

Case Report

Ducts of Luschka as a Mimicker of Well-Differentiated Adenocarcinoma of Gallbladder: A Case Report and Review of Literature

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Ducts of Luschka are small bile ducts located at the subserosal or subhepatic connective tissue of gallbladder. These ducts are commonly seen in up to 10% of routine cholecystectomy specimens. When proliferating with reactive changes as seen in the background of acute cholecystitis, they can mimic adenocarcinoma of gallbladder. However, this phenomenon is not well recognized in pathology literature, with only two articles available in English language literature. In this study, we report a case of acute cholecystitis with reactive Ducts of Luschka that is difficult to distinguish from gallbladder adenocarcinoma. We described the clinical and pathologic findings in this case and discussed the morphologic features that are helpful in establishing the correct diagnosis.

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INTRODUCTION

Differentiating malignancy from reactive atypia can be very challenging in gallbladder pathology. Morphologic features that are typically associated with malignancy, such as epithelial pseudostratification, loss of polarity, nuclear enlargement and variation in size, prominent nucleoli, and gland fusion can be focally present in acute cholecystitis (**Figure 1**). In addition, well-differentiated adenocarcinoma of gallbladder can be deceptively bland and difficult to distinguish from reactive or even normal bile ducts. Practicing pathologists are well aware of reactive atypia in the presence of acute cholecystitis, and typically use extreme caution when diagnosing malignancy in the presence of acute inflammation. Still, ducts of Luschka are less recognized as a mimicker of well-differentiated adenocarcinoma. Only two English language articles are available in the literature, which described a total of 7 cases of ducts of Luschka with morphologic features that could be mistaken for adenocarcinoma.^{1,2}

Ducts of Luschka, also known as peribiliary mucous glands and supervesicular ducts, are microscopic small bile ducts found in the subhepatic or subserosal connective tissue.³

These ducts are considered a developmental abnormality and are seen in up to 10% of cholecystectomy specimens.⁴ These ducts drain directly into the right hepatic duct or subsegmental branches of segment 4 and 5. As transecting these ducts during cholecystectomy can cause bile leaking and peritonitis, ducts of Luschka are well-studied in surgery and radiographic literatures. However, they are not well known to pathologists. To our knowledge, only four pathology articles exist in the literature, with two articles describing ducts of Luschka mimicking adenocarcinoma of gallbladder and two articles reporting adenocarcinoma arising from ducts of Luschka.^{5,6} Histologically, ducts of Luschka are glands lined by a single layer of cells similar to intrahepatic bile ducts. The diameter of these ducts varies significantly, from several microns to a few millimeters. Characteristic features include linear and/or lobular arrangement and distinctive concentric periductal fibrosis.⁷

In this study, we report a challenging cholecystectomy specimen with mucosal florid reactive epithelial atypia and ducts of Luschka at the subserosal connective tissue. The ducts of Luschka show morphologic features that are difficult to distinguish from adenocarcinoma of the gallbladder. We described features that are important for correct recognition of this benign entity. Awareness and proper recognition of ducts of Luschka are important for practicing pathologists to avoid mis-diagnosing ducts of Luschka as adenocarcinoma.

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CASE REPORT

A 50-year old Caucasian male with no significant past medical history presented to the emergency department with right upper quadrant abdominal pain and anorexia. The pain started one week ago and was getting progressively worse. No other symptom, such as fever, chill, or weight loss, was

present. Computed Tomography (CT) examination showed an obstructing stone within the cystic duct and small amount of fluid collection surrounding the gallbladder. No other abnormality was seen. These CT findings as well as symptomatic presentation were consistent with acute cholecystitis.

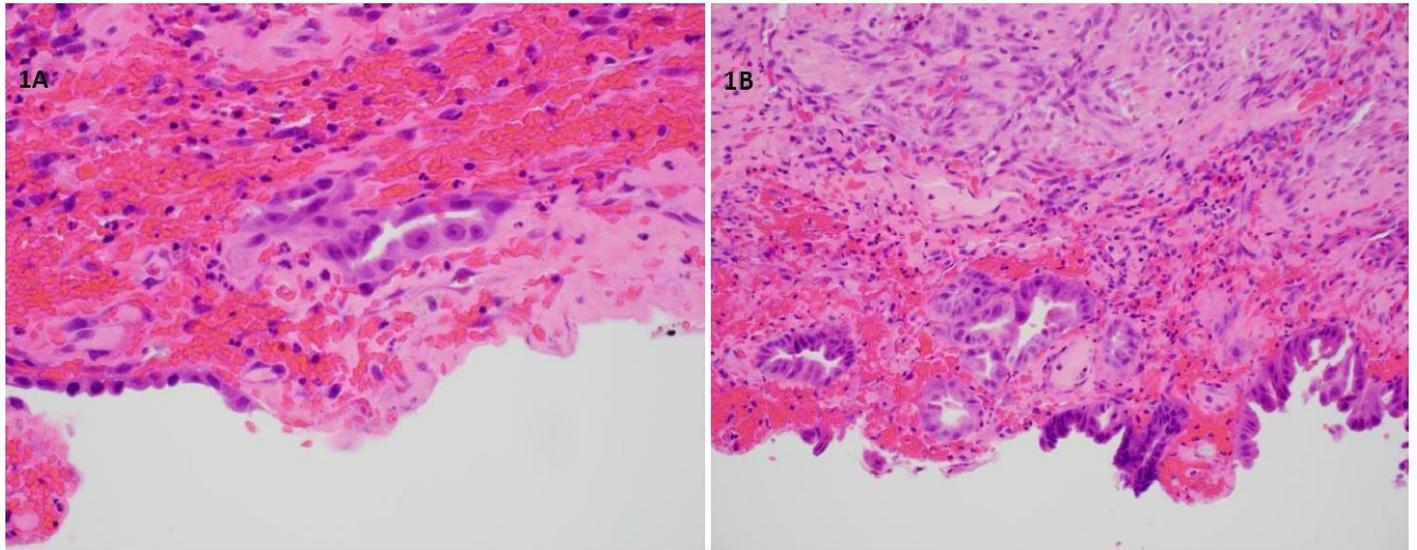


Figure 1. **1A.** Reactive epithelial atypia with nuclear size variation and prominent nucleoli. The surface shows ulceration and stroma has hemorrhage and acute inflammation. In addition, the residual epithelium (lower left) shows maturation and less atypia. All these findings support a reactive process. **1B.** Reactive epithelium shows pseudostratification, tufting, and focal glandular fusion. Again, the surface ulceration, stromal inflammation and hemorrhage indicate that this is a focus of injury.

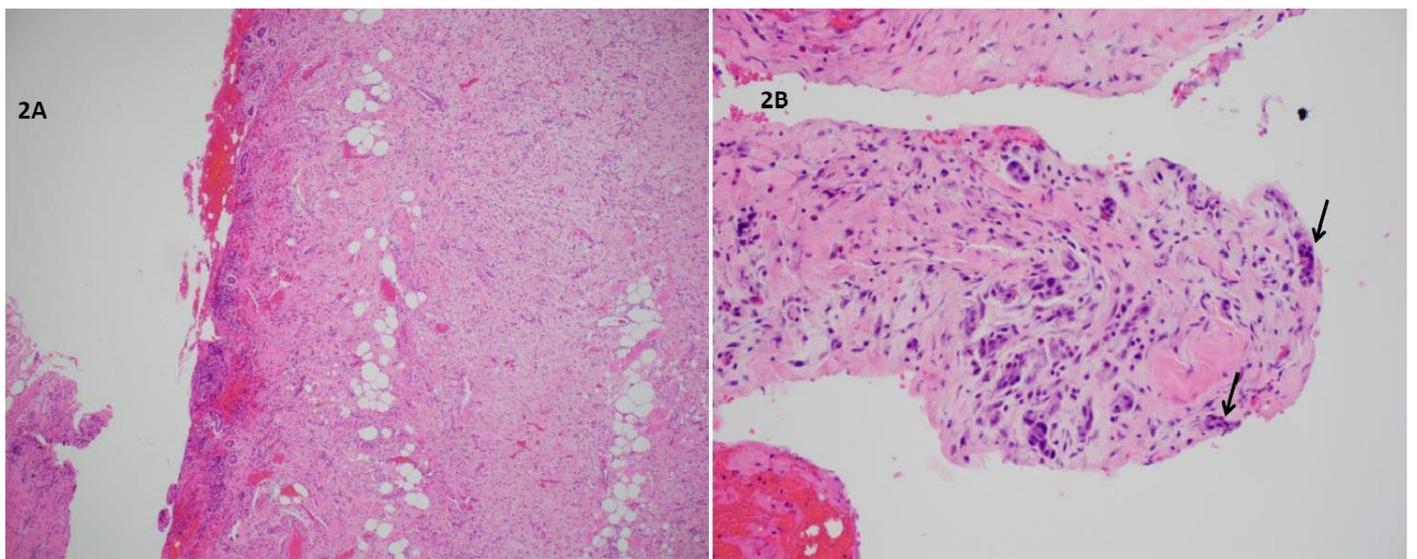


Figure 2. **2A.** Ducts of Luschka with a linear arrangement at serosa surface. The hemorrhage and acute inflammation is prominent. **2B.** Ducts of Luschka shows a vaguely lobular configuration. Careful examination reveals individually irregularly spreading glands (arrows), imparting a worrisome impression.

The patient underwent laparoscopic cholecystectomy. During the procedure, extensive adhesion involving the gallbladder was noted, which took more than one hour to lyse and expose the gallbladder. No other abnormality was present and cholecystectomy was performed subsequently. The patient developed a large hematoma at the right upper quadrant postoperatively, probably caused by the extensive adhesion lysing process. He was otherwise doing well and was discharged home at the third day after the surgery.

Pathologic Findings

The gallbladder measures 9.0 x 4.9 x 3.0 cm. It was opened and severely disrupted during surgery. Multiple green-brown gallstones were present. The mucosa was fragile with hemorrhagic and ulcerated areas. No mass or nodule was identified. The gallbladder wall was thickened, fibrotic and firm. The serosal surface was similarly hemorrhagic with edematous change. No attached liver tissue was present.

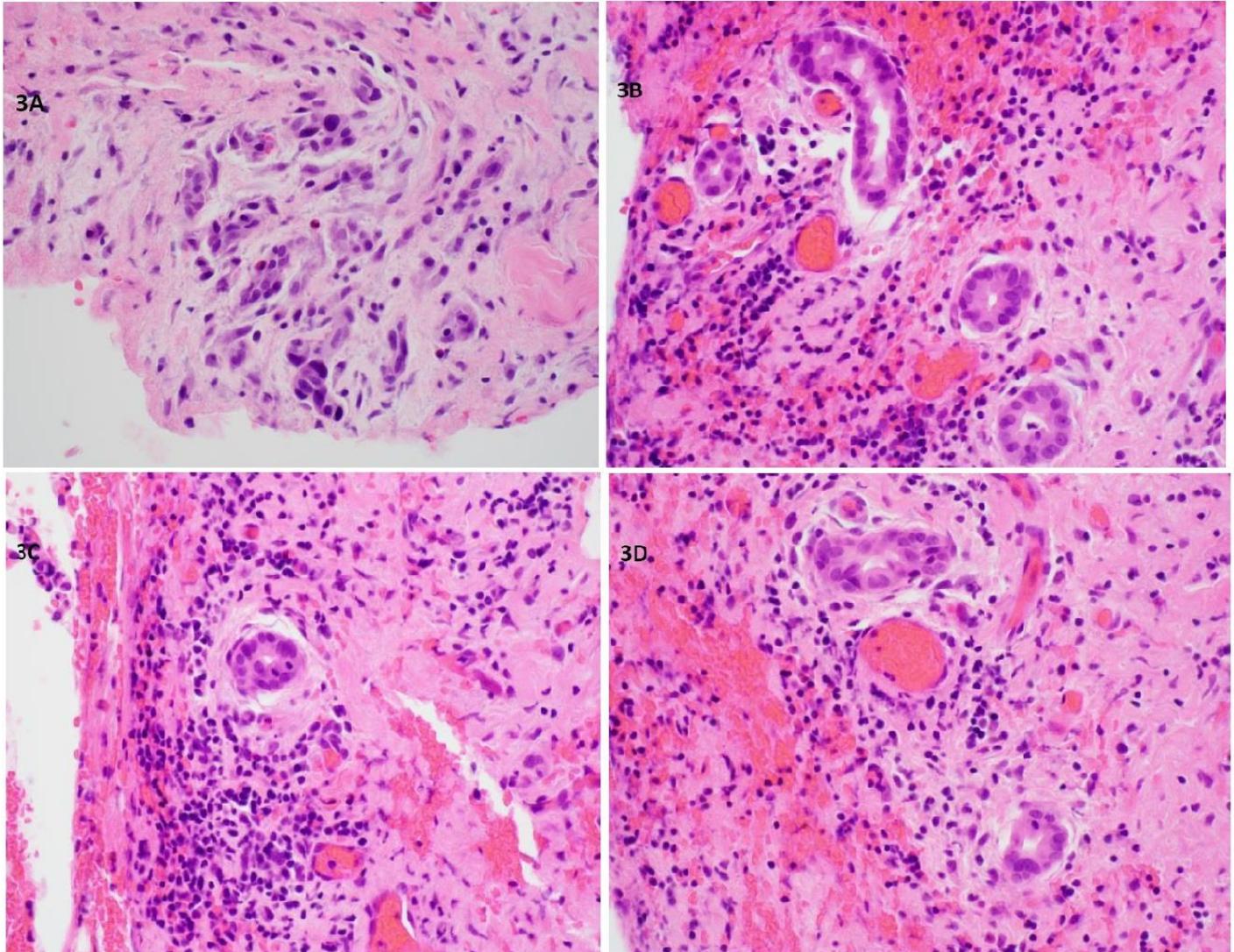


Figure 3. 3A. Cluster of small ducts with nuclear pleomorphism, hyperchromasia, and poorly formed glands. The clues to a benign diagnosis are the lobular configuration and the overall small nuclear size (the largest nucleus is less than three times the size of a lymphocyte nucleus). 3B, 3C, 3D. High power view of Ducts of Luschka (400 x). The linear configuration is less obvious at high power. There is prominent acute inflammation. Nuclear pleomorphism, mitoses and focal loss of cellular polarity are also seen (B, C and D).

The entire gallbladder with a total of 40 sections was submitted for microscopic examination. The mucosa had multiple foci of ulceration with hemorrhage, dense chronic

and acute inflammation (**Figure 1**). The epithelium was focally denuded with the remainder epithelium showing florid reactive changes. Nuclear enlargement with prominent

nucleoli was diffusely present at sites with acute inflammation and hemorrhage. Some foci of epithelium showed nuclear pseudostratification, tufting, and slight loss of polarity. Fused and crowded glands were also focally present. While these changes are morphologically difficult to distinguish from dysplasia, the background of dense inflammation, marked congestion and hemorrhage in the stroma were clues that these were reactive changes. In addition, whenever present, the surface epithelium overlying these reactive glands showed maturation with less atypia, which was another important clue of reactive change.

Atypical glandular proliferation was also present at the serosa and subserosal area. At low magnification, these glands showed a vaguely linear (**Figure 2A**) and lobular configuration (**Figure 2B**). However, individually irregularly spreading glands were also present, imparting a worrisome impression. These glands were lined by a single layer of cuboidal or columnar biliary-type epithelium. One focus showed significant nuclear pleomorphism and hyperchromasia (**Figure 3A**). Other worrisome features, such as mitotic activity, and focal loss of cellular polarity, were also focally present (**Figure 3B, 3C, 3D**). The degree of cytologic and structural atypia were sufficient to raise a differential diagnosis of adenocarcinoma, although definitive features of malignancy, such as desmoplasia and invasive growth, were not present.

This case was discussed intradepartmentally. A diagnosis of adenocarcinoma was considered by several pathologists, while others insisted a benign diagnosis. The features that were consistent with adenocarcinoma were the significant nuclear pleomorphism, hyperchromasia, and mitotic activity. The variation in nuclear size was almost 4-to-1 in a single gland as shown in **figure 3A**. In addition, mitotic activity was reported to be absent in Ducts of Luschka.⁸ Scattered mitoses were present in this case in these subserosal ducts, which was against a benign diagnosis of Ducts of Luschka. In addition, the typical concentric fibrosis surrounding Ducts of Luschka was not present. The features arguing against a diagnosis of adenocarcinoma were the typical location of these ducts at the serosa and subserosa area and the vague linear and lobular configuration of these ducts. In addition, nuclear atypia was relatively focal with hyperchromasia and nuclear pleomorphism present only at several foci out of these 40 sections. More importantly, there was no convincing dysplasia in the mucosal epithelium and the gallbladder wall had severe acute inflammation and reactive change, but otherwise unremarkable. It was highly unlikely for adenocarcinoma to spread to serosa without involvement of the gallbladder wall. Similarly, metastasis was unlikely due to the focal atypia in this case.

Follow-Up

The patient returned 2 months later after the surgery for a subcutaneous seroma at the right upper quadrant of abdomen. The seroma was drained and about 30 ml of clear yellow fluid was collected. Abdominal and pelvic CT was performed and no abnormality was identified other than the seroma.

Hence, in limited follow-up, the patient had no progressive disease.

DISCUSSION

Ducts of Luschka are small microscopic bile ducts in the subserosal or subhepatic connective tissue. These ducts are considered a developmental abnormality seen in patients of all age groups and are present in up to 10% of routine cholecystectomy specimens. Microscopically, Ducts of Luschka consist of groups of small bile ducts with lumina of various calibers. The ducts are lined by a single layer of biliary-type epithelium similar to those of the intrahepatic bile ducts. The characteristic histologic features include a lobular or linear arrangement and distinctive concentric fibrosis surrounding these ducts. Previous studies showed that reactive Ducts of Luschka can be mistaken for adenocarcinoma of gallbladder.^{1,2} However, this phenomenon is not well recognized in the published pathology literature. To our knowledge, only two English language articles exist, which reported a total of 7 cases of Ducts of Luschka as a mimicker of adenocarcinoma of gallbladder. Only for a few of these reported cases, a diagnosis of adenocarcinoma was seriously considered.

In this study, we report a challenging cholecystectomy specimen with florid acute cholecystitis and Ducts of Luschka with reactive changes that are difficult to distinguish from adenocarcinoma. The histologic sections show irregularly proliferation of small ducts with significant cytologic atypia and scattered mitotic activity. The lobular and linear configuration is only vaguely present, while the characteristic peri-ductal fibrosis is not seen (**Figure 2** and **Figure 3**). As discussed in the previous study, compared with adenocarcinoma, mitoses and nuclear pleomorphism/size variation should be minimal in Ducts of Luschka.¹ While in our case, significant nuclear atypia and mitotic activity are focally present. We feel the most important helpful feature to distinguish Ducts of Luschka from invasive adenocarcinoma is the location of these ducts and relatively focal atypia. Ducts of Luschka are confined to the subhepatic or subserosal surface of the gallbladder, while adenocarcinoma is more concentrated at the mucosal surface. Whenever atypical glands are seen confined at the subserosal area, benign reactive Ducts of Luschka needs to be considered as a differential diagnosis. Other helpful features for diagnosing benign ducts of Luschka are lack of desmoplasia and true invasive growth pattern. In addition, there is usually significant acute inflammation associated with reactive Ducts of Luschka. Whenever there is acute inflammation, epithelial atypia should be evaluated with extreme caution.

Many somatic mutations have been detected in gallbladder adenocarcinoma, including DPC4, KRAS, BRAF, TP53, and p16/CDKN2A, genes that are frequently mutated in other pancreatobiliary carcinomas. Microsatellite instability is seen only in a subset of gallbladder carcinoma.³ However, the prevalence of these mutations in Ducts of Luschka has not been studied before.

Immunohistochemical stains are of very limited value in distinguishing benign Ducts of Luschka from adenocarcinoma. A panel of immunohistochemical antibodies consisting of p53, DPC4 and Ki-67 has been used in distinguishing between benign versus malignant biliary diseases. However, studies have shown that p53 overexpression is seen in only about 50% of gallbladder adenocarcinomas, and overexpression is also seen in areas with epithelial regenerative atypia.⁸ DPC4 is not helpful neither as it is lost in only a small fraction (11%) of gallbladder adenocarcinoma.⁹ Although previous studies showed that Ducts of Luschka have minimal or no mitoses, Ki-67 index was high in two of the cases tested.² The low sensitivity of DPC4 and the significant overlap of p53 and Ki-67 staining results prevent the effective use of these markers in daily practice.

In summary, we report a case of reactive Ducts of Luschka mimicking well-differentiated adenocarcinoma of gallbladder. We discussed morphologic features of reactive Duct of Luschka. Awareness and proper recognition are important for practicing pathologists to avoid misdiagnosis of this benign condition as adenocarcinoma.

CONFLICT OF INTEREST

None.

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