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Case Report

Multiple endocrine neoplasia type 1 (MEN1) presenting with renal stones: Case report and review

Mohamed N. Ibrahim, MD*, James Liem, MD, Ahmed ElKady, MD

Department of Diagnostic Radiology, Rotherham General Hospital, Moorgate Road, Rotherham, South Yorkshire S60 2UG, United Kingdom

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ABSTRACT

Multiple endocrine neoplasia type 1 (MEN1) is a complex, autosomal dominant inherited syndrome characterized by 3 different tumors (parathyroid, anterior pituitary, and pancreatic islet). The diagnosis is defined clinically by the presence of 2 or more primary tumors. We report the case of a 35 years old patient who presented with recurrent renal stones and imaging findings for MEN1. Computed tomography pancreas revealed a mass in the tail which was confirmed by magnetic resonance imaging. Ultrasound of her neck showed a mass on the left side and MIBI scan diagnosed a parathyroid adenoma which was later pathologically confirmed.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a complex, autosomal dominant inherited syndrome caused by mutations in the MEN1 tumor suppressor gene. The diagnosis is defined clinically by the presence of at least 2 primary MEN1 tumors (parathyroid, anterior pituitary, and pancreatic islet). We described a case of MEN 1 who presented with 3 types of tumors showing classic imaging studies. Written consent from the patient was taken and approval of the research office of the hospital.

Case report

A 35-year-old female presented to the Urgent and Emergency care center with left flank pain and vomiting. The urine dipstick was negative. Her past medical history included a prolactinoma for about 12 years and recurrent renal stones for a few years. She has a family history of parathyroid diseases and unknown abdominal tumors. She was on 500 mcg cabergoline once per week to treat hyperprolactinemia with the previous noncompliance to medication.

Her blood tests were – Calcium: 3.48 mmol (2.1–2.6), Phosphate: 0.6 mmol (0.8–1.5) Parathyroid: 54.37 pmol/L (1.95–8.49). Her kidney function tests and eGFR were normal.

* Corresponding author.

E-mail address: mohamednabil2005@gmail.com (M.N. Ibrahim).

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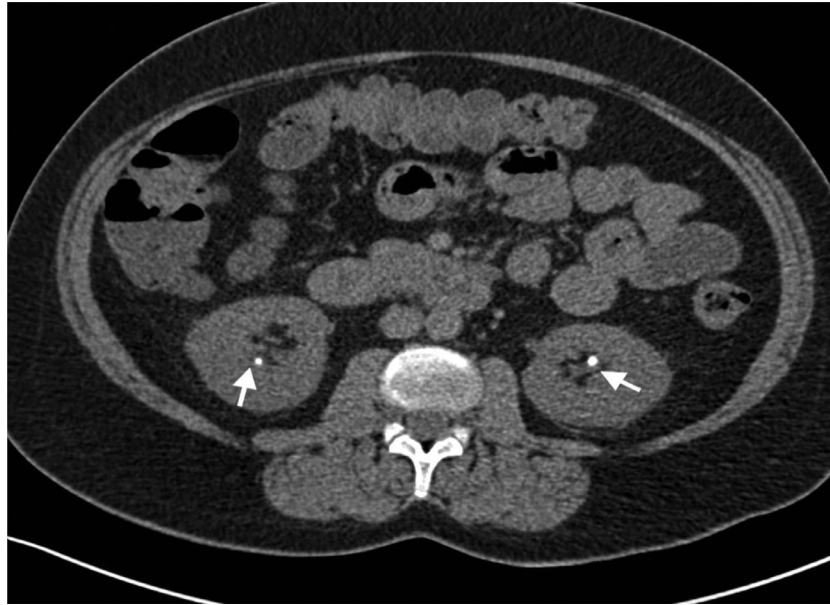


Fig. 1 – Noncontrast CT KUB showing bilateral small renal stones (white arrows). No hydronephrosis.

Vitamin D level was 30 nmol/L (<25 nmol/L) and the Prolactin level was 3341 mIU (0–646). TSH was normal. Computed tomography KUB was requested shortly in urgent and emergency care center (Fig. 1).

The patient was admitted to the hospital under the medical team to treat her hypercalcemia. Two days after admission a CT pancreas was performed (Fig. 2).

An magnetic resonance imaging Pancreas 3 days later confirmed the findings (Fig. 3).

She had a previous magnetic resonance imaging pituitary gland 6 years ago (Fig. 4).

Two weeks after admission a neck ultrasound followed by a MIBI scan was requested (Figs. 5 and 6).

Our patient had a history of a pituitary prolactinoma and newly discovered pancreatic and parathyroid tumors, meeting the clinical criteria for the diagnosis of MEN. Her young age at presentation and family history of parathyroid disease suggest familial MEN1.

Parathyroidectomy was done after 1 month and histopathology confirmed the parathyroid adenomatous tissue with some atypical features but no evidence of invasive neoplasia.

Afterward, she had developed a new episode of renal stone disease and hydronephrosis after which a nephrostomy tube was inserted.

Discussion

MEN1 is a rare autosomal dominant hereditary tumor syndrome with a high degree of penetrance, that is caused by inactivating mutations of the tumor suppressor gene *MEN*, and is characterized by a predisposition to a multitude of endocrine and nonendocrine tumors [1].

MEN1 syndrome is most commonly inherited as an autosomal dominant condition (90%) but can occur sporadically, with an incidence of 0.25% from random postmortem studies [2,3].

The diagnosis of MEN1 can be made clinically based on family history, or directly with genetic testing for a MEN1 mutation [2]. The clinical diagnosis of MEN1 includes the presence of 2 or more primary endocrine tumors associated with MEN1 (parathyroid adenomas, enteropancreatic tumors, and pituitary adenomas) [2,4]. The diagnosis based on family history requires only 1 of the associated primary endocrine tumors in someone who has a first-degree relative with diagnosed MEN1 (Table 1) [2].

Parathyroid adenomas are the most frequently occurring tumor in patients with MEN1, occurring in 90% of patients by age 40 [3,5]. These tumors can cause primary hyperparathyroidism and patients may present with hypercalcemia, nephrolithiasis, and osteitis fibrosa cystica [2,4,6]. The age at symptoms onset of parathyroid adenoma is earlier in patients with MEN1 compared to those without and typically occurring at approximately 20–25 years of age compared to 55 years of age, respectively [2].

Furthermore, it is estimated that 1%–18% of patients diagnosed with primary hyperparathyroidism will have MEN1. The degree of hypercalcemia in these individuals is usually mild and patients may be asymptomatic or present with polydipsia, polyuria, constipation, malaise, altered mentation, hypertension, shortened QT interval, peptic ulcer disease, urolithiasis, and/or decreased bone mineral density with increased fracture risk. There is a high prevalence of urolithiasis and early bone mineral loss in young individuals with MEN1-associated primary hyperparathyroidism, and bone or renal complications are progressively more frequent, extensive and severe in long-standing primary hyperparathyroidism cases and those associated with gastrinoma [7,8].

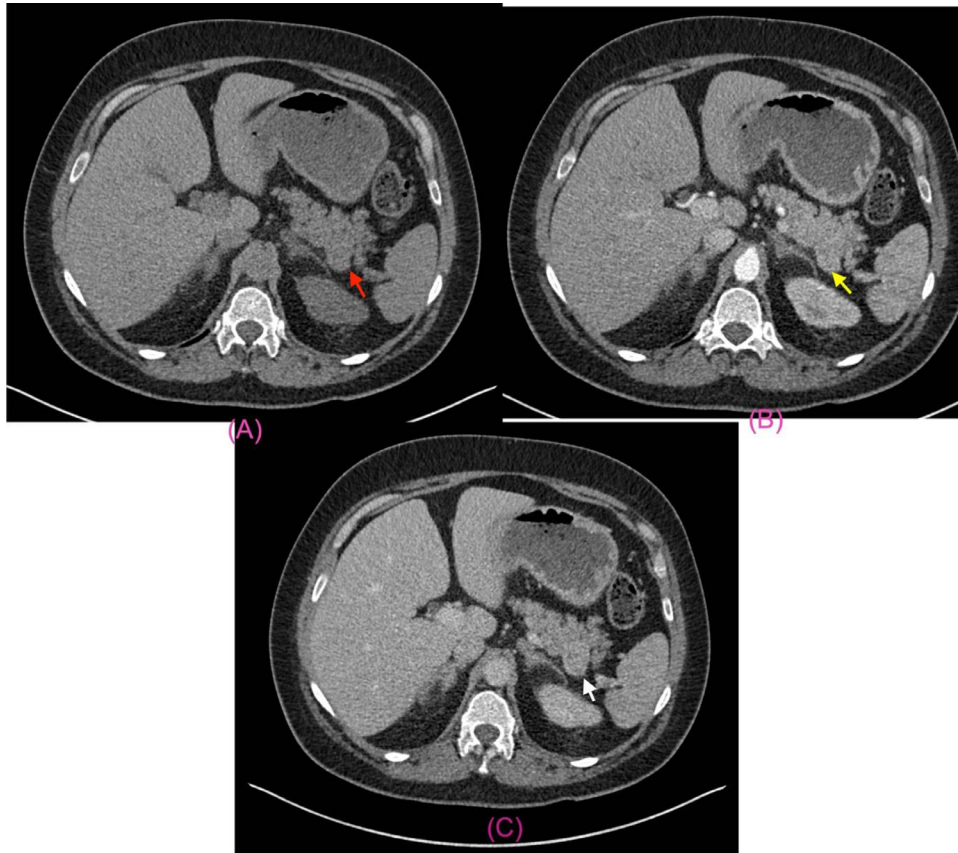


Fig. 2 – (A) Pre-contrast CT pancreas: showing a solid isodense mass compared to the pancreatic parenchyma in the tail of the pancreas measuring 2.5 × 2.1cm (red arrow). (B) Postcontrast arterial phase: the mass demonstrates Iso to mild high attenuation compared to the pancreatic parenchyma (yellow arrow) (C) Venous phase: the lesion is also seen as a well-circumscribed hyperdense mass (white arrow). (Color version of figure is available online.)

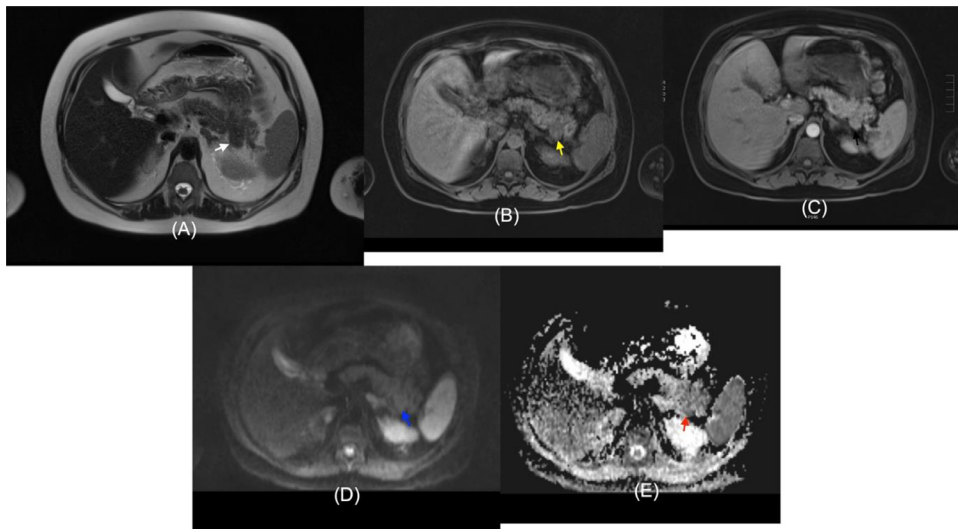


Fig. 3 – (A) MRI pancreas axial T2 WIs: confirms the mass in the pancreatic tail appearing iso-intense compared to the pancreatic parenchyma (white arrow) (B) Axial T1WIs precontrast: the mass appearing hypointense compared to the rest of the pancreas (yellow arrow). (C) Postcontrast arterial phase: enhancement similar to pancreatic parenchyma (black arrow). (D) MRI pancreas DWIs (B value 400): the mass shows mild diffusion restriction (blue arrow). (E) ADC map: shows a relative signal loss (red arrow). (Color version of figure is available online.)

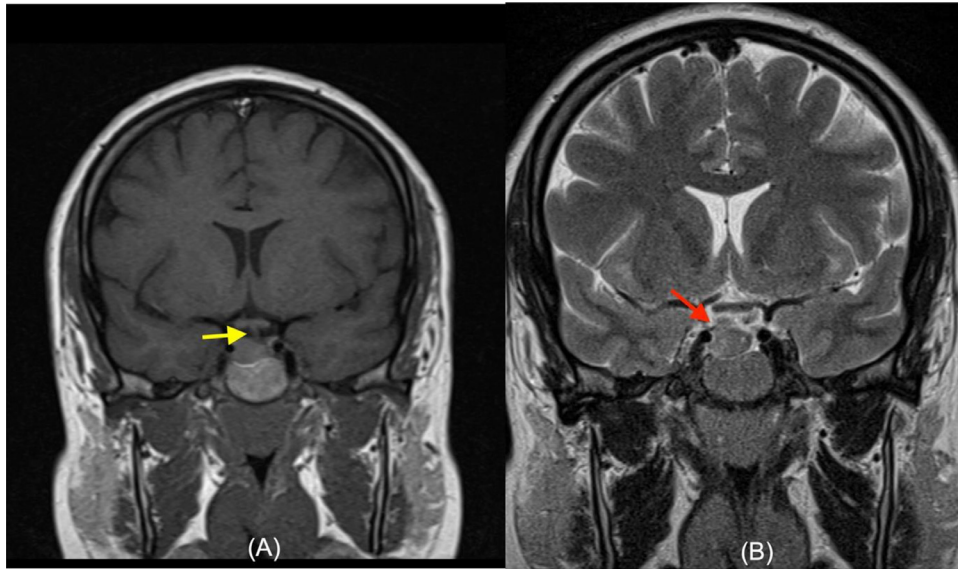


Fig. 4 – (A) MRI pituitary gland coronal T1WIs: reveals deviation of the pituitary stalk to the left side (yellow arrow) (B) Coronal T2WIs: shows a small mass of isointense signal to the grey matter in the right aspect of the pituitary gland measuring 7 mm (red arrow), the appearance is consistent with a microadenoma. (Color version of figure is available online.)

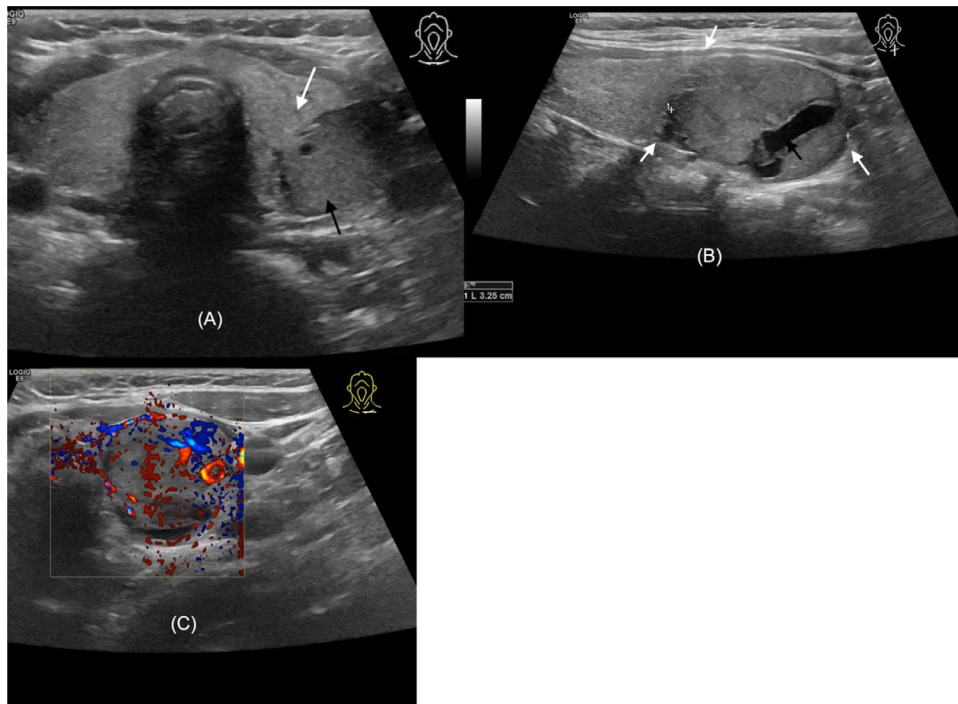


Fig. 5 – (A) Transverse greyscale U/S image of the neck: shows a hypoechoic nodule compared to the thyroid parenchyma in the left side of the neck measuring 3.3 x 2.2 cm (black arrow) with a normal appearance of the left thyroid lobe (white arrow) (B) Longitudinal greyscale image: the nodule lying close to the inferior aspect of the left thyroid lobe (white arrows) with anechoic central areas representing cystic changes (black arrow) (C) Doppler mode image of the neck: the nodule showing increased vascularity.

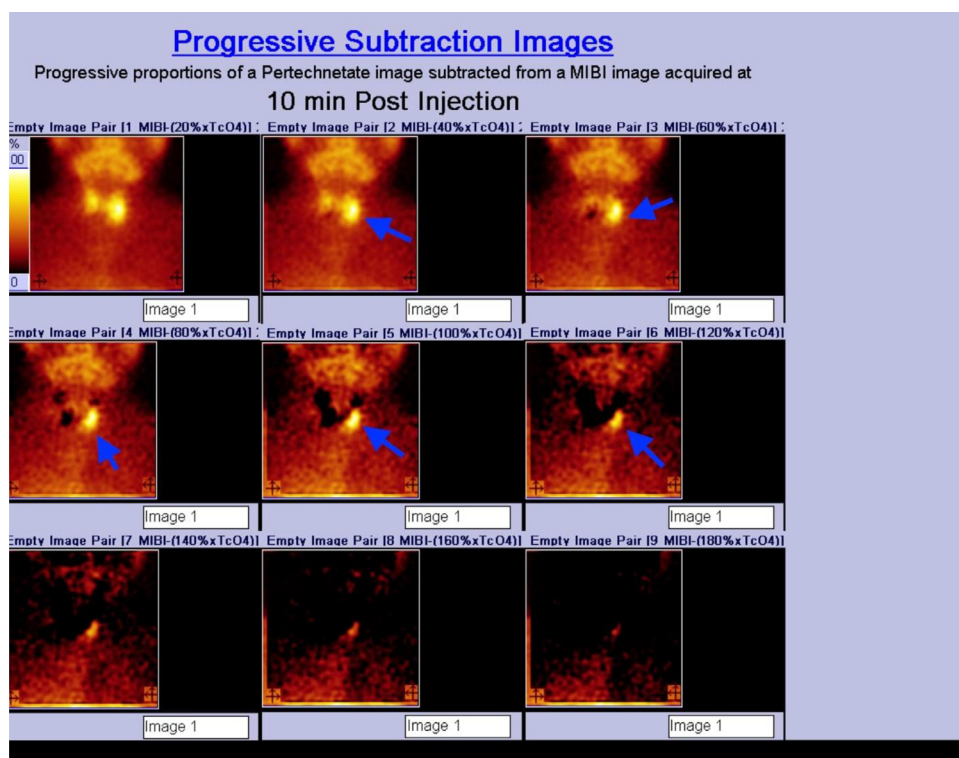


Fig. 6 – Progressive proportions of pertechnetate image subtracted from MIBI image acquired at 10 min post-injection demonstrating persistent activity on the subtraction images related to the left lower pole in keeping with a parathyroid adenoma (blue arrow). (Color version of figure is available online.)

Table 1 – Diagnostic criteria for MEN1* [2]

1. The occurrence of two or more primary MEN1-associated endocrine tumors (ie, parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma)
2. The occurrence of one of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN
3. Identification of a germline MEN1 mutation in an individual who may be asymptomatic and has not yet developed serum biochemical or radiological abnormalities indicative of tumor development

MEN1, multiple endocrine neoplasia type 1.

* To make a diagnosis of MEN1, a patient must fulfill at least one of three criteria.

Our patient presented in her mid-thirties but she had previously experienced 2 episodes of nephrolithiasis during her late twenties with calcium-rich stones. During workup, the patient's serum calcium and parathyroid hormone levels were both elevated.

Evaluation for patients with hyperparathyroidism typically includes an ultrasound scan as an initial screening for underlying parathyroid adenoma followed by nuclear technetium Tc-99m sestamibi scintigraphy for confirmation. Sestamibi scintigraphy has a sensitivity and specificity of >90% for lesions that demonstrate retention of sestamibi radiotracer on delayed imaging [9].

Management of parathyroid adenomas is typically surgical, with the removal of the overactive glands with either a subtotal or total parathyroidectomy; however, noting that patients with MEN1 have an increased risk of persistent or recurrent hypercalcemia after subtotal surgery, which is thought to be

secondary to their tendency toward multiglandular disease, is important [2,10].

In our case, one parathyroid adenoma was identified by initial ultrasound screening and confirmed with sestamibi scintigraphy.

Biochemical screening for primary hyperparathyroidism in patients with MEN1 should be performed annually with an assessment of serum calcium and parathyroid hormone levels [2].

Pancreatic neuroendocrine tumors (pNETs) are estimated to occur in 30%-80% of patients with MEN1, and up to 80%-100% of patients in postmortem studies. MEN1 is the most common hereditary syndrome associated with pNETs with approximately 10% of all pNETs being associated with MEN1 [11].

Although not the most common tumors, malignant enteropancreatic neuroendocrine tumors are the leading cause

of mortality in patients with MEN1 [5]. Associated tumors of the pancreatic islet cells can be either functioning (hormone-secreting) or nonfunctioning (non-hormone-secreting). Hormone-secreting tumors include gastrinomas (40% incidence), insulinomas (10% incidence), and vipomas and glucagonomas (2% incidence) [3].

Gastrinomas, the most commonly occurring enteropancreatic tumor in patients with MEN1, are often multiple, with metastases identified in approximately 50% of these patients at the time of diagnosis [3]. Malignant gastrinomas account for the majority of neuroendocrine tumor-related MEN1 deaths [5]. Clinically, gastrinomas cause gastric acid hypersecretion and recurrent peptic ulcers with diarrhea, known as Zollinger-Ellison syndrome [12,13]. Nonfunctioning pNETs are among the most common enteropancreatic tumors in MEN1 [14].

Our patient did not have symptoms or laboratory findings to suggest that the pancreatic tail tumor is hormonally functioning.

Pituitary tumors may occur in up to 60% of patients with MEN1, although the frequency reported in the literature is variable [3]. Prolactinomas are the most commonly occurring pituitary tumors in patients with MEN1, with a prevalence of 20% by age 40 [3].

Patients with pituitary tumors can present with headaches and visual field deficits because of tumor size and growth. Prolactinomas in particular can cause erectile dysfunction and decreased libido in men or amenorrhea and galactorrhea in women resulting from increased prolactin [2]. The management of prolactinomas typically involves transphenoidal resection of the tumor or medical management with bromocriptine or cabergoline therapy. MEN1-associated pituitary tumors, however, tend to be more aggressive and resistant to therapy and surgery than sporadic pituitary tumors [2].

In our case, the patient had a history of galactorrhea which was treated with cabergoline and was under regular follow-up of her prolactin from 6 years before the diagnosis of MEN1 syndrome.

Conclusion

Diagnosis of MEN1 depends on having a high level of suspicion in patients who present with features of hyperparathyroidism, prolactinoma, or increased gastric acid secretion. Our patient demonstrates a classic example of MEN1 syndrome with tumors in all 3 defining endocrine organs, including pituitary prolactinoma, parathyroid adenoma, and pancreatic neuroendocrine tumor (nonfunctioning). When the clinical suspicion for MEN1 is high, endocrinology evaluation with appropriate laboratory workup and imaging evaluation as described for this patient is advised then follow-up and genetic counseling.

Patient Consent

Written consent from the patient was taken.

REFERENCES

- [1] Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997;276:404–7 [PubMed] [CrossRef] [Google Scholar]. doi:10.1126/science.276.5311.404.
- [2] Thakker RV, Newey PJ, Walls GV, et al. Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab* 2012;97(9):2990–3011 [PubMed] [CrossRef] [Google Scholar]. doi:10.1210/jc.2012-1230.
- [3] Almeida MQ, Stratakis CA. Solid tumors associated with multiple endocrine neoplasias. *Cancer Genet Cytogenet* 2010;203(1):30–6 [PMC free article] [PubMed] [CrossRef] [Google Scholar]. doi:10.1016/j.cancergencyto.2010.09.006.
- [4] Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). *Mol Cell Endocrinol* 2014;386(1-2):2–15 [PMC free article] [PubMed] [CrossRef] [Google Scholar]. doi:10.1016/j.mce.2013.08.002.
- [5] 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 [PMC free article] [PubMed] [CrossRef] [Google Scholar]. doi:10.1097/MD.0b013e3182954af1.
- [6] Donegan D, Singh Ospina N, Rodriguez-Gutierrez R, et al. Long-term outcomes in patients with multiple endocrine neoplasia type 1 and pancreaticoduodenal neuroendocrine tumours. *Clin Endocrinol (Oxf)* 2017;86(2):199–206 [PubMed] [CrossRef] [Google Scholar]. doi:10.1111/cen.13264.
- [7] Burgess JR, David R, Greenway TM, Parameswaran V, Shephard JJ. Osteoporosis in Multiple Endocrine Neoplasia Type 1: severity, clinical significance, relationship to primary hyperparathyroidism, and response to parathyroidectomy. *Arch Surg*. 1999;134:1119–23 [PubMed] [CrossRef] [Google Scholar]. doi:10.1001/archsurg.134.10.1119.
- [8] Lourenco DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type-1 associated primary hyperparathyroidism. *J Bone Miner Res*. 2010;25:2382–91 [PubMed] [CrossRef] [Google Scholar]. doi:10.1002/jbmr.125.
- [9] Michaud L, Balogova S, Burgess A, et al. A pilot comparison of 18F-fluorocholine PET/CT, ultrasonography and 123I/99mTc-sestaMIBI dual-phase dual-isotope scintigraphy in the preoperative localization of hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism: influence of thyroid anomalies. *Medicine (Baltimore)* 2015;94(41):e1701 [PMC free article] [PubMed] [CrossRef] [Google Scholar]. doi:10.1097/MD.0000000000001701.
- [10] Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. *World J Surg* 2004;28(11):1139–42 [PubMed] [Google Scholar].
- [11] Marx SJ, Simonds WF. Hereditary hormone excess: genes, molecular pathways, and syndromes. *Endocr Rev*. 2005;26:615–61 [PubMed] [CrossRef] [Google Scholar]. doi:10.1210/er.2003-0037.
- [12] Singh Ospina N, Donegan D, Rodriguez-Gutierrez R, Al-Hilli Z, Young WF Jr. Assessing for multiple endocrine neoplasia type 1 in patients evaluated for Zollinger-Ellison syndrome—clues to a safer diagnostic process. *Am J Med*

- 2017;130(5):603–5 [PubMed] [CrossRef] [Google Scholar]. doi:[10.1016/j.amjmed.2016.11.035](https://doi.org/10.1016/j.amjmed.2016.11.035).
- [13] Poitras P, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. *Clin Gastroenterol Hepatol* 2012;10(2):199–202 [PubMed] [CrossRef] [Google Scholar]. doi:[10.1016/j.cgh.2011.08.012](https://doi.org/10.1016/j.cgh.2011.08.012).
- [14] Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Ann Surg*. 2006;243:265–72 [PMC free article] [PubMed] [CrossRef] [Google Scholar]. doi:[10.1097/01.sla.0000197715.96762.68](https://doi.org/10.1097/01.sla.0000197715.96762.68).