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Case Report

The Largest Malignant Pheochromocytoma: A Case Report and Literature Review

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Abstract: Introduction: Malignant pheochromocytoma is a rare neuroendocrine tumor with an annual incidence of 3–8 cases per 1 million per year in the general population. Its clinical presentation can vary greatly. There are few published cases of giant pheochromocytomas. We report a case of the largest tumor in the world. The literature is reviewed to evaluate the spectrum of disease presentations and the available options for disease management and treatment. Case presentation: A 52-year-old male, originally from El Kelaa des Sraghna in the middle of Morocco, which had a 36cm mass of the left suprarenal gland with metastatic lesions. He was treated with a combination chemotherapy regimen of cyclophosphamide, vincristine and dacarbazine. Conclusion: A heterogeneous clinical presentation of malignant pheochromocytoma and a short response to chemotherapy had been observed in our case. However, controlled studies need to determine a standard of care.

Key Words: Malignant pheochromocytoma, largest, chemotherapy, case report.

INTRODUCTION

Pheochromocytoma is a rare neuroendocrine neoplasm arising from the adrenal medulla. Its prevalence can be estimated at between 1:4500 and 1:1700, with an annual incidence of 3–8 cases per 1 million per year in the general population [1]. Pheochromocytoma is usually benign; however, approximately 10% of pheochromocytomas are malignant [2]. Traditionally, malignant pheochromocytomas were described as those that had metastases, recurred, or had evidence of local invasion of surrounding structures [3,4]. Most tumors are sporadic, whereas about 25% of cases are associated with germline mutations [5]. Treatment of malignant pheochromocytoma is based primarily on surgical resection, but most cases are unresectable. A combination of cyclophosphamide, vincristine, and dacarbazine (CVD) is often used as initial chemotherapy for malignant pheochromocytoma, based on a study that reported a high response rate and improvement in symptoms. In this report, we present a case of the largest malignant pheochromocytoma in the World treated with a combined chemotherapy with CVD, with a literature review focused on the current therapeutic approaches for patients with this pathology.

Case report

A 52-year-old male, originally from El Kelaa des Sraghna in the middle of Morocco, with no personal or family history was referred for evaluation of a growing intra-abdominal tumefaction. He was asymptomatic. His weight was 65 kg for 1.72 m. He was normotensive at 120/80 mmHg and normocarde with a heart rate of 72/min. Physical examination revealed a tender mass of 25cm in the left upper quadrant extended to the hypogastric region with a collateral venous circulation on the abdominal wall. Thoracoabdominal computerized tomography (CT) scan demonstrated a 26.7 x 24.5 x 36cm mass located in the left retroperitoneum, which occupied the entire abdominal cavity (Fig.1,2).

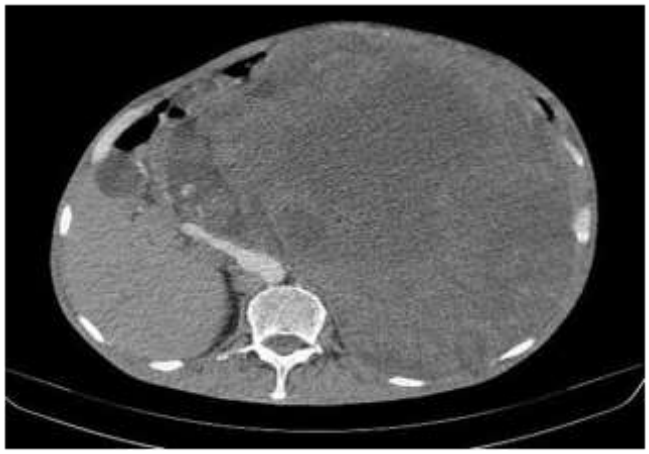

Fig.1. Axial **contrast-enhanced CT scan of the abdomen showing a large mass of the left flank with locoregional infiltration and mass effect on adjacent structures.**

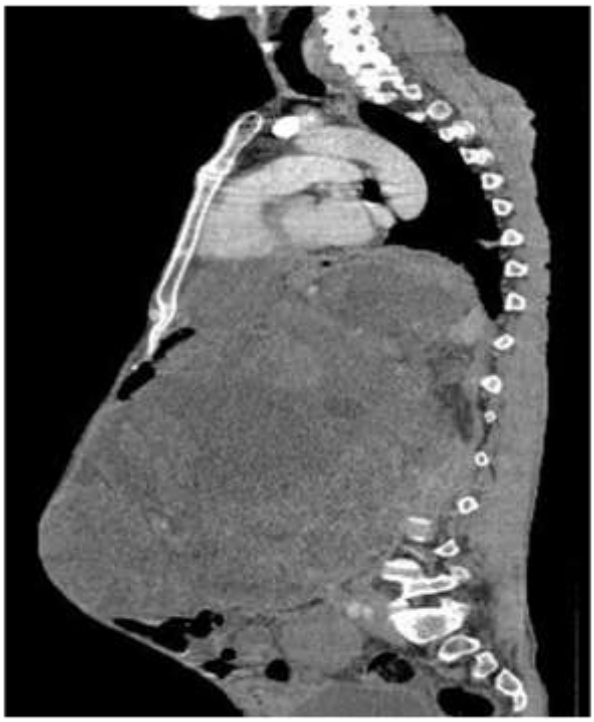

Fig.2. Sagittal reconstruction CT scan showing a large heterogeneous abdominal mass.

It had an abnormal vascularization and displaced the adjacent structures. The left suprarenal gland could not be identified. This tumor was associated with deep lymph nodes, multifocal hepatic lesions and lung nodules (Fig.3).

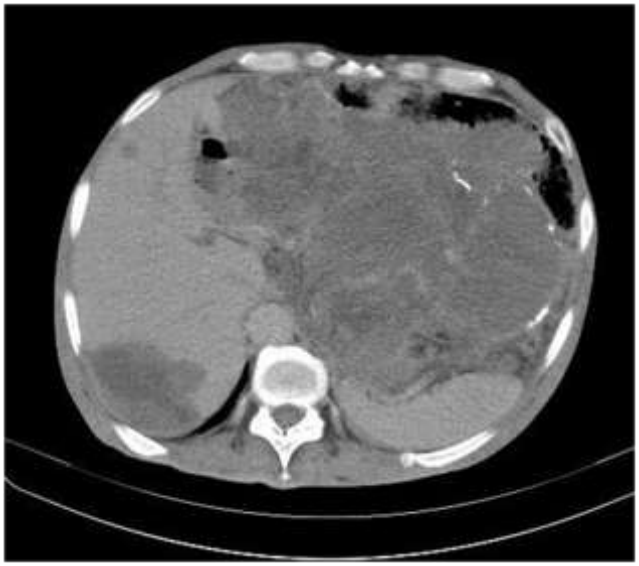

Fig.3. Axial CT scan showing a large heterogeneous mass of the left flank with two liver lesions.

Because the origin of the mass was unknown, a surgical exploration was performed. The tumor was hypervascular and adherent to vascular axes. Pathologic evaluation of a biopsy revealed a pheochromocytoma. Biochemical tests include measurements of urinary and plasma catecholamines, urinary metanephrines (normetanephrine and metanephrine), and urinary vanillylmandelic acid were normal, while Ambulatory blood pressure monitoring (APBM) were also normal. Scintigraphy showed no 123I-MIBG uptake in suprarenal area (Fig.4).

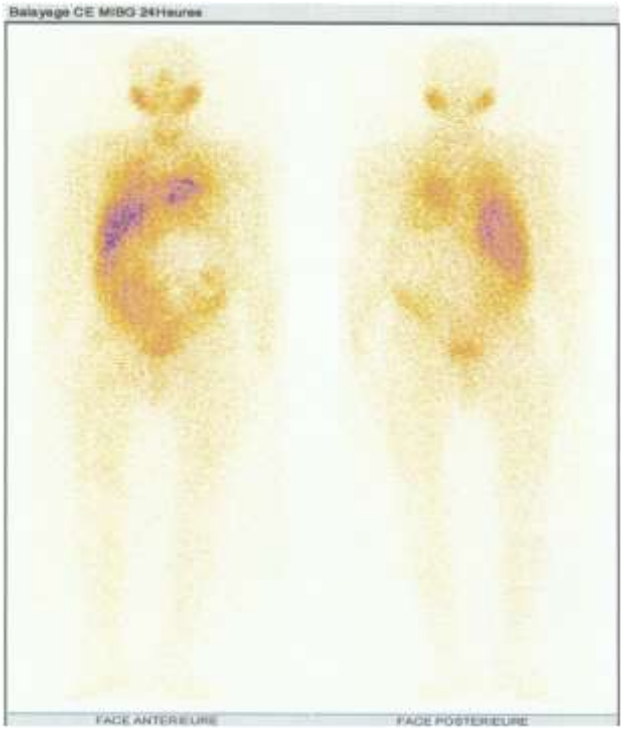

Fig.4. 24-hour delayed scintigraphy showed no 123I-MIBG uptake in left suprarenal area.

No associated diseases were present at diagnosis. Especially; the fundus of the eye showed no retinal hemangioblastoma which may be present in Von Hippel Lindau disease. Cervical ultrasound and calcitonin dosage were normal excluding medullary thyroid carcinoma may be associated with pheochromocytoma in a context of multiple endocrine neoplasia type 2. The patient was referred to genetics consultation for mutation research on SDH and VHL genes, research made necessary because a third of pheochromocytoma are associated with a familial disease.

Whereas negative result of 123I-MIBG scintigraphy, the patient was treated with CVD chemotherapy as originally described by Averbuch et al. [6]: a combination of cyclophosphamide (750 mg/m2 body surface area) on day 1, vincristine (1.4 mg/m2 body surface area) on day 1 and dacarbazine (600mg/m2 body surface area) on days 1 and 2 every 21days. The patient remained stable until the 9th cycle of the chemotherapy when a CT scan showed a progressing retroperitoneal tumor. The situation began to worsen and he died three months later.

Discussion

Malignant pheochromocytoma is an uncommon tumor which accounts for 10-20% of all cases of pheochromocytoma [7,8]. It may occur sporadically or as part of hereditary syndrome. According to the latest studies, up to about 24% of tumors may be hereditary [9-11]. Hereditary pheochromocytoma is associated with multiple endocrine neoplasia type 2, neurofibromatosis type 1, von Hippel-Lindau syndrome, and familial pheochromocytomas due to germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D [11].

Clinical presentation of pheochromocytoma can vary greatly

but most commonly presenting with episodes of headaches, sweating, palpitations, and hypertension [12,13]. Normal blood pressure or even hypotension is also common in these patients, in whom diagnosis is often based on the space-occupying complications of tumours.28,29 Presumably as a consequence of their asymptomatic nature, as in our patient, these tumors tend to be large; most present with metastases [13]. There are few published cases of pheochromocytomas larger than 20 cm; the biggest pheochromocytoma, with a size of 29 × 21 × 12 cm, was presented by Basso and colleagues [14]. There are studies that try to define variables to determine malignant behaviour, such as the tumour size. According to Sturgeon and colleagues, sizes greater than 6 cm could be a predictor of malignancy [15]. However, other authors disagree [16]. Currently, malignancy is defined by the existence of metastasis, local recurrence or invasion of adjacent structures. The most common metastatic sites are the bones, lungs, liver, and lymph nodes [17].

In malignant pheochromocytoma, palliative surgery is usually performed in order to release tumor pressure on surrounding tissues or to decrease tumor mass [18]. However, a survival advantage of surgical debulking is not proven. 131I-MIBG is used for patients in whom 123I-MIBG scintigraphy is positive with only about 30% of responses [19].

Chemotherapy, with a combination of cyclophosphamide, vincristin and dacarbazine(CVD), can provide tumor regression and symptom relief in up to 50% of patients, but the responses are usually short and in only 30% of patients[6]. Chemotherapy is preferred in patients with negative 123I-MIBG scintigraphy and in those with rapidly progressing tumors [20,21]. Several studies have demonstrated overexpression in malignant pheochromocytoma of angiogenic molecules, such as VEGF [22], leading strong evidence that targeting this pathway with antiangiogenic therapies could represent a new promising treatment option. Accordingly, sunitinib, a receptor tyrosine kinase inhibitor, has been used in the treatment of malignant pheochromocytomas, with promising results [23,24].

Conclusion

Malignant pheochromocytomas are very rare and aggressive tumors with a heterogeneous presentation. Only isolated cases are published rather than large series, so it is difficult to determine the outcomes. A short response to chemotherapy was observed in our case. Hopefully, a larger study must be created in the near future with enough power to determine a standard of care.

Declarations

A. Acknowledgements

We are grateful to the patient‘s next of kin for giving us permission to publish the report.

B. Authors’ contributions

JD, EE, RB, AE and MK carried out medical management and the writing of the manuscript. NCIG performed the patient's radiological examination. HR performed the histological examination of the patient’s biopsy. All authors read and approved the final manuscript.

C. Competing interests

The authors declare that they have no competing interests.

D. Consent for publication

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

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