Clinical case

Hypercalcitonemia revealing a somatostatinoma

Hypercalcitoninémie révélatrice d’un somatostatinome

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Résumé

Les somatostatinomes sont des tumeurs très rares, développées aux dépens de cellules endocrines duodénales ou pancréatiques. En général bien différenciées, elles ont un fort potentiel de malignité et sont responsables d’une sécrétion tumorale de somatostatine. Les somatostatinomes co-secrétant la calcitonine et la somatostatine sont exceptionnels et moins de 20 cas ont été rapportés dans la littérature. Nous présentons l’observation d’une patiente de 57 ans adressée pour amaigrissement, diarrhée et déséquilibre d’un diabète connu. Une élévation franche de la calcitoninémie est mise en évidence, associée à la découverte de lésions hépatiques hypervasculaires d’allure secondaire. Les investigations font suspecter une hypercalcitoninémie d’origine extrathyroïdienne et conduisent au diagnostic de somatostatinome métastatique sécrétant à la fois de la somatostatine et de la calcitonine. Le dosage de la calcitonine pourrait compléter le bilan d’une tumeur endocrine de la région duodéno-pancréatique et constituer un marqueur biologique de diagnostic et de suivi.

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Mots clés : Calcitonine ; Somatostatinome ; Diabète

Abstract

Somatostatinoma are rare well-differentiated endocrine tumors with malignant behavior arising from the pancreas and duodenum. They are defined by somatostatin positive immunostaining of the majority of tumor cells. The main clinical features are diabetes, diarrhea and biliary lithiasis related to somatostatin production. Somatostatinoma secreting both calcitonin and somatostatin may be unrecognized as a small number of such observations have been published. We report the case of a 57- year-old woman referred for weight loss, diarrhea and worsening diabetes. Computer tomography scan revealed multiple hypervascular liver lesions suggestive of metastases. High plasma calcitonin level was evidenced, with normal chromogranin-A value, and high plasma somatostatin results lately communicated. Calcitonin secretion of extra-thyroidal origin was suspected leading to the identification of a pancreatic mass by further multiphase CT. The patient underwent left pancreatectomy with surgical hepatic resection. Histological and immunostaining studies confirmed definitive diagnosis of somatostatinoma secreting both somatostatin and calcitonin. Plasma calcitonin should be measured in the assessment of duodeno-pancreatic endocrine neoplasm. Calcitonin determination is available, more reproducible than other specific pancreatic endocrine markers and could be effective for diagnosis and follow-up of such foregut-derived endocrine neoplasia.

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1. Introduction

Neuroendocrine tumors (NETs) of the duodenum and pancreas account for 1–2% of pancreatic neoplasms. Their prevalence and incidence are low, a concern for approximately 1/100,000 inhabitants [1]. Most of them occur sporadically,
though some may involve genetic predisposition to their development. Tumor stage at diagnosis and histopathological differentiation are the two main prognostic factors [2]. Tumor differentiation, location and spread also determine the functional characteristics, the clinical features and disease revelation. Thus, in 15–35% of cases, endocrine tumors of the pancreas may not be functional, being discovered incidentally, or diagnosed at late stage with symptoms due to tumor burden. Conversely, functional pancreatic endocrine tumors (65–85% of cases) can cause specific clinical manifestations related to excessive hormone production (gastrin, insulin, glucagon, vasopeptide, somatostatin, serotonin, ACTH, GHRH) [1,2].

Among the group of functional duodeno-pancreatic endocrine tumors, somatostatinoma remains very rare, with an approximate incidence of one new case per year per 40 million inhabitants. This tumor is basically defined by the predominant production of somatostatin; however, as most foregut-derived-NETs, it can also secrete other varieties of hormones and neuropeptides. It commonly develops in the pancreas and the duodenum and may occur in the setting of Recklinghausen disease [3]. The characteristic somatostatinoma secretory syndrome includes steatorrhea, diabetes mellitus and biliary lithiasis, though clinical presentation may vary. We report on the case of a female patient with a metastatic pancreatic endocrine tumor secreting both somatostatin and calcitonin, which was firstly recognized on liver disease and calcitonin elevation.

### 2. Clinical case

A 57-year-old diabetic woman was admitted for glycemic dysregulation (glycosylated hemoglobin increased up to 10%). Type 2 diabetes mellitus had been discovered two years earlier in an overweight woman (BMI = 33 kg/m²), and had been well controlled with metformin and glibenclamide, until recent months.

On examination, an alteration of the patient’s general health was evident; she presented asthenia, rapid weight loss of 10 kg in 4 months, and a polyuro-polydipsic syndrome. The patient complained of worsening diarrhea, previously attributed to adverse effects of biguanides. Insulin was started, restoring glycemic control but without improvement in the digestive symptoms.

Routine biochemistry was normal. Abdominal ultrasonography and a thoraco-abdominal contrast-enhanced CT scan showed hepatic hypervascular nodules inaccessible to biopsy and did not reveal any apparent abdominal mass. Regarding endocrine tumor markers, all were within normal limits excepted calcitonin, which was increased to 874 pg/ml (N < 3) (serum chromogranin-A = 27 ng/ml [N < 120], ACE = 2 μg/l [N < 10], plasma serotonin and 5-hydroxy-indolacetic urinary acid levels in the normal range).

Cervical ultrasonography did not identify either thyroid nodules or lymph nodes ruling out medullary thyroid carcinoma. Accordingly, the rise in calcitonin level on pentagastrin IV stimulation was modest, peaking to 980 pg/ml after 5 min. Scintigraphy with ¹¹¹In-octreotide (OctreoScan™) demonstrated a single moderate uptake in a mediastinal lymphadenopathy.

A careful study of abdominal organs was again performed on multiphasic CT, with spiral images obtained during the hepatic arterial phase, the portal venous phase and at equilibrium. This time, the dynamic sequences revealed a large hypervascular mass in the pancreatic tail during the early arterial phase, measuring 6 × 4 cm, not delimited from the normal pancreatic parenchyma on the first imaging studies (Fig. 1), and previously diagnosed liver metastases.

The following measurements of pancreatic hormones were normal: gastrin, insulin, C-peptide, glucagon, vasopeptide, pancreatic polypeptide and hormone α subunit. Plasma somatostatin determination, received a few months later, was > 125 UI/l (N < 20).

Due to the distal localization of the tumor, laparoscopic surgery was possible; combining splenopancreatic caudal resection, removal of accessible liver nodules, and cholecystectomy to treat lithiasic cholecystitis discovered intraoperatively.

On histological examination, the pancreatic tumor was 4.4 cm long; the five resected liver nodules were all metastatic and chronic cholecystitis was confirmed. A well-differentiated NET of the pancreas was described according to the 2004 WHO/ENETS grading classification, exhibiting 1 mitosis / 10 HPF and a Ki67 proliferative index of 5%. A strong expression of chromogranin-A and somatostatin was detected by immunohistochemistry staining; there was also an intense immunoreactivity for calcitonin expressed by 70% of the tumor cells (Figs. 2–5).

Within weeks following the intervention, there was a general improvement with disappearance of the diarrhea. Better glycemic balance was achieved under oral treatment. One month after surgery, calcitonin and somatostatin measures decreased to 358 pg/ml and 51 UI/l respectively, declining by more than 50% from preoperative levels. Given the residual hepatic disease, and the occurrence of hypercalcemia due to tumoral PTHrp secretion, somatostatin long-acting analogues were introduced.
to maximize secretory control and slow tumor progression. Six months after surgery, reascension of calcitonin to 1200 pg/ml was observed without any functional signs. CT scan and 18FDG-PET showed tumor progression with 18FDG uptake of known remaining bilobar liver lesions, leading to the indication of hepatic chemo-embolization.

3. Discussion of diagnosis

Endocrine tumors of pancreas are difficult to diagnose, with the exception of insulinoma and gastrinoma harboring suggestive clinical criteria. The sensitivity of standard imaging is low when no characteristic features can help clinicians to focus search. Even spiral contrast CT scan can fail to recognize small pancreatic NETs, or to assess adequately a large tumor appearing almost isodense to the pancreas. As illustrated in this report, multiphase CT enables more accurate characterization and location of pancreatic NETs, especially when using the early plus late arterial phase and the portal-venous time [4]. Somatostatin receptor scintigraphy dedicated to the imaging of NETs expressing somatostatin receptors 2 and 5 may be helpful for localizing gastrinoma (Se: 75–100%), but is disappointing for detecting insulinoma (Se: 50–60%). Its usefulness has been poorly studied in somatostatinoma [5–7]. New generation radiotracers, like DOTA-Tyr(3)-octreotide or DOTA-lanreotide, seem to be more accurate as diagnostic tools [8].

Analyzing the secretory profile of an endocrine tumor may also help to identify the originating site [9]. Well-differentiated pancreatic endocrine tumors arise from a wide range of endocrine cells (α, β, delta...) and therefore have the capacity
to synthesize numerous peptides and hormones. NETs are considered as non-functional whenever biological screening fails to show evidence of significant hormone production or shows that produced peptides have no biological activity, for example, in case of chromogranin-A single secreting tumors. By contrast, functional endocrine tumors (like gastrinoma, insulinoma, vipoma, glucagonoma...) fulfil two conditions: first secreting bioactive peptides, then producing them in sufficient quantity to determine clinical consequences. Interestingly, effects of excessive somatostatin release can lead to steatorrhea by inhibition of pancreatic enzymes, biliary tract lithiasis as gallbladder contractions are weakened, and diabetes if inhibition of insulin is predominant over glucagon.

Calcitonin is a polypeptidic hormone mainly secreted by thyroid parafollicular cells (C-cells). Its measurement, both sensitive and specific, has diagnostic and prognostic value in medullary thyroid cancer. Other circumstances for acute or chronic calcitonin elevation include septic states (procalcitonin), renal failure, reactive C-cell hyperplasia and non-thyroid endocrine tumors mostly of foregut-derived origin [10]. High elevation of calcitonin could mislead to the assumption of medullary thyroid carcinoma, in particular if calcitonin is the only measured hormone [11,12]. A major calcitonin peak within minutes after pentagastrin testing is predictive of medullary thyroid carcinoma, whereas low stimulation is seen in hypercalcitoninemia of other causes, like in our report [13]. Calcitonin measurement has been recommended for the biological work-up of foregut-derived (bronchial, gastric, duodenal, pancreatic) NETs [9,14]. However, few observations of pancreatic NETs secreting calcitonin have been reported. Pancreatic NETs can secrete multiple peptides resulting in co-production of calcitonin and somatostatin [15–18], or demonstrating a pluri-hormonal secretory profile with elevated intestinal vasopeptide [19–21], increased insulin, proinsulin, glucagon, somatostatin, gastrin, pancreatic polypeptide, serotonin, ACTH... [22]. Routine measurement of calcitonin in patients with NETs should be offered thereby, at least once, to assess best biologic tumor markers for follow-up. As emphasized in the study of Fleury and Flejou, who performed systematic calcitonin screening in NETs, an increase of calcitonin was noted in 6/66 patients (9%), associated in half of cases with elevation of somatostatin [23].

4. Management and treatment

Somatostatinoma has malignant behavior, with inaugural lymph node involvement and/or synchronous distant metastases found in 66–88% of patients at the time of diagnosis [24]. According to the meta-analysis by Soga, patients with pancreatic somatostatinoma were more symptomatic with plurihormonal secretion and larger lesions at diagnosis. As expected, duodenal somatostatinoma were associated with neurofibromatosis; and showed more frequently psammoma bodies on histological examination [25]. Mixed tumors may also coexist, composed of both endocrine and glandular components [26]. A prognostic score (G1 to G3), taking into account the number of mitosis and index of cell proliferation, was proposed by expert pathologists of the European Neuroendocrine Tumor Society. Grade 3 defined by mitotic count > 20 (10HPF) and Ki-67 index > 20% might be associated with reduced secretion of chromogranin-A [27]. In our case, prognostic score was G1-G2. Though immunoreactivity for chromogranin-A was strongly evidenced, serum chromogranin-A was normal at the stage of metastatic diffusion.

Surgery is still the most effective treatment of somatostatinoma, aiming at complete excision of the primitive tumor, lymph node dissection and surgical removal of resectable metastases [28]. In the field of medical treatment of NETs patients with liver metastasis, current strategies are interferon-alpha therapy, long-acting somatostatin analogues [29], percutaneous radio-frequency destruction, embolization of hypervascular lesions, peptide-receptor radionuclide therapy and systemic chemotherapy [30,31]. Sunitinib oral anti-angiogenic therapy, licensed for kidney cancer and GIST, had also demonstrated activity against pancreatic NETs [32].

Somatostatin analogues treatment was paradoxically proposed to our patient while presenting Octreoscan™ negative liver metastases of her resected somatostatin secreting tumor. Positive Octreoscan™ may not be a prerequisite in the choice of directing patients to somatostatin analogues treatment as some studies have shown that patients with initial negative scintigraphy findings can unexpectedly respond to therapy [33]. Moreover, some limited data suggest that somatostatin analogues have a small antitumor effect [29]. On follow-up, the patient developed symptomatic hypercalcemia due to neoplastic PTHrp release in the context of progressive disease. Somatostatin treatment was continued to alleviate hypercalcemia in association with biphosphonate therapy. Somatostatinoma syndrome did not worsen under long-acting somatostatin analogues.

Assessment of tumor progression in patients with well-differentiated endocrine tumors that may have an indolent course or develop slow growing metastases is sometimes challenging. Sensitive and specific biological markers therefore can play a critical role in the prediction of tumor progression. Chromogranin-A seems clinically useful with sensitivity ranges from 57 to 69% and specificity ranges from 68% to 100% in functional and non-functional foregut NETs [34]. However, its real effectiveness has been recently questioned because of high percentage of false positive results [35]. Measurement of plasma somatostatin, although specific for our patient’s follow-up, is expensive and not routinely available. By contrast, calcitonin testing, easily and widely available, may be cost-effective particularly when chromogranin-A is useless. Plasma calcitonin concentration is proven to be related to tumor burden in medullary thyroid cancer, both at diagnosis and at follow-up, incrementing proportionally with disease evolution. A part from some first data given by one study [34], no large-scale prospective work has yet been undertaken to assess whether calcitonin levels reflect accurately tumor burden of calcitonin secreting NETs, in consideration of tumor differentiation and tumor topography. In the present case-report, calcitonin measurement was decisive for the diagnosis and the therapeutic strategy. The correct diagnosis was reached because of the elevated calcitonin, which later varied in parallel with the evolution of the disease.
5. Conclusion

Endocrine malignant tumors can produce many peptides, implying a choice for available, reproducible and efficient biological markers for oncologic follow-up. In clinical practice, calcitonin measurement should be included in the work-up of foregut-derived NETs, as illustrated here. Information on the exact prevalence of calcitonin secreting NETs is still limited. Whether this marker is indicative of tumor burden and has prognostic value in extra-thyroidal NETs also needs to be clarified.

Conflict of interest

None.

References