

## Hepatic focal nodular hyperplasia developing in a fanconi anemia patient: a case report and literature review

**Fanconi anemia, an autosomal recessive and X-linked disorder, is known to be associated with a variety of neoplasms. Liver tumors are one of the most frequently observed neoplasms but the association between the two disorders remains obscure. We present a case of a 27-year old female Fanconi anemia patient diagnosed with a mass on the right lobe of the liver measuring 90×75×60 mm. Histopathological examination of the mass after right hepatic lobectomy revealed focal nodular hyperplasia. This appears to be the first reported case of a hepatic focal nodular hyperplasia of such proportion associated with Fanconi anemia. Previously reported cases of liver tumors in association with Fanconi anemia in the English Literature were either hepatocellular carcinomas or hepatic adenomas.**

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Fanconi anemia (FA) is an autosomal recessive as well as X-linked disorder characterized by bone marrow failure, skin pigmentation, congenital abnormalities and increased susceptibility to cancer development. At least 12 genetic subtypes (FA-A, B, C, D1, D2, E, F, G, I, J, L and M) have been described and all, except FA-I, have been linked to a distinct gene.<sup>1</sup> The most frequently reported neoplasms associated with FA are myeloid leukemias, liver tumors, head and neck carcinomas and gynecological malignancies.<sup>2,3</sup> Several studies and case reports have shown a direct connection between androgen use and development of liver tumors in both FA and non-FA patients.<sup>4-11</sup> Almost all reported cases of liver tumors in FA patients are either hepatocellular carcinomas (HCC) or hepatic adenomas (HA).<sup>2</sup> Reported here-in, is a case of a female FA patient found to have focal nodular hyperplasia (FNH) after hepatic resection of a liver tumor diagnosed following several years of androgen use. This might be the first reported case of a benign liver tumor without any potential for malignant transformation found in an FA patient, in the English Literature.

A 27-year old female patient, while at age of 8, presented with symptoms of pancytopenia and failure to thrive. Physical examination revealed short stature (height less than 3rd percentile), micrognathia and café-au-lait spots on her skin. Her hemoglobin was 9.9 g/dL, leukocyte count of  $2.8 \times 10^9/L$  and platelets of  $28 \times 10^9/L$ . The bone marrow was mildly hypoplastic with moderately suppressed erythroid and megakaryocytic lineages. This clinical picture, in addition to a history of her sister been previously diagnosed with FA, led to the suspicion of FA. Subsequent cell analysis using DEB (diepoxybutane) test revealed numerous chromosomal breaks confirming the diagnosis of FA. She was started on androgen (oxymetholone 3 mg/kg/day) and prednisolone (1 mg/kg/day) therapy at the age of 8. Two years later, her blood count remained satisfactory and the doses of oxymetholone and prednisolone were tapered to 25 mg/day (1 mg/kg/day) and 2.5 mg/day (0.1 mg/kg/day), respectively. After 19 years without any major incident, except four red blood cell (RBC) transfusions in the last two years and neutropenic fever for which she received a 5-day course of G-CSF treatment, she presented with a complaint of abdominal discomfort which she indicated

started several months earlier. Physical examination revealed a slight right upper quadrant tenderness and a palpable liver. Her blood chemistry revealed elevated liver function parameters (ALT of 57 U/L, AST of 49 U/L, GGT of 1279 U/L, ALP of 281 U/L and total bilirubin of 0.57 mg/dL). Her white blood cell count was  $3 \times 10^9/L$ , hemoglobin 4.5 g/dL and platelets  $18 \times 10^9/L$ . Levels of tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were normal except serum alpha-feto-protein (AFP) which was slightly elevated [9.73 IU/mL, (normal range of 0-5.8 IU/mL)]. An abdominal ultrasound followed by magnetic resonance imaging (MRI) of the liver revealed a homogeneous hyperechoic mass measuring 88×80 mm on the right side of the liver. The radiological features of the mass were interpreted to be consistent with FNH (see Figure 1). In addition, the body and tail of the pancreas were noted to be absent (congenital agenesis). Histological analysis of a tru-cut needle biopsy specimen showed liver tissues separated by fibrotic bands and containing abnormally walled vascular structures. There were no portal tracts and hepatocytes were positively immunoreactive for cytokeratin 8 and 18 but negative for cytokeratin 7 and 19. This morphology was interpreted as reflecting a regenerative process secondary to developmental vascular anomaly (FHN or hamartomatous lesion). However, the possibility of malignancy could not be ruled out. Because of this and due to the large size of the mass with potential risk of malignancy, complete surgical resection was considered. After a careful preoperative hematological evaluation and preparation, she underwent a successful right hepatic lobectomy surgery. She received 8 units of RBC, 18 units of platelets transfusion perioperatively. Her postoperative course was uneventful and was discharged 8 days after surgery. Macroscopic examination of the specimen revealed an encapsulated mass measuring 90×75×60 mm with fibrous septae and central scar. Microscopy revealed typical features of classic FNH including central stellate zone containing numerous abnormally thick-walled vessels, marked proliferation of biliary structures surrounded by inflammatory cells and hepatic plates containing normal appearing hepatocytes. No foci of hepatoma or adenoma were found (see Figure 2, 3.). The patient is currently doing well clinically.

Fanconi anemia, like other cancer predisposition disorders, is known to be associated with increased risk of a variety of neoplastic disorders. Most commonly reported neoplasms include myeloid leukemias, head and neck carcinomas, liver tumors and gynecological malignancies.

The development of liver tumors in FA was initially suggested to be associated with underlying genetic abnormality, rather than with the therapy. However, earlier reports suggested a possible connection between androgen use and liver tumors in FA patients.<sup>4,12,13</sup> The review by Alter BP and also by Velazquez et al, in which 36 out of 37 FA patients with liver tumors received androgen treatment, support the opinion of a potential role of androgens in the risk of liver tumor development in these patients.<sup>2,14</sup> The role of androgens in the pathogenesis of liver tumors has not been fully explained. Androgen and estrogen receptors have been identified in HA and HCC and surrounding normal liver cells suggesting that these steroids may play a significant role in the induction and growth of these tumors.<sup>15-17</sup> Another suggestion that anabolic steroids may induce liver tumors through intermediate hyperplastic lesions; a sequence similar to that seen during induction by carcinogens in experimental animals,<sup>18</sup> may explain why almost all reported cases of liver tumors in FA and non-FA patients

**Figure 1.** Post-contrast T1 weighted Magnetic resonance imaging of the liver showing hyperintense mass (arrow heads) measuring 8.8 cm with a hypointense central scar (thin-arrowed).

**Figure 2.** Cross section of freshly resected specimen showing encapsulated mass (arrow heads) with nodules of variable size and septa.

**Figure 3. A.** Photomicrograph showing central stellate scar with ductular proliferation surrounded by normal hepatocytes and absence of portal triad (H&E stain: x200). **B.** Cross section of resected specimen showing nodular appearing mass (arrow heads) measuring 90x75 mm.

are either HA or HCC.

The pathogenesis of FNH (the second most common benign solid tumor of the liver) is not well known. However, it is generally regarded as a hyperplastic or regenerative lesion often as a result of abnormal vasculature.<sup>19</sup> With the exception of one case report, no association has been established specifically between androgen

use and FNH.<sup>20</sup> Whether long-term androgen therapy can cause the development of FNH is not known, but the identification of both estrogen and androgen receptors in both normal and tumoral liver cells may suggest that androgens may also accelerate the growth of FNH.

Patients with FNH are mostly asymptomatic, however, the most common clinical symptoms are epigastric and right upper quadrant pain. Spontaneous rupture leading to hemorrhage is extremely rare. There is no evidence that FNH is a precursor of any malignant liver tumor.<sup>21</sup> Because of its benign course most patients are generally managed conservatively. Surgical resection is indicated for those with significant symptoms or in cases where malignancy cannot be excluded by radiologic and histologic studies.

The most distinguishing feature of this case is the diagnosis of FNH (see Figure 3), as against other reports which were either HCC or HA. Although benign, surgical resection was carried out because preoperative tru-cut needle biopsy failed to exclude malignancy and also because of the large size of the tumor carrying a potential risk of concurrent foci of HCC. Conservative follow-up was considered inappropriate for the patient because of her symptoms. However, the decision to carry out a major surgical hepatectomy in an already pancytopenic patient is debatable. Nonetheless, inability to exclude malignancy preoperatively and the large size of the tumor with potential risk of spontaneous rupture, however rare, in an already pancytopenic patient, could result in a remarkably high mortality rate making the decision for surgery *sine qua non*.

As part of the disease process, patients with FA per se, have an intrinsic tendency to develop variety of malignancies which is thought to be further augmented by treatment modalities such as androgens and stem cell transplantation with associated increased risk of liver tumors and head and neck carcinomas, respectively. Successful surgical resection of malignant or premalignant lesions in FA patients can be carried out favorably provided all necessary perioperative replacement of blood components is carefully orchestrated. Finally, further studies are needed to investigate role of androgens in the formation and/or growth of FNH.

\*Nabil M. Nuamah, <sup>1</sup>Erhan Hamaloglu, <sup>1</sup>Arif Ozdemir, <sup>1</sup>Ahmet Ozenc, <sup>2</sup>Havva Solak Ozseker, <sup>2</sup>Canek Sokemensuer  
Hacettepe University School of Medicine  
<sup>1</sup>Department of General Surgery  
<sup>2</sup>Department of Pathology

\*Correspondence: Nabil M. Nuamah  
Hacettepe University School of Medicine  
Department of General Surgery  
Sihhiye, Ankara 06100 Turkey  
Tel: +90-532-7676421  
E-mail: Drnuamah@Yahoo.Com

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