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Case Report

Serial Cancer Development Three Times in a Patient with Fanconi Anemia

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Keywords
Squamous cell carcinoma · Radiotherapy · Secondary malignancy · Lung cancer · Hematopoietic stem cell transplantation · Fanconi anemia

Abstract
Fanconi anemia (FA) is characterized clinically by bone marrow failure, congenital malformations, sensitivity to DNA cross-linking agents, and increased risk of malignancy. Hematological cancer is the best-described malignancy in patients with FA, but the susceptibility to the development of solid tumors is also well documented, especially after hematopoietic stem cell transplantation (HSCT). With regard to the development of solid tumors in patients with FA, head and neck, esophageal, and anal squamous cell carcinoma are well known, but reports of lung cancer are extremely rare. Here, we describe an FA patient with a history of HSCT that developed 3 serial cancers – oral, esophageal, and nonsmall cell lung cancer – over a period of 6 years. The third lesion was nonsmall cell lung cancer and its location corresponded closely to the field of irradiation treatment for prior esophageal cancer. The occurrence of lung cancer in patients with FA is uncommon, but FA patients should be screened regularly and serially. Our case also indicated the importance of the irradiated field as a location for subsequent cancer development.

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Introduction

Fanconi anemia (FA) is a rare autosomal recessive DNA-repair disorder characterized by bone marrow failure, congenital malformations, and sensitivity to DNA cross-linking agents. It is also well established that FA patients are prone to malignancies. Leukemia is the most common type of cancer, but FA patients are also at substantially increased risk of developing solid tumors [1–5], with a 28% cumulative incidence of solid tumors by the age of 40 years [1]. In particular, head and neck squamous cell carcinoma (SCC) is significantly more common in FA patients than the general population, with some reports indicating a hundredfold increased risk in these patients [3, 6]. In addition, a history of hematopoietic stem cell transplantation (HSCT) has been suggested to increase the risk of head and neck SCC in FA patients [3–8]. Several case series report described synchronous and/or chronological second SCCs following head and neck cancer in patients with FA, such as esophageal and anogenital cancers [4, 5, 9–11]. However, the development of second lung cancer is extremely rare [2, 3, 12, 13] and the occurrence of over second primary malignancies has not been elucidated because of the rarity of FA.

We encountered a case of FA with a history of HSCT that developed 3 serial cancers – oral, esophageal, and nonsmall cell lung cancer – over a 6-year period. Here, we describe the clinical course and present a review of secondary primary malignancies in patients with FA.

Case Presentation

The patient was a 30-year-old Japanese woman with a history of FA. The initial diagnosis of FA was made at 4 years old because of presence of anemia and malformation. She received HSCT from a full-matched unrelated donor at the age of 13 years. The conditioning regimen included cyclophosphamide (10 mg/kg × 4 days), anti-lymphocyte globulin (25 mg × 2 days, 50 mg × 2 days), fludarabine phosphate (25 mg/m^2 × 6 days), and thoracoabdominal irradiation (3 Gy), and steroid therapy was continued about for 4 years after HSCT. Then, she and her family moved to our prefecture and she had been regularly followed up at our hospital. She developed type II diabetes requiring insulin therapy in 2007 (at the age of 18 years). In 2014, she noticed a tongue protrusion and was diagnosed with tongue cancer (left tongue margin, T2N0Mx, SCC, negative for human papillomavirus). Complete partial tongue resection without reconstruction was performed. Subsequently, she had been regularly followed up by magnetic resonance imaging (MRI) examination every 6 months. However, in 2017, swelling and mass lesion on the cervical esophagus were detected by magnetic resonance imaging and endoscopic examination revealed esophageal SCC (Fig. 1a). The stage was T3N1M0 and she refused surgery because of vocal code removal at the surgery. On physical examination, dwarfism with central obesity-like body shape was observed (height 132 cm, weight 34.5 kg). Radiation therapy (1.8 Gy × 23 fractions, total 41.4 Gy) was performed without any specific toxicities and complete response was achieved (Fig. 1b). In 2019 (at the age of 30 years), she presented with a cough that gradually worsened. She sometimes complained of stridor and was referred to our respiratory department. She had no history of smoking or drinking alcohol. Her parents had no hematological abnormalities and there were no specific relevant findings in her family history, including cancer. Body weight (36 kg) was also similar after the radiotherapy for esophageal cancer. Wheezing was detected on lung auscultation. Fasting blood sugar and HbA1c were 166 mg/dL and 9.3%, respectively, and other blood chemistry findings were almost within normal limits. Tumor markers, including carcinoembryonic antigen (14.5 ng/mL), SCC antigen (2.4 ng/mL), and cytokeratin 19 fragments (CYFRA 21-1; 7.4 ng/mL) were elevated. Chest computed tomography showed nodular shadows in the

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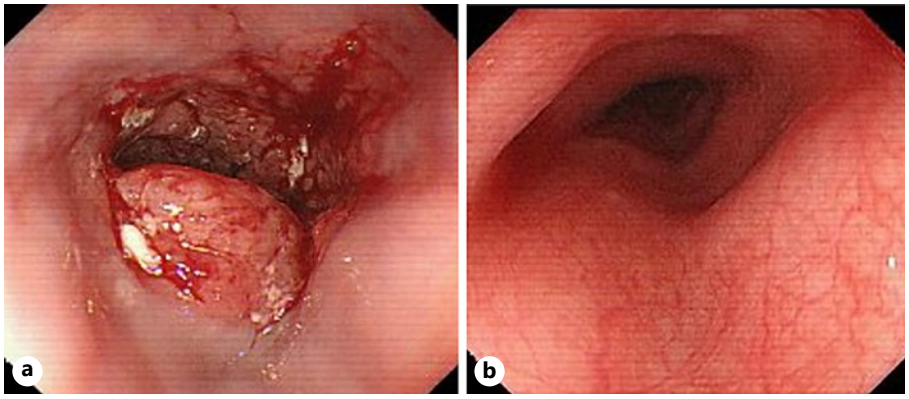

Fig. 1. Endoscopic examination showed a bulging lesion in the upper part of the esophagus before radiotherapy (**a**) and a disappearance of the lesion after radiotherapy (**b**).

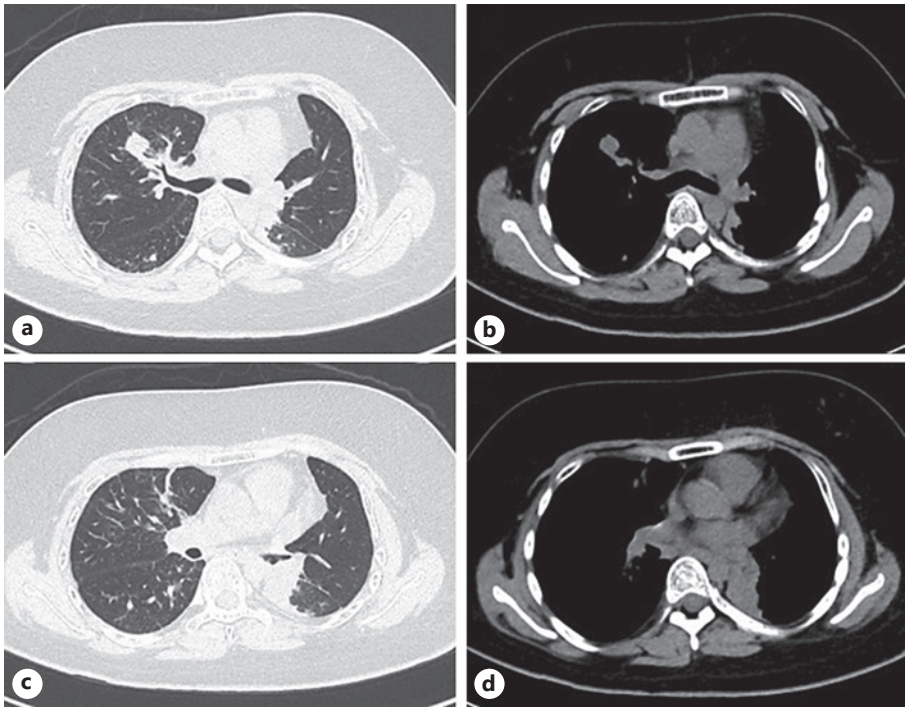

Fig. 2. Chest CT showed nodular shadows in the right upper lobe (**a**, **b**) and atelectasis in the left lower lobe of the lung (**c**, **d**). CT, computed tomography.

upper lobe of the right lung, and atelectasis and a mass shadow in the lower lobe of the left lung (Fig. 2) suggesting lung cancer. Bronchoscopic findings revealed reddish and swollen mucosa causing stenosis of left upper and lower bronchi and a polypoid white mass in the left upper lobe (Fig. 3). Histological examination indicated SCC (Fig. 4). Immunohistochemical examination of the biopsy specimen indicated that the lesion was positive for p40 and p63 and negative for thyroid transcription factor-1. The tumor cells were negative on immunohistochemical staining with anti-PD-L1 antibody. Genetic analysis revealed that EGFR-sensitive mutations (exons 18, 19, and 21), BRAF, ALK, and ROS-1 fusions were negative. In the present case, the left lung cancer lesions were located very close to the field of previous

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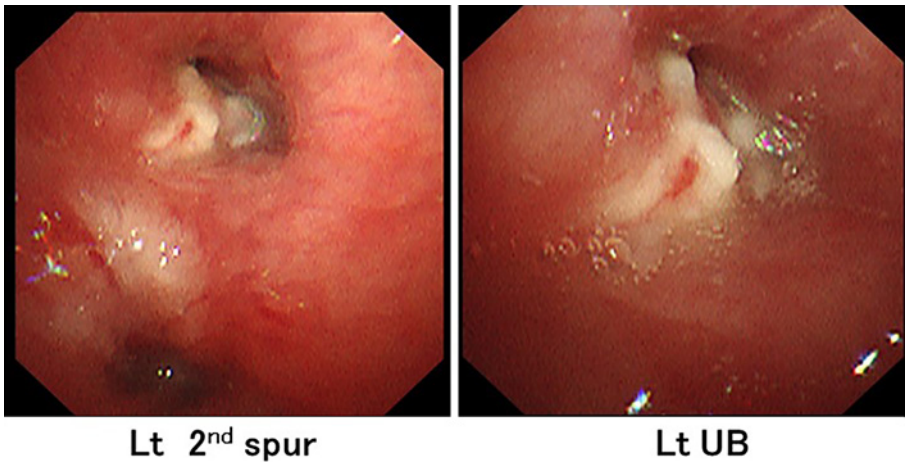

Fig. 3. Bronchoscopic findings at left second spur showing reddish and swollen mucosa causing stenosis of the left upper and lower bronchi and a polypoid white tumor lesion in the left upper lobe.

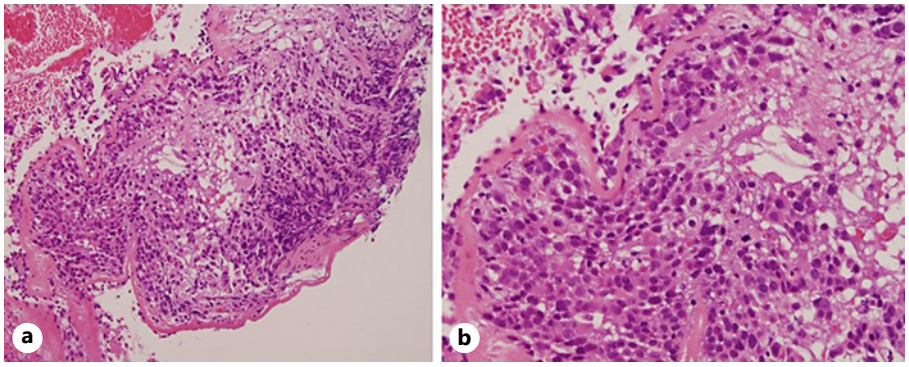

Fig. 4. Histological examination of the transbronchial biopsy specimen revealed SCC (hematoxylin and eosin staining, ×10 (**a**), ×40 (**b**)). SCC, squamous cell carcinoma

irradiation for esophageal cancer (Fig. 5). Chemotherapy using cytotoxic agents was not recommended based on her performance status of 2, respiratory condition, and background diseases, including diabetes and FA. Her respiratory condition deteriorated gradually and she died 3 months after the diagnosis of lung cancer.

Discussion

We described a case of FA with a history of HSCT that developed 3 serial SCCs – oral, esophageal, and nonsmall cell lung cancer – over a period of 6 years. The third lesion of nonsmall cell lung cancer corresponded closely to the field of irradiation therapy for prior esophageal cancer.

Oral SCC is the most common type of cancer to develop in patients with FA [1–6]. Furquim et al. [6] summarized 121 cases of oral cancer in FA and reported that >75% of patients receiving HSCT developed oral cancer before 25 years old, whereas 73% of non-HSCT patients developed oral cancer after 25 years old. In addition, female patients tend to develop cancer at an older age than male patients, although the incidence of oral cancer was not significantly

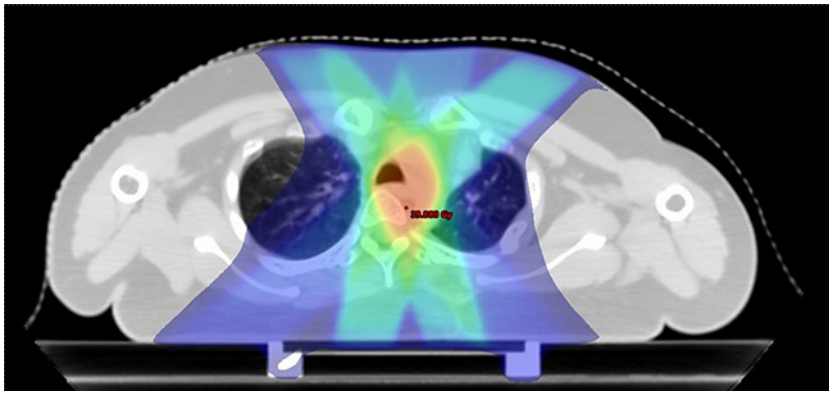

Fig. 5. Radiation dose distribution over 1 Gy for previous esophageal cancer. The irradiated area corresponded closely to the site of development of left lung cancer.

different between sexes. They also reported that 34 patients (28%) had >1 primary tumor, and half of the patients developed secondary malignancies in the mouth. Synchronous and/or chronological development of esophageal carcinoma was also documented in several case studies [4, 5, 9–11]. Thus, oral and esophageal cancers, as seen in our case, are relatively common cancers in patients with FA. However, lung cancer in patients with FA has rarely been reported. Alter [2] summarized 92 solid tumors in patients with FA reported between 1927 and 2001 and reported the development of lung cancer in 3 patients. Subsequently, they further analyzed a cohort study of 163 patients with FA from 2002 to 2015, and reported 1 case of the development of lung cancer [3]. Clinical information about these cases was not available. However, we found 2 additional case reports of lung cancer developing in FA patients [12, 13]; both were male, in their 30 s, with 10-pack year smoking history, and no history of previous cancers. The histological type was squamous cell lung cancer. Thus, lung cancer is an extremely uncommon primary solid tumor in FA.

Our patient was female and a never smoker, including no family history of smoking. We speculated that the development of lung cancer in the present case was associated with previous radiotherapy for HSCT and esophageal cancer as well as the presence of susceptibility to malignancies of the FA gene pathways. In addition, it is a noteworthy that the lesions were located in the bilateral lungs corresponding closely to the field of irradiation therapy for prior esophageal cancer and that lung cancer developed after short interval (3 years) following the prior radiotherapy. Radiotherapy remains a key therapeutic strategy for various cancers, including esophageal cancer and it is well known that the absolute excess risk increases with time from treatment for as long as 20–25 years after chemoradiotherapy in the case of Hodgkin's lymphoma [14]. The precise mechanism contributing to the development to malignancy in such as short interval remains unclear in patients with FA, our case suggests that careful and short-term screening of the irradiated area should be performed in patients with FA.

It has been shown that toxicities in chemotherapy and/or radiotherapy are poorly tolerated and considered prohibitive in FA patients. Indeed, several reports indicated unexpected severe toxicities during radiotherapy and/or combined with chemotherapy, leading to treatment-related death [15, 16]. Thus, limited information was available about therapeutic strategies and outcomes in cases of solid tumors developing in FA. Recently, Dudek et al. [13] reported a well-tolerated neoadjuvant chemotherapy with a reduced dose of carboplatin and gemcitabine in a patient with nonsmall cell lung cancer. Hosoya et al. [11] also reported successful treatment outcome in a case of esophageal carcinoma treated with a low

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dose of cisplatin and 5-fluorouracil plus radiotherapy (30 Gy). Only radiotherapy at a total dose of 41.4 Gy was performed for esophageal cancer in the present case, which was apparently insufficient for disease control in general patients with esophageal cancer. However, the toxicity was well managed and the esophageal cancer was well controlled for 3 years after radiotherapy. The optimal cytotoxic chemotherapy and/or radiotherapy regimens remain unclear, and further studies to determine therapies for solid malignancies in patients with FA are required.

Conclusion

We described the clinical course of the serial cancer development 3 times in a patient with FA with a history of HSCT. Regular and careful screening for solid malignancies as well as cytogenetic abnormalities in patients with FA should be performed even from infancy. Our case also indicated the importance of irradiated area as a site of subsequent cancer development.

Statement of Ethics

All treatment procedures in this patient were performed in accordance with written informed consent. Ethical approval of institutional research committee was not relevant or applicable to this case report. Consent for publication was obtained from the parents.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

K.Y., T.H., A.M., H.K., T.N., N.S., S.K., and T.K. took care of the patient and participated in the conception of the study. H.S. and I.I. participated in the pathological diagnosis. K.Y., S.K., and T.K. wrote the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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