and 6) familial inheritance pattern (2). Although FA is a rare disease, it is one of the most common hereditary bone marrow failure syndromes, occurring in approximately 1 per 100,000-250,000 live births (3) and with no sex predilection (4). The prevalence is higher in Ashkenazi Jews, Spanish gypsies, South African blacks, and Afrikaners than in others (5, 6).

In 1964, Schroeder et al. discovered chromosomal abnormalities in lymphocytes of FA patients (7). Furthermore, Sasaki et al. found that this chromosomal abnormality is significantly increased by DNA cross-linking agents, such as mitomycin C, and that this disease is caused by chromosomal instability (8). FA was shown to be a dysfunction of the Fanconi pathway, 1 of the 2 major pathways involved in DNA damage repair (9), and 22 responsible genes in the pathway have been identified thus far. Except for two of these genes, the inheritance mode is autosomal recessive (10).

More than 80% and 90% of FA patients develop aplastic anemia by ages 10 and 40, respectively. The transition to myelodysplastic syndrome and acute myeloid leukemia often occurs from puberty to adulthood (11). FA is a hematopoietic genetic disorder of the stem cell and is thus resistant to immunosuppressive therapy. Anabolic steroids are effective in approximately half of the patients, but the effect is temporary in most cases (12). The only effective therapeutic option against FA is allogeneic hematopoietic cell transplantation (HCT) (13). The prognosis of FA patients has markedly improved in developed countries since the year 2000, mainly due to improvements in the treatments for bleeding and infectious complications occurring in severe pancytopenia (4, 11).

Although HCT can prevent the progression to hematopoietic tumors, there is another risk of developing solid tumors (e.g., head and neck cancer), and such risk increases

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after 20 years old (13). FA patients have low tolerability to chemotherapy and/or radiation therapy and are thus primarily treated with endoscopy or, if possible, surgery (14, 15). We herein report three very rare cases of FA combined with esophageal cancer.

Case Reports

Case 1

A 30-year-old woman was diagnosed with FA at 7 years old, and she underwent an allogeneic bone marrow transplant at 13 years old. The conditioning regimen was thoraco-abdominal irradiation (TAI) 3 Gy, fludarabine (Flu) 25 mg/m^2×6, cyclophosphamide (CY) 10 mg/kg×4, and antithymocyte globulin (ATG) 1.25 mg/kg×4. Post-transplant graft versus host disease (GVHD) was managed initially with immunosuppressive drugs, followed by prednisolone 3 mg/6 mg every other day. She was referred to our clinic because of a feeling of stuffiness during swallowing of six months' duration and back pain during swallowing for a month. She had no history of drinking or smoking. Her younger brother was also diagnosed with FA. Upper gastrointestinal endoscopy revealed a type 3 lesion in the esophagus 24-27 cm from the incisor that was diagnosed as squamous cell carcinoma (SCC) on a biopsy (Fig. 1a). Along with the computed tomography (CT) findings (Fig. 1b), she was preoperatively diagnosed with cT3cN1cM0c cStage III esophageal cancer. A right thoracoscopic total thoracic esophagectomy, laparoscopic-assisted posterior sternal route cervical esophagogastric tube reconstruction, and bilateral cervical lymph node dissection were performed. The pathological diagnosis was SCC, moderately differentiated Type 2, size 40×30 mm, pT3, INFb, ly1, v1, pIM1, pPM1, pDM0, and pRM0 (Fig. 1c), ultimately diagnosed as pT3pN1pM0 pStage III. However, multiple bone metastases were found in her skull six months after the surgery, and the patient was readmitted. She developed sepsis owing to empyema and died eight months after the operation.

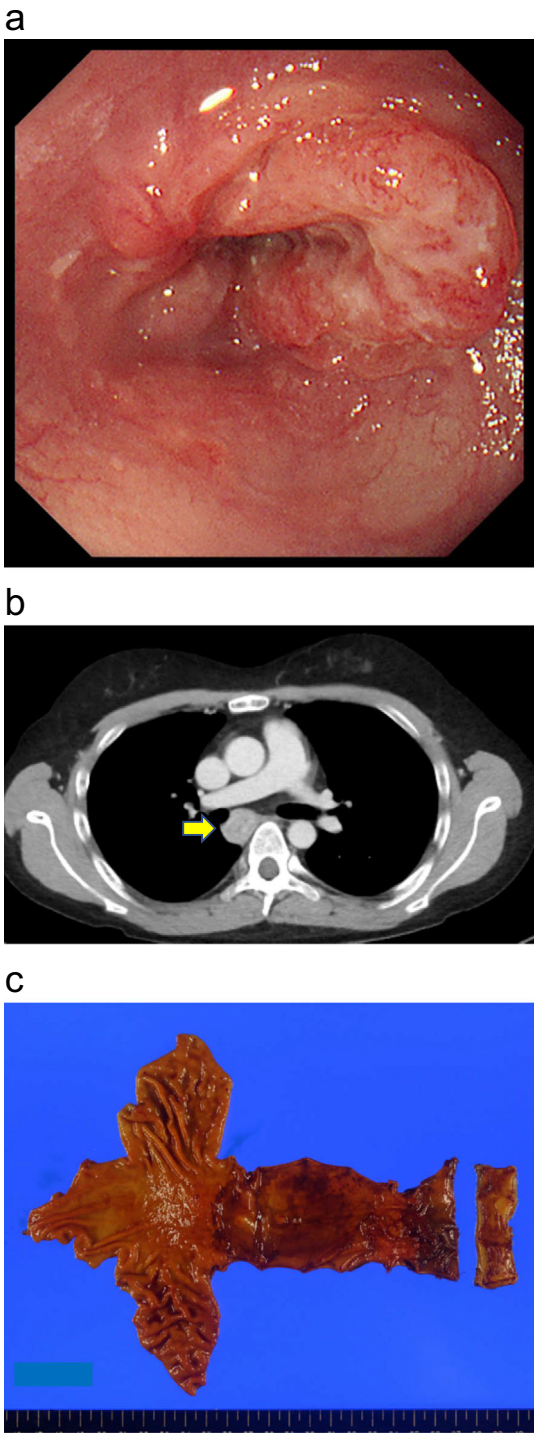

Figure 1. a: Upper gastrointestinal endoscopic image of esophageal cancer in Case 1. Irregular ulcerative lesions 24-27 cm from the incisors. b: Cross-sectional chest CT image of Case 1 shows thickening of the thoracic esophagus wall. CT: computed tomography. c: Surgical specimen of esophageal cancer. The cancer is part of the Lugol non-stained area.

Case 2

A 21-year-old woman underwent surgery for esophageal atresia immediately after birth; she had been diagnosed with FA when she was 5 years old, and allogeneic bone marrow transplantation had been performed at 12 years old. The conditioning regimen was TAI 3 Gy, Flu 25 mg/m^2×6, Cy 10 mg/kg×4, and ATG 1.25 mg×4. No GVHD occurred after transplantation. The patient was referred to our clinic because of swelling of the right cervical and supraclavicular lymph nodes detected via cervical ultrasound during follow-up for benign thyroid nodules. She had no history of drinking or smoking. Her grandmother had pancreatic cancer. Upper gastrointestinal endoscopy revealed an approximately half-circumferential 0-IIc+III lesion in the cervical esophagus 14 cm from the incisor, and she was diagnosed with SCC via a biopsy (Fig. 2a, b). Along with the CT findings (Fig. 2c), she was clinically diagnosed with cT1cN2cM0 cStage III esophageal cancer. The first-line treatment modality was surgery, including total laryngectomy; however, this was refused by the patient due to aphonia. Thus, chemoradiotherapy comprising low-dose 5-fluorouracil (5-FU)/cis-

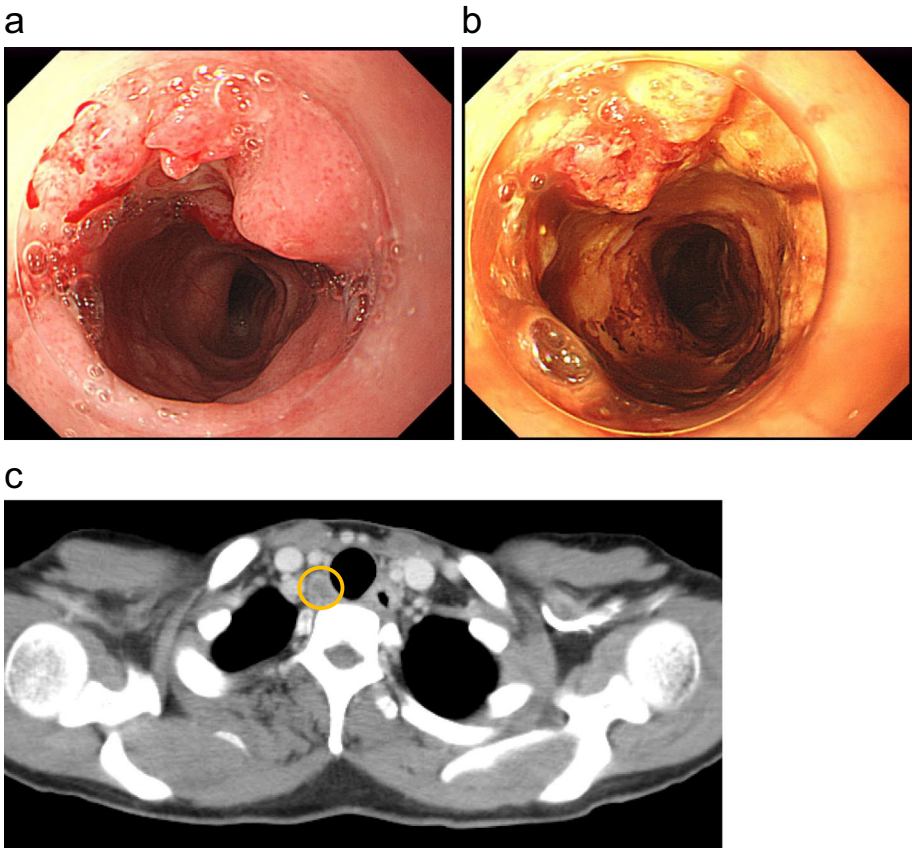

Figure 2. **a: Upper gastrointestinal endoscopic image of esophageal cancer in Case 2. Irregular ulcerative and surrounding ridges are seen on the left wall of the esophageal entrance. b: Lugol staining showing the area has almost no staining. c: Cross-sectional CT image near the neck of Case 2 showing circular right cervical para-esophageal lymphadenopathy. CT: computed tomography**

platin (CDDP) (5-FU 330 mg/m^2 and cisplatin 3.3 mg/m^2 for 5 days) and irradiation with a total of 57.2 Gy (1.1 Gy×2/day for 26 days) was performed, based on a study by Hosoya et al. (15). She developed adverse effects, such as nausea, a poor oral intake, and myelosuppression, so chemotherapy required a longer break of one to two months. As such, only four courses were administered over six months. Treatment markedly reduced both the lymphadenopathy and primary lesions; no lesions remained except for superficial and small primary lesions. After endoscopic ablation with argon-plasma coagulation followed by two additional courses of chemotherapy, a complete response was achieved.

However, she developed recurrence of the lymph node metastases after 10 months. Oral drug treatment with S-1 (tegafur, gimeracil, and oteracil potassium, 100 mg/day, administered for 4 weeks) was administered at the patient's preference. However, severe adverse effects, including diarrhea and nausea, were observed followed by vision loss. Therefore, the dose was reduced several times, and a very low dose of S-1 (20 mg/day) was administered for 9 courses total over 13 months. Although the lymph node metastasis shrank temporarily, CT and ultrasound after nine courses of S-1 therapy showed an increase in the right supraclavicular lymph node metastasis, which was judged to be progressive disease. The treatment was changed accordingly to low-dose 5-FU/cisplatin again. After eight courses, the metastatic lesions had enlarged further. At 26 years old, she opted for best supportive care and died 5 months later.

Case 3

A 26-year-old woman had been diagnosed with FA when she was 2 years old and undergone allogeneic bone marrow transplantation at 20 years old. The conditioning regimen was TAI 3 Gy, Flu 25 mg/m^2×6, Cy 10 mg/kg×4, and ATG 1.25 mg×4. Chronic GVHD developed after the transplantation but improved after tacrolimus administration. She had no history of drinking or smoking and had an unremarkable family history. She was referred to our clinic because of a swallowing discomfort of six months' duration. Upper gastrointestinal endoscopy revealed a circumferential 0-IIc+IIa lesion in the esophagus 19-25 cm from the incisor that was diagnosed as SCC on a biopsy (Fig. 3a, b, c). Along with further examinations, including CT, she was diagnosed with cT1cN0cM0 cStage I esophageal cancer. Right thoracoscopic total thoracic esophagectomy, laparoscopic-assisted posterior sternal route cervical esophagogastric tube reconstruction, and bilateral cervical lymph node dissection were performed. The pathological diagnosis was SCC, moderately differentiated, size 40×30 mm, Type 0-IIa+IIc, pT1b-SM2, INFb, ly0, v1, pIM0, pPM0, pDM0, pRM0, and pN0

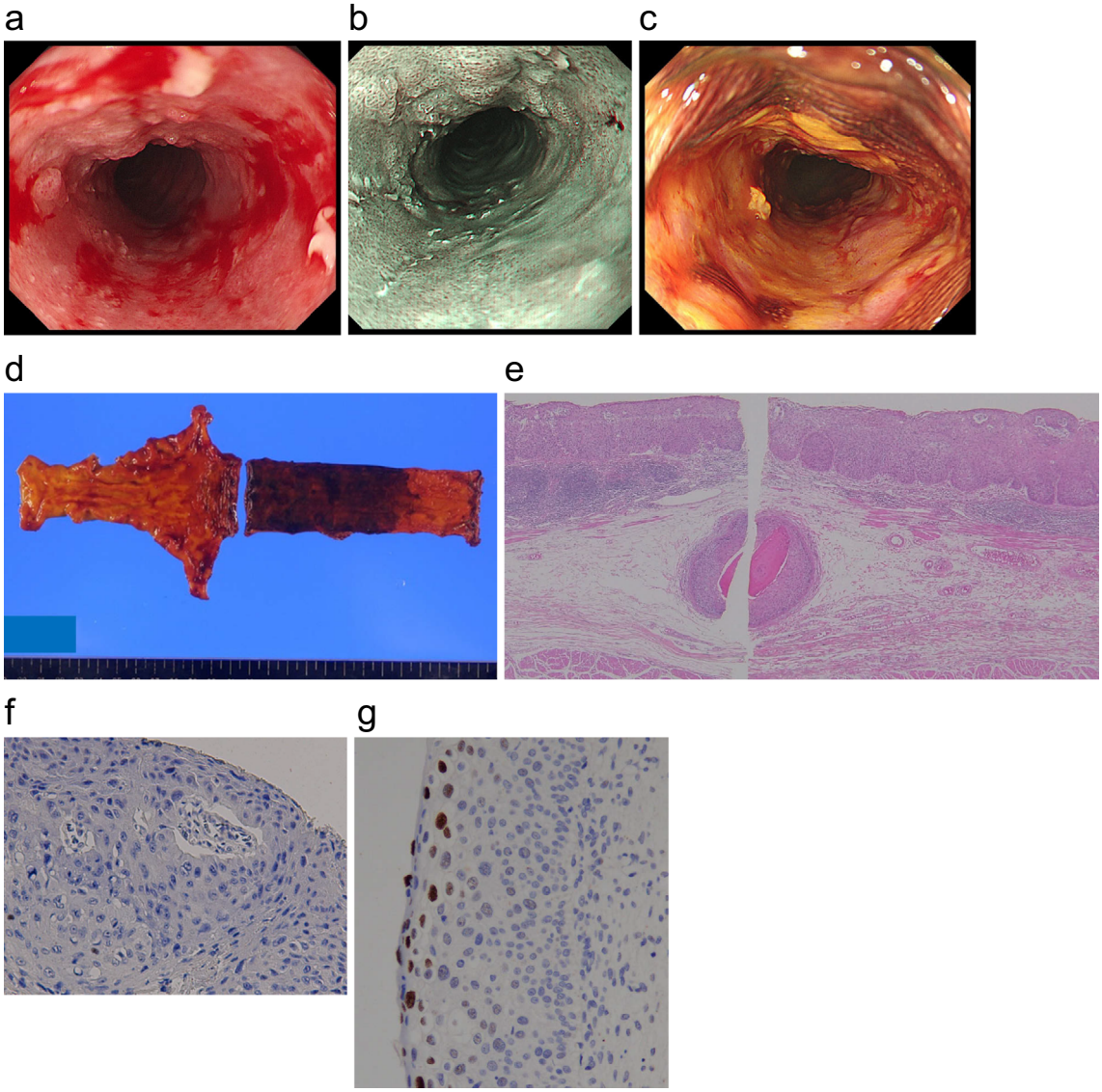

Figure 3. **a: Upper gastrointestinal endoscopic image of esophageal cancer in Case 3. Bleeding-prone, full-circumferential wall irregularities, and redness were found 19-25 cm from the incisors. b: NBI endoscopic image of the same site. The cancer lesion was observed as a brownish area in almost whole circumstances. c: Lugol staining showing the area has almost no staining. There is a protruding area and no "tatamime" sign in the IIc lesion, suggesting submucosal invasion. d: Surgical specimen of esophageal cancer. The cancer is part of the Lugol non-stained area. e: Histopathological findings by Hematoxylin and Eosin staining: cells with a high N/C ratio proliferate and extend mainly in the lamina propria with invasion into the vein submucosa. This is a moderately differentiated squamous cell carcinoma. f, g: HPV *in situ* hybridization: The nucleus is negative for a signal in the resected specimen (f), while a positive signal is apparent in the cervical dysplasia as a positive control (g). NBI: narrow-band imaging**

(Fig. 3d, e), ultimately deemed to be pT1pN0pM0 pStage I. At one year and eight months after the operation, she underwent surgery for tongue cancer, followed by two additional surgeries for other tongue cancers. No esophageal cancer recurrence occurred, and she is currently alive at 5 years and 10 months after the esophageal operation.

Discussion

Malignant tumors are a serious complication in FA, with the most common solid carcinomas being SCCs of the head and neck, esophagus, and gynecological organs (16). The ratio of observed to expected cancers is 50 for all malignant tumors, 48 for solid tumors, 785 for leukemia, 4,317 for vulvar cancer, 2,362 for esophageal cancer, 706 for head and neck cancer, 386 for liver cancer, and 17 for brain cancer (17).

The high incidence of esophageal, head, and neck cancers in FA may be due to several factors. First, drinking and smoking are well-known risk factors for esophageal

squamous epithelial cancer and head and neck cancers. The International Agency for Research on Cancer considers ethanol in alcoholic beverages, acetaldehyde associated with alcoholic beverage intake, and smoking as carcinogens (18). Both animal and human studies have shown that the Fanconi pathway plays an important role in repairing DNA damage caused by acetaldehyde (19, 20). These results suggest that FA patients are vulnerable to aldehyde-induced DNA damage, resulting in a higher incidence of SCC.

Second, the age-adjusted incidence of SCC of the head, neck, and esophagus is higher in FA patients who undergo HCT than in those who do not (21). The incidence was shown to be 4.4 times higher, and the patients were significantly younger in the transplant group (median, 18 years old) than in the non-transplant group (median, 33 years old). Furthermore, acute and chronic GVHD is an important risk factor for SCC in the head/neck and esophagus (21). Azathioprine therapy and irradiation as pretreatment for HCT have also been reported as risk factors for solid tumors among patients with severe aplastic anemia treated with allogeneic bone marrow transplantation (22). FA is a genetic disorder at the stem cell level, and HCT is currently the only effective treatment. Thus, although it may increase the risk of solid tumors, it remains an indispensable treatment for FA.

Third, human papillomavirus (HPV) infection is reported to be involved in the carcinogenesis of SCC of the esophagus (23, 24), although conflicting findings have also been reported (25). However, HPV is detected frequently not only in cervical cancer but also in SCC of the head and neck (16). Furthermore, HPV-16 promotes the cell proliferation of esophageal cancer cells (26) and is related to esophageal SCC (27). Thus, the possibility of HPV infection being a cause in the carcinogenesis of esophageal cancer cannot be ruled out. In the USA, FA patients are recommended to receive HPV vaccination, regardless of sex (16).

None of the three cases in this report had a history of alcohol or smoking, but two cases developed GVHD, and all three underwent HCT with pretreatment before transplantation. It is possible that HCT is a factor that caused the SCC of the esophagus. Pathological specimens showed negative results for HPV in immunohistochemical studies and *in situ* hybridization assays (Fig. 3f), and no relationship with HPV infection was found in any of the three cases.

Esophageal SCC is treated with endoscopic resection or surgery, chemoradiotherapy, radiotherapy, or chemotherapy alone, or palliative therapy, depending on the cancer stage and patient preference and condition (28). FA patients tend to develop severe adverse effects and have a low tolerability for chemotherapy and/or radiation therapy (29). Therefore, the treatment options for solid tumors complicated with FA are limited (15). We found 15 cases of esophageal cancer cases combined with FA in PubMed in addition to the 3 cases in this report (Table). Eleven patients had stage I/II disease; of these, 8 died within 2 years after diagnosis, indicating a worse prognosis than the current 5-year survival rate of 62.7% for stage II esophageal cancer in Japan (30). Only two patients survived for five years: the patient described in Case 3 of this report and another patient who underwent endoscopic submucosal dissection. There are no sex differences in FA, but esophageal cancer mergers were observed more commonly in women than in men among the 18 cases. Esophageal cancers in FA patients developed at markedly younger ages (20-47 years old) than in non-FA cases (31). Alcohol and smoking are known risk factors for esophageal cancer. However, of the four known cases (including the three in this study) that listed the patient histories of tobacco and alcohol consumption, none had any such history. The pathogenesis of esophageal cancer may therefore differ between FA and non-FA patients.

There have been several reports on chemotherapy techniques for solid tumors associated with FA, such as a reduced carboplatin dose for non-small cell lung cancer (32) and low-dose 5-FU/CDDP for esophageal cancer (15). In addition, postoperative radiotherapy was reported for 12 cases of SCC of the head and neck, but treatment was terminated due to severe adverse effects (33). No treatment guidelines for FA-associated solid tumors have yet been established. FA patients with solid tumors who undergo radiotherapy should be monitored closely for hematological disorders and severe mucositis (33).

In the present study, Case 1 did not undergo preoperative chemotherapy due to side-effect concerns, and only surgery was performed. She died of bone metastases eight months after surgery. Case 2 underwent reduced-dose chemoradiotherapy that yielded temporary efficacy. She developed relapse and died five years after cancer onset. Case 3 had Stage I esophageal cancer that could be cured by surgery alone. Given the outcomes of this case and a similar previous case with superficial esophageal cancer curatively resected by endoscopic submucosal dissection (34), a long-term survival might be expected if FA-associated esophageal cancer can be resected curatively. The early detection of esophageal cancer that can be treated by curative resection is thus extremely important for FA patients. In the future, it might be reasonable to consider periodic screening with upper gastrointestinal endoscopy for FA patients over 20 years old, particularly those with histories of HCT.

Regarding the optimal interval of screening endoscopy, there are no data on the endoscopic screening of high-risk patients for esophageal cancer. The clinical practice guidelines for esophageal cancer proposed by the European Society for Medical Oncology (ESMO) recommend appropriate action be taken when there are developments of symptoms or other abnormalities, as there is no evidence showing that regular follow-up improves the outcomes (35). If there are no abnormalities in symptoms or on endoscopic findings, screening once a year seems acceptable. We believe it is reasonable for patients across the country to be examined by endoscopy when they visit a pediatrics department once a year. Endoscopic screenings should be performed at shorter intervals, depending on the symptoms or the endoscopic

Table. **Esophageal Cancer Related to Fanconi Anemia.**

	ref	age/sex	Stage	FA diagnosis	BMT	Location★	chemotherapy	radiation	operation	prognosis	other tumors
1	37	26/F	pStage IVb	26y.o	-	unknown	-	+	+	death	
2	38	26/M	above Stage II	26y.o	-	Ce	-	+	-	death	
3	39	20/F	unknown	9y.o	-	unknown	-	+	-	death	
4	40	28/M	above Stage II	12y.o	-	Te	-	-	+	unknown	
5	41	31/F	pStage IVb	12y.o	-	Te	-	-	-	death	Hepatocellular Ca
6	42	29/F	pStage I	18y.o	-	Ce	-	+	+	death	
7	43	28/M	cStage III	10y.o	-	Te	-	-	+	death	
8	44	25/F	cStage II	10y.o	10y.o	Ce	5-FU (25%dose)	+	-	death	
9	15	35/F	cStage IVa	10y.o	23y.o	Te	cisplatin (3.3 mg/m^2) +5-FU (330 mg/m^2)	+	+	alive	
10	34	30s/M	pStage0	5y.o	6y.o	Te	-	-	+(ESD)	alive	Pharyngeal Ca
11	45	32/F	cStage II	32y.o	-	Ce	carboplatin and paclitaxel	-	-	death	
12	46	35/F	unknown	6y.o	-	unknown	-	-	+	death	
13	46	47/F	cStage I	19y.o	-	Te	-	-	+	death	Lung Ca/ Tongue Ca
14	47	unkown/F	cStage I	unkown	+	Te	-	+	-	death	Tongue Ca
15	47	unkown	cStage I	unkown	+	Ce	-	-	+	death	
16	*	30/F	pStage III	7y.o	13y.o	Te	-	-	+	death	
17	*	21/F	cStage I	5y.o	12y.o	Ce	cisplatin (3.3 mg/m^2) +5-FU (330 mg/m^2), S-1	+	-	death	
18	*	26/F	pStage I	2y.o	20y.o	Te	-	-	+	alive	Tongue Ca

*our cases

★ Ce: cervical esophagus, Te: thoracic esophagus

findings. We would like to analyze more cases before considering the most appropriate interval for endoscopic screening. Narrow-band imaging is a standard and useful tool for the early detection of superficial cancer in the esophagus (36), and it should be applied for screening endoscopy.

In the future, we hope to promote the early detection of esophageal cancer in FA patients and contribute to improving the prognosis of these patients.

Author's disclosure of potential Conflicts of Interest (COI).
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