Somatostatinoma: Beyond neurofibromatosis type 1 (Review)

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Abstract. Somatostatinoma is a tumour mainly originating from pancreas or duodenum; overall with an incidence of 1/40 million persons. We introduce a narrative review of literature of somatostatinoma including the relationship with neurofibromatosis type 1. Clinical presentation includes: Diabetes mellitus, cholelithiasis, steatorrhea, abdominal pain, and obstructive jaundice while papillary tumour may cause acute pancreatitis. The neoplasia may develop completely asymptomatic or it is detected as an incidental finding during an imaging or a surgical procedure. It may be sporadic or associated to genetic backgrounds especially for duodenal localisation as neurofibromatosis type 1 (*NF1* gene with malfunction of RAS/MAPK pathway) or Pacak-Zhuang syndrome (*EPAS1* gene encoding HIF). Surgery represents the central approach if feasible but the prognostic depends on location, and grading as indicated by WHO 2017 classification of neuroendocrine tumours. Previously known as Von Recklinghausen disease, neurofibromatosis type 1, the most frequent neurocutaneous syndrome, is an autosomal dominant disorder including: Café-au-lait spot, skin fold freckling on flexural zones, and neurofibromas as well as tumours such as gliomas of optic nerve, gastrointestinal stromal tumours (GISTs), iris hamartomas and brain tumours. Duodenal somatostatinoma is associated with the syndrome which actually involves more often a duodenal tumour of GIST type than a somatostatin secreting neoplasia. Other neuroendocrine tumours are reported: Gastrointestinal NENs at the level of rectum or jejunum and pheocromocytoma. Overall, one quarter of subjects have gastrointestinal tumours of different types. Somatostatinoma, when not located on pancreas but in duodenoum, may be registered in subjects with neurofibromatosis type 1 most probably in addition to other tumours. Overall, this type of neuroendocrine tumour with a challenging presentation has a poor prognosis unless adequate radical surgery is promptly offered to the patient.

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Abbreviations: ACTH, adrenocorticotropic hormone; CCK, cholecystokinin; ^{68}Ga, gallium; GIST, gastrointestinal stromal tumours; HIF2A, hypoxia-inducible factor; NGS, next-generation sequencing; pNEN, pancreatic neuroendocrine neoplasia; PET, positronic emission tomography; PRRT, peptide receptor radionuclide therapy; SR, somatostatin receptors; SSA, somatostatin analogues; SRI, somatostatin receptor imaging; TSH, thyroid stimulating hormone

Key words: somatostatinoma, neurofibromatosis, somatostatin, neuroendocrine, duodenal tumour

Contents

1. Introduction

Somatostatinoma is a tumour mainly originating from two organs: On the one hand are the δ cells of the pancreas which produce somatostatin, being a part of pancreatic neuroendocrine neoplasia (pNEN), and on the other hand, there is the

duodenum source; overall with an incidence of 1/40 million persons (1). Clinical presentation includes diabetes mellitus, cholelithiasis, steatorrhea, abdominal pain, vague symptoms, and some describe the specific triad as: Glucose metabolism anomalies, steatorrhea and aclorhydria (2,3). Hypoglycemia also has been reported potentially related to insulin co-secretion from pancreas tumour or as a functional release (3). Obstructive jaundice is caused by masses located at the level of ampulla of Vater, and papillary tumour may also cause acute pancreatitis (including repetitive episodes) (4,5). However, the neoplasia may develop completely asymptomatic or it may be detected as an incidental finding during an imaging technique of an endocrine/non-endocrine organ or during a surgical procedure for abdominal pain of unknown cause or other non-related synchronous conditions (2,6,7). The tumour may be sporadic or associated to different genetic backgrounds as neurofibromatosis type 1 for duodenal localisation (8). Blood somatostatin assays as well as others less specific neuroendocrine markers such as chromogranin A or neuron specific enolase are useful for initial diagnosis but also as prognostic parameters during follow-up (9). The hormonal excess is similar between pancreatic and duodenal localisations, but the admission may be due to local compressive symptoms because of the tumour mass itself (2,6,7). The immunostain for somatostatin confirms the diagnosis, noting that many cases may have a silent evolution or associate local non-specific symptoms and thus the post-operative histological and immunohistochemical report is crucial for adequate disease recognition (10). Surgery such as pancreatico-duodenectomy represents the central element of approach if feasible but the prognostic depends on location, and grading as pointed out by WHO 2017 classification of neuroendocrine tumours (8,10).

2. Method

Our aim was to introduce a narrative review of literature of somatostatinoma, also stressing the relationship with neurofibromatosis type 1. The data research used mostly PubMed database, and a selection of 57 articles was included.

3. Pancreatic neuroendocrine neoplasia

pNENs might produce glucagon, insulin, gastrin (causing Zollinger-Elison syndrome), vasoactive intestinal polypeptide (VIP), rarely calcitonin, serotonin, adrenocorticotropic hormone (ACTH) and, recently, cholecystokinin (CCK)-oma syndrome has been reported considering the tumour-related production of CCK (11,12). Somatostatinoma represents 5% of pNENs thus it is one of the rarest pathological secretions of the pancreas (13). Both pNEN and gastrointestinal NEN are the main group of NENs (11,12). They all have the capacity to produce specific and non-specific neuroendocrine markers/hormones and to express somatostatin receptors (SR) which are targeted by somatostatin analogues (SSA) (11,12). The main line of therapy for pNENs is surgery with curative intention or, in severe cases, there is a need for debulking procedure involving the primary lesion and/or metastasis such as hepatic metastasis in association with medical therapy (depending of grading, tumour size and site, and histological profile) as well as peptide receptor radionuclide therapy (PRRT) especially for NENs with a poor level of differentiation (14).

4. Somatostatin: A general perspective

Somatostatin of pancreatic/duodenal origin is a hormone with a biochemical structure of tetradecapeptide (15). It inhibits exocrine and endocrine functions such as gut and pancreatic hormones, but also intestinal motility and local nutrients absorption, and gastric acid secretion (15). Pancreatic δ cells exhibit paracrine actions of β and α cells especially with the purpose of glucose regulation (16). Central somatostatin is produced by hypothalamus and it displays also inhibitory effects on pituitary growth hormone, thyroid stimulating hormone (TSH) and prolactin (17). SRs are widespread in the brain and their activation communicates with the modulation of food and water intake and recently they have been linked with obesity pathogenesis (17-19). Further innovative approaches of obesity are currently under development and they include anti-obesity vaccines with hormone analogues such as somatostatin or ghrelin (20).

5. Somatostatin secreting tumours

Pancreas site is involved in 70% of all the somatostatin producing tumours (36% at head level, 14% at the body, and 32% at the pancreatic tail) in addition to 19% at the duodenum area, 3% at ampulla of Vater, and 3% at small bowel, while exceptional localisations at pulmonary area, thyroid lobes or renal parenchyma have been reported (21-23). Gastric location complicated with gastrointestinal bleeding is also uncommon (24).

Somatostatinoma has been reported in association with genetic conditions. For instance, polycythemia-paraganglioma-somatostatinoma syndrome (also called Pacak-Zhuang syndrome) is a very rare underlying paraganglioma/pheocromocytoma and somatostatin producing tumour (mostly of duodenal origin) in addition to the mentioned haematological disorder in children and mutations such as *EPAS1* gene encoding hypoxia-inducible factor (HIF2A) or *von Hipple-Lindau* gene (25-27). Recently the gain of function involving the mutation of *EPAS1* gene (oxygen degradation domain) has been identified as aetiology of the Pacak-Zhuang syndrome (28). Moreover, non-mosaicism somatic mutations of *HIF2A* seem to induce the same syndrome but with late onset (29).

Somatostatinoma syndrome includes: Diabetes mellitus, diarrhoea and gallstones (30-32). Less frequently other features are found such as hypochlorhydria/achlorhydria, dyspepsia and weight loss (30). These are caused by inhibitory effects of the somatostatin on the other pancreatic hormones including insulin or on gastrointestinal parameters as gastric acid secretion (1,30). Duodenal location of the somatostatinoma causes anaemia and gastrointestinal haemorrhage (30-33).

Increased blood levels of somatostatin are found in different amounts depending on tumour production (30). Neuroendocrine markers that are less specific such as chromogranin A, neurron specific enolase, and 5-hydroxytryptamine might help the diagnosis and follow-up (30,31,34). Imaging techniques are widely variable such as ultrasound, computed tomography, magnetic resonance imagery, positronic emission

tomography (PET), and somatostatin receptor imaging (SRI) such as octreoscan/^{68}Ga (Gallium)-DOTATATE (30,35). Immunohistochemistry in somatostatinomas is positive for somatostatin and also for chromogranin A and synaptophysin as hallmark of the neuroendocrine component (36,37). Non-specific somatostatin assay is also found in medullar thyroid cancer and pheocromocytoma (30). Somatostatinomas are positive for SR type 2 and 5 out of the five SR types (30).

Surgery is the only option with curative intention and techniques such as partial/total pancreatectomy, duodenectomy, pancreaticoduodenectomy, cholecystectomy, endoscopic papillectomy are used (30,33). However surgery is not feasible in many cases because of the tumour anatomy or rapid invasion or because of deteriorated clinical status, delayed diagnosis (30). SSAs such as octreotide or lanrerotide exhibit both tumour and hormonal control (30,37). In addition to SSAs, PRRT like ^{177}Lu-DOTATATE may improve the poor survival while thyosine kinase inhibitors express a certain response (38). However, the current standard management is still far from optimal.

6. Neurofibromatosis type 1

Previously known as Von Recklinghausen disease, neurofibromatosis type 1, the most frequent neuro-cutaneous syndrome, is an autosomal dominant condition [mutations of neurofibromatosis type 1 (*NF1*) gene] with a relative high frequency in general population (for a genetic disorder) (39,40). The reported incidence is 1/2500-1/3000 (39,40). The mutation causing the condition is at the level of *NF1* gene (on chromosome 17) which induces a malfunction of RAS/MAPK (known as Ras-Raf-MEK-ERK) pathway since normally neurofibromin down-regulates RAS expression (41). Somatic mutations of the same gene have been found in non-syndromic cancers such as melanoma as well as in chemotherapic resistance for various neoplasia (41).

The skin lesions are café-au-lait spots (or macules), and neurofibromas which are both benign (40,41). Their clinical recognition is enough for diagnosis based on three aspects: Café-au-lait spots, skin fold freckling on flexural zones, and neurofibromas (which have the best positive prediction) (42). Lipomatous neurofibroma is a variant of neurofibromas containing an increased number of adipocytes, being more frequent in females and in larger neurofibromas lesions (43). Usually, there are numerous neurofibromas with onset at different ages; some of them causing local pain and pruritus; a major impact regarding the quality of life is registered because of them (42,44). No standard management has yet been considered, the approach varies from conservative to different procedures of removal including electrodessication (44).

The tumours with a higher risk in neurofibromatosis type 1 are benign or malignant such as gliomas of optic nerve, gastrointestinal stromal tumours (GISTs), somatostatinomas, and potentially adenocarcinomas of different origins (37,39,45). An increased risk of breast cancer and leukaemia has been reported (41). Also, iris hamartomas, brain tumours and bone anomalies (including scoliosis) represent a specific configuration seen in neurofibromatosis type 1 which also increases the risk of learning and intellectual dysfunctions (46). Others morbidities such as peripheral nerve sheath malignancies, supranumerary teeth of permanent dentition, have been reported (39,46).

These associated tumours require a multidisciplinary team involving a dermatologic, oncologic, surgical, orthopaedic, cardiovascular, gastrointestinal and endocrine approach in association with imaging and laboratory assessments. A certain level of heterogeneity is described even among individuals belonging to the same family (46). This represents a real challenge to practitioners following the subject's trough their lifespan despite the general level of awareness regarding the potential co-morbidities (39,46). Of course, the challenge also is reflected by adequate and prompt interventional therapy for multiple neurofibromatosis type 1-associated disorders (39,46). The most probable explanation of the phenotype variations of wide area is the gene that encodes neurofibromin 1 protein which was proven extremely heterogeneous, as well (39,46). The tumour suppressor gene effects are different between various gene regions in addition to sex-hormones and germline influences (39,46). Further gene targeted studies will help the clinicians to forecast the clinical complications and potentially to prevent them through gene manipulation. The importance of the topic is reflected by the relative high frequency of the disorder among inherited conditions.

The condition is distinct from neurofibromatosis type 2 which is an autosomal dominant disorder with NF2 tumour suppressor gene mutations on chromosome 22 (47-49). It is found in 1/25,000 births (48,49). The statistical data shows that by the age of 60 years the penetrance is almost 100%; 50% of subjects inherit the mutation and 50% have acquired mutations (48,49). The associated neoplasia with a high risk involves nervous central system such as schwannomas (especially bilateral vestibular location), astrocytomas, meningiomas, ependymomas and neurofibromas (48,49). Moreover, the most frequent eye anomalies are cataract, retinal hamartomas, and epiretinal membranes (48,49). Skin conditions found in neurofibromatosis type 2 are cutanous schwannomas and mild pattern of café-au-lait patches (not so frequent as in neurofibromatosis type 1) (48,49). Other morbidities have been reported including malignant mesothelioma and sarcomas (48,49). A multidisciplinary approach is needed as well as genetic counselling (48,49).

Another disorder which is similar with type 1 and type 2 neurofibromatosis is schwannomatosis but it displays a distinct syndrome from type 1 and 2 neurofibromatosis (47-49). All three conditions together represent the class of neurofibromatoses with neurofibromatosis type 1 as the most frequent group (47-50).

7. Somatostatinoma and neurofibromatosis type 1

Neurofibromatosis type 1 is a complex and heterogeneous syndrome and the associated risk of neoplasia is *sine qua non*. The presence of a duodenal somatostatinoma has a higher risk than general population but this is not the most significant tumour association seen in patients with *NF1* gene mutations. Duodenal somatostatinoma is associated with neurofibromatosis type 1 (which actually involves more often a duodenal tumour of GIST type and very rarely a somatostatin secreting neoplasia), and also with Von Hippel-Lindau syndrome or with tuberous sclerosis (4). Some reports include synchronous diagnosis of

GIST and somatostatinoma in subjects with neurofibromatosis type 1, a combination called 'A triad worth remembering' by Njei and Sanchez (51). Hiesgen and Variava (52) reported for the first time a case of an HIV positive woman with a synchronous metastatic somatostatinoma and a gastrinoma presenting with diabetes mellitus, chronic diarrhoea and recurrent peptic ulcer. Somatostatinoma of ampulla of Vater and minor papilla has rarely been reported (53,54). Neuroendocrine tumours other than somatostatinomas, for instance, gastrointestinal NENs at the level of rectum or jejunum have been reported in neurofibromatosis type 1 (55,56). As mentioned, a subject with *NF1* gene mutations has a higher risk of pheocromocytoma in general population (37,57). Overall, one quarter of patients with the syndrome have gastrointestinal tumours of different types (51).

8. Discussion

Three different aspects involving somatostatinoma without/without neurofibromatosis type 1 are discussed. One point of view includes current controversies; another is related to the body of evidence with a spectacular recent increase of NEN field, and also some genetic considerations as one more step to the future.

Controversies. There are still subjects regarding somatostatinoma that are a matter of debate or are not completely understood at present. The clinical picture at presentation might associate local compressive symptoms due to the tumour mass which are different between pancreatic and duodenal site. However, the symptoms strictly associate with hormonal excess are similar between the two main locations of the somatostatinoma and, unless there are local symptoms, there is no clue to specify the source. The general prognostic is poor despite the fact that somatostatinoma may be silent for a period of time. Which is the optimal approach is still inconclusive. Moreover, the specific prevalence of duodenal somatostatinoma in patients with neurofibromatosis type 1 is unknown; also the question related to the association with duodenal, not pancreatic site, is still unanswered (58). The use of first generation somatostatin analogues such as prolonged formulas of octreotide and lanreotide seems a paradox for a somatostatin secreting neoplasia but actually their role in tumour growth and function has been proven (59).

Neuroendocrine tumours. Somatostatinoma is part of a generous topic of neuroendocrine neoplasia. A large amount of publications are currently available since the progress of diagnosis and therapy has given an increasing trend to the subject. Gastroenteropancreatic neuroendocrine tumours represent the majority of NENs. The poor prognosis is related to non-rectal location, high grading (according to WHO criteria 2017 based on Ki67 proliferation marker and mitotic index), large tumour mass at diagnosis, metastases at any level including liver and bone, potential dedifferentiation processes in metastases involving a more aggressive profile than reflected by the primary lesion (60-62). Duodenal NENs underline this pattern as well as a potential curable approach based on surgery especially in early stages and in well differentiated NENs; if possible, less aggressive surgical approach decreases the risk of complications (63). The level of awareness improves the overall survival due to early recognition and therapy (63,64). In this type of tumours the functional aspects are frequently positive thus the endocrine profile might help the early detection (63,64). Opposite to non-neuroendocrine tumours, the neuroendocrine paraneoplastic syndromes are associated with both benign and malignant neoplasia and they do not necessarily represents a poor prognostic marker (64,65). Somatostatinoma through the above mentioned presentation displays this scenario.

Genetic background. Both NENs and neurofibromatosis type 1 are related to genetic backgrounds which are known for neurofibromin 1 gene and less known as NEN implications for neurofibromatosis type 1. Loss of its function causes cells proliferation as contributor to different tumour formations (66,67). The gene is difficult to be analysed because it is large and next-generation sequencing (NGS) seems promising to help the genetic diagnostic by covering the Ras-related signalling elements (66,67). Novel variants of NF1 gene such as p.(Gln181Profs*20) have been recently reported (68). Aggressive breast cancer in females with neurofibromatosis type 1 involves germline mutations of neurofibromin 1 in association with other somatic mutations of TP53 or KMT2c (69). However, some of neoplasia associated mutations are described in non-neurofibromatosis cases (70-74).

9. Conclusions

Somatostatinoma, when not located on pancreas but in duodenum, may be registered in subjects with neurofibromatosis type 1 most probably in addition to other tumours. Overall, this type of neuroendocrine tumour with a challenging presentation has a poor prognosis unless adequate radical surgery is promptly offered to the patient.

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Authors' contributions

FS critically revised the manuscript for its content and was involved in the conception of the study. MC wrote the manuscript and was involved in the conception of the study. AV was also involved in the conception of the study. SEA and RCP were responsible for the literature research and were involved in the conception of the study. MCD critically revised the manuscript and was involved in the conception of the study. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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