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## Single Case

# Successful Treatment of Hepatocellular Carcinoma Complicated by Fanconi Anemia

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## Keywords

Fanconi anemia · Hepatocellular carcinoma · Transcatheter arterial embolization

## Abstract

A 42-year-old woman with liver tumors was referred to our hospital. Her condition was complicated by Fanconi anemia, and she had undergone total laryngectomy 8 years ago. On admission, contrast-enhanced computed tomography revealed hypervascular tumors in the right hepatic lobe. Ultrasound-guided tumor biopsy revealed that the tumor comprised moderately differentiated hepatocellular carcinoma. Although the patient exhibited preserved liver function (Child-Pugh A), complete blood count revealed severe pancytopenia. Eventually, the tumor was successfully treated by transcatheter arterial embolization (TAE). Both platelet transfusion and systemic administration of antibiotics were performed. She was discharged 35 days after TAE.

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## Introduction

Fanconi anemia (FA) is an inherited aplastic anemia that is characterized by congenital abnormalities such as skeletal defects and hypopigmentation, progressive bone marrow failure, and susceptibility to malignancies [1]. FA is considered to be caused by mutations in genes regulating replication-dependent removal of interstrand DNA crosslinks [2]. Apoptotic induction in hematopoietic stem cells (HSCs) caused by unrepaired DNA damage resulted in depletion of HSCs; this further leads to pancytopenia [3]. It has been shown that 75–90% of the patients demonstrate pancytopenia. Allogeneic HSC transplantation, which is the only curative modality for bone marrow failure in patients with FA, has been reported to contribute to favorable survival [4].

FA patients frequently develop hematological and nonhematological malignancies [5]. It has been reported that these patients carry a more than 500-fold higher risk of developing hematological malignancies such as leukemia and myelodysplastic syndrome compared with healthy people. Among solid tumors, the development of head and neck squamous cell carcinoma has been well documented, but the incidence of hepatocellular carcinoma (HCC) appears to be less common [6]. Therefore, the clinical condition and treatment approach for HCC in FA patients remain to be elucidated.

Here, we describe an unusual case of HCC complicated by FA, wherein the patient was successfully treated with transcatheter arterial embolization (TAE).

## Case Report

A 42-year-old woman was admitted to our hospital for the treatment of liver tumors. Her condition had been complicated by aplastic anemia 33 years ago, and at that time, she was treated with anabolic steroids. She did not get the opportunity to receive HSC transplantation. She was ultimately diagnosed with FA based on the findings of mitomycin C-induced chromosomal breakage analysis in lymphocyte cultures 8 years ago. In the same year, she developed laryngeal cancer and received total laryngectomy. Three months prior to admission to our hospital, she developed multiple pyogenic abscesses in pelvic muscles. Although she was successfully treated with the systemic administration of antibiotics, multiple liver tumors were detected.

On admission, she exhibited a short stature (143.1 cm) and systematic pigmentation of skin. She has no family history of inherited disorders. Blood count tests showed severe pancytopenia. White blood cell count, hemoglobin concentration, and number of platelets were 400/ $\mu$ L, 7.3 g/dL, and 3,000/ $\mu$ L, respectively. Serum levels of aspartate transaminase and alanine transaminase were within their normal ranges (Table 1). However, serum levels of alkaline phosphatase and  $\gamma$ -glutamyltranspeptidase was elevated (842 and 486 U/L, respectively). Both hepatitis B surface antigen and hepatitis C virus antibody were negative. The levels of  $\alpha$ -fetoprotein and des- $\gamma$ -carboxy prothrombin were 109.6 ng/mL and 21,377 mAU/mL, respectively. The patient's Child-Pugh score was 5 (class A).

Contrast-enhanced computed tomography (CT) demonstrated multiple hypervascular tumors in the right hepatic lobe (Fig. 1). The diameter of the main tumor was approximately 90 mm. The lesions were clinically determined to be stage III (T3N0M0). Tumor biopsy re-

vealed that the tumor comprised of moderately differentiated HCC (Fig. 2a). Nontumor tissue showed scarce inflammation and fibrosis, although iron deposition was observed in hepatocytes (Fig. 2b). In view of the tumor stage and liver function, hepatic resection or transcatheter arterial chemoembolization (TACE) was recommended according to the guidelines for HCC treatment proposed by the Japan Society of Hepatology [7]. However, taking into consideration severe pancytopenia, the treatment approach appeared not to be suitable. We obtained informed consent before treatment and conducted TAE, but not TACE. Concordant with the findings of contrast-enhanced CT, these tumors demonstrated enhancement on CT hepatic angiography and perfusion defect on CT during arterial portography. Lipiodol-CT after TAE exhibited lipiodol deposition in the tumors (Fig. 3). To reduce the risk of complications, both platelet transfusion and intravenous administration of antibiotics were performed prior to TAE. Because she exhibited persistent fever after TAE, the administration of antibiotics was continued. She was eventually discharged 35 days after TAE.

## Discussion

FA, which was first reported in 1927, is a bone marrow failure syndrome characterized by progressive lethal pancytopenia and skeletal abnormalities [8]. FA is attributed to chromosomal instability, and 19 genes responsible for FA have been identified to date [9, 10]. Although *FANCB* gene represents an X-linked deleterious mutation in FA complementation group B, the remaining FA-associated gene aberrations are autosomally inherited recessive mutations. The incidence of aplastic anemia is 80% in FA patients aged  $\leq 10$  years and 90% in FA patients aged  $\leq 40$  years [11]. The patient in the present case developed pancytopenia when she was 9 years old.

One of the most significant clinical features of FA is FA-associated malignancy. Hematological malignancies are frequently observed in patients with FA, and the incidence of this phenomenon increases with age. Leukemia or myelodysplastic syndrome develops in 30% of FA patients aged  $\leq 30$  years [12]. Although these data suggest that patients with FA should undergo HSC transplantation during childhood, the outcomes associated with this approach have been less than favorable. It has recently been reported that HSC transplantation with a conditioning regimen that includes fludarabine is associated with a favorable survival [13]. In the present case, the patient did not get the opportunity to receive HSC transplantation, and she received blood transfusion and anabolic hormone therapies. Of importance, nonhematological malignancies in FA patients are also associated with a morbidity rate of 25–30%. Squamous cell carcinomas of the head and neck and gynecological malignancies are among the most frequently observed types of cancer in this context [14]. FA in the present case study was complicated by laryngeal cancer, and the patient had previously undergone a total laryngectomy. Because the risk of solid tumor development remains high even in FA patients treated with HSC transplantation, careful attention is required.

It has been reported that the incidence of HCC complicated by FA is 46% by age 50 [5]. However, there are few reports describing an effective therapeutic intervention for such cases. Hepatic resection and liver transplantation from a compatible donor is an approach reported [15, 16] for patients with juvenile-onset FA presenting with relatively mild pancytopenia, a condition that may be considered advantageous. Considering that the success of

radical treatment in treating HCC in patients with FA is often limited by the severity of pancytopenia, FA-related HCC is associated with a poor prognosis. In the present case, the patient presented with severe pancytopenia; therefore, neither surgery nor administration of anticancer drugs was feasible treatment options. After further consideration, replacement therapy and intravenous antibiotics were administered, and TAE was conducted to control the tumors.

In cases of aplastic anemia, including patients with FA, long-term treatment with anabolic steroids and replacement therapy with blood components is commonly implemented. However, this approach requires extreme caution because of the association of anabolic steroid hormone therapy with iron deposition and hepatocarcinogenesis [17, 18]. The patient in this report presented with iron deposition resulting from transfusion dependency and long-term treatment with anabolic steroid hormones and immunosuppressants. Iron deposition was suspected to be a contributing factor to the development of HCC. Taken together, it is necessary to pay attention to HCC development in such cases.

In conclusion, this is a first report which documents a case of HCC complicated by FA wherein the patient was successfully treated with TAE. The therapeutic approach against HCC is usually determined based on the tumor stage and hepatic reserve function. In cases of HCC complicated by FA, the selection of the appropriate therapeutic strategy should be based on a comprehensive evaluation that includes the assessment of the severity of pancytopenia, performance status, and other relevant variables.

### Statement of Ethics

The authors have no ethical conflicts to disclose.

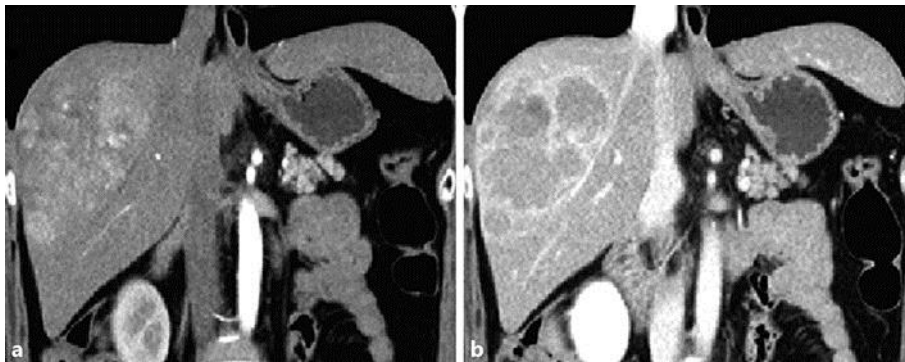
### Disclosure Statement

The authors declare no conflict of interest.

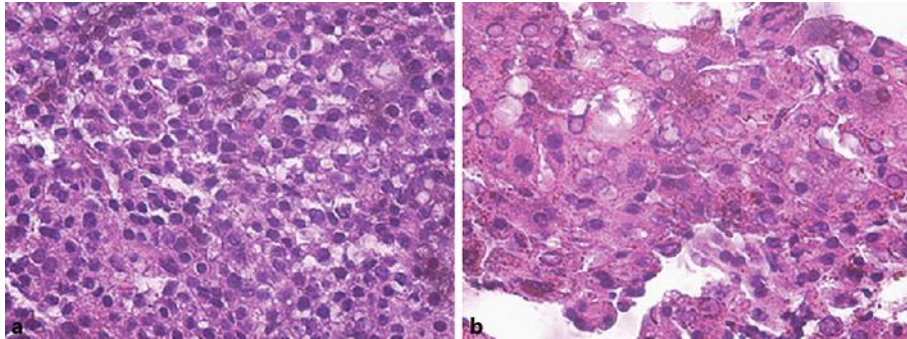
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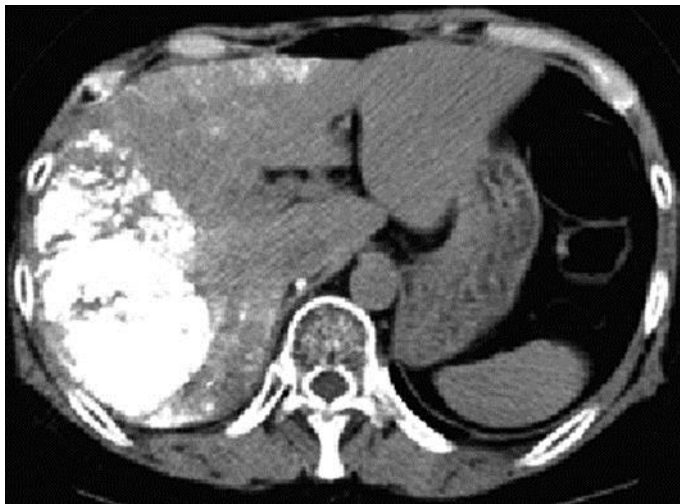
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**Fig. 1.** Contrast-enhanced CT findings. **a** The tumors in the right hepatic lobe showed enhancement in the arterial phase. **b** These lesions showed washout in the equivalent phase.



**Fig. 2.** The pathological findings of the liver biopsy specimen. **a** The tumor was composed of moderately differentiated HCC. **b** Iron deposition in hepatocytes was observed in nontumor tissue. HE.  $\times 400$ .



**Fig. 3.** Findings of lipiodol-CT. CT conducted after TAE showed lipiodol accumulation in the tumors.



**Table 1.** Laboratory data on admission

<i>Blood cell count</i>	
WBC	400/ $\mu$ L
RBC	$2.53 \times 10^4$ / $\mu$ L
Hb	7.3 g/dL
Ht	20.5%
Plt	$0.3 \times 10^4$ / $\mu$ L
<i>Coagulation</i>	
PT-INR	1.06
<i>Blood chemistry</i>	
TP	5.9 g/dL
Alb	3.6 g/dL
T-Bil	0.5 mg/dL
AST	29 IU/L
ALT	24 IU/L
LDH	189 IU/L
ALP	842 IU/L
$\gamma$ -GTP	486 IU/L
BUN	10 mg/dL
Cre	0.49 mg/dL
Fe	247 $\mu$ g/dL
<i>Serology</i>	
CRP	2.5 mg/dL
HBsAg	–
HCV-Ab	–
HIV-Ab	–
<i>Tumor markers</i>	
AFP	109.6 ng/mL
AFP-L3	45.5%
DCP	21,377 mAU/mL
Ferritin	1,671.1 mg/dL