



Porcelain gallbladder and its relationship to cancer

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Summary

Background Porcelain gallbladder (PGB) is defined as calcium deposits encrusting the internal visceral layer, which becomes hard, brittle, and bluish. Porcelain gallbladder is rare and has been found in less than 1% of routine cholecystectomy specimens. Several studies report an incidence of gallbladder carcinoma (GBC) associated with gallbladder calcification varying between 12.5 and 61%, data which have been known for 60 years. There is a lack of information concerning PGB and its association with GBC, and the aim of this study is to better define this relationship.

Methods A total of 10 patients were found to have PGB in 1050 consecutive routine surgical cholecystectomies. Clinical and laboratory findings, gallbladder histologic examination, bile culture, and bile pH were related to stone composition analysis performed by X-ray diffraction using Perkin–Elmer (Perkin Elmer Corp. Norwalk, CT, US) 1625 FTIR.

Results Among the 10 patients with PGB, complete calcification of the entire gallbladder wall was present in six cases, while four patients had partial calcification. Gallstones were present in all cases of PGB, multiple stones in nine cases and a single stone in one case. Bile culture was performed in all patients of

the series. Among the 10 cases with PGB, culture was positive in two cases.

Conclusion PGB is a disease as rare as it is subtle. Moreover, the chronic stimulation by stones can generate an initial dysplasia that will subsequently turn into a neoplasm: the cancerization risk is probably no different from long-standing cholesterol or combined stones, but as risk factor for cancer it requires early cholecystectomy.

Keywords Cholecystitis · Cholelithiasis · Surgery · Gallbladder cancer · Gallbladder stones

Introduction

Porcelain gallbladder (PGB) is defined as calcium deposits encrusting the internal visceral layer, which becomes hard, brittle, and bluish ([1], Figs. 1 and 2). The incidence is low, with PGB found in less than 1% of routine cholecystectomy specimens, with a female predominance of 5 to 1 male. Older age is a risk factor, with most occurring over the age of 60 [1–7]. Gallbladder carcinoma (GBC) is an aggressive biliary tract malignancy, rare in most Western countries, although more widespread in other regions of the world, with a particularly high incidence observed in Japan, Chile, India, and Bolivia [6–8]. PGB in children is extremely rare. Adenocarcinoma accounts for 90% of gallbladder cancers [8], while squamous cell carcinomas of the gallbladder account for 2–12%. Other rarer forms of gallbladder cancer include sarcomas, lymphomas, and carcinoids. Although gallstones are a described risk factor for development of gallbladder carcinoma, Comfort et al. showed that less than 1% of patients with asymptomatic gallstones developed gallbladder carcinoma over a 10–25-year period [9, 10]. PGB is currently considered as a late fate of chronic cholecystitis and is included among the most

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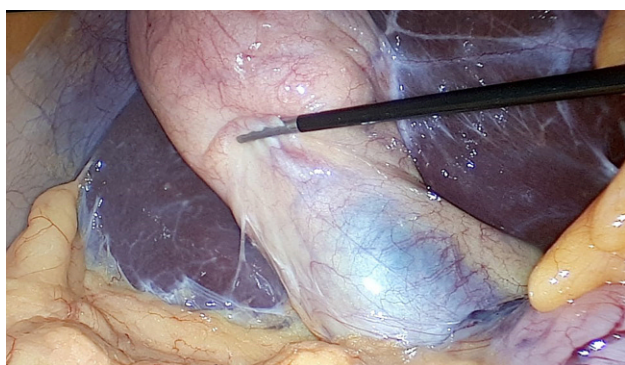


Fig. 1 Laparoscopic view of porcelain gallbladder



Fig. 2 Porcelain gallbladder

important premalignant conditions for GBC. The extent of gallbladder wall involvement varies from the presence of a single calcified plaque adhered to the mucosal layer to total full-thickness replacement of the tissue of the entire gallbladder wall with calcium [1, 8]. Several studies report an incidence of GBC associated with gallbladder calcification varying between 12.5 and 61%, data which have been known for 60 years [10–13]. Other authors think that the condition is not associated with gallbladder malignancy [1]. Actually, the reported incidence is around 2–8% [4, 5].

The aims of this study are to report not only the pathologic findings in the gallbladder wall (as in most of the retrospective studies) but also findings never reported up to now in a large series, such as stone types, structure, and composition; pattern of calcification; bile analysis (pH, culture); and the presumed time lapse between gallbladder calcification and cholecystectomy, in order to better define the relationship between PGB and GBC.

Materials and methods

A total of 1050 consecutive patients treated by cholecystectomy for benign gallbladder disease at our department between 2003 and 2018 were included in the study, 395 men (37.6%) and 655 women (62.4%). The mean age was 58.6 years (range 19–94). All patients with hyperbilirubinemia due to any cause, known bile duct lithiasis, or those previously treated by ERCP were excluded. Clinical and laboratory findings, gallbladder histologic examination, bile culture, and bile pH were related to stone composition analysis performed by X-ray diffraction using Perkin–Elmer 1625 FTIR (Perkin Elmer Corp. Norwalk, USA). Light stereomicroscopy of stones and scanning electron microscopy of stones (ISI-SX-25 SEM Pabish, Milan, Italy) were also performed in a subset of cases (85 patients with gallstones and 13 patients with GBC). 95% of the procedures were performed by a laparoscopic

approach (998 pt). Intraoperative cholangiography was performed in all the laparotomic cases (52 pt).

Results

The whole series (1050 pt) had ultrasonographically demonstrated lithiasis (Figs. 3 and 4). At histological examination a single stone was found in 15% of cases.

In 1040 cases we operated patients with gallstones but without PGB: in these cases, stones were ovoidal, single, or multiple in 34%, multifaceted in 35%, combination in 7.5%, composite or other stones in 6.7%, and pigment stones in 11.4%. However, pigment stones in association with other types of stones were found in 5% of other patients.

In particular, stones larger than 12 mm were found in 35% of the study population and in 90% of patients with PGB.

GBC was incidentally found in 27 cases (27/1050, 2.6%). Multiple lithiasis with a combination of large (size over 12 mm) cholesterol gallstones was found in 25 (92.6%) cases and small cholesterol faceted stones 3–4 mm in diameter in 2 cases.

We found 10 cases with PGB at histological examination (Table 1), 8 females (80%) and 2 males (20%). The mean age was 67 years (range 44–88 years).

Seven patients with PGB were aware of having had gallstones for at least 8 years (8–45 years). In four patients, based on abdominal ultrasound examinations performed in different periods, it was possible to establish that gallstones preceded the occurrence of PGB by 4 to 17 years. We cannot be precise on the onset of calcification of the gallbladder wall because the patients did not follow regular check-ups.

Among the 10 patients with PGB, macroscopic histologic examination showed complete calcification of the entire gallbladder wall in six cases, while four had partial calcification, in one case limited to the infundibulum and in three cases to the fundus and part

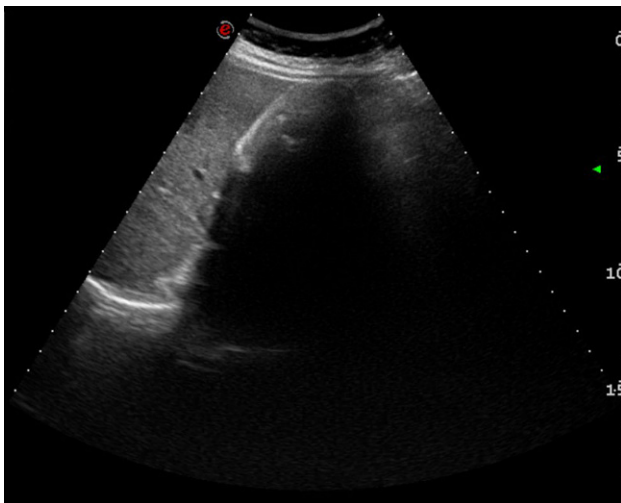


Fig. 3 Ultrasound view of porcelain gallbladder 1

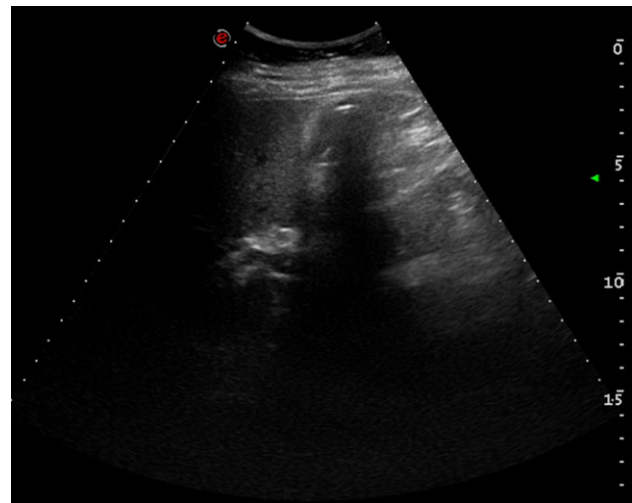


Fig. 4 Ultrasound view of porcelain gallbladder 2

of the body of the gallbladder. Microscopic examination showed the presence of intraparietal microlithiasis in the four moderate cases of PGB. Diffuse hyalinosis and atrophy of the mucosal layer with areas of complete disappearance of the epithelium was found in the six severe cases of PGB. The associated finding was chronic inflammation, often with a perivascular distribution obscuring a few residual epithelial islets.

Gallstones were present in all cases of PGB, multiple in nine cases and single in one case. In five (56%) cases of multiple lithiasis, we observed the presence of a single stone of 0.5–1.3 cm impacted in the neck of the gallbladder, where it had formed a septum in the Heister valve resulting as a separate cavity; the nucleus of the gallstones consisted of radiate cholesterol crystals. The peripheral coating of calcium carbonate was almost absent in the stones impacted in the infundibulum and progressively greater in those stones located in the body and in the fundus of the gallbladder. In the other four (44%) cases, multiple stones were found together with bile sludge and/or purulent material, with at least one stone larger than 12 mm and in one case, the gallbladder was completely filled with small-faceted stones. Of the 10 PGB patients, 9 had at least one stone larger than 12 mm.

Among the 10 cases with PGB, bile culture was positive in 2 cases (*Escherichia Coli* and *Enterobacter Cloacae* in one patient and *Klebsiella Pneumoniae* in the other).

Evident calcification of the gallbladder wall was reported in 2 (7.4%) of 27 patients with GBC, with the histological presence of adenosquamous carcinoma.

Discussion

Although the etiology of PGB is poorly understood, the chronic inflammatory process causes an alteration in calcium metabolism leading to cholelithiasis and transmural calcification of the gallbladder [5]. It is reported that PGB is associated with GBC [7], probably

due to the accumulation of carcinogens in a condition of biliary stasis or due to malignant degeneration following chronic inflammation [14, 15]. In the literature there is a lack of analysis of the relationship between PGB and GBC in large series of patients, as there are only sporadic observations [16].

Polk [13] collected reports of 100 patients with PGB and found 22 cases of GBC, Etala [12] reported an incidence of GBC in PGB of 61%.

In our experience we have identified 10 cases of PGB, 0.95% of our consecutive series of cholecystectomy, 6 with complete calcification and 4 with partial calcification. GBC was found in 27 cases (2.57%). Two of these patients had evident calcification of the gallbladder wall (7.4%).

Furthermore, there is lack of data in the literature concerning the relationship between PGB, presence of gallstones, numerical size and type of stones, bacteriology, analysis of bile and GBC.

In the present series, gallstones were present in all patients with PGB, consistent with the reported rate of 95% [13, 17].

Moreover, we found the presence of infraparietal black microlithiasis in the bottom of Rokitsansky–Aschoff sinuses (isolated or in combination with intraluminal black microstones) associated with cholesterol (or mixed) gallstones in 21 cases with rare chronic cholecystitis or biliary infection, although it is not correct to include these cases in the series of patients with parietal calcification of the gallbladder wall evident on conventional radiography or ultrasound [18].

The stones found in patients with PGB were cholesterol or with a cholesterol core, large in 90% of cases. In most cases they were of long standing and partial calcification preceded complete calcification before the age of 55 years. Even more suggestive is the relative incidence of large stones in the entire series of patients with gallstones (35%), particularly in patients with PGB (80%) and in patients with GBC (90%).

Table 1 Patients with porcelain gallbladder

Patient ID	Sex	Calcification	Mean size (mm)	Stone type	Bile pH	Culture
1	F	Complete	15	D	7.4	–
2	M	Complete	12	C	7.4	–
3	F	Complete	9	C	7.2	+
4	F	Partial	15	D	7.0	–
5	M	Complete	12	D	7.1	–
6	F	Complete	13	O	7.5	–
7	F	Complete	20	C	7.6	+
8	F	Partial	12	C	8.0	–
9	F	Partial	20	D	7.5	–
10	F	Partial	14	D	8.1	–

O ovoidal cholesterol; *C* combination with calcified periphery; *D* composite stone (different population of stones in the same gallbladder)

From our evidence, gallstones precede PGB and GBC, and those of greater size and duration are progressively more frequent in patients with PGB and GBC than in the general population. It can be hypothesized, in agreement with previous reports in the literature [19, 20], that gallstones and especially cholesterol stones larger than 1.5 cm are mainly responsible for the development of GBC and that the risk factors for GBC are the same or similar to those responsible for the formation of large stones.

Regarding the relationship between stone size and GBC, limiting the analysis to patients over the age of 50 and with stones larger than 1.5 cm, 8% of patients had GBC. On the other hand, 16.6% of all patients with evident parietal calcification had GBC.

This rate is in agreement with previously reported rates between 12 and 20% of PGB cancerization in radiological studies [21].

However, from our experience, both patients with GBC and parietal calcification were not aware that they had gallstones or PGB; therefore, it was not possible to establish a clear relationship between PGB and GBC [14], but the issue remains that the parietal calcification could be a metaplastic change in an already established GBC. None of the 10 patients with PGB had histological evidence of malignant cells. Two of the 10 patients with PGB had long-standing PGB (over 15 and 19 years, respectively).

Our results therefore suggest that the role of PGB as a precancerous condition [15, 22] has been overestimated in the past. In our opinion, PGB is not an obligatory passage in the natural history of chronic cholecystitis, but rather represents a pathological entity which correlates to an obstruction of the cystic duct, with the deposition of calcium salts both in the gallbladder wall and on previous gallstones. The low incidence of biliary infection in patients with PGB also suggests that chronic inflammation but not infection is the main factor in the development of PGB. The other mechanism that supports parietal calcification is so-called dystrophic calcification, i.e., deposition of calcium (main phosphate) and bone metaplasia in areas with previous supplicated or necrotic phenomena.

The possible mechanism by which carcinomatous changes occur in patients with PGB is unknown. Cancer could likely start from residual epithelial islets in the presence of chronic mechanical irritation and/or inflammation. The hypothesis that chronic irritation promotes neoplasia is also supported by the discovery that the lithiasic gallbladder epithelium incorporates tritiated thymidine at a level 23-times greater than normal [23]. According to Albores Saavedra et al. [24], GBC in PGB patients may be related to scar cancer phenomena, as there is usually fibrosis in addition to calcification. Histologically, calcification can involve the muscle layer or mucosa and the underlying lamina propria. It is possible to hypothesize that cancerization may occur more frequently according to the first mechanism in patients with partial or incomplete calcifications and multiple residual epithelial nests, and more frequently according to the “scar cancer phenomenon” in patients with complete calcification and diffuse hyalinosis of the different layers of the wall of the gallbladder.

Conclusion

PGB is a disease as rare as it is subtle, because the progressive replacement of the muscular part of the wall with a pattern containing calcium inhibits its contractile capacity and this explains the lack of abdominal pain characteristic of biliary lithiasis. Moreover, PGB represents the pathological evolution of a particular type of cystic duct obstruction rather than the late result of dystrophic calcification (bone metaplasia of necrotic or inflamed tissues of the parietal wall). The cancer risk is probably no different from long-standing cholesterol or combined stones (8% in our series), but as a risk factor for cancer it requires early cholecystectomy, especially because we are unable to estimate the onset of PGB and therefore neglect the presence of dysplasia or tumor, either confined or multifocal.

Main novel aspects

- PGB is a rare finding (0.8) in a consecutive series of patients with bile tract surgery, usually associated with and probably determined by gallstones, and likely represents the pathologic evolution of a particular type of cystic duct obstruction more than the late result of dystrophic calcification (bone metaplasia of necrotic or inflamed tissues of the parietal wall).
- The role of PGB as a premalignant condition has been overestimated in the past.
- PGB is a disease as rare as it is subtle, but as a risk factor for cancer it requires early cholecystectomy.

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Author Contribution CN conceived the study, participated in data collection and analysis, drafted the manuscript. SMLPF conceived the study, participated in statistical analysis, and reviewed the manuscript. LFN, MI, and FD participated in data collection and analysis, provided language help, and contributed to the manuscript draft. DM is the guarantor of the manuscript. All Authors read and approved the manuscript.

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Declarations

Conflict of interest N. Calomino, M.L.P.F. Scheiterle, D. Fusario, N. La Francesca, I. Martellucci and D. Marrelli declare that they have no competing interests.

Ethical standards Ethical approval was not required because this was an observational study that did not require any modification of the standard therapeutic protocols. All procedures performed in this study involving patients were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent to collect and consult clinical records was obtained from all patients included in the studies.

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