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Hepatocelluar Carcinoma Associated With Attenuated Familial Adenomatous Polyposis: A Case Report and Review of the Literature

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Abstract

Hepatocelluar carcinoma (HCC) has rarely been associated with familial adenomatosis polyposis (FAP). Between 1950 and 2011, only a few cases of HCC associated with classic FAP have been reported in the medical literature. Here, we report the first case to our knowledge of HCC associated with attenuated FAP (aFAP). The patient possessed a single nucleotide mutation in the noncoding region after exon 4, which is rarely observed in attenuated FAP, and not previously reported in classic FAP–associated HCC. Our patient underwent liver transplantation for a 22-cm-large HCC (in China), however, her HCC recurred 1.5 years after the transplantation. Here we review the medical literature on FAP and HCC, with a particular focus on the role of the Wnt/APC/β-catenin pathway toward a better understanding of HCC pathogenesis.

Keywords

Familial adenomatosis polyposis; Hepatocelluar carcinoma

Introduction

In 1859, Charelaigue[1] first described adenomatous polyposis in a 16-year-old girl and a 21-year-old man. Later, familial adenomatosis polyposis (FAP) was recognized to be the most common inherited polyposis syndrome. Cumulative evidence supports that, under the umbrella of FAP, classic FAP (cFAP), and attenuated FAP (aFAP), might be very different identities both clinically and molecularly. Patients with FAP can have extracolonic manifestations of their diseases, including thyroid carcinomas and central nerve system neoplasms.[2] It is rare for patients with FAP to have hepatic neoplasms, especially HCC. Here, we report the first case to our knowledge of HCC associated with aFAP.

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Case Report

A 42-year-old Caucasian woman presented with a 1-month history of early satiety and discomfort in the right upper quadrant. Her Italian-descendant paternal family history was notable for familial adenomatosis polyposis (FAP), with her father and his 5 siblings having developed multiple colon polyps while in their 40s. Her maternal family is mixed-European and had no malignancy except that her mother had head-neck cancer. By using direct DNA sequencing, she was found to have a nucleotide substitution in a noncoding intervening sequence (IVS) that occurs 5 base pairs from the end of exon 4 (IVS4+5G>A), which resulted in a truncated APC protein. Periodic screening colonoscopies (beginning at age 18 years) had been negative until she was 41 years old. At that time, she had both upper esophagogastroduodenoscopy and colonoscopy. The esophagogastroduodenoscopy revealed polyps too numerous to count in the body and fundus of the stomach. Colonoscopy showed about 2 dozen tiny adenomatous polyps (all <5 mm) in the cecum and ascending colon, few polyps in transverse colon, and no polyps in the descending colon, sigmoid colon, or rectum. She was diagnosed with attenuated FAP (aFAP) and underwent a total abdominal colectomy with ileoproctostomy 1 year before her presentation with abdominal pain. Pathology from her colectomy showed no evidence of high-grade dysplasia or malignancy.

At the time of her presentation with abdominal pain, results of a physical examination revealed palpable hepatomegaly but no scleral icterus or ascites. Blood tests showed a total bilirubin, 1.0 mg/dL; aspartate aminotransferase, 46 U/L; alanine aminotransferase, 55 U/L; alkaline phosphatase, 422 U/L; gamma-glutamyl transpeptidase, 282 U/L; and alpha-fetoprotein, 0.95 ng/mL. Unfortunately, she was found to have a large liver mass (22.5 ×12.6 cm) (Figure 1A) on magnetic resonance imaging. Biopsy of the mass revealed mature hepatocytes arranged in rosettes and thickened groups, and with mild cytologic atypia (Figure 1B). A reticulin stain showed an absence of the normal reticulin framework, which supports a diagnosis of well-differentiated hepatocellular carcinoma (HCC). She was determined not to be a candidate for liver transplantation due to disease outside the Milan criteria but subsequently obtained an orthotopic liver transplantation in Beijing, China. After liver transplantation, she received adjuvant intravenous doxorubicin every 3 weeks for 5 cycles.

Our patient had hepatitis B virus (HBV) and hepatitis C virus (HCV) serologic tests before her liver transplantation, which were negative. Shortly after liver transplantation with a Chinese liver donor, she remained seronegative for HCV but became seropositive for HBV infection, with HBV core antibodies total (anti-HBc total) positive, but hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) negative. She had no liver enzyme abnormality from 2 months to 1.5 years after the liver transplantation. At that time, the serologic test results showed that anti-HBc total changed from positive to negative, HBe antigen (HBeAg) became positive, and that hepatitis B e antibody (HBeAb), HBsAg, and HBsAb remained negative. HBV DNA viral load became detectable, at 1,090,000 IU/mL. The HBV was genotype B, and no polymerase, precore, and BCP mutations.

Routine abdominal imaging was performed after the transplantation. One and a half years after transplantation, an magnetic resonance imaging of the abdomen revealed multiple rim-enhancing masses about 3 cm in size throughout both lobes of the liver (Figure 1C) along with an extrahepatic mass in the pararenal soft tissue. Ultrasound-guided percutaneous core liver biopsies of one mass confirmed HCC (Figure 1D). She was treated with chemoembolization and subsequently with sorafenib, but her disease pursued a relatively aggressive course, and she died of progressive systemic disease approximately 1 year from the time of the documented recurrence (Figure 2).

Discussion

FAP is an autosomal dominant hereditary disease that is characterized by the presence of numerous adenomatous polyps throughout the colon and rectum. The classic FAP phenotype is characterized by the early onset of polyps beginning in the teens, adenocarcinoma by age approximately 40 years old, and hundreds to thousands of polyps in the gastrointestinal tract. The aFAP phenotype is different from the "classic" FAP in the age of onset, number and location of polyps. Patients with aFAP start to develop polyps in their 40s, and normally have fewer than 100 polyps that are right-side dominant. The clinical presentation of the patient in our case was not typical of cFAP but was consistent with aFAP, with onset at older age, larger numbers of gastric polyps, and relatively few colonic polyps.

Patients with FAP can have extracolonic manifestations of their disease: stomach and duodenal adenomas; periampullary carcinomas and carcinomas of the billiary tract; jejunal and ileal adenomas; osteomas of the mandible, skull, and long bones; soft-tissue lesions, such as epidermoid cysts and desmoids tumors; thyroid carcinomas; and central nerve system neoplasms.[2] It is rare for patients with FAP to have hepatic neoplasms.[3] Hepatic tumors reported in patients with FAP include adenoma, hepatoblastoma, fibrolamellar carcinoma, and HCC.[3,4]

FAP is caused by mutations in the *APC* (adenomatous polyposis coli) gene. The human *APC* gene is located on the long (q) arm of chromosome 5 and is considered a tumor suppressor gene. More than 800 germline *APC* gene mutations have been identified in families with classic and attenuated FAP,[5] most of which involve exon 3 to codon 1700 (exon 15), which result in truncated proteins or the absence of protein. Truncating mutations between codons 169 and 1600 are associated with the cFAP phenotype. Mutations at the 5′ and 3′ extremes of the *APC* gene are more commonly associated with aFAP. The IVS4+5 G>A mutation that our patient possessed is located at the 5′ end of *APC* and occurs in a highly conserved region that is usually necessary for proper messenger RNA processing.[6] The same mutation was seen among Greek aFAP kindred.[7] A similar mutation (IVS4+5 G>C) at this location has been shown to result in deletion of exon 4, frameshift, and a stop after the first 6 codons in exon 5, which generates a truncated APC protein, which is either unable to form the APC complex or to generate a dominant negative effect on the APC complex. It is intriguing that, in Japanese patients, gastric lesions occur in patients with aFAP with an exon 4 mutation[8]; our patient with a deletion that started from exon 4 also had numerous gastric adenomatous polyps.

With recent improvements in routine mutation detection techniques, germline *APC* mutations can be detected in 81% of patients with cFAP and in up to 30% of patients with aFAP.[9] Analysis of recent data indicates that a significant portion of patients who have *APC*-mutation-negative cFAP and aFAP have mutations of *MYH* (MutY human homology, 7% of cFAP and 40% of aFAP, respectively). MYH encodes a critical member of the DNA base-excision repair system.[9] It seems that *APC* mutation and *MYH* mutation are mutually exclusive, therefore, a *MYH* mutation test is unwarranted in a patient who has *APC*-mutated aFAP.

Between 1950 and 2011, only 10 cases of HCC associated with FAP/Gardner syndrome have been reported in the literature,[3,4,10–15] including our case (Table 1). Our report is the first to our knowledge to describe HCC associated with aFAP, and the first to document recurrence of HCC after liver transplantation in a patient with aFAP. We reviewed all cases of HCC related to FAP. Unfortunately, only 2 patients had genetic testing done. Both had germline *APC* mutations, one that occurred between codons 1099 and 1693,[4] and the other that occurred at codon 208.[3] The patient with the codon 208 germline APC mutation also

had a somatic mutation at codon 568. Our patient has a different germline mutation pattern from the above patients. It, therefore, seems that not just a single but rather a group of genetic alterations can breed HCC in FAP and aFAP. Unfortunately, our patient's liver transplantation was performed in China; we do not have sufficient HCC specimen from the biopsy for somatic mutation testing.

Cases of HCC in FAP highlight that the Wnt/APC/*β*-catenin signaling pathway could potentially be important in hepatocarcinogenesis in general. Accumulating evidence supports a crucial role of the Wnt/APC/*β*-catenin pathway not only in normal embryogenesis but also in carcinogenesis of various cancer types.[16] Wnt protein interacts with its receptors of serpentine proteins Frizzled (Fz), which then activates the downstream effector Dishevelled (Dsh), and eventually the APC protein complex. APC is considered a tumor suppressor protein, which forms a large complex with glycogen synthase kinase 3-beta (GSK-3*β*) and axin. The APC complex binds to casein kinase (CK1)-phosphorylated *β*-catenin,[17] and the GSK-3*β* component of complex phosphorylated *β*-catenin a second time, ultimately leads to its ubiquitination and degradation by proteasomes.[18] Loss of APC function, therefore, leads to stabilization and accumulation of *β*-catenin in the cytoplasm and nucleus, where it binds to the transcription factor Tcf/Lef complex and activates the transcription of Wnt target genes. About 150 Wnt target genes have been identified (ie, *MYC*, *MYB*, *CJUN*, and *CYCD1*), which play pivotal roles in cell proliferation, differentiation, migration, and interaction with the extracellular matrix.[19]

Abnormal regulation of *β*-catenin appears to be a key event in HCC carcinogenesis. *β*-catenin mutations have been discovered in about 17% of HCCs; mutated sites include the GSK-3*β*-phosphorylation site. Approximately 50%–70% of HCCs have increased levels of *β*-catenin in the cytoplasm and nucleus.[20] It has been estimated that 12%–26% of cases of *β*-catenin accumulation come from *β*-catenin gene mutation and another 8%–13% from *β*-catenin-regulating gene mutation.[21]

If the Wnt/APC/*β*-catenin pathway is important in both colorectal cancer and HCC carcinogenesis, how can we explain the exceeding rarity of HCC associated with FAP? First, there may be natural selection for APC genotypes that retain some activity in downregulating *β*-catenin signaling,[22] and, therefore, require other genetic "hits" that are more likely to occur in colonic cells. Second, germline APC mutation alone may be insufficient in determining HCC development.[3,23] Third, the Wnt/APC/*β*-catenin signaling pathway may not play a dominant role in HCC tumorigenesis but rather may create genetic instability that, when combined with other genetic or extraneous factors, results in HCC. It is of interest to note that *β*-catenin-overexpressing transgenic mice develop significant hepatomegaly but not hepatic neoplasms.[21]

Note that our patient had no known history of HBV infection before liver transplantation. Her posttransplantation laboratory results uncovered chronic active genotype B HBV infection, which likely came from the donor. HBV has long been known as a major risk factor for HCC. Results of several studies have suggested that infection by HBV genotypes B and C are associated with an increased risk of HCC.[24] The mechanism of HBV carcinogenesis likely includes the integration of HBV DNA allows persistence of the virus and induces genetic alterations. In recent years, the X gene (HBx), the smallest open reading frame in the HBV genome that encodes a 154 amino acid protein has been recognized as being essential for productive HBV infection and replication. Interestingly, HBx activates Wnt/*β*-catenin signaling by upregulating the cytoplasmic *β*-catenin.[25] Our patient was at high risk for HCC recurrence after transplantation primarily due to tumor size, but it is interesting to speculate that the HBV infection could have contributed to recurrence. However, her HBV viral load converted from nondetectable to high about the time of her

HCC recurrence, which makes us doubt the significance of the HBV infection in this case. Currently, there are no data reported about the recurrence rate of HCC in patients who are HBV seronegative and who have received an HBV-infected donor liver. Data from the National Institutes of Health HBV orthotopic liver transplantation study group summarized the final, long-term outcome of patients transplanted for HBV-related HCC. With a mean follow-up of 36.5 months after orthotopic liver transplantation, 12 (12.2%) of 98 patients developed recurrence of HCC.[26]

This patient had been healthy before her diagnosis of HCC. She had never lived in another country or had known exposure to hepatotoxins. She received 5 cycles of doxorubicin right after liver transplantation and received immunosuppressive medications, including tacrolimus, mycophenolate mofetil, prednisone, and sirolimus after transplantation. It has been reported that immunosuppressive medication, with the exception of mTOR inhibitors, may contribute to HCC carcinogenesis.[27] Yokoyama et al[28] reported that the administration of combination therapy with cyclosporine and steroid, and/or doxorubicin was associated with a significant reduction in doubling-time for HCC from 273 days to 37 days. Interestingly, a recent study showed that Wnt–β-catenin signaling in dendritic cells regulates the balance between inflammatory vs. regulatory responses.[29] Upregulation of β-catenin signaling may potentiate dendritic cells to a tolerogenic state, which may contribute to tumorigenesis. It is unclear whether APC gene mutation and immunosuppressive medication caused a mutually intensifying effect on β-catenin and resulted in higher immunotolerance and subsequent HCC recurrence in our patient.

Conclusion

To our knowledge, this is the first report of a case of HCC associated with aFAP. The role of this specific APC gene mutation in HCC development deserves further investigation toward a better understanding HCC pathogenesis.

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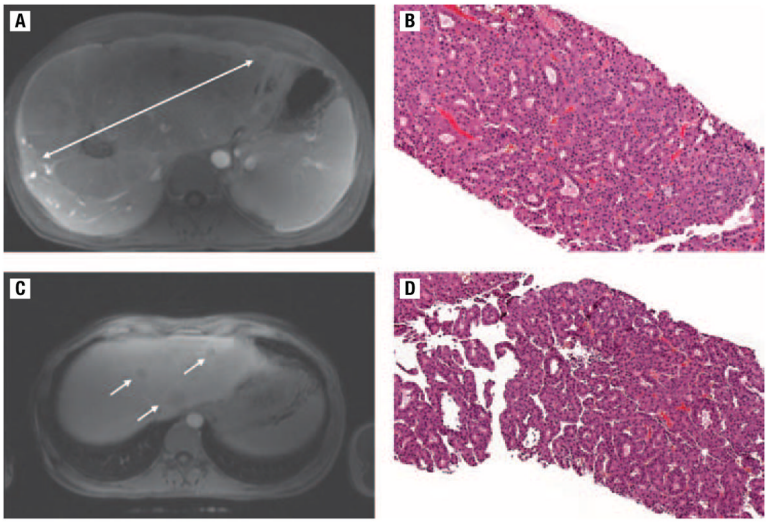

Figure 1.

(A) Magnetic Resonance Image (MRI) of the Liver, Showing a Large Primary Hepatocellular Carcinoma About 22.5 cm in Size. (B) Microscopic View of a Core Biopsy, Revealing Hepatocellular Carcinoma With Mature Hepatocytes Arranged in Rosettes and Thickened Groups, and With Mild Cytologic Atypia. Hematoxylin and Eosin Stain at ×100 Magnification. (C) MRI of the Liver Showing 3 Recurrent Lesions in the Transplanted Liver. (D) Microscopic View of a Core Biopsy, Again Confirming Hepatocellular Carcinoma at ×100 Magnification

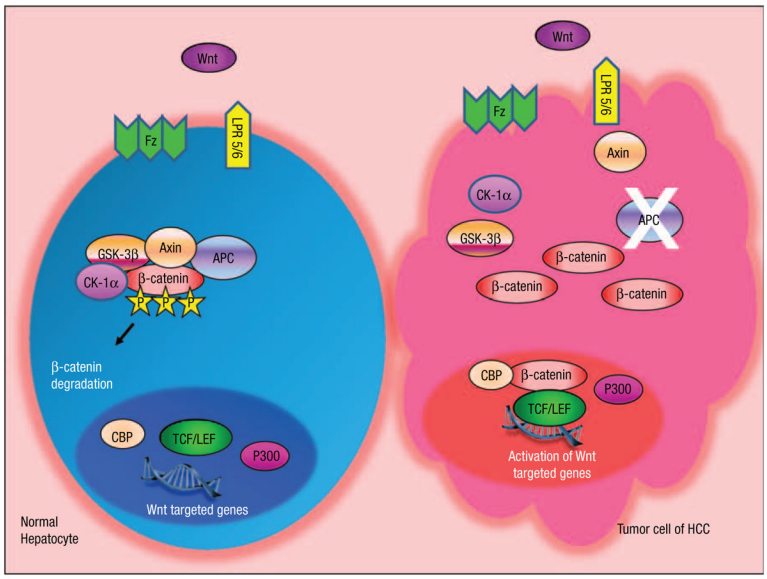

Figure 2.

The Potential Role of Wnt/APC/*β*-Catenin Pathway in APC Gene-Mutated Hepatocarcinogenesis. The Wnt-Ligand is a Secreted Glycoprotein That Binds to Frizzled Receptors (Fz), Which Trigger a Cascade and Result in the Release of the Multifunctional Kinase GSK-3*β* Form the APC/Axin/GSK-3*β* Complex. In Normal Hepatocytes, in the Absence of Wnt-Signal (Off State), *β*-Catenin, is Targeted for Degradation by the APC/Axin/GSK-3*β* Complex. *β*-Catenin Undergoes Proteasomal Degradation After Phosphorylation by CK1*α* and GSK-3*β*. In Tumor Cells, Mutated or Truncated APC Protein Cannot Form the APC/Axin/GSK-3*β* Complex, Resulting in Stabilization of the *β*-Catenin Level. *β*-Catenin Translocates into the Nucleus and is Recruited to the LEF/TCF DNA-Binding Factors and Subsequently Leads to the Activation of Wnt-Targeted Genes

Table 1

Summary of Patients With HCC Associated With FAP/Gardner Syndrome

Reference	Family History	Polyposis Syndrome	Age of FAP Dx (y)	Age of HCC Dx (y)	Other Tumors	Germline Mutation	Somatic Mutation
Veale,[10] 1965	−	FAP	—	25	—	—	—
Weinberger et al,[14] 1981	+	Gardner	20	3	Epidermoid cysts	—	—
Zeze et al,[15] 1983	+	FAP	31	33	—	—	—
Laferla et al,[11] 1988	−	FAP	43	43	Gastric carcinoma	—	—
Van Steenbergen et al,[13] 1989	+	FAP	19	19	—	—	—
Spigelman et al,[12] 1991	+	FAP	—	78	Tumors of the bile ducts, pancreas and duodenum	—	—
Gruner et al,[4] 1998	−	Gardner	18	15. Fibrolamellar HCC.	Desmoid tumor	Between codon 1099–1693	—
	+	FAP	—	9	—	—	—
Su et al,[3] 2001	+	Gardner	15	28	Desmoid tumor	Codon 208	Codon 568
Li et al, 2011	+	aFAP	41	42	—	IVS4+5G>A	—

Abbreviations: − = negative; + = positive; — = unknown; aFAP = attenuated familial adenomatous polyposis; Dx = diagnosis; FAP = familial adenomatous polyposis; HCC = hepatocellular carcinoma; IVS = intervening sequence.