Adenomas involving the extrahepatic biliary tree are rare but have an aggressive clinical course

Biliary adenomas that are usually found in surgically removed gallbladders are rare, but can also occur in the extrahepatic biliary tree. We present a case series of extrahepatic bile duct adenomas at our institution, along with a review of the literature. All three patients with extrahepatic biliary adenomas were identified, arising either in the gallbladder (20/23) or the extrahepatic biliary tree (3/23). All gallbladder biliary adenomas were detected incidentally during cholecystectomy for unrelated indications. Patient’s medical records from the three patients with extrahepatic biliary adenomas were reviewed for demographic information, clinical pre-
sentation, imaging results, operative findings, and surgical pathology results. The study was approved by the institutional review board at Baystate Medical Center, Springfield, MA. A literature review of published cases of extrahepatic biliary adenoma was performed using MEDLINE database. All identified cases were reviewed and the findings are summarized.

**Results**

**Case 1**

An 85-year-old woman with a history of atherosclerotic disease and gallstones was referred to the Gastroenterology outpatient office for evaluation of an incidental finding of biliary dilation up to 19 mm. The patient complained of intermittent abdominal pain but denied nausea, vomiting, jaundice, or weight loss. Her liver function tests (LFTs) were normal. Endoscopic ultrasound revealed a small soft-tissue non-shadowing lesion in the distal common bile duct (CBD) without evidence of a pancreatic head lesion (Fig. 1). Endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse dilation of the biliary tree with a fixed filling defect in the distal CBD without focal stricture. Forceps biopsies revealed papillary and cribriform adenomatous epithelium with high grade dysplasia (Fig. 2). A biliary stent was not placed due to normal LFTs. The patient was deemed to be a poor surgical candidate for pancreaticoduodenectomy. Five months after initial presentation, the patient represented with jaundice, decreased appetite, weakness, and weight loss, with an obstructive pattern on her LFTs. ERCP showed a 15-mm occlusive stricture in the distal CBD with diffuse proximal biliary dilation; a metal stent was inserted. Brush cytology showed atypical ductal cells suspicious for adenocarcinoma. One year later, she was found to have duodenal ulceration from underlying cholangiocarcinoma with extensive liver metastases.

**Case 2**

A 61-year-old woman presented to the hospital with abdominal pain and weakness. She had a medical history of primary sclerosing cholangitis, and idiopathic thrombocytopenic purpura status post-splenectomy, and was on chronic immunosuppression. Laboratory evaluation revealed leukocytosis, and blood cultures returned extended spectrum, B-lactamase-producing *Escherichia coli*. MRI of the abdomen showed an irregular, polypoid lesion in the common hepatic duct (Fig. 3). Direct cholangioscopy with multiple biopsies revealed a villous adenoma with extensive high grade dysplasia. Complete endoscopic polypectomy was unsuccessful, therefore she underwent total bile duct resection and Roux-en-Y hepaticojejunostomy. One year after her initial presentation, she presented with left flank pain and back pain. Imaging revealed bone metastases to the L5-S1 vertebral bodies with biopsy showing adenocarcinoma of pancreaticobiliary origin, along with liver metastases and peritoneal carcinomatosis.

**Case 3**

A 78-year-old woman with a history of reflux esophagitis presented with symptoms suggestive of gallbladder pathology. She was found to have a polypoid bile duct lesion on intraoperative cholangiogram. ERCP showed an adenomatous polyp with high grade dysplasia involving the distal CBD. The patient underwent distal bile duct resection with choledochojjunostomy. Four years after surgery, she was found to have a large mass in the roux limb of the jejunum causing obstruction of the small bowel and invading the transverse colon. She underwent transverse colectomy, partial small-bowel resection, resection of the prior hepaticojejunostomy, and creation of a new hepaticojejunostomy. Final pathology showed adenocarcinoma. The patient underwent chemotherapy which was discontinued due to poor tolerance. Two years later, she was found to have metastatic disease to the liver, brain, and skin.
| Reference          | N  | Gender | Age, years | Country | Location                  | Presentation                                | Treatment                                      | Histology                      | Outcome                                |
|--------------------|----|--------|------------|---------|---------------------------|---------------------------------------------|-----------------------------------------------|--------------------------------|---------------------------------------|
| Ariche et al. [2]  | 1  | F      | 77         | Israel  | Mid CBD                   | Recurrent abdominal pain, jaundice, fever   | Local excision, Roux-en-Y hepatojunostomy   | Villous adenoma               | —                                     |
| Burhans and Myers [3] | 1  | F      | 64         | USA     | Left hepatic duct         | Symptoms of cholecystitis, jaundice, fever  | Removal with forceps surgically              | Papillary adenoma             | Presented 4 years later with large cystic mass. Alive at 5 years |
|                    | 1  | F      | 76         | USA     | CBD (junction of cystic and bile duct) | Jaundice, fever, anorexia, n/v             | Curettage                                    | Adenoma                      | Died 6 years later from CVA          |
| Hultén et al. [4]  | 2  | M      | 61         | Sweden  | Distal CBD                | Biliary colic and jaundice                  | Local excision/choleccholecystectomy and hepaticoduodenostomy | Papillary adenoma             | Alive after 7 years                  |
| Shemesh [5]        | 1  | M      | 58         | Israel  | Distal CBD                | Recurrent abdominal pain                     | Surgically removed                           | Tubular adenoma               | Well at 2 months                    |
| Sturgis et al. [6] | 1  | F      | 81         | UK      | Distal CBD                | Intermittent right upper quadrant (RUQ) pain, nausea/vomiting | Endoscopic excision                          | Tubulovilous adenoma          | Well post-surgery                    |
| Futami et al. [7]  | 1  | F      | 40         | Japan   | Inferior bile duct        | Relapsing pancreatitis                       | Surgical excision                            | Adenoma                      | Uneventful for 18 months            |
| Jao et al. [8]     | 1  | M      | 60         | Taiwan  | Distal CBD                | Abdominal screening ultrasound               | Endoscopic excision                          | Tubulovilous adenoma          | Well at 2 months                    |
| Ibrarullah and Sreenivas [9] | 1  | F      | 33         | India   | Distal CBD                | RUQ pain, vomiting                           | Roux-en-Y hepatojunostomy                    | Adenoma                      | Asymptomatic at 38 months           |
| Katsinelos et al. [10] | 1  | M      | 58         | Greece  | Distal CBD                | Abdominal pain, jaundice, nausea/vomiting, RUQ mass | Whipple                                      | Adenoma                      | Well at 6 months                    |
| Kim et al. [11]    | 1  | M      | 55         | Korea   | Distal CBD                | Painless jaundice and pruritis               | Whipple                                      | Tubulovilous adenoma          | Multiple gastrointestinal polyps 8 months after surgery |
| Aparajita et al. [12] | 1  | F      | 75         | UK      | CBD (junction at cystic duct) | Jaundice, weight loss                         | Pancreatocoduodenectomy with Roux-en-Y reconstruction | Papillary adenoma             | Well 9 months after surgery          |
| Akaydin et al. [13] | 1  | M      | 60         | Turkey  | Proximal CBD              | Painless jaundice, pruritis, acholic feces   | Excision and Roux-en-Y hepaticojujunostomy   | Tubulovilous adenoma          | —                                     |
| Munshi and Hassan [14] | 1  | F      | 69         | USA     | Distal CBD, junction at cystic duct | RUQ pain, pruritis, light stools             | Endoscopic excision                          | Papillary adenoma             | Surveillance with no symptoms, unclear interval |
| Prachayakul et al. [15] | 1  | M      | 53         | Thailand| Distal CBD                | Recurrent fever with intermittent jaundice   | Polypectomy endoscopically                    | Tubular adenoma               | Polyp disappeared on repeat procedure |
| Sirimontaporn et al. [16] | 1  | M      | 73         | Thailand| Mid to distal CBD         | Recurrent liver abscess/Klebsiella bacteremia | Endoscopic forceps biopsy                    | Adenoma                      | Further biopsy normal, no interventions afterwards |
| Styne et al. [17]  | 1  | F      | 59         | USA     | Left hepatic duct         | Recurrent cholangitis                        | Surgical excision                            | Papilloma                     | 2 months later adenocarcinoma       |
| Cardoza et al. [18] | 1  | F      | 53         | USA     | Common hepatic duct       | Incidental LFT elevation                     | Surgical resection                           | Papilloma                     | —                                     |
| Jennings et al. [19] | 1  | M      | 58         | UK      | Common hepatic duct       | Jaundice                                     | Surgically enucleated and stalk resected     | Villous adenoma               | 16 months after presentation, recurrent villous adenoma, hepatic duct, roux-en-y |
| Colarian and Wescott [20] | 1  | F      | 78         | USA     | Common hepatic duct       | Painless jaundice                            | Hepatojunostomy                              | Villous adenoma               | Recovered from surgery              |
| Reference          | N | Gender | Age, years | Country       | Location          | Presentation                  | Treatment                                                   | Histology              | Outcome                          |
|-------------------|---|--------|------------|---------------|-------------------|-------------------------------|-------------------------------------------------------------|------------------------|----------------------------------|
| Sotona et al. [21]| 1 | M      | 58         | Czech Republic| Left hepatic duct | Painless obstructive jaundice | Local excision, Roux-en-Y hepaticojejunostomy              | Papillary adenoma     | Alive 1 year after the surgery   |
| Ho and Lee [22]   | 1 | M      | 15         | Taiwan        | Cystic duct       | Tarry stools, jaundice        | Exploratory laparotomy                                      | Papillary adenoma     | –                                |
| Loh et al. [23]   | 1 | F      | 72         | UK            | Cystic duct       | Recurrent RUQ pain, nausea    | Surgical resection with cholecystectomy                    | Papillary adenoma     | –                                |
| Liu et al. [24]   | 1 | F      | 61         | China         | Cystic duct       | Intermittent upper abdominal pain and fever | Snare polypectomy using a gastroscope | Tubulovillous adenoma | Asymptomatic at 3 months          |
| O’Shea et al. [25]| 1 | M      | 75         | USA           | Left hepatic and common hepatic duct | RUQ pain, jaundice, dark urine, weakness | Excision surgically                                             | Villous adenoma       | –                                |
| Morris-Stiff et al. [26] | 1 | F      | 73         | UK            | Common hepatic and proximal left hepatic duct | Abdominal pain, weight loss | Surgical resection, Roux-en-Y hepaticojejunostomy          | Papillary adenoma     | –                                |
| Hanafy and McDonald [27] | 1 | M      | 76         | UK            | CBD, hepatic and cystic duct | Mild jaundice and RUQ mass     | Local excision surgically                                      | Villous adenoma       | –                                |
| Xu and Chen [28]  | 1 | F      | 27         | China         | CBD and hepatic ducts | Painless jaundice and pruritis | Whipple/resection of extrahepatic bile duct and whipple   | Villous adenoma       | Well 9 months after surgery    |
| Saxe et al. [29]  | 1 | M      | 64         | USA           | Distal CBD        | Recurrent abdominal pain, jaundice, weight loss, pruritis | Whipple                                                      | Villous adenoma       | Well at 3 years                  |
| Blot et al. [30]  | 1 | M      | 84         | France        | Distal CBD        | Febrile jaundice              | Surgical excision                                             | Villous adenoma       | Well at 1 year                  |
| Inagaki et al. [31]| 1 | M      | 73         | Japan         | Distal CBD        | Epigastric pain and jaundice  | Whipple                                                     | Papillary adenoma     | Well at 12 months after surgery  |
| Chang et al. [32] | 1 | M      | 51         | Taiwan        | Distal CBD        | Febrile jaundice, RUQ pain    | Refused surgery                                              | Papillary adenoma     | Asymptomatic after 3 months      |
| Aggarwal et al. [33]| 1 | M      | 55         | India         | Mid CBD           | Recurrent abdominal pain      | Whipple                                                     | Adenoma               | –                                |
| Lou et al. [34]   | 1 | M      | 47         | Taiwan        | Distal CBD        | Fever, abdominal pain         | Local excision surgery                                       | Tubular adenoma       | Well at 8 months                 |
| Fletcher et al. [35]| 1 | M      | 74         | UK            | Distal CBD        | Painless jaundice, pruritis, weight loss | Whipple                                                   | Papillary adenoma     | Well at 1 year after surgery   |
| Present cases     | 3 | F      | 85         | USA           | Distal CBD        | Abdominal pain                | Refused surgery                                              | Papillary adenoma     | Cholangiocarcinoma 5 months after presentation |
|                   | F | 78     | USA         | Distal CBD     | Gallbladder symptoms | Distal bile duct resection with cholecystectomy | Adenoma                                                      | –                     | Adenocarcinoma involving small/large bowel 4 years after surgery |
|                   | F | 61     | USA         | Common hepatic duct | Febrile bacteremia | Local excision unsuccessful; total, subsequent bile duct resection and Roux-en-Y hepaticojejunostomy | Villous adenoma | Metastases to the bone 1 year after initial presentation |

CBD, common bile duct; CVA, cerebrovascular accident; LFT, liver function test; RUQ, right upper quadrant.
Observations and conclusions

The pathology specimen was obtained surgically in 32 cases and endoscopically in seven cases. In 22 cases, the adenomas were associated with atypia/dysplasia. The location of adenomas was in the CBD (25/39; 64%) [2–16], common hepatic duct (7/39; 18%) [3,17–24], and cystic duct (3/39; 8%) [22–24]. Four (10%) cases involved multiple ducts in continuity [25–28].

Discussion

Benign tumors of the extrahepatic biliary tree can be divided into epithelial and non-epithelial tumors. There is little uniformity in the nomenclature applied to benign epithelial lesions and various classifications have been proposed. According to the WHO classification, they are divided into five different types: tubular, papillary (also known as papillomas), tubulopapillary, biliary cystadenoma, and papillomatosis [1]. Adenomas comprise two-thirds of all benign biliary tumors [2]. For the purpose of this review, we have focused on adenomas involving the extrahepatic bile duct, excluding ampullary adenomas, cystadenomas, and papillomatosis. Three extrahepatic bile duct adenomas were diagnosed at our institution among a total of 10559 bile duct pinch biopsies and surgical specimens (0.03%) over 13 years. One of our cases has been reported previously [1]. On extensive review of the literature, we found another 36 cases making a total of 39 cases of extrahepatic bile duct adenomas reported to date [2–28] (Table 1 and Fig. 4).

Demographics and presentation

Extrahepatic biliary adenoma appears to be a disease of older patients. The age of presentation ranged from 15 to 85 years with a mean age of 62.8±15.4 years (male, 61.0±14.4 years; female, 64.6±16.3 years). The affected gender was male in 21 cases [4, 5, 8, 10, 11, 13, 15, 16, 19, 21, 25, 27] and female in 18 cases [2, 3, 6, 7, 9, 12, 14, 17, 18, 20, 23, 24, 26, 27]. The most common presenting complaints were abdominal pain, jaundice, fever, pruritus, and abnormal LFTs. One of our cases presented with recurrent bacteremia in the setting of underlying primary sclerosing cholangitis. Two reported cases were asymptomatic with incidental findings of biliary dilation on imaging [1, 8]. One case was found incidentally in a surgical resection specimen performed for duodenal adenocarcinoma [11].

Histology

The pathology specimen was obtained surgically in 32 cases and endoscopically in seven cases. In 22 cases, the adenomas were associated with atypia/dysplasia. The location of adenomas was in the CBD (25/39; 64%) [2–16], common hepatic duct (7/39; 18%) [3,17–24], and cystic duct (3/39; 8%) [22–24]. Four (10%) cases involved multiple ducts in continuity [25–28].

Treatment

Management of extrahepatic bile duct adenomas is not clearly defined. Surgical resection was the primary mode of therapy in 31 of 39 patients [2–5,7–13,17–23,25–28]. Cases in the 1970s have reported using limited surgical curettage without resection of the affected area [3,5]. Endoscopic resection with snare polypectomy or forceps has been reported in six cases [6,8,14–16,24]. There are no reports of the use of ablative therapy with radiofrequency ablation or photodynamic therapy after endoscopic resection.

Prognosis

The follow-up period varied among all the cases reported. The majority of the patients had good short-term outcomes. Long-term follow-up (>1 year) and short-term outcome (<1 year) were reported in 8 [3,7,11,19] and 17 cases [4,5,8,10,11,15–17,21,24,28], respectively. Five cases presented with interval malignancy including cholangiocarcinoma, and small-bowel adenocarcinoma was noted at follow-up [1,4,17]. The longest follow-up was reported to be 7 years with the patient still alive [4]. Associations were found with certain malignancies and syndromes either at presentation or follow-up, including Gardner’s syndrome, familial polyposis coli, or periampullary carcinoma [5,7,12].
Conclusion

We highlight the rarity of extrahepatic bile duct adenoma with three additional cases from our institution adding to the paucity of literature on the subject. All three patients in our series presented with subsequent biliary malignancy with metastases or local invasion. We recommend aggressive surgical intervention and close postoperative surveillance when diagnosis of extrahepatic bile duct adenoma is made.

Competing interests: None

References

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