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CASE REPORT

Primary aldosteronism due to adrenocortical adenoma with concurrent ileum carcinoid tumor: case report

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Abstract Primary aldosteronism (PA) with synchronous carcinoid syndrome is extremely rare occurrence. In this article, we describe a case of PA due to adrenocortical adenoma ("aldosteronoma") and concurrent malignant carcinoid tumor of ileum. The patient was treated with synchronous right adrenalectomy and resection of the ileum. This case is an example of concomitant presence of two types of tumors, effectively managed surgically. We report a case of a nonclassical form of multiple endocrine neoplasia type 1 (MEN 1) syndrome.

Keywords Primary aldosteronism · Carcinoid syndrome · Adrenocortical adenoma

Introduction

Primary aldosteronism (PA) is one of the most common correctable causes of secondary hypertension and has been estimated with a prevalence that ranges widely from 1.4% to 10% in the hypertensive population [1–4]. Patients with PA classically present with poorly controlled hypertension associated with hypokalemia [5]. Various pathological conditions have been associated with PA, due to an aldosterone-secreting adenoma of the adrenal cortex, including glucagonoma [6], pheochromocytoma [7], Crohn's disease [8], primary hyperparathyroidism [9], and a case of multiple endocrine neoplasia type 1 (MEN 1) [10].

Neuroendocrine neoplasm of gut (also called carcinoids) is very rare and originates mainly in the gastrointestinal tract [11]. These tumors are found in the appendix, small intestine (ileum), Meckel's diverticulum, rectum branches, esophagus, stomach, pancreas, gall bladder, biliary tract, teratomas of ovary and testes, and the right side of colon [12, 13]. They are usually asymptomatic or characterized by obstructive symptoms [14]. The typical clinical picture is the carcinoid syndrome that occurs in 18% of patients with ileum carcinoid [15] and it is characterized by flushing, diarrhea, abdominal pain, and cutaneous manifestation.

In this report, we present a first case of a PA due to adrenocortical adenoma concurrent with ileum carcinoid tumor.

Case report

A 55-year-old male was referred to our Department Unit of Secondary Hypertension, by his medical practitioner with a 20-year history of poorly controlled hypertension with multiple antihypertensive medications (losartan, clonidine, amlodipine) and recently severe hypokalemia (2.5 mEq/l), without diuretic therapy. Moreover, he complained of diffuse abdominal pain associated with nausea and change in bowel habits with diarrhea, palpitation and also a recent weight loss of 5 kg, over 2 months, and wheezing, flushing, and muscle weakness.

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The patient had a family history of cancer: his father died from lymphoma and a sister died from gastric carcinoma (adenocarcinoma). There were no endocrinopathies in other family members; in particular none of the family member had history of hypercalcemia.

On physical examination, our patient's vital signs were: temperature 36°C; blood pressure 160/100 mmHg; heart rate 88 b/min; respiratory rate 16 breaths/min. No alterations were found in heart and thoracic auscultation, his waist circumference was 90 cm, and BMI was 26 kg/m^2. No signs of neurological involvement were present.

Abdominal examination revealed a generalized abdominal distension but no other signs of peritonitis, rectal examination revealed no masses.

In order to perform a correct study of renin–angiotensin–aldosterone system (RAAS), a pharmacological wash out was needed, therefore a new pharmacological treatment with of calcium channel blocker (nifedipine 20 mg/day) and an alpha-blocker (doxazosin 2 mg/day) was started.

Laboratory examination was remarkable from hypokalemia (2.42 mEq/l), hypocloridemia (98 mEq/l), and a metabolic alkalosis (with a base excess of 7 mmol/l). Blood urea nitrogen (20 mg/dl) and creatinine (1.01 mg/dl) levels were normal. Calcium concentration was 9.6 mg/dl (normal range 8–10 mg/dl), albumin concentration was 4 mg/dl (normal range 3–5 mg/dl), and glucose was 86 mg/dl (normal range 70/110 mg/dl). Complete blood cell count was within normal limits.

Twenty-four hours urine, on a normal salt diet (140–150 mEq/day), revealed: sodium excretion 135 mEq/24 h, potassium excretion 80 mEq/24 h, aldosterone excretion 37.6 μg/24 h (normal value 2.8 ± 25 μg/24 h), urinary free cortisol excretion 31 μg/24 h (normal value 10–150 μg/24 h), and total urinary metanephrine 120 μg/24 h (normal value 20–345 μg/24 h), whereas supine plasma renin activity (PRA) 0.15 ng/ml/h (normal value 0.2–2.7 ng/ml/h) and plasma aldosterone concentration (PAC) 116.7 ng/dl (normal value 0.75–15 ng/dl) (giving a PAC/PRA ratio of 778 ng/ml/h:ng/dl) were altered. Plasma a.m. cortisol and ACTH levels were normal (15.8 μg/dl and 26.4 pg/ml, respectively). The saline infusion test confirmed the inappropriate aldosterone secretion (PAC > 7 ng/dl). Other hormones values were: TSH 2.1 μUI/ml (normal value 0.2–3.5 μUI/ml), calcitonin 7.8 pg/ml (normal value <15 pg/ml), prolactin 12.3 ng/ml (normal value 2–14.5 ng/ml), LH 6.2 mUI/ml (normal value 1.5–9.26 mUI/ml), FSH 5.1 mUI/ml (normal value 1–1.4 mUI7 ml). Moreover, with the suspect of carcinoid syndrome (clinical history), we performed further testing and the patient's chromogranin A was over 1400 mg/ml (normal value <90 mg/ml) and 24 h urinary 5-hydroxyindol-acetic acid levels were elevated (90 mg/24 h; normal value 2–10 mg/24 h).

Computed tomography (CT) of the abdomen and thorax revealed a hypodense lesion in ileum (diameter 2 cm) with hypervascolarization and 20 lesions located within the liver, that were consistent with metastatic tumor. The largest liver lesion measured 4 cm in diameter. The right adrenal gland was occupied by a nodular lesion that measures 2.5 cm, while the left adrenal gland presents normal dimensions and morphology.

No other lesions were presented in the abdomen, pelvis, and thorax (Fig. 1).

A whole body scan using somatostatin receptor scintigraphy (octreoscan 474 MBq e.v.) showed areas of increased uptake throughout the liver but no other regions (Fig. 2).

Based on these clinical, biochemical, and radiological images results we proposed the diagnosis of PA due to right adrenocortical lesion and suspected ileum neuroendocrine intestinal tumor with liver metastasis. The patient, with adequate potassium supplementation, antihypertensive and antialdosterone receptor treatment, was referred to Department of Surgery "P.Valdoni".

Surgery

At the laparotomy surgery, the abdominal cavity was entered through a midline incision. Exploration revealed the presence of multiple, unresectable liver lesions, located on both lobes (metastasis). As described by CT-scan, the right adrenal gland was altered by the presence of a 3 cm lesion, and the right adrenalectomy was performed (Fig. 3), the contralateral gland was normal in appearance. Moreover a liver incisional biopsy was performed.

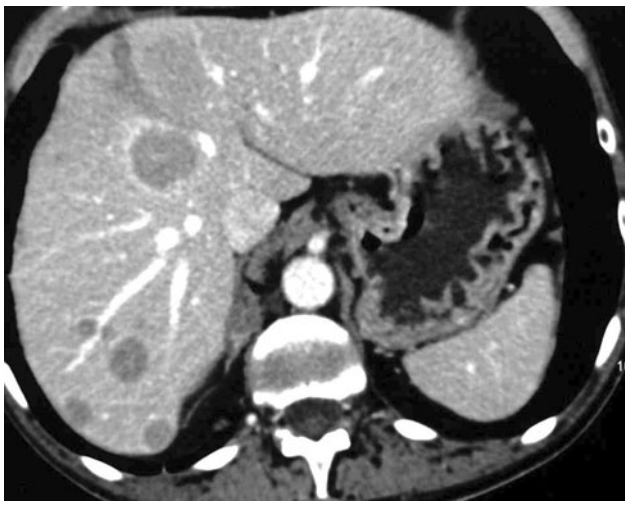

Fig. 1 CT scan reveals the presence of multiple liver metastases

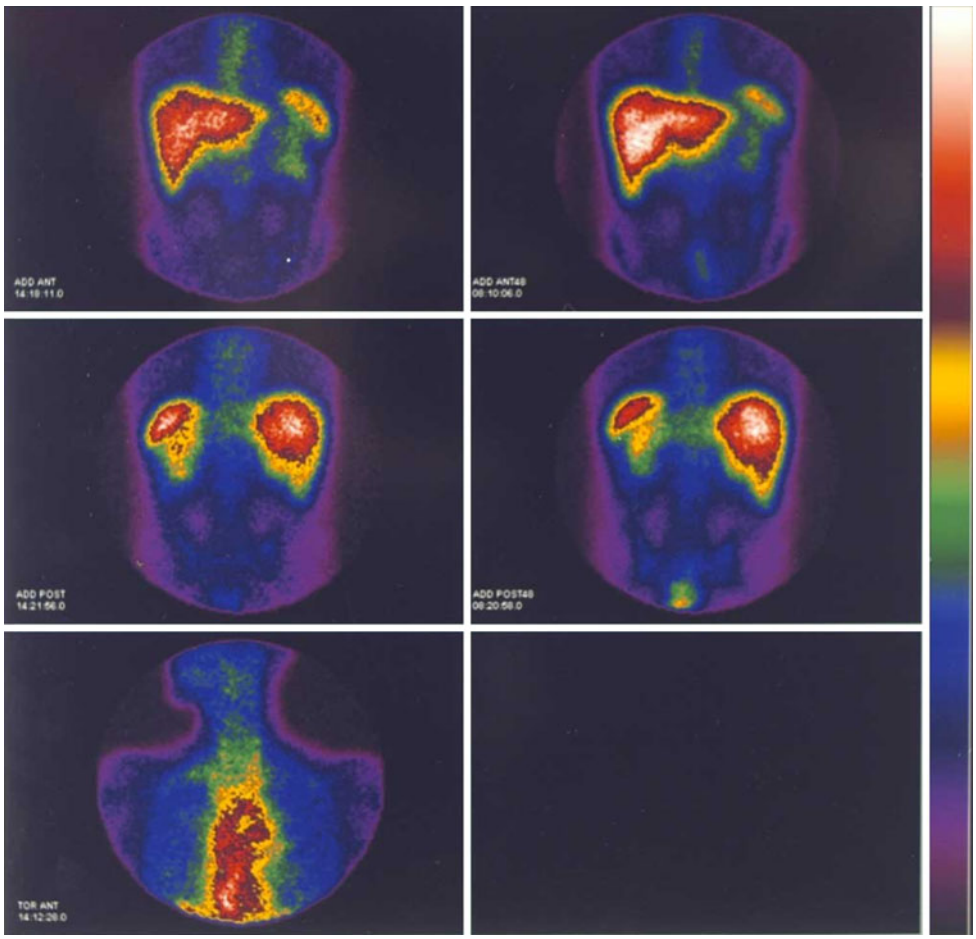

Fig. 2 Octreoscan 474 MBq total body reveals areas of increased uptake throughout the liver

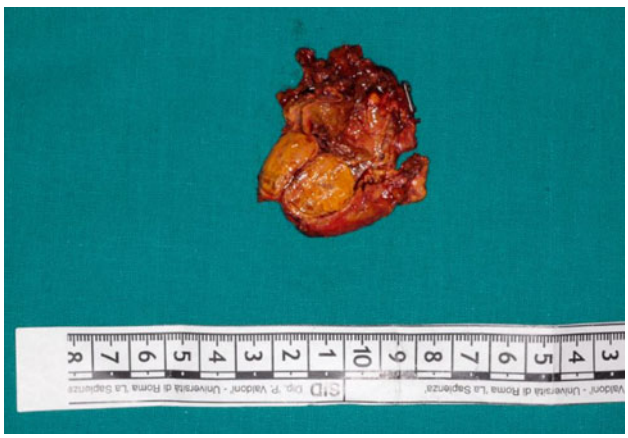

Fig. 3 The right adrenal gland with the adenoma

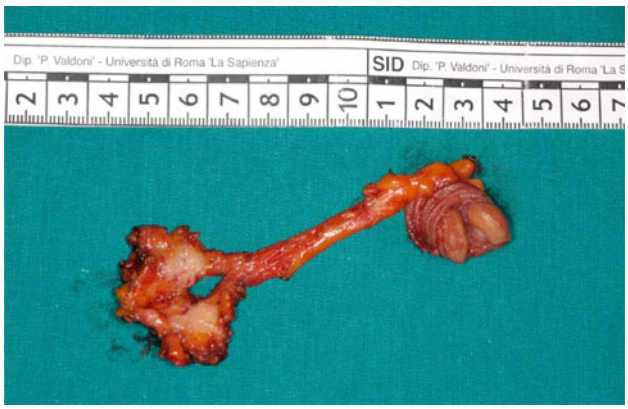

Fig. 4 The opened specimen of the resected ileum with lymphnode metastases

The exploration of the entire bowel revealed the presence of a neoplastic stenosis at the level of the distal ileum, about 60 cm distant from the ileocecal valve.

At the level, the mesentery presented gross lymphatic metastases. The ileum resection was performed associated to lymphadenectomy (Fig. 4) and a reconstruction by hand-sewn end-to-end anastomosis. No other visceral lesions were found during surgery intervention.

Pathology

Specimens consisted of (1) right adrenal gland, (2) a short tract of small bowel ileum with mesenteric adipose tissue, and (3) an incisional biopsy of liver.

The adrenal gland measured $5 \times 3 \times 1.5$ cm and had an altered profile due to the presence of a nodule, 2 cm in diameter, showing yellow color on cut section and

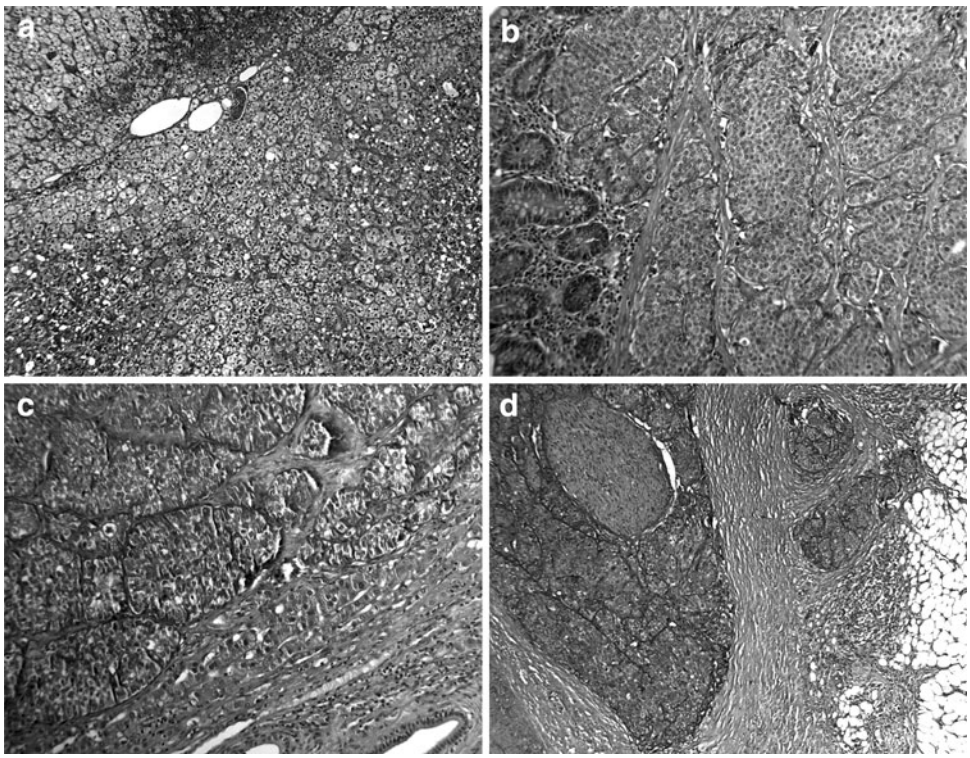

Fig. 5 Histological pictures of (**a**) cortical adrenal adenoma and of endocrine tumor of small intestine (**b**), with liver metastasis (**c**) and perineural invasion (**d**) (H&E, **a**, **b** ×100, **c**, **d** ×250)

circumscribed by a subtle fibrous capsule. On microscopic examination, this nodule was made of two cell populations, arranged in nests or trabeculas: one minor cell line had eosinophilic granular cytoplasm; the other had clear vacuolated cytoplasm. The lesion was demarcated by a thin fibrous capsule from the remaining of the adrenal gland that had no alteration in both cortex and medulla. On the basis of these findings a diagnosis of cortical adenoma was made (Fig. 5a).

The small bowel tract measured 1.8 cm in length after fixation, and the mesenteric tissue attached was 3 × 4 × 1.5 cm. On cut section, it showed a nodule of 1.3 cm in maximum diameter, yellow in color, with firm consistence, localized at the interface between the small bowel wall and the adipose tissue. This lesion had an insular pattern of growth and was made of cells with moderately pleomorphic nuclei, occasionally "bizarre", surrounded by eosinophilic cytoplasm. Frequent mitoses were seen along with perineural invasion (Fig. 5b–d). Immunohistochemical analysis revealed positive staining for chromogranin A, synaptophysin, neuron specific enolase and low molecular weight keratin, being negative for high molecular weight keratin. The liver incisional biopsy measured 1 × 0.8 × 0.5 cm and a small gray-yellow nodule under the glissonian capsule was evident. It featured histological pattern identical to small bowel lesion, allowing a diagnosis of liver metastasis of ileum neuroendocrine tumor. A diagnosis of malignant endocrine tumor of small bowel infiltrating the mesenteric tissue was made.

Genetic analysis

Genetic evaluation was performed. Peripheral blood sample (10 ml) from the patient was collected after written informed consent according to our local ethic committee approval in line with international protocol.

DNA was extracted from the peripheral blood leukocytes of each patient with the Nucleospin blood L kit (Macherey-Nagel, Duren, Germany) and analyzed for germline mutations. in the gene of MEN-1 (exons 2, 3, 4, 5, 6, 7, 8, 9, 10). For this gene, coding regions and exon-intro boundaries PCR fragments purified with a commercial kit (PCR purification kit, Qiagen, Milan, Italy) were subjected to 2% agarose gel electrophoresis with ethidium bromide staining and subsequently sequenced with a genetic analyzer (ABI PRISM 310, Applied Biosystems, Milan, Italy).

We did not find germline mutations but a polymorphism in the codon 541 (ACA > GCA, Thr > Ala, in homozygosis) exon 10 of the MEN-1 gene.

Follow-up

After the surgery intervention, short-acting octreotide analog test showed good response, so long-acting octreotide (S-LAR) was started with a dose 120 mg im every 28 days.

The patient was reevaluated 4 months later, he was taking a S-LAR therapy at a dose 120 mg i.m. every

28 days, and was still nearly asymptomatic (moderate abdominal pain was present) and he tolerated the therapy. He showed normal values of blood pressure (110/80 mmHg; amlodipine 10 mg/day) and heart rate (75 beats/min). Echocardiography revealed a moderate remodeling of left ventricle and laboratory exams returned to normal values (PRA 1.03 ng/ml/h; PAC 16.7 ng/dl; potassium 4.2 mEq/l; sodium 140 mEq/l; chloride 105 mEq/l; calcium 9.8 mg/dl; creatininemia 1.3 mg/dl). Moreover, chromogranin A (500 mg/dl) and 24 h urinary 5-hydroxyindlacetic acid (28 mg/24 h) levels significantly improved but permanent high. CT of the abdomen and thorax revealed multiple liver metastatic lesions in diameter progression. No other lesions were in the abdomen, pelvis, and thorax.

Discussion

Primary aldosteronism (PA) is characterized by autonomous overproduction of adrenal aldosterone with suppression of PRA, sodium retention, and consequent hypertension. Various primary adrenal pathological processes cause this syndrome: some of them are best treated by surgery and others by medical [1]. The aldosterone-producing adenoma (aldosteronoma) is the most important cause of hyperaldosteronism and represents one of the few curable causes of secondary arterial hypertension. These tumors are usually small (less than 2 cm in diameter) and benign [16]. Some patients are completely asymptomatic or have minimum symptoms resulting from hypertension (e.g. headache) and hypokalemia (polyuria, nycturia, muscle cramps). Occasionally excessive muscle weakness, paresthesias, tetany and even muscles paralysis may occur [17].

This is the first paper to report the occurrence of an aldosterone-producing adenoma in association of an ileum carcinoid tumor.

The neuroendocrine tumors of gastrointestinal tract (also called "carcinoids") are rare tumors [18, 19]. Carcinoid tumors were classified according to their embryologic origin as foregut (bronchial, stomach, duodenum, biliary tract, and pancreas), midgut (small intestine, appendix, cecum, and proximal colon), and hindgut (distal colon and rectum) [20]. The small intestine (ileum) is the most common site (45%) followed by the rectum (20%), appendix (16%), colon (11%), and stomach (7%) [21]. Most cases are discovered incidentally and may remain asymptomatic for many years.

Symptoms occur mainly due to local mass effect, fibrosis, or secretion of bioactive products. In fact, these tumors originate in the enterochromaffin cells of the intestine and have the ability to produce various peptides and hormones, such as biogenic amines and prostaglandins. In particular, enterochromaffin cells and carcinoid tumors have the capacity to produce 5-hydroxytryptamine (serotonin). The liver metabolizes these peptides into inactive forms but in case of liver metastases these substances secrete into the hepatic veins enter the systemic circulation causing various symptoms described as carcinoid syndrome [22, 23].

The typical symptoms of the carcinoid syndrome are diarrhea, flushing, abdominal pains, wheezing, and dyspnea and rarely intermittent bronchial obstruction and secretory diarrhea occurs in up to 80% of patients and was accompanied by abdominal cramping [24].

At one presentation our patient manifested arterial hypertension, diffuse abdominal pain, diarrhea, and severe hypokalemia.

Hypokalemia, an electrolyte disorder with multiple causes, has a prevalence of about 5% in the hospital population [25]. In most cases, the etiology is evident from the clinical picture and routine plasma biochemistry tests and there is usually no need to resort to further, more complex and expensive biochemical evaluation. In particular, in the presence of hypokalemia, a urinary potassium concentration greater than about 10 mEq/l suggests that increased renal excretion of potassium is the cause, whereas in patients with hypokalemia with high or normal plasma bicarbonate and low urinary potassium concentration <10 mEq/l, the most common cause is gastrointestinal loss (e.g. chronic diarrhea).

In our patient, the severe hypokalemia associated to metabolic alkalosis was due to the inappropriate aldosterone secretion and, in part, at the chronic diarrhea. In fact, hypokalemia has been considered as the classical hallmark in the diagnosis of PA. However, recent studies have revealed that low plasma potassium levels are uncommon [1], because less than 50% of PA shows hypokalemia.

Aldosterone-secreting adrenal lesions are quite rarely associated with endocrinopathies [26–28] and some cases were diagnosed as multiple endocrine neoplasia type 1 (MEN-1) [10]. MEN-1 is a rare (approximately one in 30,000) endocrine disorder [29], and usually consists of hyperparathyroidism and benign or malignant tumors of the pancreas and the anterior pituitary; it can also include combinations of more than 20 endocrine and non-endocrine tumors, carcinoids, lipomas tumors of the adrenals, ovaries, and thyroid [30].

The MEN-1 gene is located in chromosome 11q13 and consists of 10 exons that encode a 610-aminoacid protein, named menin [31].

The mutational hypothesis in this gene proposed that the first hit or mutation is inherited as a germline mutation and the second hit occurs as a somatic mutation in the predisposed endocrine cells. This second mutation may occur by

chromosome loss (e.g. loss of heterozygosis), chromosome loss with duplication, mitotic recombination, or another localized event such as paint mutation [32]. As a consequence of two mutations, both alleles of the MEN1 gene are inactivated, allowing the tumor growth.

In the present case, we reported a patient with an aldosterone-producing adenoma coexisting with ileum carcinoid tumor. The case may be considered a variant nonclassical form of MEN 1 syndrome, since the patient presented with two endocrine tumors. In addition, our patient presents a polymorphism in the codon 541 of exon 10 of the MEN-1 gene.

In conclusion, the concurrence of an adrenal cortical-aldosteronoma with ileum carcinoid tumor is unique. We believe that this case probably represents another variant of the non classical form of MEN 1 syndrome.

Conflict of interest This study has been realized without governmental funding.

References

1. G.P. Rossi, G. Bernini, C. Caliumi, G. Desideri, B. Fabris, C. Ferri, C. Ganzaroli, G. Giacchetti, C. Letizia, M. Maccario, F. Mallamaci, M. Mannelli, M.J. Mattarello, A. Moretti, G. Palumbo, G. Parenti, E. Porteri, A. Semplicini, D. Rizzoni, E. Rossi, M. Boscaro, A.C. Pessina, F. Mantero, PAPY Study Investigators, A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J. Am. Coll. Cardiol. **48**, 2293–2300 (2006)
2. L. Mosso, C. Carvajal, A. González, A. Barraza, F. Avila, J. Montero, A. Huete, A. Gederlini, C.E. Fardella, Primary aldosteronism and hypertensive disease. Hypertension **42**, 161–165 (2003)
3. R.D. Gordon, M. Stowasser, T.J. Tunny, S.A. Klemm, J.C. Rutherford, High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin. Exp. Pharmacol. Physiol. **21**, 315–318 (1994)
4. K.C. Loh, E.S. Koay, M.C. Khaw, S.C. Emmanuel, W.F. Young Jr, Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. J. Clin. Endocrinol. Metab. **85**, 2854–2859 (2000)
5. G.P. Rossi, A.C. Pessina, A.M. Heagerty, Primary aldosteronism: an update on screening, diagnosis and treatment. J. Hypertens. **26**, 613–621 (2008)
6. H. Abe, K. Kubota, T. Noie, W. Kimura, M. Makuuchi, A rare combination consisting of primary hyperaldosteronism and glucagonoma. Am. J. Gastroenterol. **94**, 1397–1401 (1999)
7. R.F. Berbarie, M. Emmett, N.A. Breslau, Quiz page. Secondary hypertension with contralateral pheochromocytoma and aldosteronoma. Am. J. Kidney Dis. **46**(1), A51, e1-3 (2005)
8. M. Astegiano, F. Bresso, B. Demarchi, N. Sapone, D. Novero, G. Palestro, A. Resegotti, R. Pellicano, M. Rizzetto, Association between Crohn's disease and Conn's syndrome. A report of two cases. Panminerva Med. **47**, 61–64 (2005)
9. M. Honda, T. Tsukada, T. Horiuchi, R. Tanaka, K. Yamaguchi, T. Obara, H. Miyakawa, T. Yamaji, M. Ishibashi, Primary hyperparathyroidism associated with aldosterone-producing adrenocortical adenoma and breast cancer: relation to MEN1 gene. Intern. Med. **43**, 310–314 (2004)
10. A. Beckers, R. Abs, P.J. Willems, B. van der Auwera, K. Kovacs, M. Reznik, A. Stevenaert, Aldosterone-secreting adrenal adenoma as part of multiple endocrine neoplasia type 1 (MEN1): loss of heterozygosity for polymorphic chromosome 11 deoxyribonucleic acid markers, including the MEN1 locus. J. Clin. Endocrinol. Metab. **75**, 564–570 (1992)
11. S.N. Pinchot, K. Holen, R.S. Sippel, H. Chen, Carcinoid tumors. Oncologist **13**, 1255–1269 (2008)
12. G. Aggarwal, K. Obideen, M. Wehbi, Carcinoid tumors: what should increase our suspicion? Clevel. Clin. J. Med. **75**, 849–855 (2008)
13. J.C. Yao, M. Hassan, A. Phan, C. Dagohoy, C. Leary, J.E. Mares, E.K. Abdalla, J.B. Fleming, J.N. Vauthey, A. Rashid, D.B. Evans, One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J. Clin. Oncol. **26**, 3063–3072 (2008)
14. I.M. Modlin, K. Oberg, D.C. Chung, R.T. Jensen, W.W. de Herder, R.V. Thakker, M. Caplin, G. Delle Fave, G.A. Kaltsas, E.P. Krenning, S.F. Moss, O. Nilsson, G. Rindi, R. Salazar, P. Ruszniewski, A. Sundin, Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. **9**, 61–72 (2008)
15. B. Eriksson, G. Klöppel, E. Krenning, H. Ahlman, U. Plöckinger, B. Wiedenmann, R. Arnold, C. Auernhammer, M. Körner, G. Rindi, S. Wildi, Frascati Consensus Conference participants. Consensus guidelines for the management of patients with digestive neuroendocrine tumors—well-differentiated jejunal-ileal tumor/carcinoma. Neuroendocrinology **87**, 8–19 (2008)
16. J.D. Blumenfeld, J.E. Sealey, Y. Schlussel, E.D. Vaughan Jr., T.A. Sos, S.A. Atlas, F.B. Müller, R. Acevedo, S. Ulick, J.H. Laragh, Diagnosis and treatment of primary hyperaldosteronism. Ann. Intern. Med. **121**, 877–885 (1994)
17. A. Ganguly, Primary aldosteronism. N. Engl. J. Med. **339**, 1828–1834 (1998)
18. J.K. Ramage, A.H. Davies, J. Ardill, N. Bax, M. Caplin, A. Grossman, R. Hawkins, A.M. McNicol, N. Reed, R. Sutton, R. Thakker, S. Aylwin, D. Breen, K. Britton, K. Buchanan, P. Corrie, A. Gillams, V. Lewington, D. McCance, K. Meeran, A. Watkinson, UKNETwork for Neuroendocrine Tumours. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut. **54** Suppl 4, iv1-16 (2005)
19. W.W. de Herder, Tumours of the midgut (jejunum, ileum and ascending colon, including carcinoid syndrome). Best Pract. Res. Clin. Gastroenterol. **19**, 705–715 (2005)
20. E.D. Williams, M. Sandler, The classification of carcinoid tumours. Lancet **1**, 238–239 (1963)
21. M.A. Maggard, J.B. O'Connell, C.Y. Ko, Updated population-based review of carcinoid tumors. Ann. Surg. **240**, 117–122 (2004)
22. I.M. Modlin, M. Kidd, I. Latich, M.N. Zikusoka, M.D. Shapiro, Current status of gastrointestinal carcinoids. Gastroenterology **128**, 1717–1751 (2005)
23. A.N. van der Horst-Schrivers, A.N. Wymenga, T.P. Links, P.H. Willemse, I.P. Kema, E.G. de Vries, Complications of midgut carcinoid tumors and carcinoid syndrome. Neuroendocrinology **80**, 28–32 (2004)
24. M.H. Kulke, R.J. Mayer, Carcinoid tumors. N. Engl. J. Med. **340**(11), 858–868 (1999)
25. F. Assadi, Diagnosis of hypokalemia: a problem-solving approach to clinical cases. Iran. J. Kidney Dis. **2**, 115–122 (2008)
26. G.W. Herd, A case of primary hyperparathyroidism, primary hyperaldosteronism and Cushing's disease. Acta Endocrinol. (Copenh) **107**, 371–374 (1984)
27. A. Fertig, M. Webley, J.A. Lynn, Primary hyperparathyroidism in a patient with Conn's syndrome. Postgrad. Med. J. **56**, 45–47 (1980)

28. D.E. Hellman, M. Kartchner, N. Komar, D. Mayes, M. Pitt, Hyperaldosteronism, hyperparathyroidism, medullary sponge kidneys, and hypertension. JAMA **244**, 1351–1353 (1980)
29. R.F. Gagel, S.J. Marx, Multiple endocrine neoplasia, in *Williams Textbook of Endocrinology* 11th edn, ed. by P.R. Larsen, M. Kroenenberg, S. Helmed, K. Polonsky (WB Saunders & Company, Orlando, 2007) (Section X, Chap 40)
30. A. Falchetti, F. Marini, E. Luzi, F. Tonelli, M.L. Brandi, Multiple endocrine neoplasms. Best Pract. Res. Clin. Rheumatol. **22**, 149–163 (2008)
31. S.C. Chandrasekharappa, S.C. Guru, P. Manickam, S.E. Olufemi, F.S. Collins, M.R. Emmert-Buck, L.V. Debelenko, Z. Zhuang, I.A. Lubensky, L.A. Liotta, J.S. Crabtree, Y. Wang, B.A. Roe, J. Weisemann, M.S. Boguski, S.K. Agarwal, M.B. Kester, Y.S. Kim, C. Heppner, Q. Dong, A.M. Spiegel, A.L. Burns, S.J. Marx, Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science **276**, 404–407 (1997)
32. S.S. Guo, M.P. Sawicki, Molecular and genetic mechanisms of tumorigenesis in multiple endocrine neoplasia type-1. Mol. Endocrinol. **15**, 1653–1664 (2001)