Unusual association of diseases/symptoms

A solid organising cryptogenic liver abscess and its association with a colonic tubulovillous adenoma

Christopher B Tan,¹ Mitanshu Shah,¹ Dhyan Rajan,² Seth Lipka,¹ Shadab Ahmed,³ Lester Freedman,⁴ Kaleem Rizvon,² Paul Mustacchia²

¹Department of Internal Medicine, Nassau University Medical Center, East Meadow, New York, USA

²Department of Gastroenterology, Nassau University Medical Center, East Meadow, New York, USA

³Department of Infectious Disease, Nassau University Medical Center, East Meadow, New York, USA

⁴Department of Pathology, Nassau University Medical Center, East Meadow, New York, USA

Correspondence to Dr Christopher B Tan, ctan@numc.edu, bryanmd1@gmail.com

Summary

Cryptogenic liver abscess (CLA) is a well-known disease entity that has puzzled clinicians for centuries. With the advancement of diagnostic modalities, comes the decreasing incidence of liver abscess labelled as 'cryptogenic' in nature. Colonic diseases have been identified as a possible underlying condition found in patients with liver abscesses. Although rare, tubulovillous adenomas have been implicated as one of the colonic causes of a CLA. We present a case of a CLA in a 53-year-old man with a potentially associated tubulovillous adenoma found via colonoscopy.

BACKGROUND

Pyogenic liver abscess (PLA) has been described as early as the time of Hippocrates.¹ In 1938, Ochsner *et al*² first defined the treatment and mortality of this disease process. Since then, the aetiology and management of PLAs have changed dramatically; with the advancement of diagnostic and therapeutic options made widely available to clinicians.¹

The incidence of PLA in the USA has been estimated at 2.3 per 100 000 individuals annually; with mortality from PLA ranging from 5% to 31%. The incidence of PLA is higher among men than women, and has a mean age of presentation of 55–66 years.^{1 3 4} The liver is the most vulnerable organ for the development of bacterial abscess, owing to its rich blood supply.⁵

Cryptogenic liver abscess (CLA) has been well recognised as the possible initial manifestation of a silent colorectal carcinoma.^{6 7} However, its association with tubulovillous adenomas has rarely been reported, with only one case published in the English literature.⁶ Here we present a case of a CLA possibly initiated by a tubulovillous adenoma in the colon. The diagnosis was further complicated by the absence of any identifiable organism on multiple cultures, and the solid appearing lesions in imaging studies.

CASE PRESENTATION

A 53-year-old African-American man with medical history significant for hypertension presented to the emergency room with complaints of right upper quadrant abdominal pain for the past 3 weeks. The pain was described as sharp, constant, moderate in intensity with no aggravating and alleviating factors.

On further questioning, the patient disclosed having intermittent fevers, chills, anorexia, night sweats and an unintentional weight loss of over 20 pounds in the last

3 months. The patient denied any associated symptoms of nausea, vomiting, abdominal bloating, diarrhoea and blood per rectum. The patient denied the use of tobacco, alcohol or any recreational drugs. He was born and raised in the USA and denied any recent travel or recent ill contacts.

Physical examination revealed a frail, elderly looking man in mild distress. Further examination was remarkable for tachycardia of 105 beats per minute and a right upper quadrant abdominal tenderness. There was neither sign of an enlarged liver or spleen; nor did examination reveal any palpable lymph nodes.

A routine laboratory evaluation revealed a leukocytosis of 15 600/mm³, a haemoglobin level of 10 g/dl and an elevated platelet count of 534 000/mm³. Liver function testing was remarkable for an elevated alanine transaminase of 49 U/l, an elevated aspartate transaminase of 66 U/l, an elevated alkaline phosphatase of 255 U/l and low albumin level of 2.7 g/dl. A subsequent CT of the abdomen and pelvis showed multiple, complex, lobulated, low-density, peripherally enhancing lesions within the central liver spanning the right and the left hepatic lobes measuring up to 13.5 cm in diameter; suggestive of an infectious or neoplastic process (figure 1). Blood cultures were drawn, and the patient was started empirically with ampicillin–sulbactam and metronidazole.

Considering the above findings, further work-up was performed to determine the nature of the liver lesions. A subsequent ultrasound and MRI of the abdomen showed the same inconclusive results; with MRI showing multiple confluent cystic masses with septations of the liver (figures 2 and 3). Additional laboratory evaluations including hepatitis serology, amoebic serology, tumour markers, HIV serology, C-reactive proteins and erythrocyte sedimentation rate are summarised in table 1.

The patient underwent an oesophagogastroduodenoscopy and colonoscopy with multiple biopsies to

Figure 1 CT scan abdomen. Note the multiple, complex, lobulated, low density, peripherally enhancing lesions within the central liver spanning the right and the left hepatic lobes.

determine an infectious, inflammatory or neoplastic cause that might explain the liver lesions. Colonoscopy results showed a 1.5-cm pedunculated polyp which was subsequently removed by snare polypectomy and sent for histopathological examination; which was later reported as a tubillovillous adenoma with intermediate grade dysplasia (figure 4).

Over the next 2 days, the patient continued to have persistent low-grade fevers despite adequate antibiotic coverage. Repeat blood counts were significant for a worsening leukocytosis of 16 000–18 000/mm³; while two separate blood cultures were negative for any bacterial or fungal growth. An ultrasound-guided liver biopsy was subsequently performed, with specimen being sent for both microbiological and histopathological evaluation. Cultures from the biopsied specimen did not reveal any organism. Pathological results showed highly atypical benign reactive

bile ducts, in a background of dense fibrosis with sinusoidal oedema and moderate chronic inflammation. No polymorphonuclear cells, parasitic and/or fungal organisms were identified. These findings were inconclusive of a certain diagnosis (figure 5).

With no response to the antibiotics and the unusual chronic symptoms of fever, night sweats, anorexia and weight loss; a malignant process was further entertained. Considering the possibility of an earlier stage of biliary or hepatic malignancy and the possibility of inadequate tissue sampling in the prior biopsy, a repeat CT-guided liver core biopsy was done which again showed similar results. A pathological report of the liver sample was described as a broad region of severe parenchymal fibrosis with intense chronic inflammation made up of lymphoplasmacytic cells effacing the hepatic architecture. No bacterial organisms were identified on cultures. Confounded with a complicated and uncertain diagnosis, antibiotic and antifungal were subsequently continued.

Figure 2 Ultrasound of the abdomen showing heterogeneous hypoechoic lesions in the liver suggestive of inflammatory or neoplastic process.

OUTCOME AND FOLLOW-UP

Over the next 7 days, the patient gradually improved with systemic antibiotics. Although a repeat CT of the abdomen did not show any regression of the liver mass, the patient's dramatic improvement after 2 weeks of antibiotics suggested a presumptive diagnosis of CLA. Our patient was discharged home with a 14 day course of levofloxacin.

A follow-up CT scan of the abdomen 2 months later revealed a decrease in the size and complexity of the right hepatic lesion further suggesting the diagnosis of CLA (figure 6). The presence of tubulovillous adenoma revealed by colonoscopy could have predisposed this to have a CLA, with no other risk factors and/or any known identifiable source of the abscess. A close follow-up was initiated to monitor the regression of the liver mass.

Figure 3 MRI of the abdomen, showing multiple confluent cystic masses with septations.

DISCUSSION

PLA is usually related to hepatobiliary and intra-abdominal infections such as cholecystitis, suppurative cholangitis, suppurative pylephlebitis, appendicitis, diverticulitis and peritonitis.^{1–5} However, recent reports of PLA have been associated with different colonic diseases; the most notable of which include inflammatory bowel disease, diverticulitis, colon cancer and colonic polyps, namely tubulovillous adenomas.⁵

A PLA is considered cryptogenic in nature when no obvious extrahepatic source of infection is identified.^{8–9} The majority of patients with PLAs fall into this category. In a study by Rahimian *et al*¹ on patients with PLA, most of the cases identified were cryptogenic in nature. Furthermore, the majority of patients suspected of having

a PLA who underwent CT and ultrasound studies, were also found to have their abscesses be cryptogenic in origin.⁸ However, most of the studies done on PLA are retrospective in nature and did not include colonoscopy as a diagnostic modality in identifying a colonic pathology.¹

A considerable number of PLAs are derived from portal vein pyaemia as a result of peritonitis and bowel leakage. Direct bacterial spread via the biliary ductal system is another important route of infection.^{10–11} The mechanism of PLA from a colonic origin is not clearly understood, with theories suggesting the translocation of bacteria from a damaged and compromised colonic mucosa, which may gain access to the blood stream with the subsequent hematogenous spread to the liver.^{5–9–11}

The most common isolate from a PLA infection is *Escherichia coli*. However, recent studies in the USA have shown an increasing trend of *Klebsiella pneumoniae* as the primary organism.^{1–12} Other organisms involved in PLA include *Enterococcus* spp, *Bacteroides* spp, *Streptococcus viridans*, *Staphylococcus* spp, *Pseudomonas* spp, *Proteus* spp, *Citrobacter freundii*, *Enterobacter cloacae*, *Peptostreptococcus* spp and *Clostridium* spp.^{1–10}

The earliest symptoms of PLA are insidious and non-specific; with the clinical triad of fever, chills and right upper quadrant pain being present in many patients.^{1–13} Other symptoms include nausea, vomiting, weight loss, jaundice and diarrhoea. Laboratory studies that are suggestive of a PLA are an elevated white blood count, a low albumin level, elevated alkaline phosphatase levels and increase in C-reactive proteins and erythrocyte sedimentation rates.^{1–13–14}

Blood cultures are an essential tool in supporting the diagnosis of PLA, although, they are more likely to be positive in non-cryptogenic and polymicrobial infections. Several retrospective chart reviews on the study of PLA also have demonstrated similar results.^{10–14–15} Direct cultures from the suspected liver abscesses offer a much higher yield than routine blood cultures, with recent

Table 1 Summary of laboratory results

Laboratory test	Result (normal range)
Hepatitis B surface antigen	Non-reactive
Hepatitis B core IgM antibody	Non-reactive
Hepatitis B core antibody, total	Non-reactive
Hepatitis B surface antibody	<5 mIU/ml (>10, immunity)
Hepatitis A antibody IgM	Non-reactive
Hepatitis A antibody, total	Reactive
HCV antibody screening	Non-reactive
Rapid HIV screening	Negative
Antinuclear antibody	Negative
<i>Entamoeba histolytica</i> antibody IgE	Negative
Echinococcus IgE	<0.35 (<0.35)
Stool ova and parasites	Negative
Stool occult blood	Negative
Acid fast smear/culture (tissue)	Negative
AFP, serum tumour marker	2.5 (<6.1 ng/ml)
CA 19-9	11 (0–37 U/ml)
Iron	11 (45–160 µg/dl)
Total iron-binding capacity	94 (228–428 µg/dl)
Transferrin saturation	12 (20–55%)
Ferritin	1926 (13–150 ng/dl)

AFP, alpha-fetoprotein; CA, carbohydrate antigen; Ig, immunoglobulin.

Figure 4 (A) Colonoscopy, note the 1.5 cm polyp which was removed by snare polypectomy (arrows). (B) Histopathological examination of the polyp showing long fronds of papillary epithelium springing directly from the fibrovascular core, characteristic of tubulovillous adenoma with intermediate grade dysplasia.

studies showing 77% culture positivity.^{14 16} Conversely, cultures obtained from percutaneous drainage placed more than 48 h are mostly contaminated with the normal skin flora and other organisms. Cultures obtained from

percutaneous drainage sites are unreliable, and should not be used to aid in the choice of antibiotics.¹⁶

Imaging studies play an important role in the diagnosis of PLA the most common of which include CT,

Figure 5 Liver core biopsy. (A) H&E stain $\times 2$ magnification, showing fibrosis and ductal proliferation. (B) H&E stain $\times 20$ magnification, highly atypical benign reactive bile ducts, in a background of dense fibrosis with sinusoidal oedema and moderate chronic inflammation. (C) CD56 immunohistochemistry staining, suggestive of benign bile ducts. (D) Repeat biopsy 14 days later showing severe parenchymal fibrosis with intense lymphocytic infiltration (arrow).

Figure 6 Follow-up CT scan of the abdomen 2 months later. Note the decrease in the size and complexity of the right hepatic lesion suggestive of a resolving liver abscess.

ultrasonography and MRI. The imaging finding of hepatic abscesses varies widely depending on the stage of the lesion. The classical finding of a typical abscess on imaging studies includes a central fluid pus-like collection surrounded by a multilayered hypovascular or hypervascular rim. These findings are common regardless of the type of imaging study used. However, advanced organising abscesses can demonstrate a granulomatous features with less pus fluid collection, often mistaken for other solid focal lesions; the most notable of which are peripheral cholangiocarcinoma and hepatocellular carcinoma.¹⁷ Several studies have demonstrated the use of special techniques such as the vascular involvement of tumours in colour-Doppler ultrasound,¹⁸ the use of diffusion weighted MRI¹⁹ and the notable changes in early dynamic phase of CT/MRI;¹⁷ all of which may help differentiate these potential mimics.

Over 70% of CLA are localised in the right lobe of the liver, with the remainder occurring in the left lobe. Rarely does a cryptogenic abscess involve both hepatic lobes.^{1 8 9} Moreover, investigators have suggested that solitary abscesses are more common in cryptogenic infection in contrast to multiple abscesses seen in biliary causes of PLA;⁸ while other studies have shown contrary and conflicting results.^{20–22} Our case involves multiple lesions in both lobes of the liver with signs of solid organising lesions on both MRI and CT.

Significant differences in the outcome of patients with CLA versus PLA have been suggested. Patients with CLA have shown to have earlier defervescence of fever, a better response to antibiotics and a shorter hospital stay as compared with other causes of PLA.⁵ On the contrary, patients with suspected CLA have shown to have higher risks of developing colorectal cancer on long-term follow-up. In a study by Lai *et al*⁷ on patients with CLA;

there is a 3.36 times greater risk of developing colorectal cancer in a 5 year follow-up, as compared with those who did not have CLA. A similar study by Mohsen *et al*⁴ also showed the same increased risk of colorectal cancer in CLA. These findings strongly suggest the role of colonic abnormalities as a probable cause of CLA. Several studies have now shown colonoscopy as a vital tool in both the diagnosis, as well as cancer surveillance in patients with CLA.^{4 5 7}

Colonic polyps are divided into four types, namely: hyperplastic, hamartomas, inflammatory and adenomatous polyps. Hyperplastic polyps are the most common form in adults with no malignant potential. Adenomatous polyps, however, carry a considerable risk of malignant transformation that increases exponentially with size.²³ Adenomatous polyps are further subdivided as tubular, villous or tubulo-villous, microscopically. Tubular adenomas are histologically described as tube-like glandular structure projecting from the central core. However, villous adenoma forms long finger-like fronds from the polyp surface that usually extend straight down with minimal or no branching. Tubulovillous adenomas are histologically distinct as the combination of both tubular and villous structures.^{23 24}

The risk of malignant transformation of such polyps is directly related to the degree of dysplasia. Mild dysplasia is characterised by a uniform loss of the normal appearing mucin and hyperchromatic elongated cells. Moderate dysplasia shows more prominent nucleoli with crowding of cells. In severe dysplasia, there is an increase of nuclear pleomorphism and an increase of nuclear-to-cytoplasmic cellular ratio.^{23–25} Koo *et al*⁹, in a recent study on the prevalence of colon cancer or high-grade dysplastic adenoma in PLA patients, have demonstrated higher incidence of both conditions than in normal individuals, 4.5%

and 7.4%, respectively. The group further concluded that colonoscopy should be considered as a PLA evaluation modality.⁹ In the case discussed, the degree of nuclear atypia was consistent with intermediate-grade tubulovillous adenoma, further increasing the risk of future malignant potential; thus dictates the need for frequent cancer screening surveillance.

Colonic disorders that compromise the normal protective mucosa have been shown to increase the risk of bacterial translocation and the subsequent development of hepatic abscess from hematogeneous spread. Special interest in the relationship of non-cancerous colonic lesions such as tubulovillous adenoma with CLA should be considered in greater detail. Colonoscopy is an important tool in aiding the diagnosis of CLA and should be part of the initial work-up for hepatic abscesses. Furthermore, a much more aggressive colon cancer screening surveillance is warranted in these patients. An advanced solid organising hepatic abscess can potentially mimic solid tumours. Special imaging techniques in an experienced hand can most likely differentiate these disease entities.

Learning points

- ▶ An underlying tubulovillous adenoma may potentiate the development of cryptogenic liver abscess (CLA).
- ▶ Patients with CLA have a much higher colon cancer risk than the general population.
- ▶ Endoscopic evaluation is recommended in patients with hepatic abscess.
- ▶ Solid organised abscesses of the liver may show granulomatous features that can mimic solid tumours such as cholangiocarcinoma and hepatocellular carcinoma.
- ▶ The use of advanced imaging techniques such as colour flow Doppler ultrasound, diffusion-weighted MRI and early-phase CT scan may aid in the differentiation of organised abscess versus solid tumours.

Patient consent Obtained.

REFERENCES

1. **Rahimian J**, Wilson T, Oram V, *et al*. Pyogenic liver abscess: recent trends in etiology and mortality. *Clin Infect Dis* 2004;**39**:1654–9.
2. **Ochsner A**, DeBaakey M, Murray S. Pyogenic abscess of the liver. *Am J Surg* 1938;**40**:292–314.
3. **Kaplan GG**, Gregson DB, Laupland KB. Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. *Clin Gastroenterol Hepatol* 2004;**2**:1032–8.
4. **Mohsen AH**, Green ST, Read RC, *et al*. Liver abscess in adults: ten years experience in a UK centre. *QJM* 2002;**95**:797–802.
5. **Jeong SW**, Jang JY, Lee TH, *et al*. Cryptogenic pyogenic liver abscess as the herald of colon cancer. *J Gastroenterol Hepatol* 2012;**27**:248–55.
6. **Lai HC**, Chan CY, Peng CY, *et al*. Pyogenic liver abscess associated with large colonic tubulovillous adenoma. *World J Gastroenterol* 2006;**12**:990–2.
7. **Lai HC**, Lin HC. Cryptogenic pyogenic liver abscess as a sign of colorectal cancer: a population-based 5-year follow-up study. *Liver Int* 2010;**30**:1387–93.
8. **Chen SC**, Yen CH, Tsao SM, *et al*. Comparison of pyogenic liver abscesses of biliary and cryptogenic origin. An eight-year analysis in a University Hospital. *Swiss Med Wkly* 2005;**135**:344–51.
9. **Koo HC**, Kim YS, Kim SG, *et al*. Should colonoscopy be performed in patients with cryptogenic liver abscess? *Clin Res Hepatol Gastroenterol*, Published Online First: 7 May 2012. doi:10.1016/j.bbr.2011.03.031.
10. **Davis JMM**. Pyogenic Liver Abscess. UpToDate, 2011. version 19.3 (<http://www.uptodate.com>): p. 5 May 2012.
11. **Stokes JF**. Cryptogenic liver abscess. *Lancet*, 1960;**1**:355–8.
12. **Braiteh F**, Golden MP. Cryptogenic invasive Klebsiella pneumoniae liver abscess syndrome. *Int J Infect Dis* 2007;**11**:16–22.
13. **Reid-Lombardo KM**, Khan S, Scialas G. Hepatic cysts and liver abscess. *Surg Clin North Am* 2010;**90**:679–97.
14. **Barrio J**, Cosme A, Ojeda E, *et al*. Pyogenic liver abscesses of bacterial origin. A study of 45 cases. *Rev Esp Enferm Dig* 2000;**92**:232–9.
15. **Chemaly RF**, Hall GS, Keys TF, *et al*. Microbiology of liver abscesses and the predictive value of abscess gram stain and associated blood cultures. *Diagn Microbiol Infect Dis* 2003;**46**:245–8.
16. **Everts RJ**, Heneghan JP, Adholla PO, *et al*. Validity of cultures of fluid collected through drainage catheters versus those obtained by direct aspiration. *J Clin Microbiol* 2001;**39**:66–8.
17. **Kim YK**, Kim CS, Lee JM, *et al*. Solid organizing hepatic abscesses mimic hepatic tumor: multiphasic computed tomography and magnetic resonance imaging findings with histopathologic correlation. *J Comput Assist Tomogr* 2006;**30**:189–96.
18. **Liang P**, Cao B, Wang Y, *et al*. Differential diagnosis of hepatic cystic lesions with gray-scale and color Doppler sonography. *J Clin Ultrasound* 2005;**33**:100–5.
19. **Chan JH**, Tsui EY, Luk SH, *et al*. Diffusion-weighted MR imaging of the liver: distinguishing hepatic abscess from cystic or necrotic tumor. *Abdom Imaging* 2001;**26**:161–5.
20. **Chou FF**, Sheen-Chen SM, Chen YS, *et al*. Single and multiple pyogenic liver abscesses: clinical course, etiology, and results of treatment. *World J Surg* 1997;**21**:384–8; discussion 388–9.
21. **McDonald MI**, *et al*. Single and multiple pyogenic liver abscesses. Natural history, diagnosis and treatment, with emphasis on percutaneous drainage. *Medicine (Baltimore)* 1984;**63**:291–302.
22. **Seeto RK**, Rockey DC. Pyogenic liver abscess. Changes in etiology, management, and outcome. *Medicine (Baltimore)* 1996;**75**:99–113.
23. **Alnoor R**, Katz J. Villous Adenoma. Medscape reference. Drugs, diseases and procedure (updated January 4, 2012): <http://www.emedicine.medscape.com>
24. **Gabbert H**, Hohn P. Grades of atypia in tubular and villous adenomas of the human colon. An electron microscopic study. *Virchows Arch B Cell Pathol Including Mol Pathol* 1980;**33**:1–15.
25. **Matsuda M**, Misumi A, Shimada S, *et al*. Quantitative electron microscopic study on grades of atypia in adenomas of the human large bowel. *Dis Colon Rectum* 1989;**32**:57–63.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Tan CB, Shah M, Rajan D, Lipka S, Ahmed S, Freedman L, Rizvon K, Mustacchia P. A solid organising cryptogenic liver abscess and its association with a colonic tubulovillous adenoma. *BMJ Case Reports* 2012;10.1136/bcr-2012-006431, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow