Colonisation or invasion: a diagnostic dilemma in a 'benign' gallbladder

Daniel T Field
Alan Stockman
Timothy J Kendall

Abstract

We describe the case of a 60-year-old man who underwent an elective cholecystectomy for recurrent biliary colic. On microscopic examination, an incidental intracholecystic papillary neoplasm was present at the cystic duct margin, and was also found to colonise Rokitansky-Aschoff sinuses. We discuss this diagnostic pitfall for invasion and the diagnostic and management implications for this rare lesion.

Keywords Cholangiocarcinoma; cholecystectomy; intracholecystic papillary neoplasm; Rokitansky-Aschoff sinus

This Short Case is brought to you in association with the Pathological Society of Great Britain and Ireland. Each month we feature a Short Case written by a member of the Trainees' Subcommittee of the Pathological Society of Great Britain and Ireland. This case, including its scanned slides, is published on the Pathological Society's website www.pathsoc.org/index.php/trainees/case-of-the-month (previous cases can be accessed by members via the education portal login). The Short Case includes a series of Test Yourself Questions at the end to check your understanding of the case. We hope you enjoy reading it.

Pathological Society
Understanding Disease — Guiding Therapy

Case report

A 60-year-old male underwent an elective laparoscopic cholecystectomy for symptomatic gallstones and made an unremarkable recovery.

Macroscopically, at the transection of the cystic duct there was circumferential thickening of the gallbladder formed by a superficial pale firm tumour that extended 7 mm in maximum dimension. There were small, pigmented stones within the gallbladder.

On microscopic examination of the cystic duct margin, there was an exophytic, polypoidal lesion formed of complex closely packed glands. Some of these glands contained eosinophilic debris within their lumina, with fine intervening fibrovascular cores (Figure 1a). The glands were composed of pseudostratified epithelial cells with elongated, hyperchromatic, moderately pleomorphic nuclei (Figure 1b). The architectural and cellular atypia amounted to high-grade dysplasia. The exophytic lesion encircled 80 % of the circumference of the neck and cystic duct and, in the remaining 20 %, transitioned to flat low-grade dysplasia. Neoplastic glands appeared generally confined to the mucosa. However, within the initial sections, an isolated gland deep to the muscularis was identified (Figure 2a). The gland displayed similar morphology and immunophenotype to the superficial lesion and was surrounded by chronic inflammation (Figure 2b). Dysplasia colonising deep Rokitansky-Aschoff sinuses (RAS) was identified in the lesion away from the resection margin (Figure 2c).

Following review at a pathology team consensus meeting, a diagnosis of intestinal-type intracholecystic papillary neoplasm (ICPN) with high-grade dysplasia was favoured. There was no convincing adenocarcinoma arising from the lesion. The deep gland was thought to represent colonisation of an RAS by dysplastic epithelium, with additional cross-cutting of a branching sinus. In addition, immunohistochemistry excluded the possibility that these glands represented lymphovascular space invasion.

The patient was discussed at the local hepatopancreatobiliary multidisciplinary team meeting where the decision was made for further imaging to be undertaken. CT chest, abdomen and pelvis and MRCP did not show localised or distant disease. The patient underwent excision of the residual cystic duct together with part of the bile duct which showed residual non-invasive disease.

Discussion

ICPN is a rare exophytic pre-malignant neoplastic lesion found in fewer than 0.4 % of cholecystectomies. Half of all cases are incidental findings. It has a 2:1 female to male predominance and arises in the body or fundus of the gallbladder in 88 % of such cases.[1,2] The morphology is usually that of back-to-back glands in a papillary/tubulopapillary architectural pattern. Over 95 % of lesions demonstrate at least focal high-grade dysplasia. Four main morphological patterns have been described (intestinal, gastric, biliary and oncocytic). Over half of ICPNs demonstrate associated invasive adenocarcinoma, with stages T1, T2 and T3 accounting for 32, 47 and 21 % of cases respectively.[1] Given the high incidence of invasion in these lesions, the presence of a deeply-located dysplastic gland raised concerns for malignancy.

A study looking at 49 cases of gallbladder dysplasia and carcinoma involving Rokitansky-Aschoff sinuses found several features that may help a pathologist distinguish the two[3] (Figure 3). Firstly, a visible connection between the sinus and surface epithelium (such as in Figure 2c) suggests colonisation of a RAS/peribiliary glands (Figure 3, box A) rather than invasion. Secondly, dysplastic colonisation often showed longer dilated

Daniel T Field *MBBS BSc PGCert Trainee Academic Histopathologist, NHS Lothian and University of Edinburgh, UK. Conflicts of interest: none declared.*

Alan Stockman *MBBCh BSc FRCPath Consultant Histopathologist, NHS Lothian Department of Pathology, Edinburgh, UK. Conflicts of interest: none declared.*

Timothy J Kendall *BSc BM PhD FRCPath Senior Clinical Research Fellow in Pathology, University of Edinburgh Centre for Inflammation Research, Institute for Regeneration and Repair, University of Edinburgh, UK. Conflicts of interest: none declared.*

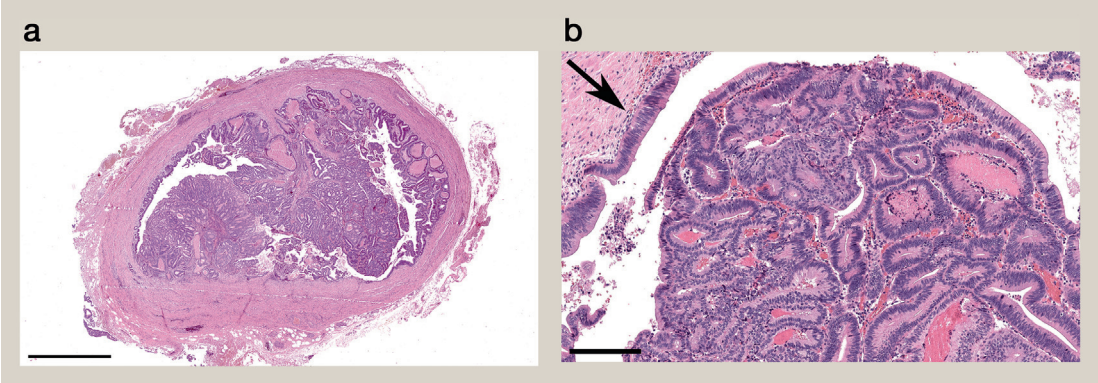

Figure 1 (**a**) The cystic duct margin showing an almost circumferential exophytic lesion composed of complex back-to-back glands. The exophytic lesion transitions to low-grade flat dysplasia on the left of the image. H&E, scale bar = 2 mm. (**b**) The cytological and architectural detail of the lesion. There are glandular structures intervened with fine fibrovascular cores. Cells display moderate to severe pleomorphism with pseudostratification. The arrow points to 'flat' dysplasia in the remaining duct. H&E, scale bar = 200 μm.

glands, sometimes with inspissated bile (Figure 3, box B) compared with the smaller invasive glands (Figure 3, box C).

Challenges were encountered with sinuses where horizontal branches were cut in a plane that left apparently isolated glands with no surface connection in the stained sections (Figure 3, box B). These glands would thus appear to penetrate the muscularis in a manner that is difficult to distinguish from invasion (as was seen in the above case). The presence of adjacent vertically orientated branches, demonstrating continuity with the lumen of the gallbladder, helped to identify these glands as non-invasive. In our case, there was significant difficulty as there were no glands in continuity with the lumen at the resection margin, the muscularis layer was distorted, and there was an inflammatory reaction around the gland. Perineural invasion, lymphovascular invasion, or nodal involvement help confirm an invasive lesion (Figure 3, box C). The absence of a desmoplastic reaction was not considered a helpful distinguishing feature, as early invasive glands were often not associated with stromal changes. Further,

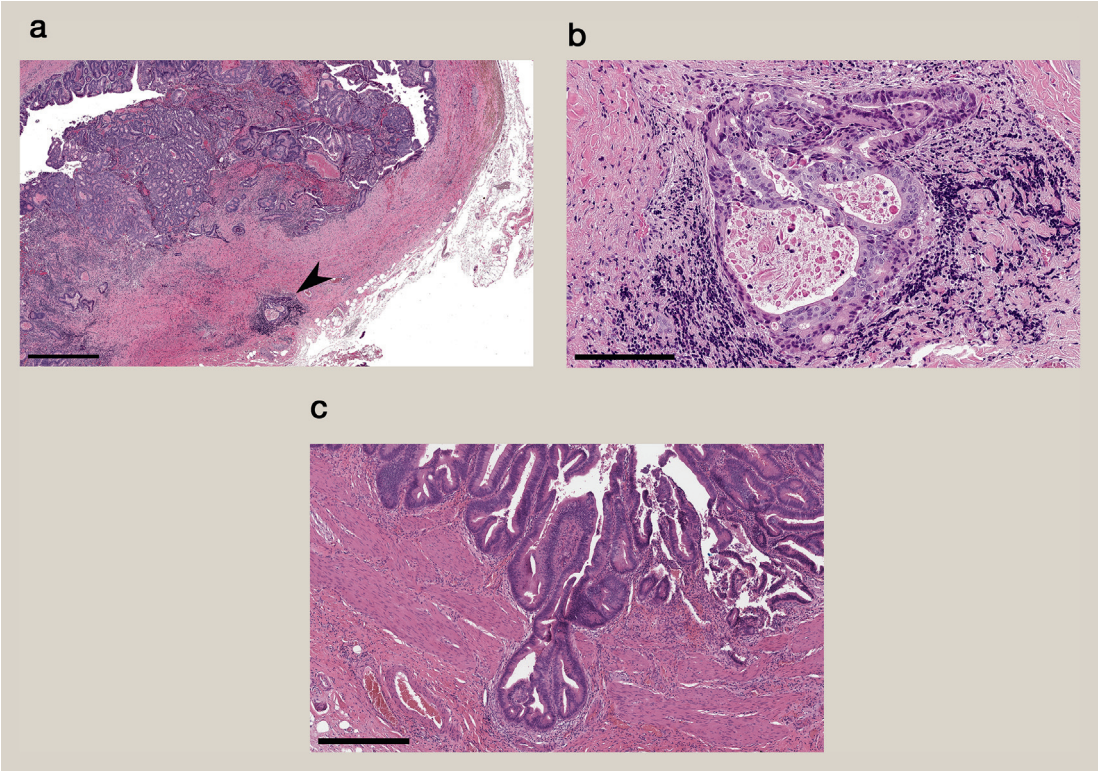

Figure 2 (**a**) The arrowhead points to an isolated gland deep to the muscularis layer that shows a surrounding inflammatory response. H&E, scale bar = 1 mm. (**b**) Close up detail of the isolated gland showing a cribriform architecture with necrotic luminal debris. The cytology recapitulates what is observed in the main exophytic lesion. A prominent lymphocytic infiltration surrounds the gland. H&E, scale bar = 150 μm. (**c**) A section towards the neck of the gallbladder which is continuous with the main lesion. There is evidence of Rokitansky Aschoff sinuses penetrating the muscularis layer. The mucosa is colonised by dysplastic epithelium. There are scattered chronic inflammatory cells around this structure. H&E, scale bar = 500 μm.

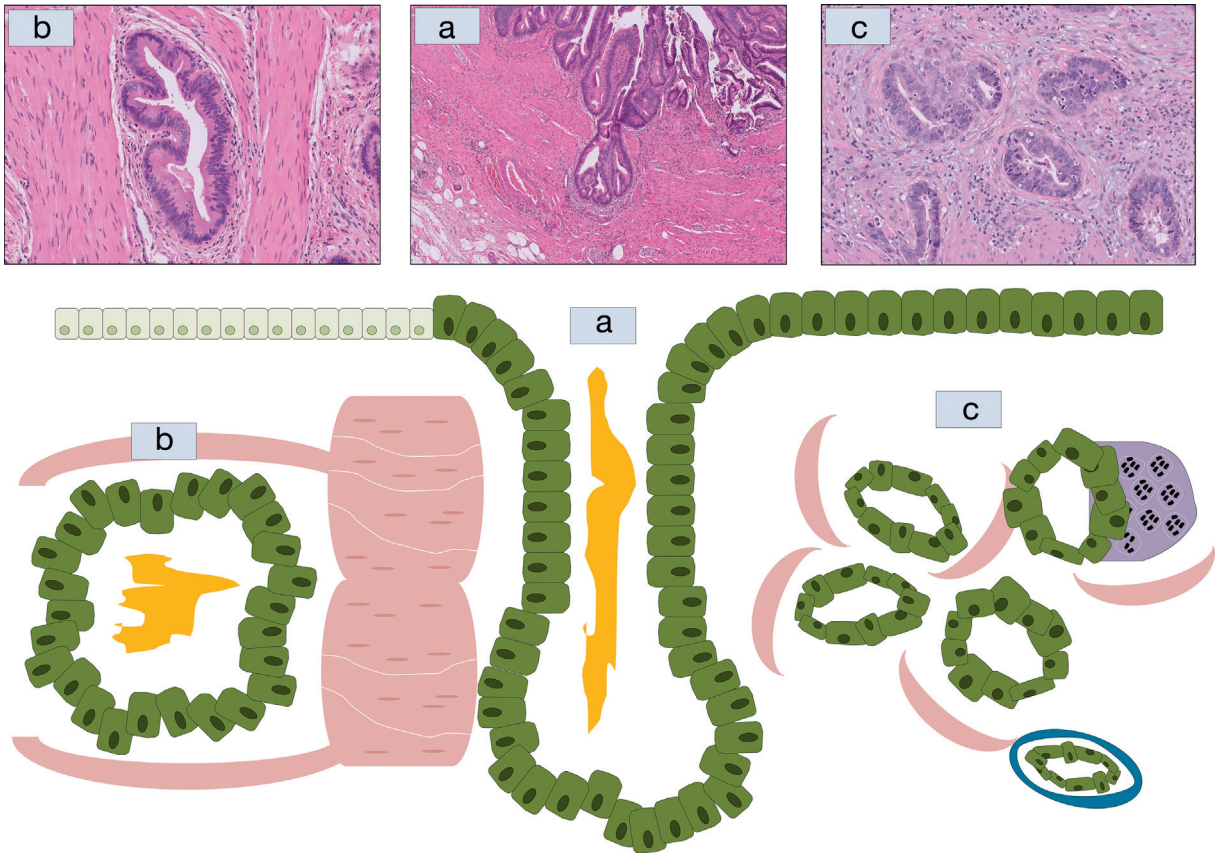

Figure 3 Schematic summarising the histological features the pathologist may use to distinguish colonisation of a Rokitansky-Aschoff Sinus (RAS) by dysplasia from invasive glands. Normal biliary epithelium can be seen on the left-hand side which transitions to dysplasia. The central RAS plunges down through a gap in the muscle and shows dysplasia. Invasive glands can be seen on the right-hand side. (**a**) Shows evidence of dysplasia in a RAS. (**b**) Shows evidence of a cross-cut dysplastic RAS with the sinus surrounded by and apparently invading through the muscularis. In isolation, this may be concerning for malignancy. However, within the context of the adjacent dysplastic sinus, the large sinus lumen and the luminal bile favour a non-invasive process. (**c**) Shows true malignant glands within the gallbladder. The glands are small, pleomorphic, surrounded by a desmoplastic stroma (although not always a helpful feature) and cause disarray of the muscularis. Features such as perineural or lymphovascular invasion can solidify an invasive diagnosis.

oedema around non-invasive sinuses may also produce a concentric stromal pattern mimicking desmoplasia.[4] A desmoplastic-like stromal reaction is therefore of limited use when assessing these early lesions.

Management of ICPN is poorly studied. Data suggest that ICPN without invasion has a 5-year survival of 78 % compared to 60 % in cases with associated invasion.[1] This latter figure is significantly better than the outcomes seen in conventional cholangiocarcinoma arising from flat BilIN. Extrapolating from incidental gallbladder cancers, it is likely ICPN, even with invasion up to T1, is best regarded as cured by cholecystectomy.[5] Higher stage tumours may warrant more aggressive therapy which is best discussed at the multidisciplinary team meeting[6] so identification of invasion within ICPN is vital. Incomplete (R1) resection, such as in our case, further complicates management as the risk of residual disease harbouring invasion must be conveyed by the pathologist in the meeting.

Conclusion

ICPN is rare but may be encountered by pathologists undertaking reporting of cholecystectomy specimens, including trainees. Given the high incidence of associated invasion, pathologists identifying ICPN must examine the specimen thoroughly and be aware of the pitfall of sinus colonisation. ◆

REFERENCES

1 Adsay Volkan, Jang KT, Roa Juan Carlos, et al. Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥1.0 cm). *Am J Surg Pathol* 2012 Sep 1; **36:** 1279–301.

2 Bennett S, Celia Marginean Esmeralda, Paquin-Gobeil M, et al. Clinical and pathological features of intraductal papillary neoplasm of the biliary tract and gallbladder. *HPB* 2015 Sep 1; **17:** 811–8.

3 Albores-Saavedra J, Shukla D, Carrick K, et al. In situ and invasive adenocarcinomas of the gallbladder extending into or arising from Rokitansky-Aschoff sinuses. *Am J Surg Pathol* 2004 May; **28:** 621–8.

4 Burt AD, Ferrell LD, Hubscher SG. MacSween's pathology of the liver. 8th edn. Elsevier, 2023.

5 Søreide K, Guest RV, Harrison EM, et al. Systematic review of management of incidental gallbladder cancer after cholecystectomy. *Br J Surg* 2018 Dec 24; **106:** 32–45.

6 Goetze TO, Paolucci V. Benefits of reoperation of T2 and more advanced incidental gallbladder carcinoma. *Ann Surg* 2008 Jan; **247:** 104–8.

Practice points

- Intracholecystic papillary neoplasms (ICPN) are rare exophytic pre-malignant lesions usually in the gallbladder fundus/body with a female predominance
- 95 % show focal high-grade dysplasia and over half demonstrate associated invasion
- Invasive disease within an ICPN appears to confer a better prognosis from conventional gallbladder cancer arising from 'flat' dysplasia
- Colonization of Rokitansky-Aschoff sinuses/periductal glands by dysplasia must be distinguished from invasive disease and cross-cut sinuses must be carefully examined (Figure 3)
- The management of incidental ICPNs with or without malignancy is poorly studied and the HPB MDT should be consulted

Multiple choice questions

1. What is the most important feature to mention when reporting an intracholecystic papillary neoplasm?

A. Presence and grade of dysplasia
B. Morphological subtype
C. Maximal size
D. The presence or absence of invasion
E. The presence of necrosis

Correct answer: D. The presence or absence of invasion. The presence and stage of invasion has a likely significant bearing on ongoing management (i.e., to undertake re-resection or not). High grade dysplasia is almost invariably present to some extent within these lesions but should be reported. The morphological subtype and necrosis do not have any significant management implications.

2. What statement concerning intracholecystic papillary neoplasms is true?

A. High-grade dysplasia is seen in around 5 % of lesions
B. Associated invasion is rare
C. If associated with invasion the prognosis is thought to be favourable compared to that of conventional gallbladder carcinoma
D. The most common molecular aberration seen is BRAF
E. They are always unifocal

Correct answer: C. Data support a favourable prognosis in ICPN with associated invasion compared with conventional gallbladder carcinoma arising from flat dysplasia. High-grade dysplasia is seen to some degree in 95 % of cases and invasion is seen in over half of cases. The most common molecular aberration are *KRAS* mutations. Multifocality with discordance between the main lesions and other areas of dysplasia is commonly encountered.

3. Which of the following is not a morphological pattern of intracholecystic papillary neoplasm (ICPN)

A. Intestinal
B. Biliary
C. Oncocytic
D. Spindle
E. Gastric

Correct answer: D. Pathologists should be aware of the varying morphologies seen in ICPN, however current evidence suggests that each subtype does not have clinical implications for patients. There is no spindle cell morphology seen in ICPN.