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REVIEW ARTICLE

Understanding multiseptated gallbladder: A systematic analysis with a case report

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Abstract

Multiseptated gallbladder (MSG) (also known as "Honeycomb gallbladder") is a rare condition that was first described by Knetsch in 1952, and there are around 150 cases described over the world. MSG has been described as a congenital anomaly in most of the cases and as acquired in a few. Moreover, the phenomenon was described with a variety of different symptoms and management. The aim of this article is to have better understanding of this condition and management approach. We are reporting a 4-year-old girl, who presented to Sidra Medicine, Qatar with MSG. We have also included 97 cases for review and analysis. The median age of presentation of the condition was 27 years but may present in neonates and in the elderly, while gender was not a risk factor. Abdominal pain is the most common presenting symptom, but it can present without symptoms. Certain congenital anomalies were detected in the pancreaticobiliary system in few patients with MSG. Medical treatment was reported in eight symptomatic patients, four of whom failed therapy. Cholecystectomy was performed in 40 patients, which resulted in resolutions of symptoms in 13 of them. Based on the available literature, congenital MSG is probably due to in-pouching of gallbladder wall to its own cavity forming septa containing muscular fibers. MSG can be diagnosed solely via imaging, and ultrasound appears to be an effective and feasible mode of diagnosis. Medical treatment efficacy is not well-known, but cholecystectomy has resulted in complete resolution in symptomatic patients.

Introduction

Multiseptated gallbladder (MSG) (also called "Honeycomb gallbladder") is a rare condition that was initially described by Knetsch in 1952,[1] and there has been less than 150 reported worldwide.

The etiology of MSG is not very clear yet and multiple embryological hypotheses have been suggested. Many of the reported cases of MSG have been diagnosed incidentally and the rest presented with a variety of different symptoms.[2,3] We present a case of an MSG seen at Sidra Medicine, the only tertiary pediatric center in the State of Qatar.

Given the rarity of incidence and the wide variation of presentations and management, we are conducting an extensive literature review and analysis of available data to have better understanding of this condition and management approach. To the authors' knowledge, this manuscript is the latest and most comprehensive review of reported cases of MSG.

Case report

A 4-year-old girl presented to the pediatric outpatient clinic complaining of chronic constipation, associated with intermittent abdominal pain, initially described as nonspecific. There was no history of fever, vomiting, diarrhea, or urinary symptoms. Past medical history was remarkable for recurrent urinary tract infections. Family history was unremarkable. Her vital signs during her first clinic visit were within normal limits for her age. Her weight and body mass index (BMI) were on the 99th centile for age (z-score 2.38). On physical examination, her abdomen was soft, with no tenderness, no masses, and no organomegaly. The rest of the physical examination was normal.

On further follow up, her constipation improved with Polyethylene glycol; however, she continued to have recurrent abdominal pain, which was ill-localized, postprandial, and exacerbated by fatty meals.

Laboratory tests showed serum white blood cells of 8.1 $\times 10$ (9)/L, hemoglobin of 125 g/L, platelets of 383 $\times 10$(9)/L, albumin of 44 g/L, aspartate aminotransferase of 31 U/L, and alanine aminotransferase of 16 U/L, total bilirubin of 9 μmol/L, C-reactive protein of 3.1 mg/L, and erythrocyte sedimentation rate of 65 mm/h. Serum glucose, creatinine, blood urea nitrogen, calcium, sodium, chloride, and potassium were normal as well as urine analysis and culture.

Ultrasonography of the abdomen was done, revealing multiseptations in the gallbladder (Fig. 1a,b). No evidence of gallbladder wall thickening, pericholecystic fluid, or cholelithiasis were found.

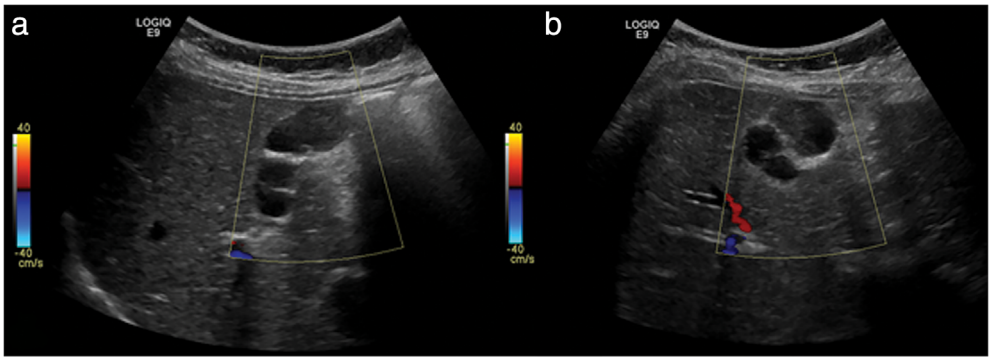

Figure 1 (a and b) Abdomen ultrasound shows multiple septations in the gallbladder in two views.

She was evaluated by the surgical team, and after discussing the risks and the benefits of surgical management with the family, laparoscopic cholecystectomy was performed. Histopathology showed normal gallbladder tissue with multiple septations. The patient was discharged on postoperative day 1 without complications. Her symptoms resolved after the surgery. She has been following in our pediatric clinic and has been asymptomatic for the last 2 years.

Methodology

We carried out a search in PubMed, Ovid, Embase, Cochrane, and Google Scholar and reviewed publications up to 15 September 2020. Terms used for searching were as follows: "Multiseptated Gallbladder," "Multiseptate Gallbladder," and "Septated Gallbladder." To maximize the search, we scrutinized the references of the identified articles. Results were screened by title to exclude nonrelevant conditions (Fig. 2). We excluded any study that reported an ultrasound appearance falsely mimicking MSG. Single gallbladder septum/diaphragm cases were also excluded. Although some articles were written in other languages, information was obtained from the abstracts written in English. Twenty-three articles were excluded (12 in Japanese, 5 in Spanish, 3 in French, and 3 in German) for having no available English report or abstract.

The remaining articles were fully reviewed separately by two reviewers (Rayan S Terkawi and Dua' Qutob), and manuscripts of nonrelevant contents were excluded after agreement by the reviewers. Reports that did not describe specific variants were considered as missing data and excluded from that specific variant. Data were extracted from 83 articles (96 patients) in addition to our case report, resulting in 97 cases.

Data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA).

The analysis aimed to better delineate the age at diagnosis, presenting symptoms, diagnostic modalities, and management. Chi-square analysis was used to explore the relation between the presence of symptoms with age groups and gender.

Results and discussion

All the reported cases are listed in Table 1.

History. While reviewing the literature, it was found that many authors have cited Simon *et al.* as the first to describe this rare condition in 1963.[4] However, scrutinizing the literature showed that this phenomenon was described 11 years earlier by Knetsch.[1,4]

Etiology and embryology. Embryological hypothesis was described by Bhagavan *et al.* in 1970,[7] who proposed that multiseptations of the gallbladder is a result of failure of disappearance of septations in the later stages of embryological development (Fig. 3a). The development, according to their hypothesis, starts with the formation of endodermal epithelial bud that will eventually wrinkle. Intraepithelial clefts will then fuse to form locules, which create spaces surrounded by septations (walls of locules) when they expand. This theory was supported by the fact that histopathology reports illustrated the presence of smooth muscles in the septations as a continuation of gallbladder wall muscles. The same authors described another theory called "Phrygian Cap" in which the embryonal gallbladder grows faster than its surrounding peritoneum forming kinks, resulting in multi-septations.

On the other hand, in 1993, Tan *et al.*[84] disagreed with the above described theory. In their study, 11 human embryos (29 days to 25 weeks of gestation) were investigated and none of them showed the phenomena of solid bud and wrinkling. Instead, they found multiple in-pouching of the lumen into the surrounding mucosa around the age of 12 weeks of gestation. These cystic outpouchings are thought to be the precursors of multiseptations in the gallbladder during the first trimester (Fig. 3b).

The suggested hypotheses might explain multiseptations of the gallbladder, but do not explain the single septation or presence of a gallbladder diaphragm such as the one described by Mathur *et al.*[85] Hence, we have decided to exclude those reports describing single septation from our review.

Furthermore, MSG has been considered a congenital abnormality until Sasaki *et al.*[2] described two patients who developed MSG secondary to inflammation in the gallbladder. Surprisingly, histopathological review of those two patients did not show muscle fibers in the walls of septations, which may differentiate acquired MSG from congenital ones. Another report described a 16-year-old boy who had a trauma to the abdomen with visceral injuries, and normal ultrasound appearance of the gallbladder.[3] He underwent chole-cysto-jejunostomy, and an

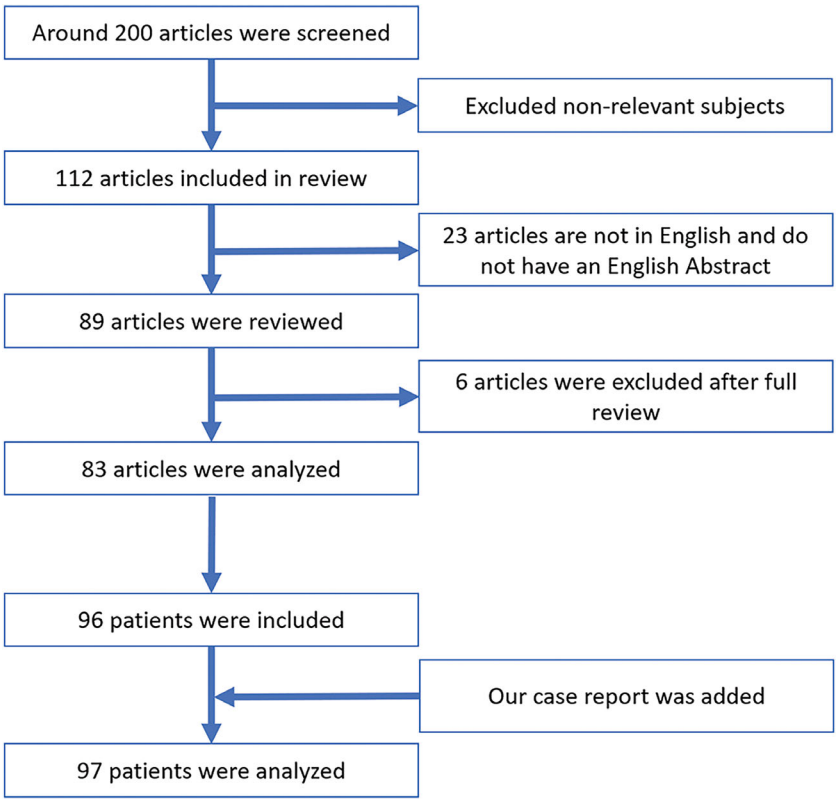

Figure 2 Inclusion and exclusion of reports.

abdominal ultrasound 1 year later showed multi-septations of the gallbladder, thus confirming the acquired form. The authors attributed the acquired form of MSG to the direct trauma to the gallbladder or by influx of gastrointestinal tract contents. The report, however, missed to publish the histopathology.

Demography of patients. Within the 92 patients included in this report, the age group ranged from newborns up to 84 years with median age of 23 years and the mean value of around 27 years (Fig. 4).

Fifty-three of them were above 18 years of age and 39 were children (18 years and below), and approximately 74% ($n = 68$) presented before the age of 40. Moreover, female patients accounted for almost 60% of the cases ($n = 53$). Turkey has the highest number of reported cases ($n = 24$), followed by United States ($n = 19$), then Japan ($n = 15$). Our case report is the first in Qatar.

Presenting symptoms. Almost one-fourth of the patients were asymptomatic at the time of diagnosis, and imaging was done for other purposes. The rest (77%, $n = 68$) presented with wide spectrum of symptoms. Our data analysis did not show statistically significant correlation when correlating symptoms, gender, or age groups (P values > 0.05). Among the symptomatic patients, 42% ($n = 28$) were males, 58% ($n = 38$) were females, and 2 cases did not report the gender.

The most common presenting symptom was abdominal pain (88.2%) in the form of nonspecific or located to the right upper quadrant. Other presenting symptoms are summarized in Table 2.

In addition, few patients described other symptoms such as dyspepsia, pruritus, weight loss, and anorexia.

As for the duration of symptoms, it was inconsistent, varying from few days to several years.

Physical examination. Half of the diagnosed patients (whether they were symptomatic or non-symptomatic) had a normal physical examination (27 patients out of 54 with reported physical examination). About one-third of diagnosed patients (33%, $n = 20$) had localized tenderness over the gallbladder area. The rest had expressed different findings in physical examination such as generalized abdominal tenderness (6.7%, $n = 4$) and palpable liver (5%, $n = 3$). Each of the following signs was reported once: jaundice, right flank tenderness, positive Murphy's sign, enlarged kidney, and poor growth.

Liver function test and other laboratory tests. Among 60 patients with reported results, 70% had normal liver function test (LFTs). Elevated alkaline phosphatase (ALP) was seen in 10 patients (14%), elevated transaminases in 8 patients (11%), elevated bilirubin in 5 patients (7%), and another 5 with elevated gamma-glutamyl transferase (GGT). Complete blood count (CBC) showed leukocytosis in 4 patients and anemia in

Table 1 Reports included in the analysis

Publication year	Author	Number of patients	Age of presentation	Gender
1963	Simon and Tandon.[4]	1	32 years	Female
1964	Bigg *et al.*[5]	1	38 years	Male
1966	Haslam *et al.*[6]	1	15.5 years	Female
1970	Bhagavan *et al.*[7]	1	27 years	Female
1972	Isdale[8]	2	10 years	Male
			15 years	Male
1973	Croce[9]	1	45 years	Female
1975	Shaw *et al.*[10]	1	31 years	Female
1977	Jena *et al.*[11]	1	28 years	Female
1979	Okuda *et al.*[12]	1	37 years	Male
1981	González Bethencourt *et al.*[13]	1	4 years	Female
1981	Alawneh *et al.*[14]	1	†	†
1982	Toombs *et al.*[15]	1	22 years	Female
1985	Pery *et al.*[16]	1	8 years	Female
1985	Oliva *et al.*[17]	1	24 years	Female
1987	Lev-Toaff *et al.*[18]	2	23 years	Female
			30 years	Male
1988	Seider *et al.*[3]	1	17 years	Male
1989	Fremond *et al.*[19]	1	13 years	Female
1990	Isomoto *et al.*[20]	1	43 years	Female
1990	Adear and Barki.[21]	1	12 years	Female
1990	Vasinrapee *et al.*[22]	1	24 years	Male
1990	Hardoff and Hardoff.[23]	1	17 years	Male
1991	Achong *et al.*[24]	1	58 years	Male
1992	Esper *et al.*[25]	1	6 years	Female
1993	Tan *et al.*[26]	1	14 years	Female
1993	Strauss *et al.*[27]	3	9 years	Female
			3 years	Male
			16 years	Male
1994	Naritomi *et al.*[28]	1	45 years	Female
1994	Song *et al.*[29]	1	49 years	Female
1994	Hahm *et al.*[30]	1	49 years	Female
1996	Saimura *et al.*[31]	1	30 years	Male
1996	Kong and Wong.[32]	1	9 years	Male
1996	Fichera *et al.*[33]	1	3 years	Male
1997	Paciorek *et al.*[34]	1	25 years	Female
1998	Saddik[35]	1	10 years	Male
1999	Joo *et al.*[36]	1	36 years	Male
1999	Mrhac *et al.*[37]	1	33 years	Male
2000	Miwa *et al.*[38]	1	70 years	Female
2001	Mouratidis and Chen.[39]	1	21 years	Male
2001	Sugawara *et al.*	3	†	†
			†	†
			†	†
2002	Koktener *et al.*[40]	1	75 years	Female
2002	Kapoor *et al.*[41]	1	21 years	Male
2003	Dalgiç *et al.*[42]	1	11 years	Female
2003	Kocakoc *et al.*[43]	1	9 years	Male
2004	Erdogmus *et al.*[44]	1	20 years	Female
2004	Nakazawa *et al.*[45]	1	56 years	Female
2004	Sasaki *et al.*[2]	2	84 years	Female
			78 years	Female
2004	Erdogmus *et al.*[46]	7	10 years	Female
			33 years	Female
			40 years	Female
			40 years	Female
			23 years	Male

(*Continues*)

Table 1 (Continued)

Publication year	Author	Number of patients	Age of presentation	Gender
			12 years	Male
			45 years	Male
2005	Yamamoto *et al.*[47]	1	46 years	Female
2006	Bahadir *et al.*[48]	1	15 days	Male
2006	Türkvatan *et al.*[49]	1	62 years	Male
2007	Fitoz *et al.*[50]	1	†	†
2008	Yamasaki *et al.*[51]	1	53 years	Female
2009	Tae *et al.*[52]	1	70 years	Female
2009	Rivera-Troche *et al.*[53]	1	19 years	Female
2010	Demirpolat *et al.*[54]	1	5 years	Female
2011	Atalar[55]	1	10 years	Female
2011	Karaca *et al.*[56]	1	29 years	Female
2011	Wanaguru *et al.*[57]	1	9 months	Female
2011	Herliczek[58]	1	11 years	Male
2011	Orokawa *et al.*[59]	1	29 years	Male
2013	Tok *et al.*[60]	1	42 years	Female
2013	Sunahara *et al.*[61]	1	20 years	Female
2013	Geremia *et al.*[62]	1	10 years	Male
2013	Aydin *et al.*[63]	1	10 years	Male
2014	Acar *et al.*[64]	1	26 years	Female
2014	Omuta *et al.*[65]	1	40s (years)	Female
2014	Afrouzian *et al.*[66]	1	29 years	Male
2015	Ortolá *et al.*[67]	1	5 months	Female
2015	Otaibi *et al.*[68]	1	54 years	Male
2016	Ozturk and Sigirci.[69]	1	12 years	Female
2016	Koc[70]	1	69 years	Female
2016	Edelman *et al.*[71]	1	16 years	Male
2016	Aydin[72]	1	7 years	Male
2017	Baram *et al.*[73]	1	25 years	Female
2017	Honrubia López *et al.*[74]	1	28 years	Male
2017	Sabra *et al.*[75]	1	12 years	†
2018	Dousse *et al.*[76]	1	30 years	Female
2018	Öztorun *et al.*[77]	1	1 years	Male
2019	Bertozzi *et al.*[78]	1	7 years	Female
2019	Our case report	1	4 years	Female
2019	Demko and Xhetani.[79]	1	6 years	Female
2019	La Mendola *et al.*[80]	1	3 years	Female
2020	Singh *et al.*[81]	1	49 years	Female
2020	Talalaev *et al.*[82]	1	60 years	Female
2020	Akbari and Putra.[83]	1	Term newborn	Male

†Means data are not available.

4 patients, while elevated pancreatic enzymes was reported in 1 patient, and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in a different patient.

Diagnostic imaging. Ultrasonography of the abdomen was performed in 75 of the reported cases, including our case. The imaging reports were suggestive of MSG in 96% ($n = 72$). One case was diagnosed via computed tomography scan,[68] and macroscopic examination intra-and postoperatively was diagnostic in the other cases.[26,48]

There were five older patients who utilized oral cholecystogram for diagnosis,[4–6,9,11] three of whom showed evidence of MSG.[4–6]

Ultrasonography of the abdomen was also helpful in detecting other associated abnormalities. Four cases reported wall thickening on ultrasound, and 2.67% ($n = 2$) reported an enlarged gallbladder. On the other hand, a small or hypoplastic gallbladder was also reported in two cases.

Changes on ultrasound following fatty meals were described in 4% of the reports. In 9.3% of cases, cholelithiasis was detected, while biliary sludge was reported in 5.3% ($n = 4$).

Histopathological features. In addition to the macroscopic findings, 22 papers reported microscopic detailed findings. Presence of muscular layers of fibers in the wall of septa was seen in 59% ($n = 13$), chronic or acute inflammatory infiltrations in 36% ($n = 8$), and fibrous tissue in the wall of septa in 32% ($n = 7$).

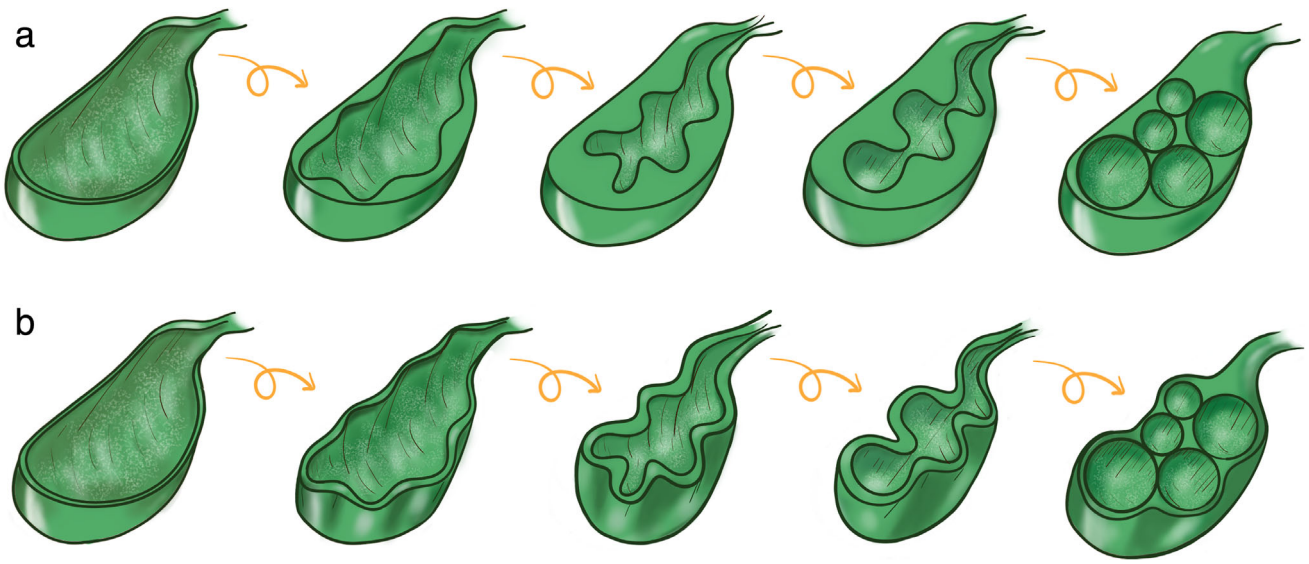

Figure 3 (a and b) Theories of multiseptated gallbladder development.

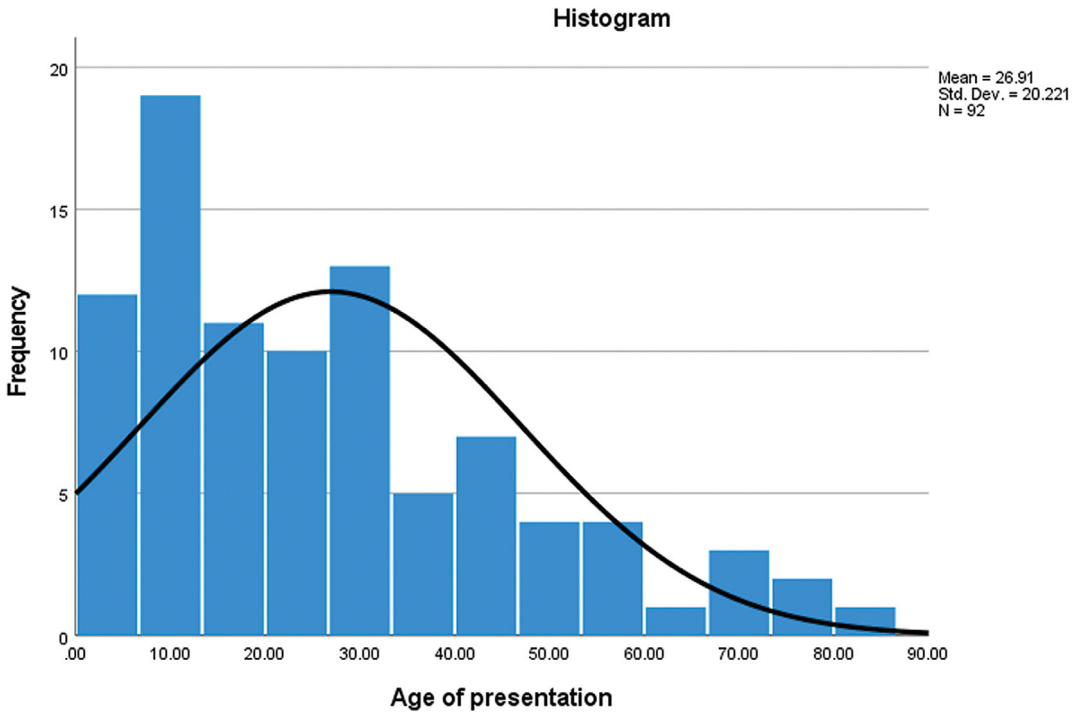

Figure 4 Age of presentation of MSG.

As Tan *et al.*[84] described earlier, presence of muscular layer supports his theory of development. On the other hand, muscular layer was not found (or not reported) in other cases, which make these data to be interpreted cautiously.

The appearance of multiseptations looks like a "honeycomb," therefore, this term was used to describe MSG.[2,27,30,31,34,35,38,41,43,57,63,64,69,70]

Other reported abnormalities. Seventeen patients had other anatomical malformations. Among these, nine patients had abnormalities related to the pancreaticobiliary system development: four with choledochal cysts, two with pancreaticobiliary ductal union before reaching the ampulla, one double cystic duct, one ectopic pancreas (together with choledochal cyst), and one gallbladder abscess/xanthogranulomatous cholecystitis.

Table 2 Main symptoms of presentation

Symptom	Frequency (*n*)
Nausea and/or vomiting	8
Jaundice	3
Poor growth	1
Back pain	1
Diarrhea	1
Pyrexia	1
Fatigue	1
Flank pain	1
Indigestion	1

This may be explained by having a common embryological origin of those structures.

Other reported anomalies were related to the urinary system (four patients) and miscellaneous gastrointestinal tract abnormalities (five patients).

The described abnormalities in urinary system are as follows: hydronephrosis of both sides, bilateral kidney duplicity, bilateral kidney cysts, ectopic right ureter implantation ($n = 3$), and partial duplication of the left ureters.

Moreover, the described miscellaneous gastrointestinal tract abnormalities are as follows: non-obstructing bands across the duodenum ($n = 2$), appearance of primary biliary cirrhosis, enlarged and inflamed liver, numerous polyps in the stomach and small and large bowel, gastric cancer, and anal fistula. None of the included reports indicated an association of MSG with gallbladder cancers.

We understand that gallbladder and pancreas originated together from the same bud,[86] which may provide a logical explanation of this linking. However, we admit the lack of knowledge about the associations between abnormalities described in other parts of the gastrointestinal and urinary tracts and the MSG. Such abnormalities may have a common etiology or may be coincidental.

Treatment options. Medical treatment was reported in eight symptomatic patients, four of them failed therapy, and the rest had no reported follow up. Medical therapy included analgesics, ursodeoxycholic acid, diphenoxylate/atropine and dicyclomine, H2 receptor antagonist, and anticholinergic medication.

Cholecystectomy was done in 40 patients (5 of them were asymptomatic and 35 were symptomatic). Out of the asymptomatic patients, three underwent other surgeries for associated abnormalities together with cholecystectomy.[47,51,83] Only 13 patients had a reported follow up after discharged. Follow up showed resolution of symptoms in all of them (100%). No one has reported failure of surgical therapy or recurrence of symptoms afterwards.

This reflect the lack of knowledge about efficacy of medical therapy and whether it is comparable with surgical therapy or not. However, available data provide promising outcomes of cholecystectomy.

Limitations

Our outcome may have been affected by the limited number of cases included in our review. This is due to the rarity of reported cases, and the exclusion of those reported in languages other than English. The lack of reporting medical treatment prevented comparison of medical with surgical treatment. Knowing that MSG is a rare condition with few case reports per year, understanding the condition may need years to achieve.

Conclusion

Congenital MSG is a rare condition that is probably a result of outpouching of gallbladder wall to its cavity forming septa with muscular fibers. Acquired cases of MSG have also been described, lacking muscular fibers in the walls of septa. Other congenital anomalies in the pancreaticobiliary system development were detected in few patients with MSG. The median age of presentation is 27 years, however cases diagnosed in neonates and elderly have been described. Males and females are almost affected in similar distribution. The phenomenon is frequently diagnosed incidentally in asymptomatic patients. However, the most common presenting symptom is abdominal pain. Physical examination is likely to be normal. It is a diagnosis of imaging, and ultrasound is an effective and feasible modality. LFTs may be affected, but most patients had normal blood tests. Medical treatment efficacy is not well-known, but cholecystectomy showed complete resolution in symptomatic patients.

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