ORIGINAL RESEARCH PAPER

Medicine

KEY WORDS: GERD – Gastroesophageal reflux disease, MEN – Multiple endocrine neoplasia, NET – Neuroendocrine tumor, PPI – Proton pump inhibitor, PUD – Peptic ulcer disease, SRS – Somatostatin receptor syntigraphy, ZES – Zollinger Ellison syndrome

AN UNUSUAL CASE OF PEPTIC ULCER DISEASE CAUSED BY ZOLLINGER ELLISON SYNDROME

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ABSTRACT

Zollinger Ellison syndrome or gastrinoma is a neuroendocrine tumor which was first reported in 1955 by the two surgeons. NETs are considered as rare disorder but now the incidence is rising and it is not due to the increase in the disease burden but due to increased no. of patients being diagnosed. Autopsy studies have reported more than 1000 fold higher incidence. So ZES is also not as uncommon and now it is being diagnosed more. We need to have a high index of suspicion especially among the patients of refractory PUD and simple and cheap tests like fasting serum gastrin levels and gastric pH estimation are enough to diagnose ZES. Early diagnosis can be very crucial as 60%-90% of the gastrinoma tumors can become malignant and there are limited treatment options for the metastatic disease. Other investigations like endoscopic ultrasonography, CT scan, MRI and SRS are useful for delineating the tumor and planning definite management.

INTRODUCTION:

Zollinger Ellison syndrome (gastrinoma) is a neuroendocrine tumor which may originate from duodenum or pancreas. This syndrome is characterized by gastric acid hypersecretion resulting in severe acid peptic disease and diarrhea1. Previously reported incidence of pancreatic neuroendocrine tumors was 1-2/1,000,000 population but for the last two decades the incidence has increased to 4-5/1,000,000 population. 20-25% of pancreatic endocrine tumors are a part of inherited syndromes like multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL), neurofibromatosis and tuberous sclerosis2,3. Gastrinoma has a higher incidence among males and most of the tumors are diagnosed between the ages of 20 and 50 years. Although gastrinoma is being classified under the group of pancreatic neuroendocrine tumor but only 25% of gastrinomas are found in the pancreas. In sporadic ZES about 50 – 90% and in MEN 1 about 70 – 90% patients of ZES have duodenal gastrinomas. In few cases the tumors have been located in other intraabdominal sites i.e. mesentry, lymph nodes, biliary tract, liver, stomach & ovary. Rarely the tumor may be found in extraabdominal sites in heart and lung cancer3. Around 80% of the gastrinoma are detected in the gastrinoma triangle which is formed by joining three points, confluence of cystic duct and common bile duct superiorly, junction of first and second part of duodenum inferiorly and head and neck of pancreas medially4. Growth of these tumors shows different patterns, in 75% there is no growth or a slow growth but in 25% the growth can be aggressive. 50 - 90% of the gastrinoma can be malignant and metastasize to regional lymph nodes, liver and distant metastasis in the bones5. Patient have severe acid peptic disease symptoms and the presenting complaints are pain abdomen (75-100%), diarrhea (35-70%), pain and diarrhea (55-60%), heartburn (40-64%), duodenal ulcers (70-90%), complications like bleeding (1-17%), perforation (0-5%), obstruction (0-5%)3,4,5. The diagnosis of ZES is established by demonstrating inappropriate hyepergatsrinemia i.e. the high gastrin levels with a gastric pH of less than 3. The gatsrin levels of more than 1000pg/ml is highly diagnostic and secretin test is not required. Secretin test is not done routinely nowadays, only in few cases where we have to rule out other causes of hypergastrinemia like atrophic gastritis, achlorhydria, H. pylori infection. On endoscopy multiple ulcers, ulcers at unusual sites and in the distal sites are seen4,5. Once the diagnosis of ZES has been established the next step is to delineate the tumor and to know the extent of the disease to further plan the definitive management. For that the endoscopic ultrasonography, CT scan, MRI and somatostatin syntigraphy are used. Endoscopic ultrasonography is the most sensitive and cost effective method. It can detect lesions as small as 2 to 3 mm in diameter. However CT scan is readily available and the contrast enhanced CT can have a sensitivity of as high as 100 percent for NETs6. Staging of the tumor can be done according to the TNM staging of AJCC/UICC (eighth edition, 2017) and further management in the form of surgery can be planned. In few cases of metastatic disease chemotherapy has been used. Here we are presenting a case of ZES, as it really poses a challenge to make a diagnosis of ZES.

CASE DETAILS:

A 28 years man was admitted in medicine ward in august 2017 with the history of pain abdomen, loose stools and vomiting for 3 years. Pain was in epigastrium, burning character, non radiating, used to increase after meals. Loose stools were episodic, 3-4 stools per day, large volume, semisolid, associated with cramps. No history of blood or mucus in stools. Vomiting was also intermittent, vomitus was yellow in color, contained food particles. No history of blood in vomitus. All these symptoms were intermittent and mild initially and used to get relieved after taking medicines (PPI). But the symptoms were increased for last one year and he used to remain symptomatic for 18-20 days in a month affecting his daily life. There was history of weight loss in the form of loosening of clothes. He was diagnosed peptic ulcer disease one and half year ago from a private centre and was treated with H. Pylori eradication therapy. He had undergone a computed tomography scan (figure 1) at a private centre one year ago, where an asymmetric duodenal thickening in the first part of duodenum was reported. General physical examination and systemic examination was normal except tenderness in the epigastrium. His complete hemogram, liver and renal function tests, serum protein, serum albumin, serum electrolytes, serum calcium and thyroid function tests were within normal limit. Routine ultrasonography of the abdomen was also normal. Upper GI endoscopy revealed multiple ulcers in the duodenal bulb and D2. After this we suspected a possibility of Zollinger Elison syndrome and did a fasting serum gastrin levels, although he was on PPIs, which came out to be 1256 pg/ml (13-115 pg/ml). As he never had any GI bleed or any other complication of acid hypersecretion it was decided to do a serum fasting gastrin levels and gastric secretion pH levels after stopping PPIs for 2 weeks. He was discharged and was readmitted after 6 weeks with a 2weeks period off PPI; this time his fasting gastrin levels were 1580 pg/ml (13-115 pg/ml) and his gastric secretion pH was 2.6, serum prolactin and iPTH levels were normal. So he was diagnosed to have inappropriate hypergastrinemia. He now required an endoscopic ultrasonography and a somatostatin receptor syntigraphy (SRS) to localize the gastrinoma and to see the extent of the disease. It is to be noted that his CT scan at a private centre has already reported a thickening in the duodenum. As the facility was not available at our centre so he was referred to PGIMER Chandigarh. His SRS revealed somatostatin receptor

expressing lesion in the peripancreatic region of a size of 2.6 cms (figure 2). Endoscopic ultrasound guided FNAC revealed cellular clusters with tumor cells which round to oval in shape with few granular chromatin, inconspicuous nucleoli and scant amount of cytoplasm, which was suggestive of neuroendocrine tumor. After three months of work up he was finally admitted in surgery department of IGMC Shimla and was operated on 22nd Feb 2018 for the gastrinoma. Enucleation of the tumor (figure 3) was done along with resection of the peripancreatic lymph nodes. Cytology of the tumor revealed epithelial cells dispersed singly, in clusters and sheets forming acini and rosette patterns. Cells were round to oval with scant cytoplasm and salt and pepper chromatin, suggestive of neuroendocrine tumor (figure 4). Patient was discharged on PPI for 1 month and on follow up the patient was asymptomatic.

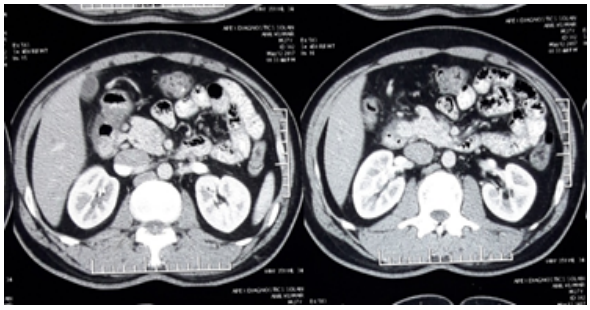

Figure 1: CT scan showing thickening of the first part of duodenum.

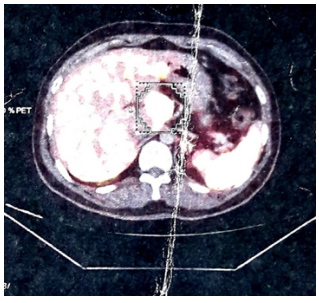

Figure 2: SRS image showing somatostatin receptor expressing lesion in peripancreatic region.

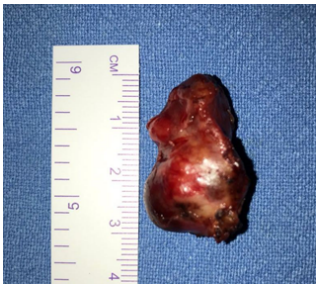

Figure 3: Tumor excised of a size of 3 cms.

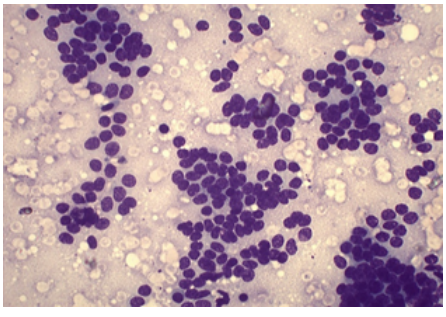

Figure 4: Cytology of the tumor showing epithelial cells dispersed singly, in clusters and sheets forming acini and rosette patterns. Cells were round to oval with scant cytoplasm and salt and pepper chromatin.

DISCUSSION:

ZES is a rare disorder characterized by gastric hypersecretion. Its symptoms are shared by many other disorders like PUD, GERD, chronic pancreatitis, gastric outlet obstruction, gastric carcinoma. So the patient may be subjected to a battery of investigations and the diagnosis is usually delayed for about 5-6 years[1,2,3]. In our case also the diagnosis was delayed for 3 years. So to diagnose ZES early we need to have a high index of suspicion. Patients usually have severe acid peptic disease symptoms and chronic osmotic diarrhea. Diarrhea is due to excessive gastric secretion, inactivation of pancreatic enzymes due to low pH, inability to absorb sodium and water due to high serum gastrin concentration[7]. In our patient also diarrhea was a prominent symptom along with the PUD symptoms. So if we have to delineate the key points for diagnosing ZES then we can say that any patient who is having recurrent PUD, no response to H2 blockers, associated with diarrhea, progressively increasing symptoms, presenting with complications like strictures or perforation, UGI endoscopy reveals multiple ulcers and ulcers at unusual sites and distal to first part of duodenum. Such patients should be suspected to have ZES. Once the ZES is established then MEN 1 should be ruled out. In our patient prolactin and iPTH levels were normal. The aim of medical treatment is to decrease the basal acid output to less than 10mEq/hr and raise the gastric pH more than 4. To achieve this the patient usually requires higher doses of PPI i.e. Omeprazole 60mg, Pantoprazole 120mg and Rabeprazole 60mg daily may be required. Most of the patients tolerate PPI without tachyphylaxis[8]. Our patient was symptom free on 40mg of pantoprazole. Sporadic cases of gastrinoma without metastatic disease should undergo an exploratory laparotomy and resection of the tumor. The surgery will decrease the need of PPI and will decrease the morbidity and risk of having malignant conversion and metastatic disease. Surgery is not routinely recommended in patients with MEN 1 syndrome because of the multifocal nature of the tumors. Jeffery A. Norton et al in their study of 151 patients observed the disease free rate immediately after surgery was 51% in sporadic cases and 16% in patients with MEN 1[9]. Our patient had undergone enucleation of the tumor along with resection of the peripancreatic lymph node excision. Guidelines from the national comprehensive cancer network recommends follow up in 3-6 months post resection with physical examination, fasting serum gastrin levels and computed tomography or magnetic resonance imaging. Long term follow up can also be done 6-12 months with physical examination and tumor markers. Imaging may be considered only if recurrence is suspected clinically[10].

REFERENCES:

1. Ellison EC, Johnson JA. The Zollinger Ellison syndrome: a comprehensive review of historical, scientific and clinical considerations. Curr Probl Surg 2009; 46:13.
2. Oberg K. pancreatic endocrine tumors. Semin Oncol 2010; 37:594.
3. J. Larry Jameson, Robert T. Jensen, et al. Harrison's endocrinology 2017; 4: 378-379.
4. David C Metz. Diagnosis of the Zollinger Ellison Syndrome. Clinical gastroenterology and hepatology 2012; 10:126-130.
5. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors : pancreatic neuroendocrine tumors. Gastroenterology 2008; 135:1469-1492.
6. Khashab MA, Young E, Leennon AM, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc 2011; 73:691.
7. Berna MJ, Hoffmann KM, Serrano J, et al. Serum gastrin in Zollinger Ellison syndrome: Prospective study of fasting serum gastrin in 309 patients from the national institutes of health and comparison with 2229 cases from the literature. Medicine (Baltimore) 2006; 85:295.
8. Jensen RT, Fraker DL. Zollinger Ellison syndrome. Advances in treatment of gastric hypersecretion and the gastrinoma. JAMA 1994; 271:1429.
9. Jeffery A. Norton, Douglus L Fraker, et al. Surgery to cure the Zollinger Ellison syndrome. N Engl J Med 1999; 341:635-644.
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. https:// www. nccn. org/ professionals/ physician gls/ pdf/ neuroendocrine.pdf (Accessed on February 20, 2018).