Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Who were those MEN hiding behind the Ulcers?: A Case Report

Shazatul Reza Binti Mohd Redzuan and Yong Sy Liang

Endocrine Unit, Medical Department, Hospital Tengku Ampuan Rahimah, Selangor, Malaysia

Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disease caused by a mutation in the MEN1 gene. We present a 65-year-old man with MEN1 who has primary hyperparathyroidism, microprolactinoma, meningioma and gastrinoma. He had undergone parathyroidectomy followed by tumour excision of meningioma. The duodenal gastrinoma lesion was inoperable as it was close to the superior mesenteric artery with high surgery risk. Medical therapy with octreotide LAR had been initiated and showed good biochemical response as well as disease progression control. Chemoembolization was proposed if the duodenum lesion reduces in size on maintenance treatment with octreotide LAR. This case highlights the challenges in managing this rare condition and octreotide LAR has shown to be effective in controlling the disease progression in MEN1 with inoperable gastrinoma.

Key words: MEN1, gastrinoma, octreotide LAR, meningioma

INTRODUCTION

MEN 1 is an autosomal dominant disorder that is due to mutations in the tumor suppressor gene MEN1 which encodes a 610 amino acid protein, menin. MEN1 is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumours. Patients with MEN1 have decreased life expectancy and the outcomes of current treatment are not as successful because of multiple tumors, which are larger, more aggressive and resistant to treatment and concurrence of metastases. The prognosis for MEN1 patients might be improved by presymptomatic tumor detection and treatment specific for MEN1 tumors.

CASE

We describe a 65-year-old male who was referred to the endocrine service initially for poorly controlled diabetes. Review of his history revealed a Zollinger-Ellison syndrome that had initially presented with persistent diarrhea, abdominal pain and vomiting when the patient was in his late forties. Gastroduodenoscopy revealed multiple duodenal ulcers and esophagitis. Elevated fasting serum gastrin without proton pump inhibitor (PPI) at 405.8 ng/L (Reference value [RV]: 44-104 ng/L), confirmed the diagnosis. CT scan of the abdomen showed a well defined intensely enhancing nodule at the third part of duodenum (2 cm from the gastroduodenal junction) suggestive of gastrinoma. However, he defaulted follow up for many years prior to his presentation to us.

During our evaluation, he was worked up for MEN associated tumors in view of the history of Zollinger-Ellison syndrome. Further work up revealed high calcium level of 2.88 mmol/L, phosphate level of 0.68 mmol/L (RV: 0.81-1.45 mmol/L) and intact parathyroid hormone (iPTH) of 22.13 pmol/L and a diagnosis of primary hyperparathyroidism was confirmed. Otherwise, he had no clinical symptoms of hypercalcaemia such as bodily ache, constipation, osteoporotic fracture or renal stone. Others relevant blood tests are shown in Table 1. The patient underwent left superior and inferior parathyroidectomy. Histopathology analysis of the parathyroid glands revealed left inferior and superior parathyroid adenoma (Figure 1). His calcium level remained normal after the removal of the glands.

Table 1. Initial blood investigations

	Initial blood test	Reference value
Corrected Ca	2.88 mmo/L	2.20-2.65 mmol/L
Phosphate	0.68 mmol/L	0.81-1.45 mmol/L
iPTH	22.13 pmol/L	1.3-9.3 pmol/L
Prolactin	7235 mU/L	<500 mU/L
FT4	15.03 pmol/L	11-22 pmol/L
TSH	1.2 mU/L	0.3-5.6 mU/L
Testosterone	13.9 nmol/L	8.0- 31.3 nmol/L
GH	0.82 µg/L	<3 µg/L
IGF-1	272 µg/L	30-210 µg/L
24 Hour catecholamine		
Norepinephrine	22.7 µg/day	12.1-85.5
Epinephrine	10.0 µg/day	1.7-22.4
Dopamine	16.1 µg/day	<498.1
Gastrin	405.8 ng/L	44-104 ng/L

Pituitary MRI was done to screen for pituitary lesion showing right parietal lobe extraaxial tumour or meningioma with suprasellar lesion (Figures 2 and 3). Prolactin level was elevated at 7235 mU/L (RV: 86-324). Otherwise, he had no headache, vision problem or hypogonadism symptoms. He has since been on cabergoline 0.5 mg twice weekly. Surgery of right parietal tumour was offered at that time but the patient refused.

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: March 31, 2020. Accepted: October 2, 2020.
Published online first: October 30, 2020.
https://doi.org/10.15605/jafes.035.02.10

Corresponding author: Shazatul Reza Binti Mohd Redzuan, MD
Endocrine Fellow, Hospital Tengku Ampuan Rahimah
Jalan Langat, 41200 Klang, Selangor, Malaysia
E-mail: shazatulr@yahoo.com
ORCiD: https://orcid.org/0000-0002-1658-1538

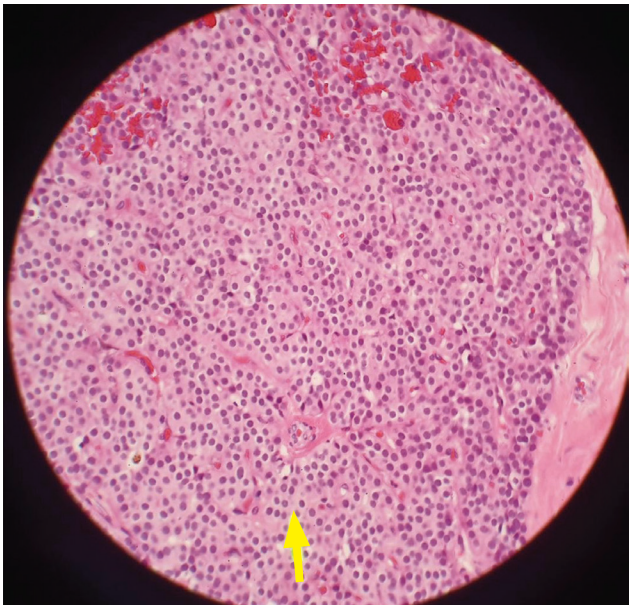

Figure 1. HPE of the parathyroid showing tumor cell with clear cytoplasm, arranged in sheets and cords traversed by delicate blood vessels (H&E, 100x).

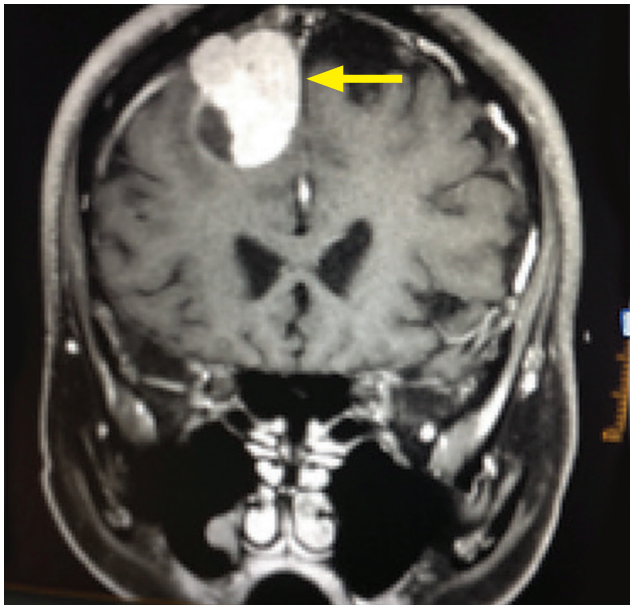

Figure 2. MRI of the brain showing a well-defined extra axial soft tissue mass in the right parietal lobe with cystic areas noted within the tumor.

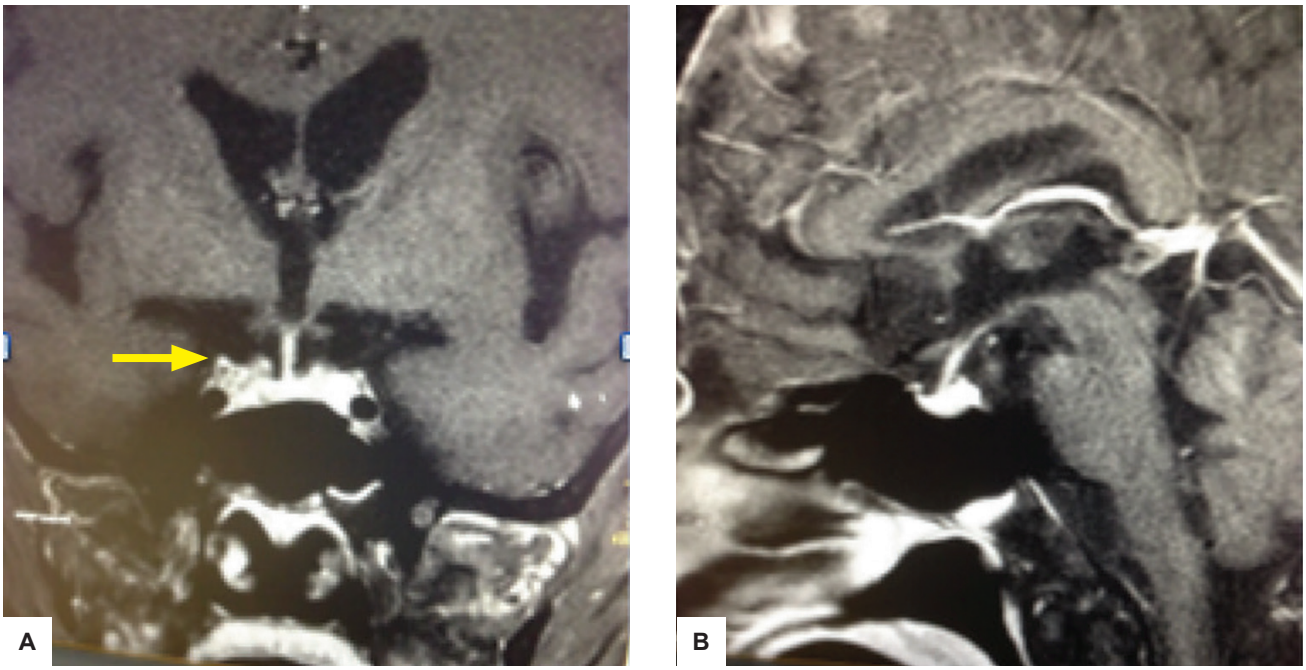

Figure 3. MRI of the pituitary showing small well-defined hypo to isointense nodules within the suprasellar region measuring 0.2x0.4x0.4 cm. **(A)** coronal view and **(B)** sagittal view.

Reassessment of the duodenal lesion with CT scan abdomen showed increasing size of the duodenal lesion at 13.0x8.1x5.1 cm (Figure 4). Repeated gastroduodenoscopy demonstrated prominent gastric fold and duodenitis. Endoscopic ultrasound was scheduled but he was not keen. He had symptoms of hypergastrinemia with peak gastrin levels 2013 pmol/L and symptoms improved with proton pump inhibitor (PPI).

He was suspected to have MEN1 due to presence of three primary MEN1 tumours which are gastrinoma, primary hyperparathyroidism and microprolactinoma. He denied having family history of MEN1 or MEN1 associated tumors. Genetic test was not performed for him due to unavailability of the test at that time. His 3 children were advised to go for health and genetic screening. One of his children tested positive for menin gene; the other 2 children's status are still unknown.

During follow-up, the patient was taking cabergoline 0.5 mg twice/week, alphacalcidol 0.25 mcg bd, esomeprazole 40 mg daily and basal bolus insulin. He was monitored clinically and CT scan abdomen was arranged in to monitor the size of the duodenal lesion.

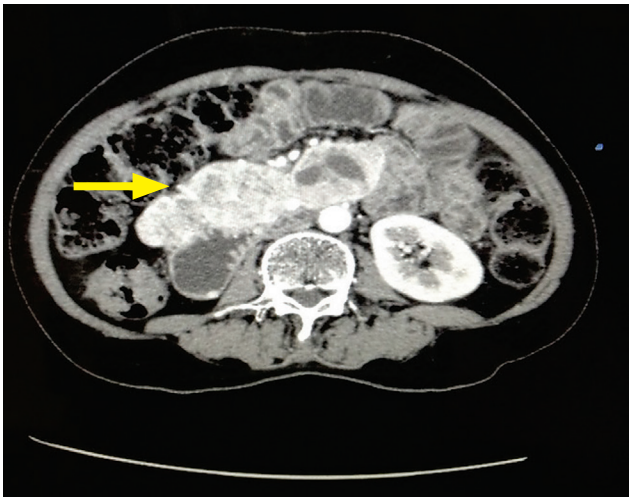

Figure 4. CT scan of the abdomen showing large well-defined multinodular and multilobulated, heterogenously enhancing mass lesion with irregular cystic component, arising from the wall of the 3rd part of the duodenum to proximal jejunum [13.0x8.1x5.1 cm (AP)].

Unfortunately, four years later, the patient developed insidious onset left sided body weakness and MRI brain showed right fronto-parietal extra axial enhancing mass with edema, mass effect with midline shift. He underwent right craniotomy and tumor excision for the right parasagittal mass. The histopathology examination of the tumor revealed right parietal lobe fibrous meningioma WHO grade 1. The surgery was complicated by massive upper gastrointestinal bleeding with hypovolemic shock.

Ga-68 Dotatate PET-CT was performed to look for metastatic lesions and showed increased uptake at the duodenum, stomach and abdominal nodes (Figure 5). There are multilobulated masses (5x12.5x9.4 cm) at the 3rd part of the duodenum (SUVmax 88.3), two foci at stomach wall at cardia (SUVmax 132), paracaval node at L1/L2 vertebral level (SUVmax 86.6) and aortocaval node at L1L2 vertebral level (SUVmax 69.7) measuring 0.9x1.2 cm and 1.5x1.2 cm respectively. The two foci in the stomach wall at cardia could be ulcer rather than metastasis to the stomach after discussion with nuclear medicine team.

The patient was started on intramuscular octreotide LAR 30 mg monthly after a multidisciplinary discussion involving his surgeon, nuclear medicine physician, interventional radiologist, oncologist and endocrine service to shrink the tumor and subsequently plan for chemo-embolization. However, patient was only keen for octreotide LAR until now. He reported improvement in symptoms especially gastric pain after treatment with proton pump inhibitor and octreotide LAR with better quality of life. His pituitary lesion, prolactin and calcium level remain stable.

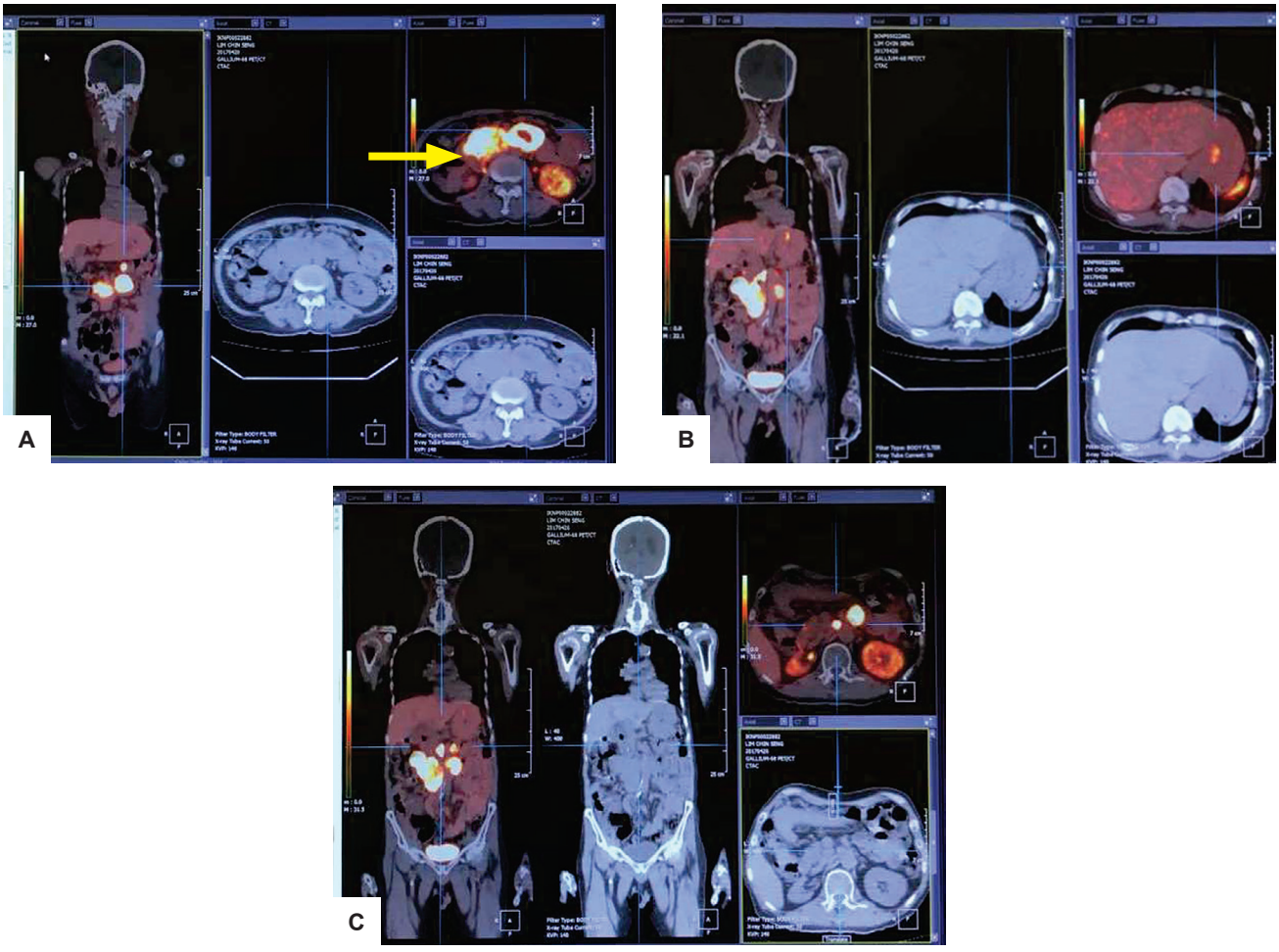

Figure 5. Ga-68 DOTATATE PET-CT showing uptake at 3rd part of duodenum (SUVmax 88.3), stomach (SUVmax 132) and abdominal nodes (SUVmax 69.7).

Table 2. Serial Investigation after octreotide LAR treatment

	Baseline	Before treatment	After octreotide LAR		
Date	2000	June 2017	September 2017	August 2018	February 2020
Gastrin (RV: 6-55 pmol/L)	405.8	2013	NA	630	680
Chromogranin A (RV: 27.0-94.0 ng/ml)	NA	14256	6564	>770	2500

NA: not available

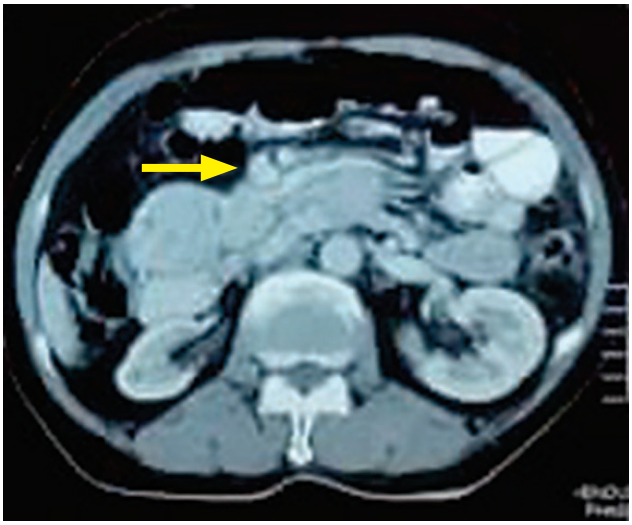

Figure 6. Repeated CT scan of the abdomen after octreotide LAR. Image showed similar size of duodenal lesion.

His serum gastrin and chromogranin A had reduced markedly after octreotide LAR (30 mg monthly) treatment (Table 2). PPI was discontinued prior obtaining the serum gastrin level. He has been maintained on this dose (Octerotide LAR 30 mg monthly) to date. Repeated CT scan abdomen after 5 months of octreotide LAR treatment revealed no significant change in the gastric, mesenteric and pancreatic lesion (Figure 6).

Currently he is being monitored closely for disease progression and symptoms of gastrinoma with yearly CT scan abdomen, Ga-68 Dotatate PET CT scan and biochemical investigations specifically fasting gastrin as well as chromogranin A.

DISCUSSION

MEN1 is a rare autosomal dominant disease caused by a mutation in the MEN1 gen (chromosome 11) encoding the tumor suppressor protein menin.[1] MEN 1 is suspected when two or more of the most common neuroendocrine tumors are found such as parathyroid tumor, pancreatic islet cell tumor and pituitary tumor. Approximately 80-90% of patients diagnosed with MEN1 show a MEN1 gene mutation.[2] The diagnosis of MEN1 can be made clinically on the basis of family history or genetic testing for a MEN1 gene mutation.[3] Our patient had gastrinoma/Zollinger-Ellison disease in his late forties, and then a few years later had primary hyperparathyroidism and micro-prolactinoma. This patient also had meningioma which is a rare tumor in MEN1. Meningiomas have been reported in about 8% of MEN1 patients and typically present later in life.[4] This case is a rare condition of meningioma in MEN1.

Genetic evaluation to confirm MEN1 gene mutation was not performed in this patient due to financial constraints as well as limited genetic tests available during that time. He denied having family history of MEN 1 or MEN associated tumor. One of his three children tested positive for menin gene.

Primary hyperparathyroidism is the most common feature of MEN 1 and occurs in approximately 95% of MEN1 patients.[5] Pancreatic neuroendocrine tumors (NET), consist of gastrinomas, insulinomas, glucagonomas, vasoactive intestinal polypeptidomas (VIPomas) and nonfunctioning pancreatic NETs occur in approximately 40-70% of MEN1 patients.[6] Anterior pituitary tumors consisting of prolactinomas, somatotrophinomas, corticotrophinomas and nonfunctioning adenomas occur in approximately 30-40% of patients.[7]

In the absence of treatment, these tumors are associated with an earlier mortality. Untreated patients with MEN1 have decreased life expectancy with 50% probability of death by the age of 50 and the cause of death in 50-70% is usually due to a malignant tumor process or sequelae of the disease.[8] In particular, malignant pancreatic NET and thymic carcinoid tumor were associated with a marked increase in the risk of death.

Subtotal parathyroidectomy has resulted in persistent or recurrent hypercalcaemia within 10-12 years after surgery in 40-60% of patients. For this case, patient had undergone parathyroidectomy and his calcium level was stable after 6 years of surgery. However, close monitoring of his calcium level together with regular assessment for symptom onset and complications are important, noting that patients with MEN1 have an increased risk of persistent or recurrent hyperparathyroidism due to tendency towards multiglandular disease.[9]

Gastrinoma is the most frequent functioning pancreato-duoedenal NET that causes gastric acid hypersecretion with the manifestation of the Zollinger-Ellison syndrome (ZES). The hypergastrinemia has a trophic effect on gastric mucosa and gastric enterochromaffin cell. It is diagnosed in at least 50% of MEN1 patients at the age of 50 and with higher prevalence in men.[8] ZES is associated with recurrent peptic ulcerations. These ulcers frequently appear small, less than 5 mms in diameter, with multiple nodular lesions arising deep in the mucosa. Gastrinomas usually grow slowly but frequently metastasize to peripancreatic lymph nodes and rarely to the liver.

The ideal treatment for a non-metastatic gastrinoma of the pancreas is surgical excision because the disease related survival in-patient with tumors that are more than 2 cm has improved after surgery.[10] In most patients with MEN1, gastrinomas are multiple and occur within the duodenum and surgical cure may be difficult. Most centers do not offer Whipple resection for the majority of MEN1 patients because fewer operations are associated with excellent survival.[11] Therefore, the surgical procedure needs

to be individualized according to preoperative findings and the patient's preference.

For this case, he was not a suitable candidate for Whipple surgery as the duodenal tumor is close to the superior mesenteric artery and is a high risk surgery. In our patient, multidisciplinary discussion involving a hepatobiliary surgeon, oncology and interventional radiologist had decided to start the patient on octreotide LAR for longer duration and then proceed with chemoembolization of the duodenal tumor.

Somatostatin analogue (SSA) has been demonstrated to control the growth of gastro-entero-pancreatic NETs but no data are available regarding their effects on the growth of MEN1 associated gastrinoma.[12] Only case reports or small series support the use of SSA in advanced gastrinoma, therefore it is difficult to quantify their ability to control tumor growth and disease progression. Tomassetti et al., had shown reduction in number and size of carcinoid tumors after 6 months of therapy and gross resolution of disease in 1 year. All the patients in the study had small tumors <1 cm in size, suggesting that LAR SSA maybe beneficial in controlling smaller disease burden.[13]

After 5 months of the somatostatin analogue treatment, our patient had reduction in the chromogranin A and gastrin level but not the size of duodenal tumor. Otherwise, clinically, the patient was feeling much better with less gastric discomfort and a better quality of life after somatostatin analogue treatment. In our patient, with a huge duodenal gastrinoma, long acting SSA appeared contributory in controlling disease progression.

CONCLUSION

We report a rare case of MEN1 with huge duodenal gastrinoma, primary hyperparathyroidism and micro-prolactinoma. The growth of gastrinoma tumor in MEN1 remained unchanged with octreotide LAR and symptoms were controlled with both the octreotide LAR and PPI. This case highlights that octreotide LAR has a potential role to control disease progression as well as improve quality of life and possibly increase survival rates in a patient with MEN1 with an inoperable, huge duodenal gastrinoma.

Ethical Considerations
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
Both authors declared no conflicts of interest.

Funding Source
None.

References

1. Christopoulos C, Papavassiliou E. Gastric neuroendocrine tumors: Biology and management. Ann Gastroenterol. 2005;18(2):127–40.
2. Falchetti A. Genetic screening for multiple endocrine neoplasia syndrome type 1 (MEN-1): When and how. F1000 Med Rep. 2010;2:14. PMID: 20948872. PMCID: PMC2948394. https://doi.org/10.3410/M2-14.
3. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990-3011. PMID: 22723327. https://doi.org/10.1210/jc.2012-1230.
4. Asgharian B, Chen YJ, Patronas NJ, et al. Meningiomas may be a component tumor of multiple endocrine neoplasia type1. Clin Cancer Res. 2004;10(3);869-80. PMID: 14871962. https://doi.org/10.1158/1078-0432.ccr-0938-3.
5. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658-71. PMID: 11739416. https://doi.org/10.1210/jcem.86.12.8070.
6. Thomas-Marques et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumor in patients with MEN1. Am J Gatroenterol. 2006;101(2):266-73. PMID: 16454829. https://doi.org/10.1111/j.1572-0241.2006.00367.x.
7. Trouillas J, Labat-Moleur F, Sturm N, et al. Pitutary tumor and hyperplasia in MEN 1: A case control study in a series of 77 patient versus 2509 non-MEN1 patient. Am J Surg Pathol. 2008;32(4):534-43. PMID: 18300794. https://doi.org/10.1097/PAS.0b013e31815ade45.
8. Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: A prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore). 2013;92(3):135-81. PMID: 23645327. PMCID: PMC3727638. https://doi.org/10.1097/MD.0b013e3182954af1.
9. Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. World J Surg. 2004;28(11):1139-42. PMID: 15490065. https://doi.org/10.1007/s00268-004-7560-8.
10. Norton JA, Jensen RT. Role of surgery in Zollinger-Ellison syndrome. J Am Coll Surg. 2007;205(4 Suppl):S34-7. PMID: 17916516. https://doi.org/10.1016/j.jamcollsurg.2007.06.320.
11. Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol. 2005;19(5):799-805. PMID: 16253901. https://doi.org/10.1016/j.bpg.2005.05.003.
12. Berardi R, Morgese F, Torniai M, et al. Medical treatment for gastro-entero-pancreatic neuroendocrine tumors. World J Gastrointest Oncol. 2016;8(4):389-401. PMID: 27096034. PMCID: PMC4824717. https://doi.org/10.4251/wjgo.v8.i4.389.
13. Tomassetti P, Migliori M, Caletti GC, Fusaroli P, Corinaldesi R, Gullo L. Treatment of type II gastric carcinoid tumors with somatostatin analogues. N Engl J Med. 2000;343(8):551-4. PMID: 10954763. https://doi.org/10.1056/NEJM200008243430805.