Case Report

Complete surgical removal of multiple tumor lesions in malignant pheochromocytomas produces a good prognosis

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Abbreviations & Acronyms
^{123}I-MIBG = ^{123}I-metaiodobenzylguanidine
CK = creatine kinase
CT = computed tomography
CVD = cyclophosphamide vincristine and dacarbazine
MPCC = malignant pheochromocytoma
PASS = Pheochromocytoma of the Adrenal gland Scaled Score

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Introduction: Malignant pheochromocytomas are rare catecholamine secreting tumors; there is no definitive strategy for the treatment of malignant pheochromocytomas, especially in cases with multiple tumors.
Case presentation: A 72-year-old woman with diabetic ketoacidosis presented with multiple malignant pheochromocytomas 16 years after undergoing adrenalectomy. After three courses of systemic chemotherapy, there was no change in the size of tumor lesions or serum catecholamine levels; surgical removal of all lesions was carried out. Eighteen months after the operation, the patient has had no recurrences and her diabetes is controlled well by oral medication.
Conclusion: Our findings indicate that complete surgical resection should be considered, even in patients with multiple malignant pheochromocytomas.

Key words: catecholamine crisis, CVD therapy, malignant pheochromocytoma, multiple recurrence.

Keynote message

Lifetime follow-up is essential for pheochromocytoma even in low risk. Surgical resection should be considered when chemotherapy fails in MPCC even in multiple tumors.

Introduction

Pheochromocytomas, which are rare catecholamine-secreting tumors, are usually benign; however, 10–20% of the cases are malignant.[1] No standard treatment has been developed for MPCC, especially in cases with multiple metastatic tumors.[2] This is predominantly due to the low incidence of this tumor type, which makes it difficult to design clinical trials. We report here an MPCC patient who developed multiple tumors 16 years after an initial primary adrenalectomy. Complete surgical resection of these tumors has given this patient 18 months of disease-free survival.

Case presentation

A 72-year-old Asian female presented with general fatigue. She had prior history of type 2 diabetes and laparoscopic right adrenalectomy for the removal of pheochromocytoma 16 years earlier. Examination revealed high blood glucose (585 mg/dL), HbA1c (8.6%). And catecholamine and metanephrine related factors levels in 24 h pooled urine was described below: adrenaline 514.8 μg, noradrenaline 273.6 μg and dopamine 25 μg; metanephrine 3.78 mg, normetanephrine 0.72 mg and vanillylmandelic acid 7.7 mg. CT revealed multiple intraperitoneal tumors (Fig. 1a–d); all were coincident with uptake of ^{123}I-MIBG scintigraphy (Fig. 2a), and without uptake on positron emission tomography at all. She was diagnosed with diabetic ketoacidosis, and suspected of MPCC. The patient was treated with a combination of CVD chemotherapy. After initiation of chemotherapy, she suddenly developed severe

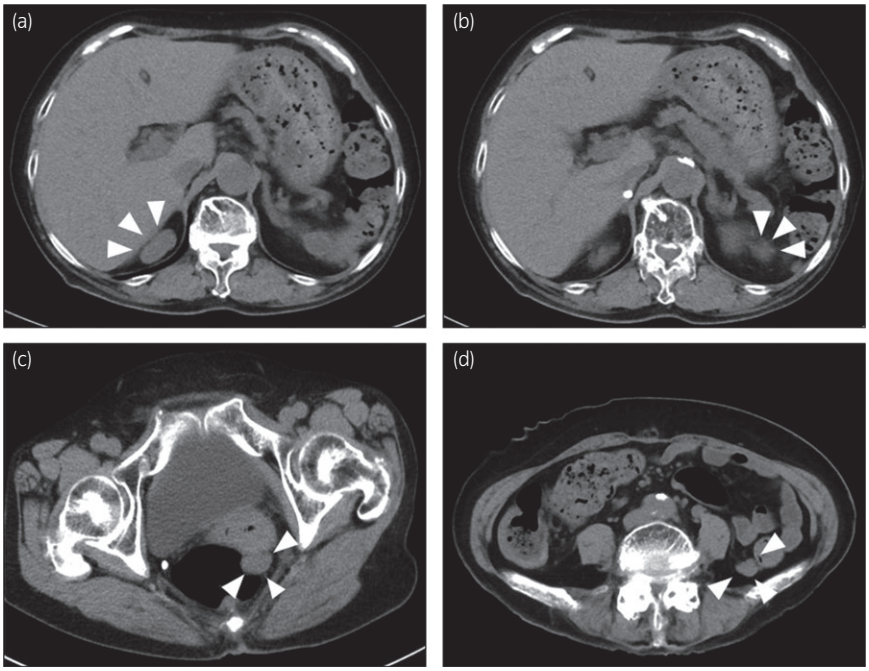

Fig. 1 Abdominal CT of tumors in the peritoneal cavity (white arrows). Tumors occurred in the lesion after right adrenalectomy (a), near the spleen (b), the para-rectum (c), and the para-descending colon (d).

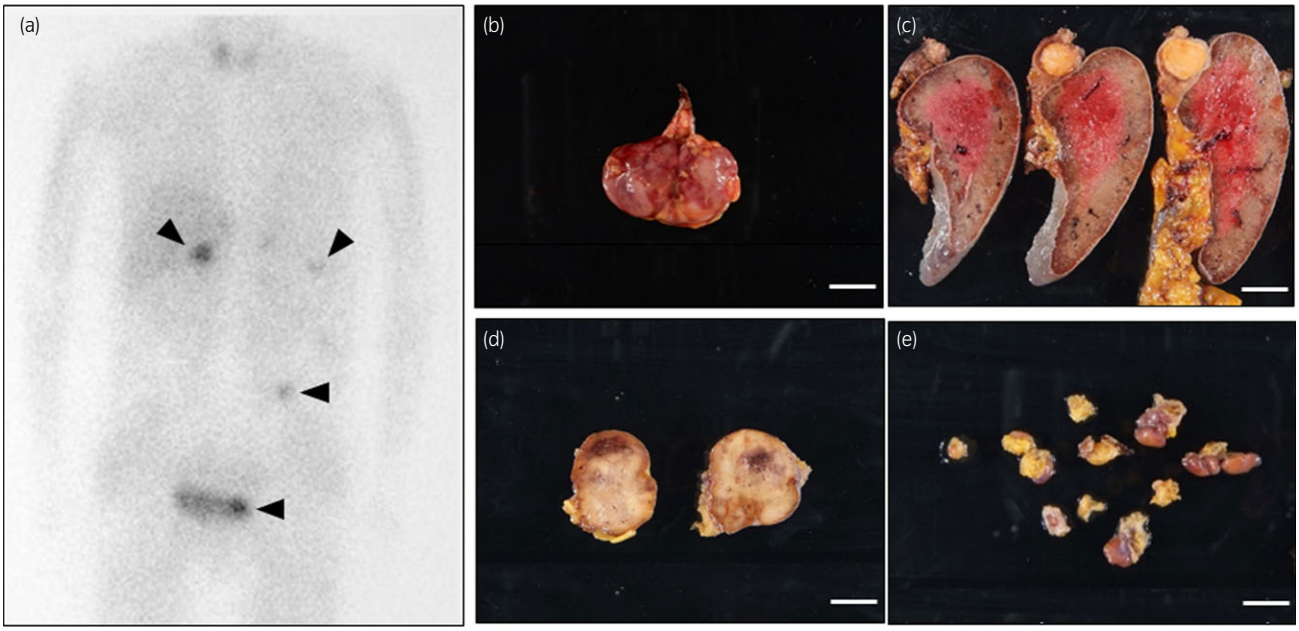

Fig. 2 (a) ^{123}I-MIBG scintigraphy. Abnormal uptakes occurred in the equivalent part of the abdominal CT (black arrows). (b–e) Macroscopic appearance of a surgically removed specimen. Tiny, yellowish brown tumors with partial bleeding were surrounded by normal tissue. The lesion after right adrenalectomy (b). Spleen and the near spleen tumor (c). The para-rectal tumor (d). The para-descending colon tumor (e). White scale bar is 10 mm.

nausea and high blood pressure (234/86 mmHg), with a high level of CK (926 IU/L) and broad-range ST changes on an electrocardiogram. An echocardiograph showed abnormal cardiac wall motion, and she was diagnosed with reverse Takotsubo cardiomyopathy. Serum catecholamine levels were extremely high (adrenaline 9904 pg/mL, noradrenaline 20 154 pg/mL and dopamine 1568 pg/mL), and thus the cardiomyopathy was attributed to catecholamine crisis. Accordingly, the next cycle of CVD was administered under ICU supervision and crisis was avoided. After three CVD cycles, there was no change in tumor volume, and serum catecholamine levels were still high. Therefore, surgery was performed under general anesthesia, and all lesions were successfully removed by strict circulatory management. The

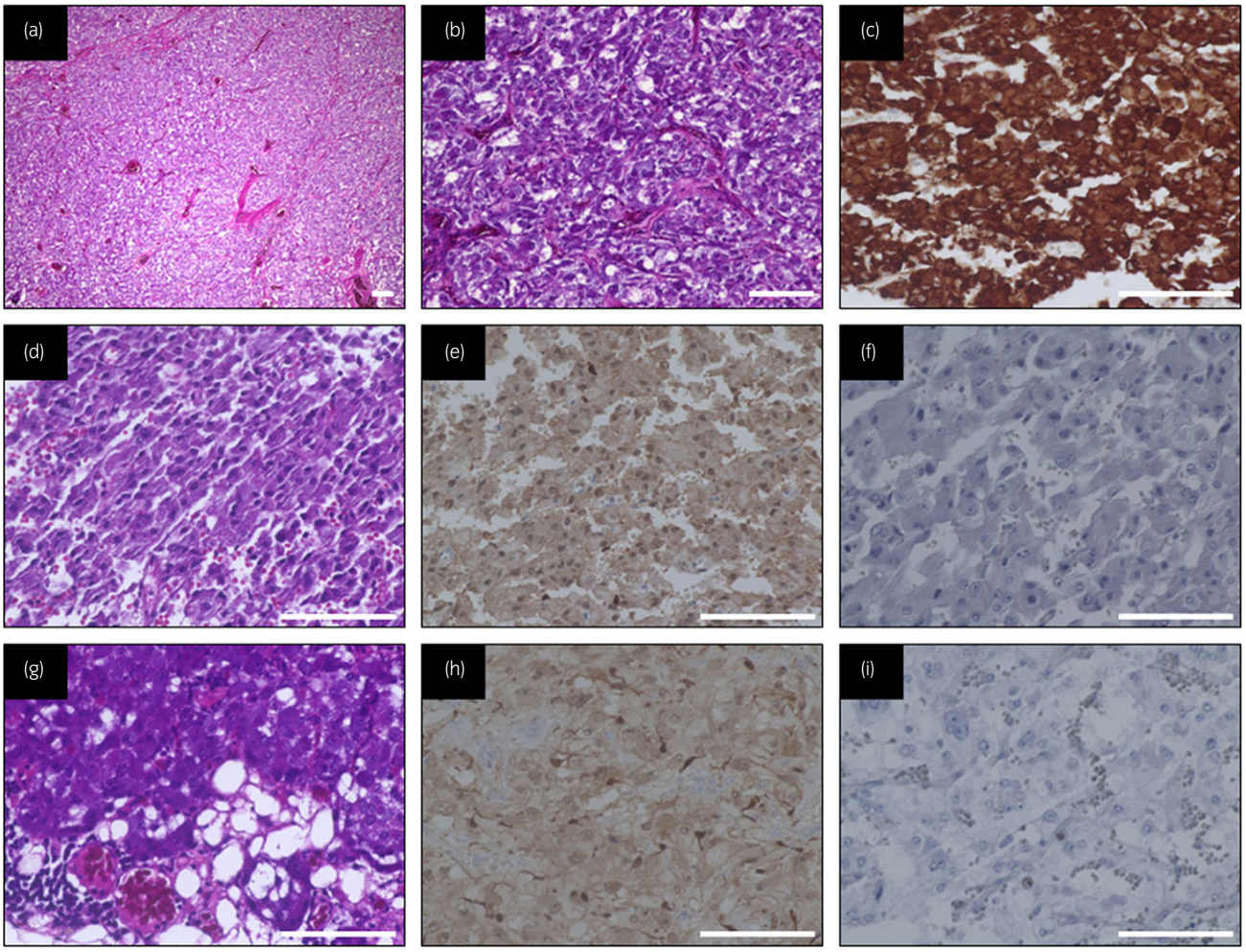

Fig. 3 (a–c, g–i) Microscopic findings of the present surgical specimen. (d–f) Microscopic appearance of 16-year-old surgical specimen. (a, b, d, g) Hematoxylin and eosin staining of the tumor specimen. A PASS score was 2 points (d) and 4 points (e). (magnification, ×4 (a), ×40 (b, d, g)). (c) Immunohistochemical staining of the tumor lesion revealed chromogranin A positivity. (magnification × 40). (e, f, h, i) Immunohistochemical staining of the tumor lesion with S-100 (e, h), and Ki-67 (f, i). The S-100 positivity rate was Grade 1 (e) and Grade 2 (h), and the Ki-67 positivity rate was 0% (f) and 1% (i). (magnification × 40).

tumor consisted of polygonal or spindle cells arranged in small nests surrounded by sustentacular cells (Fig. 3a,b). The tumor was chromogranin A-positive (Fig. 3c), and all lesions were classified as MPCC. Surgery normalized serum catecholamine levels. Eighteen months post-surgery, no additional accumulation of ^{123}I-MIBG has been identified, and the patient's diabetes has been stabilized.

Discussion

The 2017 WHO Tumor Classification states that all pheochromocytomas could have metastatic potential. However, histological prediction of MPCC from primary adrenalectomy specimens is challenging. To date, there have been few investigations; a PASS score of ≥4 points,[3] decrease in S-100 positivity rate to Grade 0,[4] and Ki-67 positivity rate of ≥4%[5] in tumor cells all correlate with a malignant prognosis. However, direct pathological comparison between primary adrenal tumor and surgical specimens after recurrence is extremely rare. Therefore, we obtained the specimen in previous operation 16 years ago, and performed immunohistochemical analysis as shown in Figure 3. As a result, the PASS score was not significantly changed. Therefore, in this case, it would have been impossible to predict the malignancy based on the primary tumor status (Fig. 3d–f). In addition, surgical specimens from the recurrent tumors were analyzed (Fig. 3g–i). Interestingly, the degree of malignancy did not differ between primary tumor and recurrent tumors. New additional biomarkers will be required to help select most likely to develop MPCC.

Malignancy is solely diagnosed when recurrence or metastasis have appeared. The mean period between primary adrenalectomy and recurrence is ~5 years (range 0.3–53.4 years).[2,6] One reason of tumor recurrence may be tumor injury during primary resection and Rafat *et al.* reported five cases of peritoneal multiple metastasis of MPCC, and all cases had tumor injury during laparoscopic surgery.[7] In our case, the patient had laparoscopic right adrenalectomy 16 years ago and the tiny capsule rupture documented in the operative note. According to the European Congress of Endocrinology, patients should be monitored at least 10 years postoperatively, particularly those determined to be at high

risk of recurrence (age <20 years at the time of surgery, patients with symptomatic/hereditary diseases, cases in which tumor diameter is ≥15 cm, paraganglioma cases). And continuous monitoring throughout a patient's lifetime is also recommended. In our case, recurrence occurred 16 years postoperatively despite the patient being at low-risk. This might be partly owing to the incidence of tiny capsule rapture during primary resection. Therefore, we suggest that lifetime follow-up should be mandatory in all pheochromocytoma patients.

There is no definitive strategy to treat MPCC with multiple tumors that have spread within the peritoneal cavity. Administration of CVD chemotherapy is an alternative treatment; however, catecholamine crisis (as in our case) is a rare but very severe adverse event.[8] In this case, although we attempted to control blood pressure by administering oral doxazosin mesylate before chemotherapy, the patient developed reverse Takotsubo cardiomyopathy. Under ICU supervision, subsequent chemotherapy was safely performed with no additional incidence of crisis, because we administered phentolamine mesylate, landiolol hydrochloride, and nifedipine while directly monitoring arterial pressure. Based on our results, we suggest that crisis management should be performed when MPCC patients are treated with CVD. This should occur in an environment where strict blood pressure management can be applied under ICU supervision, as in our case.

After three CVD cycles and no reduction in tumor size on CT and serum catecholamine levels were still high. Therefore, we diagnosed as stable disease and decided to perform surgery. Ellis *et al.*[9] reported that patients who presented with disease confined to the abdomen were significantly more likely to achieve and maintain a clinical response once tumors had been completely resected. Consistent with this, we found that once all lesions were successfully removed, serum catecholamine levels were normalized. Our conclusion is limited by the fact that it is based on only one case; however, lifetime follow-up is essential and surgical resection appears to be able to prolong survival in MPCC patients with multiple tumors.

Conclusion

We report here a case of an MPCC patient with multiple tumor lesions (which recurred 16 years after a primary adrenalectomy) who has successfully achieved 18 months disease-free survival following complete surgical resection. Lifetime follow-up is essential for pheochromocytoma occurred tumor spillage during laparoscopic surgery, and surgical resection should be considered as a viable option for multiple tumors when chemotherapy is not effective.

Conflict of interest

The authors declare no conflict of interest.

Declarations

This study was approved by the Nagoya City University Institutional Review Board; the approval number was 60-18-0178.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1 Harari A, Inabnet WB. Malignant pheochromocytoma: a review. *Am. J. Surg.* 2011; **201**: 700–8.

2 Choi YM, Sung T-Y, Kim WG *et al.* Clinical course and prognostic factors in patients with malignant pheochromocytoma and paraganglioma: a single institution experience. *J. Surg. Oncol.* 2015; **112**: 815–21.

3 Thompson LDR. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. *Am. J. Surg. Pathol.* 2002; **26**: 551–66.

4 Adler JT, Meyer-Rochow GY, Chen H *et al.* Pheochromocytoma: current approaches and future directions. *Oncologist* 2008; **13**: 779–93.

5 de Wailly P, Oragano L, Radé F *et al.* Malignant pheochromocytoma: new malignancy criteria. *Langenbecks Arch. Surg.* 2012; **397**: 239–46.

6 Hamidi O, Young WF, Nicole MI *et al.* Malignant pheochromocytoma and paraganglioma: 272 patients over 55 years. *J. Clin. Endocrinol. Metab.* 2017; **102**: 3296–305.

7 Rafat C, Zinzindohoue F, Hernigou A *et al.* Peritoneal implantation of pheochromocytoma following tumor capsule rupture during surgery. *J. Clin. Endocrinol.* 2014; **99**: E2681–5.

8 Wu LT, Dicpinigaitis P, Bruckner H, Manger W, Averbuch S. Hypertensive crises induced by treatment of malignant pheochromocytoma with a combination of cyclophosphamide, vincristine, and dacarbazine. *Med. Pediatr. Oncol.* 1994; **22**: 389–92.

9 Ellis RJ, Patel D, Prodanov T *et al.* Response after surgical resection of metastatic pheochromocytoma and paraganglioma: can postoperative biochemical remission be predicted? *J. Am. Coll. Surg.* 2013; **217**: 489–96.