Digestive and Liver Disease 51 (2019) 689–694

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Biliary stone disease in patients receiving somatostatin analogs for neuroendocrine neoplasms. A retrospective observational study

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ARTICLE INFO

Article history:
Received 20 July 2018
Received in revised form
10 September 2018
Accepted 12 September 2018
Available online 24 September 2018

Keywords:
Gallstones
Lanreotide
Neuroendocrine tumors
Octreotide

ABSTRACT

Background: Somatostatin analogs are the backbone of neuroendocrine neoplasms treatment. Biliary stone disease is a potentially severe adverse event of somatostatin analogs: an increased incidence has been reported in somatostatin analogs-treated acromegalic patients, but studies on patients with neuroendocrine neoplasms are lacking.
Aims: To evaluate biliary stone disease incidence and associated factors in a large series of patients treated with somatostatin analogs for neuroendocrine neoplasms.
Methods: A prospectively-collected database of patients with a diagnosis of neuroendocrine neoplasms of any grade and site, treated with somatostatin analogs at our Institution between 1995 and 2017, was retrospectively analyzed. Patients' demographics and disease characteristics were analyzed to evaluate the incidence and the factors related to biliary stone disease.
Results: Three-hundred patients were included; 101 (33.7%) patients underwent cholecystectomy before starting somatostatin analogs. Among 164 patients with gallbladder in situ and no history of stone disease, 60 (36.6%) developed gallstones after a mean of 36.7 months (range 1–239) from treatment start with a mean yearly incidence of 8.73%. Previous cholecystectomy was associated with a lower rate of development of gallstones ($p < 0.001$) or related complications ($p = 0.017$).
Conclusion: We observed a high incidence of biliary stone disease in patients treated with somatostatin analogs-treated for neuroendocrine neoplams. Previous cholecystectomy was the only factor associated with a lower occurrence of biliary stone disease.

1. Introduction

Biliary stone disease is a worldwide public health issue and the prevalence of gallstones is reported to be 15–20% in the Western countries [1]. Risk factors for gallstones are ethnicity (Western Caucasian, Hispanic and Native Americans), older age, female gender, pregnancy and post-partum period, obesity and rapid weight loss,

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https://doi.org/10.1016/j.dld.2018.09.013
1590-8658/

family history and genetics, cirrhosis, hemolysis, Crohn's disease, decreased physical activity, total parenteral nutrition.

Approximately, 0.7–2.5% of asymptomatic patients develop symptoms related to gallstones every year. The annual incidence of complications, mainly represented by acute cholecystitis, acute pancreatitis, obstructive jaundice, or cholangitis, is 0.1–0.3%. Once one of these conditions develops, the chance of having complications increases to approximately 30% per year.

The use of several classes of drugs, such as estrogens, oral contraceptives, clofibrate, ceftriaxone and somatostatin analogs, has been identified as a risk factor for biliary stones [1].

Somatostatin analogs (SSA) were developed to treat symptoms related to functioning neuroendocrine neoplasms (NENs) but it has been widely demonstrated that they have also an anti-proliferative activity [2–4]. Somatostatin analogs are usually well tolerated. The most frequent side effects are represented by injection-site discomfort or skin rash, blood glucose control alteration and gastrointestinal symptoms, in particular diarrhea, abdominal pain, nausea and vomiting, biliary stone disease [5,6]. Most adverse events are usually transitory and present with mild intensity; in fact, the prevalence of such effects progressively decreases during treatment. Therefore, drug discontinuations due to adverse events are rare.

Biliary stone disease is considered the most serious complication related to SSA treatment [5,7].

Several studies reported an increased gallstone incidence (up to 35%) in patients receiving SSA [8]; however, most of these studies have been conducted among patients affected by acromegaly [5–9].

Only few studies are specifically focused on this issue in retrospective analysis of NEN patients; the observed incidence of gallstone disease ranges from 52 to 63% [10,11].

In the CLARINET and PROMID trials, two phase III studies designed to evaluate the anti-proliferative effect of lanreotide and octreotide long-acting release (LAR) in NEN patients, the development of gallstones was observed as a drug-related adverse event in 10% and 14% of patients, respectively [3,4].

The European Association for the Study of the Liver (EASL) guidelines identifies SSA-treated patients as a high risk-group for developing gallstone disease [1]. However, current guidelines are inferred by small studies with low evidence, resulting in weak clinical recommendations on prophylactic cholecystectomy and ursodeoxycholic acid (UDCA) treatment.

Therefore, the aim of our study was to evaluate the incidence, clinical outcome and risk factors for biliary stone disease in a large population of NEN patients treated with SSA.

2. Material and methods

A retrospective analysis of a prospectively-collected database was performed. As part of European Neuroendocrine Tumors Society (ENETS) Centers of Excellence, the entire database including demographic and clinical information on all NEN patients is updated at every visit.

Study inclusion criteria were: histological diagnosis of NEN of any grade and site, treatment start with SSA at conventional or unconventional dose between 1995 and 2017, clinical follow-up at our Institution. Patients with known lithogenic diseases (such as chronic hemolytic anemia, cirrhosis, Crohn's disease) or with incomplete data were excluded.

The following demographic and clinical data were collected: age at the time of SSA treatment start, gender, primary tumor site, WHO classification, grade, functionality, presence of Multiple Endocrine Neoplasia Type 1 (MEN 1) syndrome, surgery of primary tumor or hepatic metastases, liver-directed treatment, type, dose and duration of treatment with SSA, history of stone disease and cholecystectomy, treatment with UDCA.

Any symptom related to the presence of biliary stones, such as biliary colic, acute cholecystitis, cholangitis, gallstone pancreatitis, odditis, gallbladder perforation, was classified as a biliary complication.

All patients or their legal representatives provided written informed consent for anonymous review of their data for research purpose. This retrospective study was approved by local Institution Review Board (Comitato Etico Indipendente, S.Orsola-Malpighi Hospital, Bologna) and was conducted in accordance with the principles of the Declaration of Helsinki (6th revision, 2008).

2.1. Statistical analysis

Continuous variables were reported as mean ± standard deviation or median and range on the basis of their distribution. Categorical variables were reported as number and frequency. The Mann–Whitney U test was used for comparison of continuous variables. Fisher's exact test or Pearson's chi square test were used for the comparison of categorical variables. The p value was considered statistically significant when <0.05. Statistical analysis was performed using a dedicated software (IBM-SPSS version 22; SPSS Inc., IL, USA).

3. Results

3.1. Baseline characteristics

Three-hundred NEN patients treated with SSA at our Institution were included in the analysis. Among patients potentially eligible for this analysis, 23 were excluded due to incomplete data (mainly concerning start or end of SSA treatment, incomplete pathology report, adequate follow up imaging for biliary stone evaluation) and 9 were excluded due to the presence of a lithogenic disease. Patients' baseline characteristics are described in Table 1.

One-hundred seventy patients (56.7%) were male; mean age at SSA start was 60.7 years (range 22–88). Primary tumor site was gastrointestinal tract in 166 (55.3%), pancreas in 95 (31.7%), lung in 19 (6.3%), unknown origin in 20 patients (6.7%). Among gastrointestinal NENs, there were 133 small bowel (44.3%), 23 gastric (7.7%) and 10 duodenal (3.3%) NENs. According to WHO 2010 classification, 294 (98%) were G1-2 NENs and 6 (2%) G3 NENs. In particular, there were 266 (88.7%) stage IIIB/IV patients, while the remaining 33 patients (11%) were stage I–IIIA (data not available in 1 patient, 0.3%). Sixty-four patients (21.3%) had a functioning tumor. In particular, 45 patients presented a carcinoid syndrome, 12 a Zollinger–Ellison syndrome, 3 insulinomas, 2 glucagonomas, 2 VIPomas. Nine patients (3%) had MEN1-associated NENs.

Among 215 (72%) patients who underwent surgery of primary tumor, 121 (56.4%) underwent small bowel resection, 50 (23.2%) distal pancreatectomy or tumor enucleo-resection, 20 (9.3%) duodeno-cephalo-pancreatectomy, 13 (6.0%) lung resection, 3 (1.4%) total gastrectomy and 8 (3.7%) other or not specified surgical procedures. Liver surgery was performed in 77 patients (25.7%), while 35 received liver-directed loco-regional treatments, such as transarterial embolization or chemoembolization or radiofrequency ablation (RF). Finally, 87 (29.0%) patients underwent prophylactic cholecystectomy.

Patients were treated with either octreotide LAR (no. 135, 45%), lanreotide (no. 107, 35.7%) or both, sequentially (no. 58, 19.3%). Conventional dose (octreotide LAR 30 mg or lanreotide 120 mg every 28 days) was administered at 287 patients (95.7%), while high-dose treatment (octreotide LAR 30 mg or lanreotide 120 mg

Table 1
Baseline characteristics of the study population.

Characteristic	Patients (No. 300)
Demographic	
Gender (male), no. (%)	170 (56.7%)
Mean age (range) at SSA start, yrs	60.7 (22–88)
Primary tumor site	
Small-bowel, no. (%)	133 (44.3%)
Stomach, no. (%)	23 (7.7%)
Duodenum, no. (%)	10 (3.3%)
Pancreas, no. (%)	95 (31.7%)
Lung, no. (%)	19 (6.3%)
Unknown, no. (%)	20 (6.7%)
WHO 2010 classification	
Well differentiated, no. (%)	294 (98.0%)
Poorly differentiated, no. (%)	6 (2.0%)
MEN 1 syndrome, no. (%)	9 (3.0%)
Functioning tumors, no. (%):	64 (21.3%)
Carcinoid syndrome, no.	45
Zollinger–Ellison syndrome, no.	12
Insulinoma, no.	3
Glucagonoma, no.	2
VIPoma, no.	2
Primary tumor surgery, no. (%)	215 (72%)
DCP, no.	20 (9.3%)
Distal pancreatectomy or enucleoresection, no.	50 (23.2%)
Small bowel resection, no. (%)	121 (56.4%)
Lung resection, no. (%)	13 (6.0%)
Total gastrectomy, no. (%)	3 (1.4%)
Other/not specified, no.	8 (3.7%)
Liver-directed procedures	
Surgery, no. (%)	77 (25.7%)
Loco-regional treatments, no. (%)	35 (11.7%)
SSA treatment characteristics	
Octreotide LAR, no. (%)	135 (45%)
Lanreotide, no. (%)	107 (35.7%)
Both, no. (%)	58 (19.3%)
Conventional doses, no. (%)	287 (95.7%)
High doses, no. (%)	13 (4.3%)
Mean duration of treatment (range), mo.	41.6 (1–263)
Previous cholecystectomy, no. (%)	101 (33.7%)
Prophylactic cholecystectomy, no. (%)	87 (29%)
Due to pre-existing gallstones, no.	14 (4.7%)
Known gallstones at SSA start, no. (%)	35 (11.7%)

Abbreviations: yrs: years; WHO: World Health Organization; MEN 1: Multiple Endocrine Neoplasia Type 1; DCP: duodeno-cephalo-pancreatectomy; SSA: somatostatin analogs; mo: months.

every 21 days) to 13 (4.3%). Mean treatment duration was 41.6 months (range 1–263).

Forty-nine (16.3%) patients had gallstones before the start of SSA; of them, 14 (4.7%) underwent cholecystectomy before starting SSA because of biliary symptoms due to the presence of gallstones. The remaining 35 (11.7%) patients had gallstones at the time of SSA treatment start. Three patients (1%) received UDCA before SSA start because of known gallstones.

3.2. Study results

Overall, 101/300 (33.7%) patients underwent cholecystectomy before the start of SSA: 87 during NET-related surgery and 14 for symptomatic biliary stone disease.

Of these 101, 3 (3%) developed common bile duct stones during SSA therapy; all 3 of them developed cholangitis and were treated accordingly.

Among the 199 patients (66.3%) with gallbladder *in situ* at SSA start, 35 patients (17.6%) had gallstones before SSA treatment, 60 (30.1%) developed stone disease during treatment, 104 (52.3%) did not develop gallstones at any time during the study period (Study flow chart — Fig. 1).

Among patients with gallbladder *in situ* and no history of stone disease before SSA start (no. 164), 60 (36.6%) developed gallbladder stones after a mean of 36.7 months (range 1–239) from SSA start with a mean yearly incidence of 8.73%.

Twenty-two patients with gallbladder *in situ* developed biliary complications, including biliary colic, acute cholecystitis, cholangitis, gallstone pancreatitis, odditis, gallbladder perforation; 5 of them, had a previous history of biliary stones, while 17 developed stones during SSA treatment. We observed a greater rate of complications in patients who developed stones during SSA treatment if compared to those with known gallstone disease before SSA start, although this was not statistically significant (28.3% vs. 14.3%; $p = 0.14$). Among these 22 patients developing complications, eighteen (81.8%) required cholecystectomy.

In the group of 199 patients with gallbladder *in situ*, none of the analyzed factors (gender, age, MEN1 syndrome, tumor site, functioning tumor, primary tumor surgical resection and type of surgery, hepatic surgery or liver-directed loco-regional ablative treatments, type and dose of SSA) were associated to the development of gallstones nor to biliary complications.

Among the entire study population (no. 300), previous cholecystectomy was the only factor associated with a lower occurrence of biliary stone disease ($p < 0.001$), while age, gender, MEN1 syndrome, site, functionality or resection (and type of surgery) of primary tumor, hepatic surgery or liver-directed loco-regional ablative treatments, type and dose of SSA were not.

Similarly, in the overall population, previous cholecystectomy was associated with a lower occurrence of biliary complications ($p = 0.017$), while the other above cited factors were not (Table 2).

4. Discussion

To our knowledge, this is one of the largest study focusing specifically on biliary stones development during SSA treatment in NEN patients, compared to those on acromegalic patients or to retrospective studies on small samples of NEN patients [5–11].

In our analysis, we observed that the only factor associated with a lower occurrence of biliary stone disease and related complications is prophylactic cholecystectomy.

The high incidence (36.6%) of gallstones and related complications in patients receiving SSA in our analysis is also higher than in general population [1] and in SSA registration studies (PROMID and CLARINET) [3,4]. On the opposite, the incidence reported in our study is slightly lower than that reported in other retrospective studies on NEN patients [10]. Studies on acromegalic patients treated with SSA, reports a higher incidence of biliary stone disease, but with very variable incidence rates. However, these data are not comparable to our results, in particular due to the fact that acromegaly is a risk factor for the development of gallstones *per se* [5,7,9].

The most commonly used SSA in NEN patients are octreotide LAR and lanreotide that are commonly used for the treatment of NENs of different origins, with both antiproliferative effect and for symptoms control.

In our series, SSA were also used for the treatment of 6 G3 NEN patients. SSA were used to achieve symptom-control in these patients (4 had a carcinoid syndrome and 2 a Zollinger–Ellison syndrome), since they expressed SSTR and had Ki67 20–25%.

SSA are usually well tolerated and side effects are usually of mild intensity and progressively decrease during treatment. One of the most severe side effects is represented by biliary stone disease.

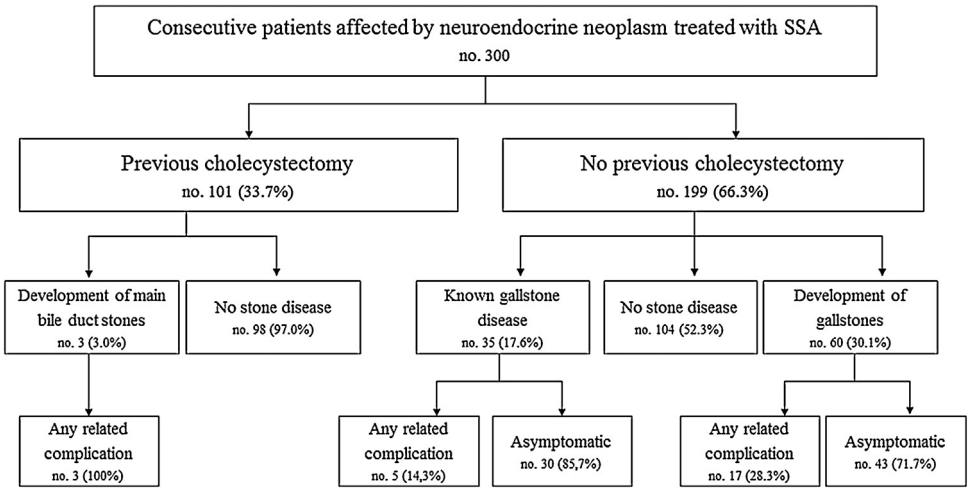

Fig. 1. Study flow chart.

Table 2
Association between patients' demographic and clinical characteristics and development of biliary stone disease (left column) and of stone-related complications (right column).

Characteristic	Development of stone disease			Development of stone-related complications		
	Yes	No	p*	Yes	No	p*
Gender						
Male, no.	35	135	0.841	16	154	0.440
Female, no.	28	102		9	121	
Primary tumor site						
Gastro-intestinal tract, no.	40	126	0.315	17	149	0.403
Pancreas, no.	14	81		7	88	
Lung, no.	5	14		0	19	
Unknown, no.	4	16		1	19	
MEN1 syndrome						
Present, no.	2	7	0.923	1	8	0.759
Absent, no.	61	230		24	267	
Functioning tumors						
Yes, no.	15	49	0.589	4	60	0.497
No, no.	48	188		21	215	
Primary tumor surgery						
Yes, no.	43	173	0.456	18	198	0.999
No, no.	20	64		7	77	
Primary tumor surgery type						
DCP, no.	2	18	0.178	2	18	0.778
Distal pancreatectomy or enucleoresection, no.	7	43		3	47	
Other, no.	34	111		13	132	
Hepatic surgery						
Yes, no.	11	66	0.093	3	74	0.102
No, no.	52	171		22	201	
Liver-directed loco-regional treatment						
Yes, no.	5	31	0.264	2	34	0.520
No, no.	58	206		23	241	
Previous cholecystectomy						
Yes, no.	**3**	**98**	**<0.001**	**3**	**98**	**0.017**
No, no.	60	139		23	177	
SSA type						
Octreotide LAR, no.	30	105	0.870	14	121	0.411
Lanreotide, no.	22	85		6	101	
Both, no.	11	47		5	53	
SSA dose						
Conventional dose, no.	60	227	0.851	24	263	0.932
High dose, no.	3	10		1	12	

Abbreviations: MEN 1: Multiple Endocrine Neoplasia Type 1; DCP: duodeno-cephalo-pancreatectomy; SSA: somatostatin analogs.
Statistically significant associations ($p < 0.05$) in bold.

* p value from the comparison between patients developing stone disease or related complications during SSA treatment and patient without any evidence of stone disease or complications.

The pathogenesis of gallstone disease is related to several mechanisms which impair gallbladder emptying and induce supersaturated bile formation [5,9,12,13].

In CLARINET study [4], cholelithiasis was reported in 10/101 (10%) patients who received lanreotide and 3/103 patients (3%) who received placebo. In particular, among the patients with cholelithiasis, 4 patients had new gallbladder sludge (3/101 (3%) in the lanreotide group and 1/103 (1%) (in the placebo group) and 10 patients had new lithiasis (7/101 (7%) and 3/103 (3%) patients, respectively).

In the PROMID study [3], 5/42 (12%) patients developed gallstones in Octretide LAR arm and 1/43 (2%) patient in the placebo arm.

We report a high incidence of stone disease in our series (36.6%), especially if compared to historical controls and general population data (15–20% [1]); this is consistent with what was observed in CLARINET and PROMID trials. Data from these two studies are remarkable considering the relatively short exposure to SSA and follow up period (14 months in PROMID and 24 months in the CLARINET study) and the high rate of new onset biliary events. Nevertheless, the absolute number of observed biliary adverse events and the incidence in these particular populations were lower compared to our results, probably due to a longer median follow up in our study and to the fact that the population in our series is probably less selected than that enrolled in CLARINET and PROMID trials.

In our study, however, we did not find any correlation between treatment duration and higher risk of biliary stone disease, but the median time of SSA therapy was much longer (41.6 months).

Very few retrospective studies on a population comparable to ours are present in literature and they report a higher prevalence of gallstone disease, ranging from 52 to 63% [10,11].

In Norlen's series a high incidence of stone disease was reported (63%) [10]. This could possibly be because Norlen's series comprises only patients affected by midgut carcinoid, with a high proportion of ileal surgery for primary resection, and it is reported how patients who underwent ileal resection have an increased risk of stone disease due to an altered metabolism of biliary acids [14,15]. On the contrary, in our series, we considered patients affected not only by midgut carcinoid, but also pancreatic, gastro-duodenal, thoracic and unknown origin NENs. However, site of primary NEN did not result related to an increased risk of developing stone disease or related complications.

When considering gallstone-related complications requiring treatment, in the above cited series by Norlen, the 5-year cumulative risk to undergo cholecystectomy or drainage gallstone complications was 2.3% for untreated patients and 19% for SSA-treated patients [10]. Similarly, in our series, the rate of occurrence of biliary stone disease complication, although not negligible (14.3% and 28.3% in patients with and without history of biliary stone disease, respectively), seldom required intervention or specific treatment. In fact, 18 (9.0%) among the 199 patients with gallbladder *in situ* receiving SSA had to undergo cholecystectomy due to stone disease or related complications. In our series, patients not treated with SSA were not included, but when comparing the data with general population, a clear trend to an increased number of cholecystectomy indications in SSA-treated patients can be observed. In fact, in Western population affected by asymptomatic gallstones, approximately the 0.7–2.5% of patients develop symptoms every year and the annual incidence of related complications is 0.1–0.3% [1,16].

In our series, prophylactic cholecystectomy was the only factor associated with a lower occurrence of biliary stone disease and related complications.

Concurrent cholecystectomy at time of resection of midgut NEN is not associated with significantly higher morbidity or mortality [17,18]. On the opposite, cholecystectomy performed after primary resection may present more complications because of postoperative adhesions; moreover, in patients with midgut carcinoids, the tendency of abdomen fibrosis formation needs to be taken into account [10].

Current ENETS guidelines suggest that prophylactic cholecystectomy should be considered in cases of planned surgery for primary tumor or metastases, or abdominal surgery unrelated to NEN [2]. However, this indication is supported by few, relatively small case series addressing the matter of the indications of prophylactic cholecystectomy in NEN patients treated with SSA [10,11,17].

Previous literature reports observed an increased risk of gallbladder related complications (perforation, cholecystitis and hemocholecyst) in patients undergoing liver-directed treatment (RF ablation or trans-arterial embolization or chemo-embolization) [19]; on the other hand, other reports have indicated that RF ablation is a safe treatment for liver metastases near the gallbladder [20,21]. In our series, no correlation between biliary disease and liver-directed procedures or hepatic surgery has been found.

Shortcomings of our study mainly derive from its retrospective nature. In particular, some confounding factors with a potential or known role in gallstone disease, such as body mass index, were not retrievable. Since this is a retrospective study, we had no control on biliary stone-directed work up, but we revised available clinical reports and imaging studies. In our Center, patients treated with SSA are usually assessed every 4–6 months by means of thorax and abdomen CT scan. If symptoms of biliary stone disease were reported, patients were referred for abdomen US. This accounts for two contrasting limitations: on the one hand, there is a risk to underestimate the presence of biliary stone disease since CT scan has a lower sensitivity than US; on the other hand, we could have overestimated the incidence in asymptomatic patients by performing radiological exams for other reasons (*i.e.* disease evaluation of underlying NET).

However, our findings on the percentage of patients developing stone disease are consistent, if not inferior, with previous studies on patients treated with SSA for acromegaly [5,22–24].

According to ENETS guidelines [2], patient followed at our center did not receive UDCA prophylaxis. Therefore, we could not draw any conclusion about the use of UDCA in biliary stone prophylaxis from our study.

In conclusion, we analyzed biliary stone disease in a large series of patients treated with SSA for NENs and observed that the only factor associated with a lower occurrence of biliary stone disease and related complications was prophylactic cholecystectomy. Nevertheless, despite the high occurrence rate, only few patients developed symptoms requiring intervention or specific treatment. Thus, the indication to this procedure is still under great debate.

Prospective studies are needed to understand more clearly the role of prophylactic cholecystectomy and of UDCA therapy and to stratify the patients that could benefit from these treatments. Considering the progressively longer survival of these patients due to the improvement of available treatments and therefore the prolonged exposure to SSA, these issues become of great interest and clinical impact, especially because current evidence is scarce and mostly inferred by studies focusing on patients treated with SSA for acromegaly.

Conflict of interest

Davide Campana has received grants and speaker honoraria from Ipsen and Novartis. The other authors declare that they have no conflict of interest.

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