

Neuroendocrine tumors' patients treated with somatostatin analogue could complicate with emergency cholecystectomy.



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Neuroendocrine tumors' patients treated with somatostatin analogue could complicate with emergency cholecystectomy.

BACKGROUND: *Gastro-entero-pancreatic neuroendocrine tumors are gradually seeing their incidence increase, probably due to their low-rate mortality.*

Surgery and subsequent medical therapy through octeotride and somatostatin analogues is the recommended approach for hypersecretive hormonal forms, showing an effective control of symptoms and improved survival outcomes.

AIM: *The present study aims to evaluate the occurrence of gallbladder lithiasis, and its complications, in patients underwent upfront surgery for neuroendocrine tumors and subsequent long-term administration of somatostatin analogues.*

MATERIAL OF STUDY: *We included four adults affected by neuroendocrine (gastric, appendiceal and ileal) tumors and without previous evidence of gallbladder stones, who needed an emergency cholecystectomy after long-term somatostatin treatment.*

RESULTS: *The patients showed complicated conditions sustained by cholelithiasis, such as acute cholecystitis, gangrenous cholecystitis, or intestinal occlusion, which required emergency surgery.*

DISCUSSIONS: *Somatostatin analogues may influence the cascade of enzymes that guarantee the gallbladder motility, and consequently cause the precipitation of cholesterol and calcium bilirubinate crystals. Therefore, higher and sustained levels of somatostatin may result in higher rates of gallstone development.*

CONCLUSIONS: *The prophylactic cholecystectomy, during upfront surgery for neuroendocrine tumors, might prevent an emergency cholecystectomy for gallstones complications.*

KEY WORDS: Gallbladder stones, Neuroendocrine tumors, Somatostatin analogues

Introduction

Neuroendocrine tumors (NETs) are steadily increasing worldwide. They may affect any organ, although the most

frequent arise from the gastro-entero-pancreatic tract (GEP-NETs) and lungs, in 65% and 25% of cases respectively ¹.

In recent years, NETs are gaining broader interest due to their low-rate mortality ²⁻⁴, especially when compared with more aggressive neuroendocrine carcinomas, and novel technologies revealed new molecular and histopathological aspects ⁵.

Interestingly, low grade neoplasms and nonfunctioning forms are usually occasional discoveries in common radiological investigations or during surgical procedures.

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While more advanced tumors, metastatic diseases and hypersecretive hormonal forms need to be treated with a surgical approach, including exeresis, liver surgery or thermal ablation ⁶, patients with nonfunctioning, low grade, incidentally discovered GEP-NETs might benefit from a nonsurgical management consisting of active surveillance ⁷.

In 1989, Food and Drug Administration (FDA) approved octreotide as the first drug for the control of symptoms of carcinoid syndrome and VIPoma. Both the PROMID and the CLARINET randomized control trials highlighted an improved progression-free survival upon somatostatin analogues treatment (SSAs), compared to placebo ^{8,9}. Nowadays, SSAs, such as octreotide and lanreotide, remain the first-line therapy for early stage functional and non-functional NETs ¹⁰. Research on this topic has described how long-term treatments with somatostatin-like drugs in patients with neuroendocrine tumors could decrease gallbladder motility and raise the risk of gallstone (GS) occurrence¹¹. According to recent studies the rate ranges from 10% to 63% ¹².

The aims of the present study are to evaluate the occurrence of GS in patients underwent upfront surgery for NETs followed by SSAs long-term administration, in order to assess the advisability of a prophylactic cholecystectomy.

Material and Method

STUDY DESIGN

This study is a monocentric retrospective case series of patients, affected by hypersecretive hormonal forms GEP-NETs, underwent interval emergency cholecystectomy after receiving SSAs treatment, admitted to Azienda Ospedaliera-Universitaria Senese, in Siena (Italy), between January 2012 and January 2022. All patients were adults, without evidence of GS before the GEP-NETs diagnosis, then described in CT scans after surgical and long-term treatment with octreotide or lanreotide.

Demographic and clinico-pathologic features were described. PROCESS Guidelines have been adopted and reported in Supplementary Material ¹³. The study was conducted in accordance with the Declaration of Helsinki (1996).

STATISTICAL ANALYSIS

For normally distributed continuous variables, the data are expressed as the mean and SD; for non-normally distributed variables, the data are expressed as the median (minimal value, maximal value). Categorical variables are expressed as counts and percentages. SPSS 25.0 software was used for all statistical analyses.

Results

A total of 4 patients with complicated GS undergoing emergency surgery have been included in our report (Table I).

The first patient, a 49-year-old male, underwent emergency operation for intestinal occlusion due to small bowel adhesion to porcelain gallbladder. The porcelain gallbladder contained large, faceted cholesterol GS, one of which was impacted in the organ neck. The patient had appendectomy and ileal resection for NET of the appendix 13 years before. Somatostatin was added as a part of the therapeutic regimen during the last seven years. The other 2 patients, both males, aged 53 and 55, with previous unknown GS, had gangrenous cholecystitis, with concomitant liver abscess and peritonitis, within 2 and 3 days after the onset of symptoms. Both required wedge liver resection of IV and V segment. Conspicuous lymphocytic infiltration was found in the surrounding liver tissue. The GS were multiple: faceted mixed in the former, spheroidal cholesterol in the latter. The former patient had a subtotal gastrectomy for perforated ulcer (NET with lymph node, but not hepatic metastasis) 5 years before; the latter had received a previous diagnosis of intestinal NET with liver metas-

TABLE I: Demographic and clinico-pathologic features of patients.

	M/F	Age (years)	BMI (Kg/m ²)	GEP-NETs Location	Drugs administration	Cholecystectomy time interval	Histological examination after cholecystectomy
Case 1	M	49	24.8	appendiceal	Somatostatin (7 years)	13 years	Porcelain gallbladder with intestinal occlusion
Case 2	M	53	28.3	gastric	analogue	5 years	Gangrenous cholecystitis
Case 3	M	55	26.9	ileal	analogue	7 years	Gangrenous cholecystitis
Case 4	F	71	22.7	ileal	analogue	2 years	Cholecystitis complicated by perforation

BMI: Body Mass Index, GEP-NETs: Gastro-Entero-Pancreatic NeuroEndocrine Tumors.

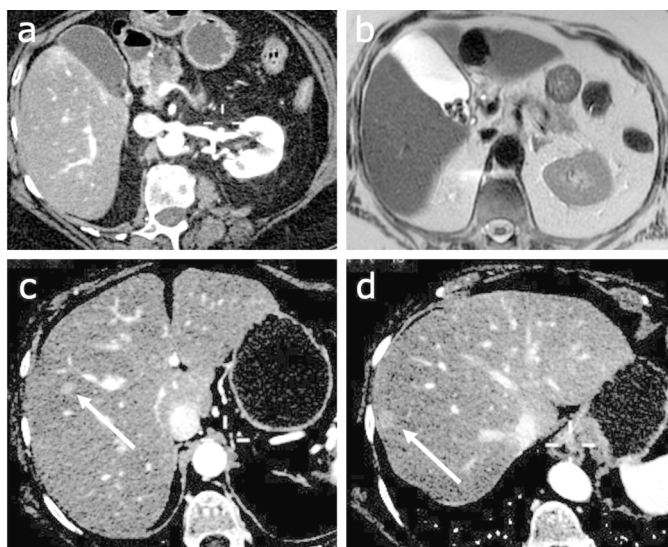


Fig. 1

tases 7 years before (Fig. 1). Both had undergone a long-term treatment with somatostatin-like drugs, as a part of therapeutic regimen. The last patient was a 71-year-old female, underwent surgery for intestinal NET, with secondary liver metastatic lesion, treated with somatostatin analogue. A CT-scan and MR control showed a cholesterol lithiasis typical of the gallbladder. Gallstones were transparent to the CT scan and more visible to the MR (Fig. 2). Six months later, the patient arrived at the emergency department with a severe cholecystitis complicated by perforation and needed an emergency cholecystectomy.

Discussion and Comments

The Surveillance, Epidemiology and End Results (SEER) Program of the US National Cancer Institute has detected a gradual increase in the incidence of NET, with GEP-NET accounting for 61% of all tumors, and the rectum and small bowel the most common sites¹⁴. They may present in benign or malignant form and show variable metastatic potential and grade of differentiation⁶. To date, the cornerstone of metastatic NETs' therapy is based on SSAs, even though several researchers propose alternative molecules with multiple lines of therapy, such as liver-directed therapy, cytotoxic chemotherapy or interferon^{15,16}.

Somatostatin analogues have demonstrated a favourable safety profile and an effective control of symptoms associated with hormone hypersecretion^{17,18}, even with a limited antiproliferative effect¹⁹. On the other hand, Caplin et al. highlighted the antiproliferative effect of lanreotide, showing a prolonged progression-free survival among patients with advanced, grade 1 (Ki-67 < 3%) or grade 2 (Ki-67 3-20%) GEP-NETs treated with SSAs⁹.

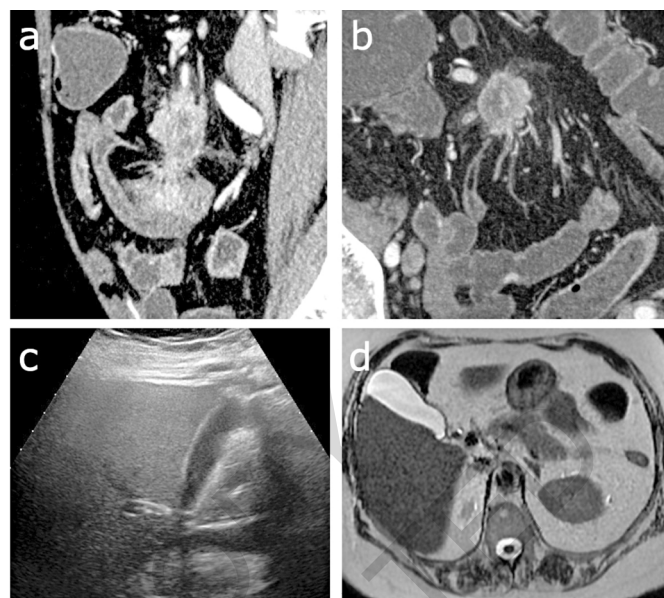


Fig. 2

Interestingly, about 10% of patients treated with lanreotide showed the occurrence of GS or gallbladder sludge. Moreover, somatostatin, together with analogues, has been described to stabilise the growth of neuroendocrine tumour metastases, probably by arresting neo-angiogenesis²⁰.

However, SSAs are known to influence the cascade of enzymes that ensure the motility of the biliary tree and gallbladder. Somatostatin is considered a secretory pan-inhibitor, suppressing many different hormones, such as cholecystokinin and secretin²¹. The cholecystokinin allows the gallbladder contraction, pushing bile through the cystic duct and common bile duct. The secretin stimulates biliary and pancreatic ductular cells to secrete bicarbonate and water, in response to the presence of acid in the duodenum and promotes the release of bile into the intestinal tract²². Therefore, higher and sustained levels of somatostatin may affect the lack of gallbladder contractility, hepatic bile secretion and motility of the sphincter of Oddi, resulting in an altered composition of bile and the precipitation of cholesterol and calcium bilirubinate crystals, which ultimately form GS^{23,24}. Similarly, obesity has been associated with high incidence in the occurrence of GS²⁵. Obese patients have a marked hyposensitivity of the wall receptors to cholecystokinin, an hyperincretion of somatostatin and, therefore, invariably form GS²⁶. Once the GS have formed, they can move inside the gallbladder up to close the cystic duct and therefore trigger an inflammatory cascade, with a quick induction of acute cholecystitis and a rapid progression to gangrene.

Despite in our series no obese patients were registered, all subjects complicated with a gangrenous or perforated gallbladder that forced emergency surgeries, prolonged

hospitalization, and increased the risk of mortality. In other series, patients suffering from acromegaly under treatment with somatostatin were also an excellent field of study²⁷. Several Authors indicate that octreotide injections impair postprandial gallbladder contraction for at least four hours, and it is partly restored only eight hours after injection²⁸. Moreover, Moschetta analysed the effects of a long-acting octeotide formulation in acromegalic patients: the occurrence of GS was observed in six out of seven patients within 8 months of therapy, probably due to the profound suppression of cholecystokinin release and gallbladder emptying²⁹. Interestingly, the SSAs withdrawal is likewise associated with increased risk of symptomatic GS and acute biliary problems³⁰. A close and careful monitoring of gallbladder ultrasound is therefore recommended in patients receiving SSA for medical treatment of acromegaly³¹.

Our patients were submitted to pre-operative imaging examination, before upfront surgery for GEP-NETs, without evidence of cholelithiasis. After hospital discharge, a long-term therapy with somatostatin or analogue was administered⁶. Nonetheless, they were admitted to the emergency department for delayed gallstones complications and underwent emergency/urgent surgery. Besides the most frequent complications of cholelithiasis, another rare but insidious evolution is the porcelain gallbladder. This condition is usually associated with GS occupancy, and more likely represents the pathologic evolution of a cystic duct obstruction rather than the result of a dystrophic calcification. The cancerization risk of a porcelain gallbladder emphasises even more the need for a closer clinical surveillance and an elective prophylactic cholecystectomy³².

Additionally, surgery for NET is mostly conducted with minimally-invasive approach, and prophylactic cholecystectomy does not lengthen the average postoperative hospital stay and limits the risk of emergency intervention for GS complications³³⁻³⁵.

Conclusions

The introduction of SSAs in most recent treatment guidelines led to increased survival outcomes, as well as increased risk of gallbladder lithiasis and related complications, between NET patients. "Everything becomes urgent if you wait long enough" (Danny Cox). Therefore, a prophylactic cholecystectomy before starting medical therapy could be recommended.

Riassunto

Casistiche recenti hanno registrato un progressivo aumento del numero di tumori neuroendocrini. L'aumentata incidenza di tali tumori sarebbe associata da un lato al ridotto tasso di mortalità, dall'altro alla migliore accu-

ratezza diagnostica delle attuali metodiche strumentali. Ciò ha determinato un crescente interesse da parte del chirurgo generale, e la necessità di discutere l'approccio terapeutico più opportuno a livello multi-specialistico. I tumori neuroendocrini di alto grado, con maggiore potenziale metastatico o in forma ipersecernente meritano un approccio chirurgico di prima istanza, e successiva terapia medica con somatostatina e suoi analoghi (octeotide e lanreotide). Diversi trial hanno dimostrato come la somministrazione di analoghi della somatostatina determinerebbero un netto aumento della sopravvivenza libera da malattia. Tuttavia, un trattamento a lungo termine è stato associato ad una maggior prevalenza di litiasi biliare. Il meccanismo fisiopatologico sembrerebbe ricollegato all'effetto della somatostatina su contrattilità della cistifellea, secrezione biliare e motilità dello sfintere di Oddi, i quali, a loro volta, determinerebbero una alterazione della composizione della bile e la precipitazione dei cristalli di colesterolo e di bilirubinato di calcio.

Il nostro studio si è proposto di analizzare l'incidenza delle complicanze della litiasi biliare in pazienti sottoposti a intervento chirurgico per tumore neuroendocrino e successiva terapia a lungo termine con analoghi della somatostatina.

Complessivamente, quattro pazienti, già noti per aver eseguito l'asportazione di un tumore neuroendocrino del tratto gastro-intestinale presso la nostra Unità, hanno acceduto in Pronto Soccorso dell'Azienda Ospedaliero-Universitaria Senese, con quadro infiammatorio sostenuto da colica biliare, quali colecistite acuta, gangrenosa e occlusione intestinale in colecisti a porcellana. Ciascun paziente ha necessitato di un intervento chirurgico di colecistectomia in regime d'urgenza.

La colecistectomia profilattica eseguita durante la chirurgia del tumore neuroendocrino primitivo e/o prima di iniziare la terapia medica, avrebbe evitato una lunga ospedalizzazione, un aumentato rischio di morbilità e mortalità, e, in ultima istanza, uno scadimento della qualità della vita.

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