

## Case Report

# Man with sporadic MEN1 and Zollinger Ellison syndrome: A case Report

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- Sporadic
- Diarrhea
- PNET
- Zollinger-Ellison
- Everolimus
- Somatulin

## Abstract

**Background:** MEN1 is a rare hereditary syndrome which manifests a variety of endocrine and non-endocrine neoplasms and lesions.

**Introduction:** A 59 year-old male with good clinical status was referred to our hospital due to chronic episodes of diarrhea. Imaging studies revealed multiple polyps in various parts of the colon, a pancreatic tail tumor, 2 hepatic lesions, bilateral adrenal hyperplasia and pituitary microadenoma. The parathyroid sestamibi scan showed abnormal concentration of radioactivity. He was submitted to peripheral pancreatectomy/ splenectomy. Biopsy revealed a well differentiated NF, G2 pNET. Blood examination showed high PTH and gastrin levels. Gastroscopy suggested Zollinger Ellison syndrome. Genetic examination demonstrated a pathogenic MEN1 mutation and further exams supported this diagnosis. His brother was also tested and found negative for any gene mutation. He was treated postoperatively with Everolimus and RFA for local hepatic control. On progression he was treated with Somatulin Autogelin monthly. His hypergastrinemia subsided and he remains asymptomatic on close follow up.

## ABBREVIATIONS

PPIs: Proton Pump Inhibitors; WBCs: White Blood Cells; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; ALP: Alkaline Phosphatase;  $\gamma$ GT:  $\gamma$ -Glutamyltranspeptidase; LDH: Lactate Dehydrogenase; CRP: c- Reactive Protein; ESR: Erythrocyte Sedimentation Rate; SYN: Synaptophysin; VIP: Vasoactive Intestinal Peptide; PP: Pancreatic Polypeptide; PTH: Parathyroid Hormone; ACTH: Adreno-Corticotrophic Hormone; PNET: Pancreatic Neuroendocrine Tumor; MEN1: Multiple Endocrine Neoplasia; MRI: Magnetic Resonance Imaging; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular hemoglobin; INR: International Normalized Ratio; DHEA: Dehydroepiandrosterone; RFA: Radiofrequency Ablation; NF: Non Functional

## INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a syndrome

phenotypically characterized mainly by tumors in the anterior pituitary, parathyroid, adrenal glands and the presence of gastrointestinal neuroendocrine tumors. It may occur in either familial (90% of cases), or sporadic forms. Germline or somatic mutations of the tumor suppressor gene MEN1 (11q13), encoding menin protein, are responsible for the syndrome. Considerable phenotypic variability of tumor type, clinical manifestations and age at diagnosis has been reported [1].

## CASE PRESENTATION

A 59 year-old male, retired driver, was admitted to the Oncology Department of Evangelismos General Hospital for the investigation of intermittent episodes of diarrhea. In his medical history type 2 diabetes mellitus under antidiabetic treatment since 2009 and episodes of symptomatic urolithiasis, due to which he underwent lithotripsy, are reported. Smoking (60 p/y) and consumption of 2-3 spirits (50 gr of alcohol daily) until last

year is worth stating concerning his social history. With regards to his family history, he has a healthy younger brother. His father died at the age of 78, with the cause of his death remaining unclear and his mother at the age of 65 from multiple myeloma.

He was afflicted by his disease 7 years ago with the occurrence of almost daily, 2-3 watery diarrheas, which were attributed at first to irritable bowel syndrome. He started therapy with PPIs and anti-diarrheal drugs and an impressive retrieval of symptoms was noted; nevertheless, diarrhea relapsed after medical therapy cessation. The patient underwent gastroscopy on April 2007 which revealed gastritis of the antrum, mild duodenitis and 2<sup>nd</sup> degree esophagitis. Biopsies from the second part of the duodenum showed normal mucosa. At colonoscopy (1/2008), multiple polyps were found at the sigmoid, descending colon and rectum. The histological examination indicated tubulovillous adenomas without elements of dysplasia or malignancy. On April 2013, he was hospitalized at the local hospital due to relapse of daily diarrheas and vomiting. There was no positive sign at physical examination. The blood examination results were: WBCs: 7070/ $\mu$ l (45% neutrophils, 39% lymphocytes), hemoglobin: 11gr/dl (MCV: 83 ), platelets: 256.000/ $\mu$ l, INR: 1,1, urea: 58mg/dl, creatinine: 1,15 mg/dl, Na<sup>+</sup>: 135 mmol/l, K<sup>+</sup>: 4,8 mmol/l, albumin: 3gr/dl, AST: 15 IU/lit, ALT: 13 IU/lit, ALP: 103 IU/lit,  $\gamma$  GT: 33 IU/lit, LDH: 150 IU/lit, amylase: 79 IU/lit, Ca<sup>++</sup>: 10,4 mg/dl, P<sup>++</sup>: 2,9 mg/dl, CRP: 3,4 mg/dl, ESR: 35 mm/h. Fecal culture and parasitological exam disclosed no findings. Both computed and magnetic resonance tomography scan showed a polycystic tumor of the pancreatic body and tail, focal hepatic metastatic lesions at segments I and II ,multiple cysts of both kidneys, bilateral adrenal hyperplasia and a lipoma at the region of the right rhomboid muscle. The dimensions of the pancreatic tail tumor were 5x3 cm and those of the nodular lesions of the right and left adrenal gland 3, 4x2, 1 and 2, 3x1, 2 cm, respectively. Biopsy was attempted twice with the use of endoscopic ultrasound, but failed due to technical reasons. Acute abdomen resulted as a complication of the handlings and the patient was operated urgently. Excisions of the 2nd part of the duodenum with part of the jejunum and jejuno duodenal anastomosis were performed. The histological examination of the excised material was negative for malignancy. On July 2013 the patient was submitted to peripheral pancreatectomy and splenectomy. Biopsy revealed a well differentiated pancreatic neoplasm G2, pT1 (1-6 mitoses/10 HPF, Ki67:10%) with immuno phenotype: Syn (+), CD56 (+), lack of expression of glucagon, VIP, PP, gastrin, serotonin, somatostatin, PTH, ACTH, calcitonin, CK19, vimentin,  $\beta$ -catenin, a-1-Antithrypsin and CD10. There was no retrieval of the symptoms postsurgically and the patient started treatment with PPIs again. At an octreoscan there was increased radio drug intake in two hepatic lesions, whose biopsy indicated the presence of neoplastic proliferation from the same malignancy. Serum chromogranin values were consistently higher than 100 nmol/lit. Serum gastrin levels fluctuated between 1092 and 4265 pg/ml postsurgically. A gastroscopy was performed again because there was no gastrin staining at the histological preparation. Hyperplasia of neuroendocrine cells of the stomach antrum and body, mild gastritis, HP (-) were found, which were compatible with Zollinger- Ellison syndrome. MEN1 syndrome was suspected due to the consistent imaging of the

adrenal enlargement in a patient with PNET and gastrinoma. A hypophysis MRI was conducted which exposed the presence of a microadenoma, while the values of cortisol, free T4, testosterone, prolactin and IGF-1 were normal. At a parathyroid ultrasound, two sub-echo formations 2, 1 and 0, 7 cm were noted. The blood examination showed increased PTH (200 pg/ml) with normal Ca<sup>++</sup> levels. A 99m Tc sestamibi scan was performed, which disclosed 3 abnormal lesions on the thyroid (2 on the left lobe and 1 on the right). The functional control of adrenal activity demonstrated conservation of the secretion rate (normal values of cortisol, ACTH, aldosterone, renin, DHEA and no suppression of cortisol with Dexamethazone). The confirmative molecular control illustrated heterozygote mutation c1A>T (p M1L) at the exon 2 of the MEN-1 gene. The molecular examination of his 53 year old brother was negative.

He started on treatment with Everolimus 10 mg daily [2,3], on 1/4/2014. He was also submitted to liver RFA for local control. On 1/2016, progressive disease was documented at an octreoscan with the portrayal of a new lesion at the pancreas. There were two lesions at the liver with low uptake of the drug, probably due to the prior treatment with RFA. The patient was treated with a monthly intramuscular injection of Somatulin autogel 120  $\mu$ g [4,5]. Reevaluations after 3 and 6 months respectively indicated stable disease. On October 2016, the patient was submitted to parathyroidectomy, which disclosed hyperplasia.

The patient follows treatment with Somatuline Autogel 120  $\mu$ g once a month, without evidence of progressive illness at a new octreoscan on 2<sup>nd</sup>/2017. He suffers from no gastrointestinal symptoms and his hormone values are in the normal range.

## DISCUSSION

We present a case report of a 59 year old male patient with sporadic MEN1 syndrome. The age of diagnosis was absolutely compatible with the experience from other authors [6]. Examination for Von Hippel Lindau and other related autosomal syndromes was negative.

Hyperparathyroidism is the main feature of MEN1 in about 80% of patients. Our patient had elevated PTH with normal serum Ca<sup>++</sup>. Parathyroid scan demonstrated two sub-echo lesions. In bibliography parathyroid tumors are reported in patients with MEN1 syndromes [7].

Pancreatic endocrine tumors occur in 70% of patient with MEN1. In more than 60% gastrinomas are diagnosed, which are manifested as Zollinger Ellison syndrome. The clinical findings of this syndrome such as epigastric pain, diarrheas were present in our patient. Esophageal reflux and peptic ulcer symptoms were absent probably due to use of PPIs [6].

Pituitary tumors in sporadic MEN1 syndromes are symptomatic in 25% of cases [6]. Our patient had a small, asymptomatic solitary pituitary tumor which was diagnosed during the investigation at clinical and biochemical basis.

Skin lesions such as angiofibromas, collagenomas and lipomas occur in 90%, but can be easily overlooked because of their subtle appearance [6]. In our case a right rhomboid muscle lipoma of no clinical significance was found. The clinical diagnosis of MEN1 is based upon the occurrence of two or more primary

MEN1 tumors types (parathyroid glands, anterior pituitary and enteropancreatic).

As for screening is concerned, first and second degree relatives should be checked genetically. Early screening reduces the age of detection by many years. In our patient his 53 year old brother was found negative for any known mutation [8].

The usefulness of surgical treatment of PNET with MEN1 remains unclear. Cytoreductive surgery is crucial for controlling symptoms and reducing the risk of metastasis. Our patient underwent peripheral pancreatectomy / splenectomy and RFA for the hepatic lesions with response of his diarrhoical syndrome. According to the bibliography, in metastatic PNETs curative resection involves at least 90% of the metastatic lesions. Postoperatively he received systematic therapy with Everolimus at first and on progressive disease with Somatulin Autogel, according to the NCCN guidelines and remains on close follow up.

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