

Co-Existence of Intrahepatic Bile Duct Adenoma and Colonic Adenocarcinoma

Gülen AKYOL¹

Nüket ÜZÜM¹

Nusret AKYÜREK²

Bülent MENTEŞ²

Abstract: Intrahepatic bile duct adenoma (BDA) is a rare benign tumor of the liver that is usually diagnosed by microscopic examination. Most cases are incidentally discovered during surgery or autopsy. Here, we report the co-existence of colonic adenocarcinoma and intrahepatic BDA mimicking metastasis in a 62-year-old man. The patient underwent metastasectomy because of the presence of colonic adenocarcinoma diagnosed at almost the same time. The diagnosis was benign in frozen sections intraoperatively and total colectomy was performed during the same operation. BDA should be included in the diseases to be differentiated from hepatic primary or metastatic tumors.

Key Words: Bile duct adenoma, liver, immunohistochemistry

İntrahepatik Safra Duktus Adenomu ile Kolonik Adenokarsinom Birlikteliği:

Özet: İntrahepatik safra duktus adenomu, genellikle mikroskopik inceleme ile tanı alan, karaciğerin seyrek görülen benign bir tümürüdür. Çoğu olgu operasyon sırasında ya da otopsi ile tesadüfen saptanır. Burada, 62 yaşındaki erkek hastada metastazı taklit eden safra duktus adenomu ile kolonik adenokarsinom birlikteliğini sunduk. Olguda aynı zamanda kolonik adenokarsinom olması nedeniyle metastazektomi operasyonu yapıldı. Frozen kesitlerle intraoperatif olarak benign tanısı kondu, sonra aynı operasyonda total kolektomi yapıldı. Safra duktus adenomu, karaciğerin primer ya da metastatik tümörlerinin ayırıcı tanısında yer almalıdır.

Anahtar Sözcükler: Safra duktus adenomu, karaciğer, immünhistokimya

¹ Department of Pathology,
Faculty of Medicine,
Gazi University,
Ankara - TURKEY

² Department of General Surgery,
Faculty of Medicine,
Gazi University,
Ankara -TURKEY

Introduction

Bile duct adenoma (BDA) is a small, well-circumscribed mass composed of small acini and tubules set in fibrous stroma (1). Most cases reported previously were incidentally discovered during laparotomy or autopsy (1-4). BDA is also referred to as peribiliary gland hamartoma, benign cholangioma, or cholangioadenoma (2,5).

Macroscopically, they are well circumscribed but not encapsulated, gray-white or tan, flat or slightly elevated, subcapsular nodules (4). Nearly 40% of cases were originally considered either suggestive or diagnostic of adenocarcinoma (primary or metastatic) at the time of referral in one series, emphasizing the importance of familiarity with this lesion (6).

Herein, we report the co-existence of colonic adenocarcinoma and intrahepatic BDA in a 62-year-old man. The diagnosis of BDA was later established pathologically. These rare benign lesions should be included in the differential diagnosis of hepatic masses in addition to metastatic lesions even if the patient has a history of malignancy.

Case Report

A 62-year-old man was admitted to our hospital with a long history of constipation, rectal bleeding, and weight loss (about 18 kg per 3 months). He had a past medical history of hepatitis C, gastritis, and appendectomy performed 40 years before. Rectoscopy was performed and a vegetative lesion was seen at the level of 40 cm. Colonic adenocarcinoma was identified by endoscopic biopsy.

Received: November 12, 2007
Accepted: March 25, 2008

Correspondence

Nüket ÜZÜM
Department of Pathology,
Faculty of Medicine,
Gazi University,
06500 Beşevler,
Ankara - TURKEY

nuketuzum@yahoo.com

On admission, liver function tests were normal except for a gamma-glutamyl transpeptidase level of 129 U/l (normal: 0-50 U/l). His serum albumin, bilirubin, and coagulation parameters were within normal limits. Serum tumor markers were higher than normal (carbohydrate antigen 19-9, 47.92 U/ml, carcinoembryonic antigen 19.85 ng/ml, carbohydrate antigen 72.4, 9.7 U/ml). Anemia and a decreased serum ferritin level were found. Ultrasonography and computed tomography revealed a well-circumscribed mass 1 cm in diameter in the posterior segment of the right lobe of the liver (Figure 1). Thus, the lesion was preoperatively diagnosed as an intrahepatic metastasis of the colonic adenocarcinoma and he was considered to have Dukes' stage D tumor. His family history was negative for familial colon cancer syndromes.

Pathological Findings

Metastasectomy was planned and a wedge liver biopsy was sent for frozen section. A solitary subcapsular, well demarcated but nonencapsulated tan nodule measuring 1.1

cm in diameter was surrounded by liver parenchyma (Figure 2a, b). A frozen section of the liver mass was interpreted as consistent with a benign lesion. Then left total colectomy was performed during the same operation.

After fixation in 10% buffered formalin solution, the left total colectomy and wedge liver biopsy material were processed conventionally and paraffin embedded. Sections, 4-µm thick, were stained with hematoxylin and eosin.

An endophytic-ulcerative predominantly intramural tumoral lesion 5 cm in diameter was observed in the sigmoid colon. Histological examination revealed moderately differentiated adenocarcinoma with atypical epithelial cells forming glandular structures exhibiting great variability in size and configuration (Figure 3). The tumor was invading all layers of the bowel and extending into the serosal surface, but no metastasis in regional lymph nodes was present. Therefore, the tumor was considered Dukes' stage B2.

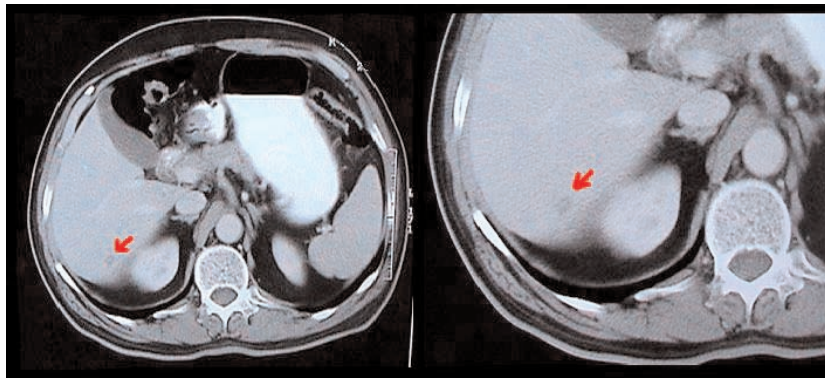


Figure 1. Abdominopelvic computerized tomography at the time of diagnosis showed a hypodense lesion (arrows) in the posterior lobe of the right lobe of the liver.

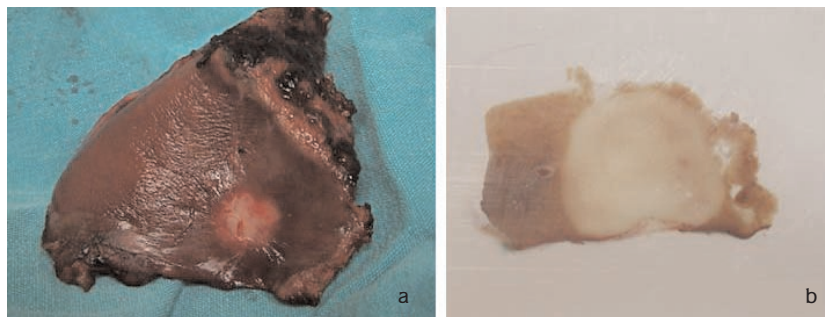


Figure 2. (a) A wedge liver biopsy demonstrating a solitary subcapsular, well demarcated but nonencapsulated tan nodule and (b) the same lesion in paraffin block.

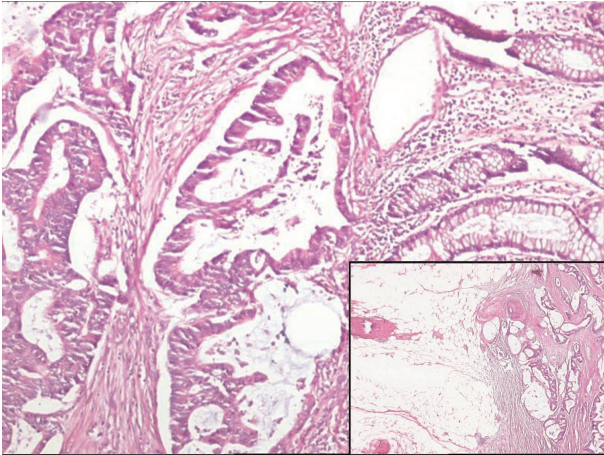


Figure 3. Moderately differentiated adenocarcinoma with atypical epithelial cells forming glandular structures exhibiting great variability in size and configuration in colon. (inset: demonstrating extension of tumoral cells into serosal surface) (Hematoxylin-eosin $\times 200$).

The microscopic study of the nodule from the liver showed an increased number of small, normal appearing bile ducts lined with a single layer of cuboidal cells and surrounding fibrotic stroma. The bile ducts had no or little lumina (Figure 4). The fibrous stroma showed varying degrees of chronic inflammation and collagenization.

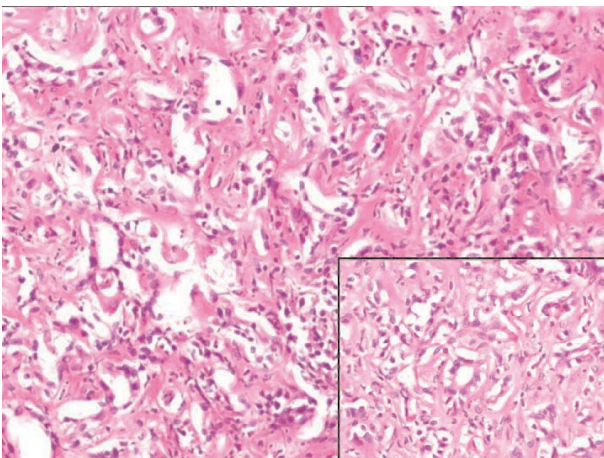


Figure 4. Photomicrograph of bile duct adenoma characterized increased number of small, normal appearing bile ducts lined with a single layer of cuboidal cells and surrounding fibrotic stroma. The bile ducts had no or little lumina. (inset: showing a bile duct with lumen formation) (Hematoxylin-eosin $\times 400$).

In addition, histochemistry and immunohistochemistry using the labeled streptavidin-biotin peroxidase complex method were performed. A standard protocol and commercially available reagent were used (Dako, Neomarkers). Cytokeratin 7, cytokeratin 20, factor-VIII, CD-34, and CEA were used. For some antibodies, the tissue was protease-digested using proteinase. Negative control slides were run in parallel. A chromogenic precipitate was obtained through incubation with AEC (3-amino-9-ethyl-carbazole) substrate chromogen. After counterstaining with Mayer's hematoxylin, the sections were coverslipped.

Mucin positivity was observed in some of the bile duct lumina (Figure 5a). Enclosed in the lesion were normally spaced portal tracts. Strong and diffuse immunoreactivity to cytokeratin (CK) 7 was observed in the BDA (Figure 5b), whereas CK20, factor-8, and CD34 stains were negative. It also showed cytoplasmic reactivity for CEA.

Peripheral liver parenchyma showed the pathology of hepatitis C virus infection including cytotoxic degenerative injury to hepatocytes, sinusoidal cell proliferation, mononuclear inflammatory cell infiltration in portal tracts, and focal necrosis, but there was no evidence of cirrhosis.

The patient had an uneventful recovery, and has been well for 2 years postoperatively.

Discussion

The incidence of benign hepatic tumors other than hemangioma is relatively low (4). BDA, previously called cholangioma or cholangioadenoma, and simply bile duct adenoma, is one of the benign lesions in the liver (3).

BDAs usually appear as solitary nodules but can also occur as multiple nodules throughout the liver, with either lobe of the liver being involved (4) BDAs are usually located on the surface of the liver and are <10 mm in diameter (2-4).

Neither familial occurrence nor occurrence in children is uncommon. No symptoms or signs are attributed to the lesion (4). In the largest reported series of 152 cases, all were found during either intra-abdominal surgery or (103 cases) or autopsy (49 cases), with 89 (58.6%) males and 63 (41.4%) females (2).

The nature and cell origin of bile duct adenomas have been a subject of controversy. Some authors suggested

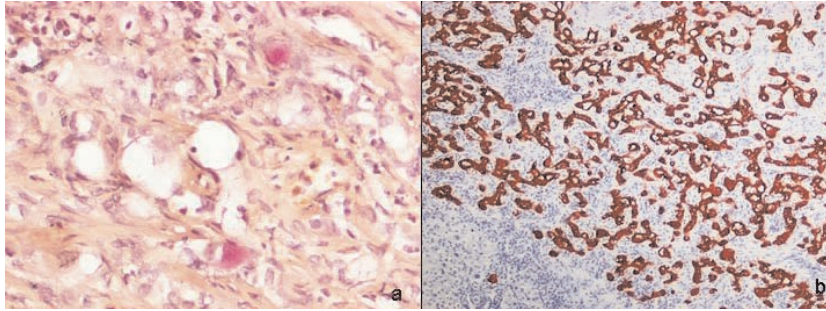


Figure 5. (a) Histochemically mucin positivity was observed in some of the bile duct lumina ($\times 200$ at magnification). (b) Cytokeratin (CK) 7 staining confirmed that these cuboidal cells forming no or little lumina were indeed bile duct in origin (Streptavidin peroxidase, AEC chromogen $\times 100$).

that they are reactive processes and a result of hepatocellular damage that induces inflammation, bile duct proliferation, and scarring as observed in hepatic cirrhosis (2). Some think that they arise from the peribiliary glands and have suggested the term “peribiliary hamartoma” for this lesion, based on immunohistochemical findings (5). Others state that these lesions are true neoplasms. The identification of K-ras mutations in a small proportion of cases and malignant transformation of others supports this view (7).

It remains unknown whether benign hepatic tumors are related to alcoholic or viral hepatitis, although cases of complication with hepatitis C or B or alcoholic hepatitis, including those found by the authors, have been reported (4). In our case, hepatitis C virus infection was detected at the same time, but we do not know if there is any relationship between them.

Bile duct adenomas are well circumscribed but not encapsulated, firm, gray-white or tan, subcapsular nodules, although they sometimes appear as subcapsular scars. At microscopic level, one sees a compact network of ductal structures with a simple tubular appearance or a more complex tortuous arrangement embedded in a variable amount of fibrous stroma that may be sclerotic or edematous and infrequently is calcified or contains granulomas. The tubular lumina are often very small or inapparent, indistinguishable on histologic evaluation from bile ductules. Cystic changes are uncommon (6). Cells of the tumor are low columnar or cuboidal, containing light colored transparent cytoplasm. They do

not show atypia or mitotic activity (4). Intracytoplasmic mucin can be found, while cytoplasmic or intraluminal bile is absent (6). The cuboidal/low columnar lining epithelium has more cytoplasm and paler nuclei than the interlobular bile ducts present within portal tracts in the adjacent liver or trapped within the lesion. Focal clear cell change has been described in these tumors (8). Inflammatory cells—particularly lymphocytes, but also neutrophils—may be noted both within and at the periphery of the lesion. Lymphocytic aggregates may be conspicuous at the interface with the adjacent liver (6).

The potential for malignant transformation cannot be entirely excluded, although it is benign in nature (4). Cases of malignant transformation have been reported (4,9). Follow-up of resected bile duct adenomas has indicated that it has a benign clinical course; however, the potential for malignant transformation has not been excluded (4).

Pathological differential diagnosis includes bile duct hamartoma (if multiple, “von Meyenburg complexes”), cholangiocarcinoma, metastatic tumor from adenocarcinoma, reactive bile ductile proliferation, hepatic abscess, inflammatory pseudotumor, and hepatic granuloma (3,4,6).

Two types of intrahepatic benign bile duct proliferations have been characterized: bile duct hamartomas (von Meyenburg complexes) and bile duct adenomas (8). Von-Meyenberg complexes or biliary microhamartomas are collections of irregularly shaped bile ducts in the liver surrounded by a dense collagenous

stroma. They are typically 0.1 to 0.3 cm in diameter and are well-circumscribed, unencapsulated lesions that are recognized most easily when in a subcapsular location. The ductular structures are often dilated cystically and contain inspissated bile. They are also frequently mistaken grossly for metastatic tumors, abscesses, or granulomas (10).

Reactive bile ductile proliferation is typically encountered in the context of cirrhotic septa or biliary tract disorders. It is distinguished from BDA based on the context of the lesion as well as histological features. It typically has no dense sclerosis, except with collapse, and has possible bile and frequent finding of periductular neutrophils. Mild atypia and rare mitoses in broad scars can be observed (6).

In our case, we also considered hemangioendothelioma in the differential diagnosis, but the lack of infiltrative margin and lack of intracytoplasmic lumina containing red blood cells in addition to immunohistochemical CD34 negativity were helpful for differentiation.

Extremely well differentiated cholangiocarcinomas have been confused with bile duct adenomas by pathologists. This diagnostic distinction is further complicated by the fact that well-differentiated cholangiocarcinoma may follow a prolonged clinical course (8). Pathological differentiation from cholangiocarcinoma with mild cellular atypia is very difficult (3). Except for Ki-67, immunohistochemical stains are not useful for distinguishing BDAs from cholangiocarcinomas (8). Nuclear pleomorphism and hyperchromasia, prominent nuclei, mitosis, and vascular/lymphatic invasion are all absent in BDAs, supporting its distinction from adenocarcinoma (6). Inflammatory pseudotumor, granuloma, and hepatic abscess were not considered in our case.

In summary, recognition of this unusual co-existence of BDA and gastrointestinal tumors will enable surgeons to avoid diagnostic confusion with metastatic carcinomas. This lesion is still confused with metastatic carcinomas by both surgeons and pathologists during frozen sections performed in patients with known carcinomas.

References

1. Goodman ZD, Terraciano L. Tumors and tumor-like lesions of the liver. In: Burt AD, Portmann BC, Ferrell LD, editors. *Macsween's Pathology of the Liver*. 5th ed. Churchill Livingstone Elsevier: 2007. p.761-814.
2. Allaire GS, Rabin L, Ishak KG, Sesterhenn IA. Bile duct adenoma: a study of 152 cases. *Am J Surg Pathol* 1988; 12: 708-715.
3. Cho C, Rullis I, Rogers LS. Bile duct adenomas as liver nodules. *Arch Surg* 1978; 113: 272-274.
4. Tajima T, Honda H, Kuroiwa T, Yoshimitsu K, Irie H, Aibe H et al. Radiologic features of intrahepatic bile duct adenoma: a look at the surface of liver. *J Comp Assisted Tomog* 1999; 23: 690-695.
5. Bhathal PS, Hughes NR, Goodman ZD. The so-called bile duct adenoma is a peribiliary gland hamartoma. *Am J Surg Pathol* 1996; 20: 858-864.
6. Washington K. Masses of Liver. In: Mills SE (senior ed), Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH. *Sternberg's Diagnostic Surgical Pathology*, 4th ed. Lippincott Williams & Wilkins, Philadelphia, 2004. p.705-1774.
7. Hruban RH, Sturm PD, Slebos RJC, Wilentz RE, Musler AR, Yeo CJ et al. Can K-ras codon 12 mutations be used to distinguish benign bile duct proliferations from metastases in the liver: a molecular analysis of 101 liver lesions from 93 patients. *Am J Pathol* 1997; 151: 943-949.
8. Albores-Saavedra J, Hoang MP, Murakata LA, Sinkre P, Yaziji H. Atypical bile duct adenoma, clear cell type. A previously undescribed tumor of the liver. *Am J Surg Pathol* 2001; 25: 956-960.
9. Hasebe T, Sakamoto M, Mukai K, Kawano N, Konishi M, Ryu M et al. Cholangiocarcinoma arising in bile duct adenoma with focal area of bile duct hamartoma. *Virchows Arch* 1995; 426: 209-213.
10. Jain D, Sarode VR, Abdul-Karim FW, Homer R, Robert ME. Evidence for the neoplastic transformation of Von-Meyenberg complexes. *Am J Surg Pathol* 2000; 24: 1131-1139.