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Case Report

Navigating the uncommon: a comprehensive case study of multiple gastroduodenal neuroendocrine tumor

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ABSTRACT

Neuroendocrine tumors (NETs) have varied pathophysiological characteristics, location, clinical presentation, management & outcome. Unfortunately, most NETs are non-functional and therefore, either remain asymptomatic until incidentally detected or present very late with pressure symptoms, adding up to the associated morbidity and mortality. Here we presented a case of a 43-year gentleman, who presented to gastroenterology OPD with chief complaints of heartburn and pain in the upper abdomen for one year. He had an equivocal clinical examination and laboratory parameters. Upper GI endoscopy and computed tomography revealed multiple nodular growths in the D1 segment and pylorus of the stomach. He was successfully managed by wide local excision of D1 and distal stomach (pylorus) followed by Polya gastrojejunostomy reconstruction. Histopathology confirmed well-differentiated NETs, low Ki67, and positive for chromogranin and synaptophysin. This case draws attention to the early age of presentation of multifocal NETs with vague symptoms and equivocal clinical examination. Coexisting gastric NETs with duodenal NETs in itself is very rare, never the less non-functional status and pre-operative diagnostic dilemma. Here, we have also drawn attention to the pros and cons of various diagnostic tools and how their utility can sometimes limit the approach of clinicians, apart from a high index of suspicion.

Keywords: Neuroendocrine tumor, Duodenal NET, Duodenum, GIST, Small intestine malignancy

INTRODUCTION

Apart from its rarity, NETs arising from neuroendocrine differentiation in epithelial cells and peptide neurons have a wide spectrum of pathophysiological characteristics, number, size and location, clinical presentation, management and outcome. The majority of NETs arise from the gastrointestinal tract (55-70%), followed by the lungs (30%). Amongst gastro-entero-pancreatic NET (GEP-NET), gastric NETs constitute 5-15% and duodenal NETs account for only 2-3% of all GEP-NETs. In the United States, the commonest sites of GEP-NETs are the small intestine and rectum, in England small intestine and appendix, and in the Asian population pancreas and rectum are the common sites of GEP-NETs.[1] In a study by Palepu et al among Indian COHORTs, the pancreas is the commonest site of NETs (37.8-48.5% of all NETs), while the stomach constitutes 6.4-11% and duodenum along with ampulla account for 8.1-11.1%. None of the 407 patients studied between 2001 and 2016, had a combination of gastric and duodenal NETs coexisting in the same patient.[2] Thus, the presence of both gastric and duodenal NETs in the same patient is extremely rare, and the exact incidence is unknown. In the same study mean age of presentation is more than fifty years with male preponderance.

Patients with NETs may manifest several symptoms owing to various peptides and hormones secreted by these tumors such as carcinoid syndrome, Zollinger-

Ellison syndrome, Whipple's triad in insulinoma, WDHA syndrome in VIPoma. Unfortunately, most NETs are non-functional and therefore, either remain asymptomatic until incidentally detected or present very late with pressure symptoms, adding up to the associated morbidity and mortality. The cases of GEP-NETs have significantly increased due to advancements in imaging and endoscopic techniques.[3] Here we reported a case of multiple non-functional gastro-duodenal NETs in a gentleman in his early forties.

CASE REPORT

A 43-year-old male patient presented to gastroenterology OPD with chief complaints of heartburn and pain in the upper abdomen for one year, The patient was asymptomatic 1 year back when he developed dull aching pain in the epigastric region, mild in intensity, non-radiating and was relieved on taking medication. The pain was not associated with nausea or vomiting. No history of fever, jaundice, melena, or hematemesis. He has been a known case of hypertension for 1.5 years which was well controlled on anti-hypertensives. There was no history of surgical intervention in the past. On examination abdomen was soft, non- tender with no palpable organomegaly or evidence of free fluid on percussion. His routine hematologic and biochemical tests were within normal limits. An ultrasound whole abdomen was requested which did not reveal any significant abnormality. His contrast-enhanced computed tomography (CECT) whole abdomen revealed a heterogeneously enhancing nodular lesion, present in the duodenum at the duodenal bulb in partial thickness of the wall, with projection into the lumen along with adjacent pylorus of the stomach and shows diffuse wall thickening as seen in Figure 1, and multiple sub-centimetric nodes in the peri-choledochal and retro-duodenal region were seen. The patient then underwent upper GI endoscopy which reported, multiple nodular lesions of variable sizes with normal overlaying mucosa, the largest 1.6×1.4 cm in the D1 segment, and less prominent D2 folds with scalloping. Guided biopsy revealed non-specific inflammatory changes.

Considering the size of the largest lesion (more than 1 cm) and multiple lesions in the pyloric region and D1 segment, the patient was referred to the surgical unit. Based on the above CT and UGI endoscopy findings and discussion in a multidisciplinary panel, the patient was scheduled for elective resection of the tumor. On intraoperative exploration, multiple nodular growths (largest 1.6×2 cm) were present in the D1 segment of the duodenum and pylorus as seen in Figure 2.

Multiple sub-centimetric retro-duodenal, peri-choledochal, and peri-portal lymph nodes were noted, dissected, and sent for the frozen section that turned out to be negative. Hence, wide local excision of D1 and distal stomach (pylorus) was done followed by Polya gastrojejunostomy reconstruction. Histopathology from the specimen revealed a grade-1, well-differentiated neuroendocrine tumor, and immunohistochemistry was positive for synaptophysin and chromogranin A (CgA) with low Ki 67. The post-operative recovery was uneventful and he was discharged on postoperative day 7. His last follow-up was at 6 weeks, he had no complaints and was doing well.

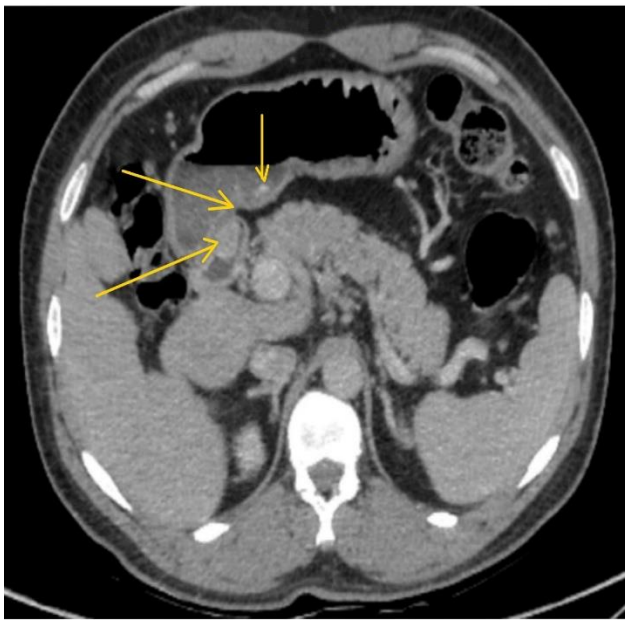

Figure 1: CECT scan of the whole abdomen, axial section showing heterogeneously enhancing nodular lesion in the duodenum shown with the yellow arrow.

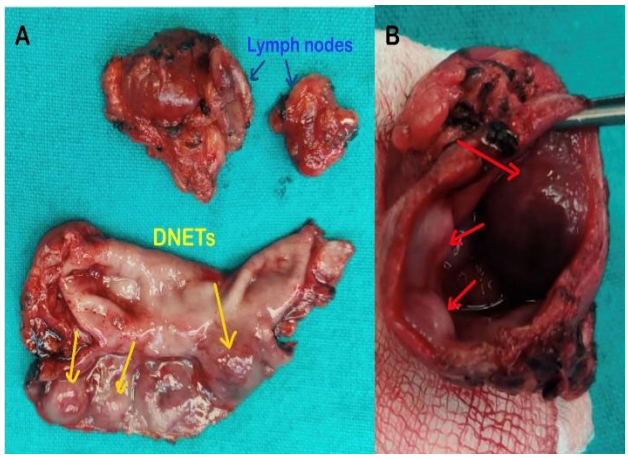

Figure 2: Post-operative resected specimen of pyloric region of Stomach and first part of duodenum showing multiple nodular lesions (yellow arrows in figure A and red arrows in figure B); the blue arrow in (A) shows dissected retro-duodenal, peri-choledochal, and peri-portal lymph nodes.

DISCUSSION

Non-functional NET may have subtle clinical presentation confused with common diagnoses such as

GERD, gastritis. Unless complete gastric outlet obstruction (GOO), GI lumen compromise may present variably from vague complaints like heartburn to the classic presentation of GOO.[4] Intra-lumen protrusion may not manifest classically as GOO like in our case where subtle complaints may be misleading until evident from UGIE or CECT.

CECT having variable sensitivity and specificity cannot distinguish amongst the spectrum of gastro-intestinal neuro-endocrine neoplasm. Furthermore, they are not a functional study.[5] While the sensitivity of UGIE depends upon the location & size of the lesion, at the time of presentation UGIE is helpful, not just to detect, demonstrate and locate the lesions but also to procure a sample for confirmatory histopathological diagnosis.[3] Though UGIE-guided biopsy plays a crucial role in clinching the diagnosis, may sometimes turn inconclusive like in our case due to its technicality. Gastroduodenal polyps do stand as differential given clinical presentation, above said UGIE, CECT, and even intraoperative findings unless histopathology says otherwise. Functional NETs are relatively easier to diagnose because of specific hormone-related symptoms and demonstration of various serum markers. The absence of this makes the diagnosis of non-functional NETs rather more challenging. In the latter case, immunohistochemical markers like chromogranin, synaptophysin, cytokeratin CD56 can be handy especially where histopathology is equivocal.[6]

The role of somatostatin receptor positron emission tomography (SSTR PET) including Ga-68 DOTATATE scans is a useful tool in staging/restaging of residual or recurrent disease, for prognosis, assessment of eligibility for Peptide radio-receptor therapy (PRRT) with 177-Lu or 90-Y DOTA peptides and therapy response monitoring (surgery, radiotherapy, chemotherapy, or PRRT).[5] In our case, we did not subject the patient to SSTR PET/CT as our patient had complete resection with HPE confirming Well-differentiated NET-grade 1, that do not require any medical treatment or PRRT. However, its usefulness is often limited as it is available only in a handful of centers.

Chromogranin A (CgA) estimation in the serum of a patient is a useful marker with sensitivity varying between 60-92%, however, it is non-specific and can be raised in bowel diseases, chronic hepatitis, renal insufficiency, heart failure, benign prostatic hypertrophy, prostatic cancer, hyperthyroidism, atrophic gastritis, and many other inflammatory diseases.[7] Proton pump inhibitors and histamine H2 receptor blockers also affect its level. Moreover, it has shown higher sensitivity and specificity in pancreatic NETs, functional NETs, and metastatic NETs as compared to their respective non-pancreatic, non-functional, and non-metastatic counterpart. We could not do serum CgA level in our patient due to the unavailability of this test at our institute. Given the literature and postoperative HPE report, we firmly believe that pre-operative CgA estimation in our case could have made any difference in the line of management.

When treating a neuroendocrine tumor it is important to determine two characteristics of the tumor: the grade of that tumor and its functional status. G-NETs have been traditionally sorted into three types: type 1 (80-90%, female preponderance) constitute small (<1 cm), multifocal tumors associated with autoimmune atrophic gastritis with high gastric pH (>4) and serum gastrin level, having low metastasis potential (1-3%) and excellent prognosis. Type 2 (5-7%, no gender predilection) small (<2 cm) multifocal lesions associated with gastrinoma/Zollinger-Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN1) syndrome, and low gastric pH (<2), high gastrin level, moderate metastatic potential (10-30%) but fair prognosis. Type 3 (10-15%, male predilection) is large (>2 cm) and arises sporadically, usually with a unifocal lesion, normal gastric pH and gastrin level, highly metastatic (50-100%), and has the worst prognosis.[8] D-NETs per se do not have specific types and are rather described according to their WHO (2022), which is not exclusive to D-NETs for that matter. The WHO classification (2022) has divided the new endocrine tumor into Well-differentiated NET (grade 1, 2, and 3), poorly differentiated neuroendocrine carcinoma (small cell NEC and large cell NEC) and mixed NEN (MiNEN). This distinction is based on the size of the tumor, lymphovascular invasion, mitotic index, Ki 67 index, invasion of adjacent organs, and presence of metastasis.[6] In our patient, small multiple lesions (1-2 cm) were noted involving both stomach & duodenum. As UGIE did not show any evidence of atrophic gastritis or ulceration, HPE of the specimen confirmed normal gastric mucosa apart from Well-differentiated NETs and he did not undergo serum gastrin level in the preoperative period, our patient cannot be classified under the above-mentioned types of G-NETs. However, based upon WHO classification, he had grade 1 well-differentiated NET with Ki67 of less than 2%.

Management of NETs can be done both endoscopically and surgically based on size criteria by ENETS guidelines.[9] Non-functional, non-ampullary localized NETs up to 1 cm size (small) can be resected endoscopically, 1-2 cm (intermediate) D-NETs management is controversial, and large (>2 cm) D-NETs or any size NET with lymphadenopathy should be managed with limited resection. The NCCN guidelines also recommend endoscopic resection for a small (<1 cm) well-localised DNET.[8] Based on ENETS guidelines patient will be followed up with multislice CT, SRS, and chromogranin A levels at 6 and 12 months and then annually for a minimum of 3 years. There is no consensus for how long one should follow-up such patients, at what interval follow-up should be done, and with what modalities it should be done remains unclear. What authors can agree upon is that the answer to these questions will vary based upon the biological behaviour

of the tumor, location, and stage at presentation, the treatment offered, histopathology reports.

CONCLUSION

This case draws attention to vague symptoms and equivocal clinical examination that NET may present with. Coexisting gastric NETs with duodenal NETs in itself is very rare, never the less its non-functional status and pre-operative diagnostic dilemma can often mislead clinicians. Here, we have drawn the attention of clinicians to the pros and cons of various diagnostic tools and how their utility can sometimes limit the approach of clinicians, despite of high index of suspicion.

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