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CASE REPORT

A new association – multiple endocrine neoplasia type 1 and malignant peripheral nerve sheath tumor

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Key Clinical Message

We report a patient with multiple endocrine neoplasia type 1 (*MEN-1*) and an aggressive malignant peripheral nerve sheath tumor (MPNST) arising from a ganglioneuroma of the adrenal gland. Patients with *MEN-1* require careful consideration of other tumor associations, including MPNST, as it can portend a poor prognosis. *MEN-1* and MPNST have not been reported.

Keywords

Adrenal, malignant peripheral nerve sheath tumor, MEN-1, neuroendocrine tumors, sarcoma.

Introduction

Multiple endocrine neoplasia type 1 MEN-1 (please note MEN-1 denotes the condition and *MEN*-1 denotes the gene defect) is an autosomal dominant familial tumor syndrome (Wermer Syndrome). It is characterized by parathyroid tumors or hyperplasia, anterior pituitary adenomas, and pancreatic neuroendocrine tumors. A clinical diagnosis of MEN-1 is reached in the presence of two of three of these, or one of these tumors in the context of a family history of MEN-1. The prevalence in the population of *MEN-1* is 1 in 30,000. The estimated penetrance is 98% by the age of 40 years. The *MEN-1* gene is on chromosome band 11q13. Genetic testing is only successful in identifying ~70–90% of mutations in the *MEN-1* gene. Other associations with MEN-1 include: adrenal cortical tumors, carcinoid tumors, lipomas, pheochromocytomas, malignant melanoma, testicular teratoma, and multiple (>3) angiofibromas [1]. Adrenal lesions are present in up to 10–15% of patients with MEN-1 [2]. To date, there has not been, to our knowledge, an association with malignant peripheral nerve sheath tumor (MPNST).

Case Report

A 69-year-old man presented with a history of poor libido on a background of long-standing type II diabetes mellitus. His diabetes had been managed with metformin 1 g daily since the age of 56 years. He had a prior duodenal ulcer, for which he was on proton pump inhibitor therapy. Biochemical investigation revealed an elevate RL prolactin (PRL) of 72,000 mIU/L (0–450), low testosterone of 4.3 nmol/L (9.1–25.0), elevated parathyroid hormone (PTH) 11.6 pmol/L (1.0–7.0), elevated calcium 2.76 mmol/L (2.10–2.60), low phosphate 0.61 mmol/L (0.72–1.36), and normal gastrin 26 pmol/L (<50). Magnetic resonance imaging (MRI) demonstrated a large parasellar mass 31 × 15 mm with elevation of the optic chiasm and invasion of the right sphenoid sinus. Clinically he was diagnosed with MEN-1 based on the findings of: hyperparathyroidism, a pituitary prolactinoma, and skin lesions (lipomas and angiofibromas). Genetic testing found no mutation; however, *MEN-1* testing at the time did not cover large deletions and has been repeated with multiplex ligation-dependent probe amplification (MLPA). This revealed a heterozygous pathogenic dele-

tion NM_130799.2(MEN1): c.1-?_1833+del.p(?). The MLPA method detects deletions and duplications that account for ~1–4% of individuals with MEN-1. *MEN-1* mutations are classified using nomenclature recommended by the Human Genome Variation Society.

Our patient has four brothers, two sisters, and one son, all of whom are unaffected clinically and biochemically to date. Both his parents are deceased from cardiovascular disease. To date, the *MEN-1* gene testing on his son has been negative. On the basis of the recent MPLA results from our patient, *MEN-1* testing is underway for his son.

His hyperparathyroidism was managed with a three-and-a-half gland parathyroidectomy. He maintained calcium homeostasis (Ca 2.63 mmol/L, PTH 6.3–9.4 pmol/L) with the remaining half of the right inferior parathyroid gland. The pituitary macroprolactinoma reduced considerably in size with cabergoline therapy 1 mg twice weekly, from 31 × 15 to 11 × 7 mm. Similarly, the PRL level dropped to 500 mIU/L (2013). The secondary hypogonadism (lutinizing hormone (LH) 0.4 mIU/L [0.4–5.1], follicle stimulating hormone (FSH) 0.9 IU/L [3.7–8.1]) from the macroprolactinoma was treated with testosterone replacement (troches and subsequently Reandron® 1000 Bayer Australia Ltd every 3 months).

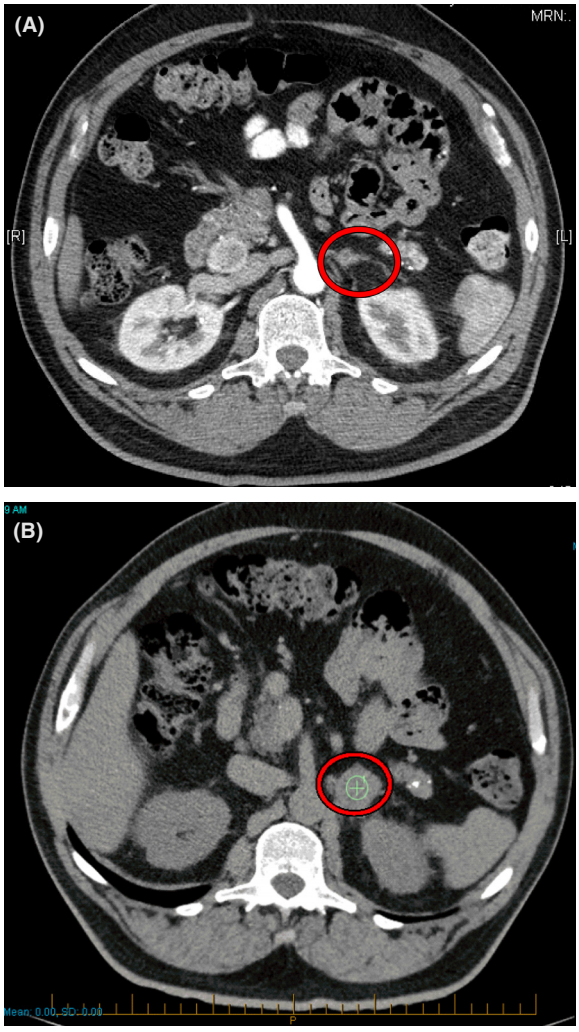

Figure 1. (A) Left adrenal mass – demonstrating initial size on imaging for gastrinomas. (B) Left adrenal mass – 18 months after (A) – significant increase in size.

Annual fasting gut peptides were performed, all of which were normal but he was lost to follow-up for a number of years. On return to the clinic, he was noted to have secondary hypothyroidism with a TSH of 0.4 mIU/L (0.4–3.9), T4 11.9 pmol/L (10–20) which was treated with thyroxine 150 μg daily. Gastrin levels rose on proton pump inhibitor therapy and multiple pancreatic lesions were noted on imaging. They were Dotatate-avid on CT/PET scanning. Metastatic disease involving the left humerus and 11th thoracic vertebra was also seen. Formal gastroscopy was attempted on two occasions to enable endoscopic ultrasound with biopsy, but was aborted due to patient intolerance, despite sedation. The presumed gastrinomas were successfully managed with Sandostatin LAR 20 mg® IM monthly Novartis Pharmaceuticals Australia Pty Ltd therapy, with a stabilization of the gastrin levels (varying between 432–700 ng/L) and tumor size (largest measuring 2.4 cm). Multifocality made the pancreatic lesions unsuitable for surgery.

On serial imaging, an enlarging left adrenal mass was noted (Fig. 1A and B), which was functionally inactive and interestingly non-Dotatate-avid. At the age of 69, he underwent left retroperitoneoscopic adrenalectomy, on the basis of its rapidly increasing size (from 9 to 50 mm). To the surprise of the surgeon, histopathology (Fig. 2) demonstrated a MPNST: Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade 3 [3].

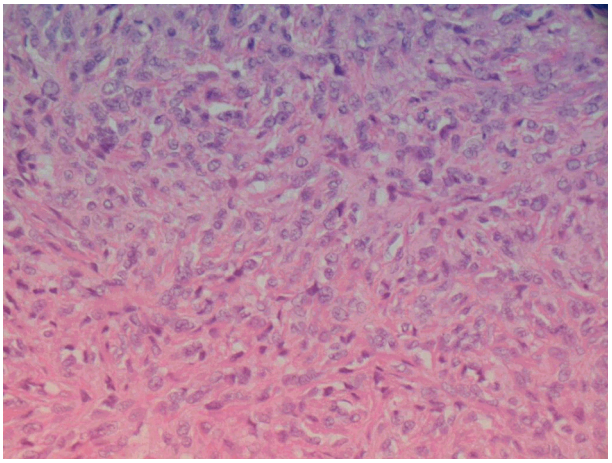

Figure 2. H&E stain demonstrating haphazard arrangement of the bland spindle cells and nerve fiber bundles of the MPNST 40 ×.

The Ki 67 proliferative index was 20% indicative of a high-grade neuroendocrine tumor. Postoperatively adjuvant radiotherapy to the adrenal bed was administered. Despite this, there has been extensive recurrent sarcoma with mass effect on left kidney, pancreas, and celiac trunk in addition to extension into paraspinal muscles. Our patient is now being palliated.

Discussion

MPNST are thought to evolve along a spectrum of disease. They are characterized by arising from a peripheral nerve, mostly Schwann cells, and are often associated with neurofibromatosis [4]. Interestingly, the cytogenetic mutations that have been described have included the 11q13 break point, which coincides with the locus of the mutation on the *MEN-1* gene [5] . MPNST is a rare malignancy with an incidence of less than 1 in a million in the general population. According to the a large series of MPNST by Ducatman et al., the Ki 67 index is not necessarily relevant to tumor biology prognosis [6]. MPNST share similar prognostic factors with patients who have other soft tissue sarcomas and have some of the poorest clinical outcomes. [7]. It is therefore unlikely that the coincidence of MPNST and MEN-1 in this patient is serendipitous. We suggest that clinical investigation is warranted in all other MEN-1 cases with consideration for a possible association with MPNST.

Conclusion

We report a novel association between MEN-1 and MPNST. The tumor arising from a ganglioneuroma of the adrenal gland is important to note in the constellation of associations with MEN-1, particularly given its malignant behavior. MEN-1 patients should be followed carefully to detect all disease manifestations and associations as early as possible.

Conflict of Interest

None declared.

References

1. Thakker, R. V., P. J. Newey, G. V. Walls, J. Bilezikian, H. Dralle, P. R. Ebeling, et al. 2012. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J. Clin. Endocrinol. Metab. 97:2990–3011.
2. Gatta-Cherifi, B., O. Chabre, A. Murat, P. Niccoli, C. Cardot-Bauters, V. Rohmer, et al. 2012. Adrenal involvement in MEN1. Analysis of 715 cases from the Groupe d'etude des Tumeurs Endocrines database. Eur. J. Endocrinol. 166:269–279.
3. Italiano, A., F. Delva, S. Mathoulin-Pelissier, A. Le Cesne, S. Bonvalot, P. Terrier, et al. 2010. Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. Ann. Oncol. 21:2436–2441.
4. Stucky, C.-C. H., K. N. Johnson, R. H. Gray, B. A. Pockaj, I. T. Ocal, P. S. Rose, et al. 2012. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. Ann. Surg. Oncol. 19:878–885.
5. Fletcher, C. D., C. P. Dal, I. de Wever, Mandahl, N., F. Mertens, F. Mitelman, J. Rosai et al. 1999. Correlation between clinicopathological features and karyotype in spindle cell sarcomas: a report of 130 cases from the CHAMP study group. Am. J. Pathol. 154:1841–1847.
6. Ducatman, B. S., B. Sheithauer, D. G. Piepgras, H. M. Reiman, and D. M. Ilstrup. 1986. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. Cancer 57:2006–2021.
7. Anghileri, M., R. Miceli, M. Fiore, L. Mariani, A. Ferrari, C. Mussi, et al. 2006. Malignant peripheral nerve sheath tumors. Cancer 107:1065–1074.

