Case report

Multifocal pancreatic PPoma in the setting of MEN1: Case report and review of literature

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1. Introduction

Neuroendocrine tumors (NETs) are diverse neoplasms that most often originate in the gastrointestinal tract, lungs, and pancreas. Pancreatic NETs (pNETs), which account for 7% of all NETs, and stem from various cells within the islets of Langerhans [1], are relatively rare but their incidence has been increasing over the past decade, from 1 to 7 per 100,000 per year across North America [2,3]. pNETs range from low-grade indolent tumors to high-grade malignant tumors with high metastatic potential [4] and are further categorized into functioning or non-functioning based on their clinical manifestations. Functioning pNETs are named based on their predominant hormone-related syndrome, such as insulinomas, gastrinomas, vasoactive intestinal polypeptide-secreting tumors (VIPomas), glucagonomas, somatostatinomas, and other rare functional tumors including pancreatic polypeptide-producing tumor (PPoma).

Pure PPomas, immunostaining for PP only, are one of the rarest forms of pNETs with <15 cases reported to date [5–7]. PPomas arise from F cells, which are diffusely located within the uncinate and head of the pancreas and produce >90% of the body’s pancreatic polypeptide (PP) [8]. PP is a regulatory substance that modulates somatostatin release and inhibits pancreas exocrine secretions. Consequently, PPomas

**ARTICLE INFO**

**Keywords:**
- Case report
- PPoma
- MEN1
- Multifocal
- pNET
- Ga68-DOTATATE PET/CT

**ABSTRACT**

**Introduction and importance:** Functioning pancreatic neuroendocrine tumors (pNETs) that express pancreatic polypeptide—PPomas—do not yet have a pathognomonic clinical syndrome associated with them due to their overall rarity and diverse symptoms. Moreover, in patients with MEN1, the often multifocal nature of pNETs presents a unique clinical issue.

**Case presentation:** We report a case of a 22-year-old man with a known MEN1 gene mutation who was suffering from severe diarrhea (7–8 bowel movements per day) and was found to have only elevated PP levels on biochemical work-up. Ga68-DOTATATE PET/CT showed multifocal tumors in the body and tail of the pancreas that were not evident on contrast-enhanced CT. The patient underwent a successful laparoscopic radical antegrade modular pancreatosplenectomy (RAMP) and recovered well post-operatively with complete resolution of his diarrhea. Immunohistochemistry showed multiple pure PPomas.

**Clinical discussion:** This case highlights the unique propensity for multifocal disease in patients with MEN1 mutations and the utility of functional imaging by somatostatin analogs, i.e., Ga68-DOTATATE PET/CT, in order to perform oncologic laparoscopic pancreatic resections.

**Conclusion:** PPomas in the setting of MEN1 mutations are a unique clinical entity due to their diverse associated clinical syndromes and propensity for multifocal disease.

1. Introduction

Neuroendocrine tumors (NETs) are diverse neoplasms that most often originate in the gastrointestinal tract, lungs, and pancreas. Pancreatic NETs (pNETs), which account for 7% of all NETs, and stem from various cells within the islets of Langerhans [1], are relatively rare but their incidence has been increasing over the past decade, from 1 to 5–7 per 100,000 per year across North America [2,3]. pNETs range from low-grade indolent tumors to high-grade malignant tumors with high metastatic potential [4] and are further categorized into functioning or non-functioning based on their clinical manifestations. Functioning pNETs are named based on their predominant hormone-related syndrome, such as insulinomas, gastrinomas, vasoactive intestinal polypeptide-secreting tumors (VIPomas), glucagonomas, somatostatinomas, and other rare functional tumors including pancreatic polypeptide-producing tumor (PPoma).

Pure PPomas, immunostaining for PP only, are one of the rarest forms of pNETs with <15 cases reported to date [5–7]. PPomas arise from F cells, which are diffusely located within the uncinate and head of the pancreas and produce >90% of the body’s pancreatic polypeptide (PP) [8]. PP is a regulatory substance that modulates somatostatin release and inhibits pancreas exocrine secretions. Consequently, PPomas

**Abbreviations:** CgA, chromogranin A; ISGIPS, International Study Group in Pancreatic Surgery; MEN1, multiple endocrine neoplasia; pNET, pancreatic neuroendocrine tumors; PPoma, pancreatic polypeptide-producing tumor; RAMP, radical antegrade modular pancreatosplenectomy; VIPoma, vasoactive intestinal polypeptide-secreting tumors.

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https://doi.org/10.1016/j.ijscr.2021.106008

Received 26 April 2021; Received in revised form 17 May 2021; Accepted 17 May 2021
Available online 23 May 2021

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have not been clearly associated with a clinical syndrome. Due to their quiescent progression, they are often found incidentally or at advanced stages due to mass effect, causing non-specific pain or hepatobiliary obstructive symptoms [9].

Although PPomas often occur sporadically, they have been associated with multiple endocrine neoplasia type 1 (MEN1). MEN1 syndrome is caused by a germline mutation in the MEN1 gene, a tumor suppressor. MEN1 syndrome is traditionally defined by a triad of parathyroid, pancreatic and pituitary manifestations. MEN1 is inherited in an autosomal dominant fashion and may confer a varying combination of more than 20 endocrine and nonendocrine tumors, rarely known to include multifocal pNETs. The most common pNET in MEN1 is gastrinoma (~40%), with PPoma found in <2% of cases [10]. Consequently, the malignancy potential of PPomas in the setting of MEN1 is unclear.

Herein, we report an unusual case of multifocal PPoma in the setting of MEN1. This case is reported in line with the Updating Consensus Surgical Case Report (SCARE 2020) guidelines [11].

2. Case presentation

A 22-year-old Caucasian man, with a known family history of MEN1 in his father and sister, was found to have a pathogenic mutation in the MEN1 gene, a tumor suppressor. MEN1 syndrome is traditionally defined by a triad of parathyroid, pancreatic and pituitary manifestations. MEN1 is inherited in an autosomal dominant fashion and may confer a varying combination of more than 20 endocrine and nonendocrine tumors, rarely known to include multifocal pNETs. The most common pNET in MEN1 is gastrinoma (~40%), with PPoma found in <2% of cases [10]. Consequently, the malignancy potential of PPomas in the setting of MEN1 is unclear. Herein, we report an unusual case of multifocal PPoma in the setting of MEN1. This case is reported in line with the Updating Consensus Surgical Case Report (SCARE 2020) guidelines [11].

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immunostain (200× magnification) shows positive immunoreactivity in the tumor compared to the adjacent normal pancreatic tissue. (D) Chromogranin immunostain (200× magnification) shows positive immunoreactivity in tumor cells. (E) Synaptophysin immunostain (200× magnification) shows positive immunoreactivity in tumor cells. (F) Ki-67 immunostain (200× magnification) shows scattered positive cells; 3–5% proliferative index.

3. Discussion

Our patient's case highlights a unique presentation of multi-focal pancreatic PPoma in the setting of a known MEN1 genetic mutation with complete resolution of longstanding diarrhea after resection. A characteristic feature of pNETs in MEN1 is the presence of multi-focal intraparenchymal pancreatic tumors, in contrast to the solitary pNETs found in sporadic cases [14,15]. The finding of microadenomatosis, defined by the presence of multiple pNETs measuring ≤0.5 cm, or microadenomas mixed with macroadenomas (>1 cm), is present in almost all MEN1 cases [14,15].

Our patient's clinical manifestation of severe diarrhea that resolved with resection is unique among published cases of pure multifocal PPoma. Historically, PP-secreting tumors were thought to cause severe diarrhea but conflicting PPoma case reports subsequently showed only a third of published cases documenting diarrhea [16]. Thus, the heterogeneous symptoms of documented PPomas have not yet resulted in an identifiable clinical syndrome and are often managed clinically as non-functional pNETs.

To date, approximately 30 patients with PPomas have been reported, 13 with histopathologic confirmation of pure PPomas (Supplementary Table 1). Even rarer is the presence of pure, multifocal PPoma in the setting of MEN1, as in our patient. Because of this rarity, the malignant and metastatic potential of PPoma in the setting of MEN1 is unknown. PPomas have been thought to confer higher local recurrence and distal metastases rates, but that may be due to the non-functioning nature of the tumor and difficulty in diagnosing it, rather than to tumor biology [9]. For instance, previous studies sought to ascertain if a 2 cm cutoff for resection candidacy used in sporadic pNETs should apply to pNETs in MEN1 patients. A study with >10 years of follow-up data for 46 patients with MEN1 and non-functioning pNETs (NF-pNETs) ≤ 2 cm who did not have surgery at the time of diagnosis reported that 28 (61%) patients had stable disease and 16 had progression, seven of whom required surgery [17]. One patient died of metastatic disease, but none of the living patients had evidence of metastatic disease at last follow-up. The authors concluded that conservative management without surgery in patients with MEN1 and NF-pNETs measuring ≤2 cm results in low disease-specific mortality [17]. The number of PPomas that may have been included as NF-pNETs in that study is unknown.

Because surveillance and early diagnosis may decrease the morbidity and mortality, biochemical markers such as serum CgA and PP are important to include in all MEN1 and potential pNET evaluations. Increased levels of serum CgA, PP and pancreastatin combined have a sensitivity of up to 95% [8]. Additionally, as illustrated in our patient, functional imaging by somatostatin analogs, i.e., Ga68-DOTATATE PET/CT, refines the diagnostic sensitivity of preoperative identification of multifocal pNETs.

Although our patient had no radiographic evidence of additional intra-pancreatic or distant metastatic disease, he remains at significant risk for additional or recurrent disease due to his known multifocal disease and MEN1 mutation and will require close follow-up. At our center, we recommend bi-annual Ga68-DOTATATE PET/CT surveillance scans for the first 5 years and then yearly. Careful surveillance for metastatic disease within the liver is crucial because debulking and metastasectomy have improved survival in patients with pNETs [18,19]. The role of systemic therapy, specifically somatostatin analogs, in patients with pNETs and MEN1 mutations remains controversial, with ongoing studies underway to assess their potential suppressive utility long-term [20].

4. Conclusion

Herein, we report a case of a young patient with multifocal PPoma causing severe diarrhea in the setting of MEN1. Screening with biologic
markers of pNETs and Ga68-DOTATATE PET/CT imaging, provided timely diagnosis, enabling R0 resection of the tumors by laparoscopic IOUS and distal RAMPs. We recommend complete immunohistochemistry with complete histological hormonal markers post-operatively to confirm diagnosis. Post-operative surveillance pancreatic imaging of MEN1 patients is crucial, especially since nonfunctioning pNETs like PPoma are known to grow quiescently. Our patient had significant improvement in his quality of life with laparoscopic distal RAMPs and will be followed closely by a multi-disciplinary team.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijscr.2021.106008.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Not applicable, and patient data is de-identified.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Guarantor

CC.

Research registration number

Not applicable.

CRediT authorship contribution statement

AM, CW, and CC jointly designed the study. CW and CC performed the surgery. CW, CC, AY and AM contributed to patient management. AM and AY performed data and evidence collection, respectively. AQ reviewed the pathology specimens. AM and CW created the initial draft of the manuscript. All authors discussed the results and contributed to manuscript revision.

Declaration of competing interest

None.

Acknowledgements

We would like to thank Pamela Derish for editing of manuscript.

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