International Journal of Surgery Case Reports 125 (2024) 110537

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Malignant pheochromocytoma with vascular invasion and metastasis: A case report and review of treatment options

Youssef Zaoui *, Salim Ouskri, Imad Boualaoui, Ahmed Ibrahimi, Hachem El-Sayegh, Yassine Nouini

Urology A department, Ibn Sina Hospital, Rabat, Morocco

ARTICLE INFO

Keywords:
Malignant pheochromocytoma
Metastatic pheochromocytoma
Pheochromocytoma

ABSTRACT

Introduction: Pheochromocytoma is a rare neuroendocrine tumor that arises from chromaffin cells in the adrenal medulla, with an incidence of 2–8 cases per million adults.

Case presentation: This case study presents the case of a 39-year-old male patient who experienced recurrent headaches, palpitations, and hypertension, ultimately diagnosed with malignant pheochromocytoma after imaging revealed a large adrenal mass with vascular invasion and metastasis.

Discussion: Despite the rarity of malignant pheochromocytomas, they present significant clinical challenges. Diagnosis typically relies on imaging and biochemical tests, with management necessitating a multidisciplinary approach.

Conclusion: This case underscores the importance of early recognition and comprehensive management strategies for malignant pheochromocytoma and reviews the available therapeutic strategies including debulking surgery, chemotherapy and other novel therapies such as Iobenguane I-131 and tyrosine kinase inhibitors.

1. Introduction

Pheochromocytomas are uncommon neuroendocrine tumors derived from chromaffin cells of the adrenal medulla. These tumors, though rare, can be malignant in about 10 % of cases, posing significant clinical challenges due to their potential for metastasis and regional invasion. Patients often present with symptoms like headaches, palpitations, and persistent hypertension. Accurate diagnosis involves biochemical tests and imaging, while effective management requires a multidisciplinary approach, combining surgery, pharmacotherapy, and, in advanced cases, systemic treatment options to optimize outcomes and improve patient prognosis.

2. Case presentation

A 39-year-old north-African male patient with no significant medical history presented to the emergency department of our hospital with recurrent pulsating headaches, palpitations, tinnitus, phosphenes, and upper right quadrant abdominal pain. Upon examination, he was diaphoretic, with blood pressure recorded at 210/124 mmHg and a heart rate of 124 bpm. Laboratory tests indicated mild hyperglycemia and hypokalemia, while inflammatory markers were negative.

A thoraco-abdominal computed tomography (CT) scan with intravenous contrast was performed, revealing a large right adrenal mass (12 × 9 cm) characterized by significant peripheral contrast uptake and central necrosis (Fig. 1) and kidney parenchymal invasion (Fig. 2). Additionally, a secondary hepatic lesion and tumor extension into the inferior vena cava with a right intra-auricular thrombus were noted (Fig. 3). The CT scan didn't reveal any other malignancies.

The diagnosis of pheochromocytoma was confirmed through elevated serum levels of free catecholamines with epinephrine measured at 295 pg/ml (2,5 times the normal value). The 24 h urinary methoxylated derivatives metanephrine and normetanephrine were also elevated at 136 μg/24 h (2,2 times the normal value) and 678 μg/24 h (1,8 times the normal value).

The patient received intravenous nicardipine to manage his severe hypertension. The tumor was deemed inoperable due to its extensive vascular invasion and metastasis.

The patient was thoroughly informed about his medical condition, including the prognosis and the potential outcomes of various therapeutic options tailored to his specific case. All available treatments were presented to him, covering their potential benefits, risks, and expected

* Corresponding author.
E-mail address: zaoui.youssef@outlook.com (Y. Zaoui).

https://doi.org/10.1016/j.ijscr.2024.110537
Received 13 September 2024; Received in revised form 24 October 2024; Accepted 25 October 2024
Available online 28 October 2024

outcomes. Given the particularly poor prognosis and the limited chances of achieving a significant improvement in his condition with more aggressive therapies, the patient made an informed decision to pursue palliative care. This choice reflects his understanding of the situation and his preference for a focus on comfort and quality of life, rather than undergoing treatments aimed at extending life with potentially burdensome side effects. The patient succumbed to an acute myocardial infarction 42 days later.

3. Discussion

Pheochromocytomas are rare neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla, with an estimated annual incidence of 2 to 8 per million adults [1]. Approximately 10 % of these tumors are classified as malignant, defined by the presence of metastases or local invasion into surrounding tissues [2].

The Menard triad—headaches, palpitations, and sweating—is a classic presentation, although it is not always complete. High blood pressure is the cardinal sign of pheochromocytoma. It is more likely to be permanent, severe, extremely unstable, and refractory to medical treatment. Paroxysmal hypertension accesses are more evocative of a pheochromocytoma. They are often associated with diffuse pain with intense headaches, anxiety and diaphoresis. In certain cases they result in serious acute accidents (acute pulmonary edema, acute myocardial infarction or transient blindness).

Metanephrine assays are conducted as a first-line diagnostic procedure, measuring either the free plasma metanephrines or the fractionated plasma or urinary metanephrines [3]. Plasma free metanephrines assess the direct secretion produced by the tumor continuously as opposed to the episodic secretion of catecholamines, which is indicative of the tumor mass. Their measurement would be little affected by sympathoadrenal excitation.

Abdominopelvic computed tomography scans are the primary diagnostic tool, with high sensitivity for detecting adrenal tumors as small as 1 cm with 87 % to 100 % sensitivity [4]. The diagnosis of malignant pheochromocytoma is often challenging and relies on various criteria, including tumor size, invasion of neighboring organs, and the presence of lymphadenopathy. Imaging plays a crucial role in the assessment of pheochromocytomas. In this case, the CT findings of a large adrenal mass with central necrosis and peripheral contrast uptake, along with hepatic lesions and intravascular extension, were indicative of a malignant process. Imaging characteristics can significantly aid in differentiating malignant from benign pheochromocytomas. Features suggestive of malignancy on imaging include [5]:

- Venous or contiguous invasion
- Presence of lymphadenopathy
- Metastasis
- Slow washout
- Density greater than 20UH
- Size: a correlation between the size and malignancy was described with larger lesions being more frequently malignant.

In the absence of metastases or massive periglandular growth, it is histopathologically difficult to distinguish a malignant from a benign pheochromocytoma [6].

Management of malignant pheochromocytomas typically requires a multidisciplinary approach. Treatments for malignant

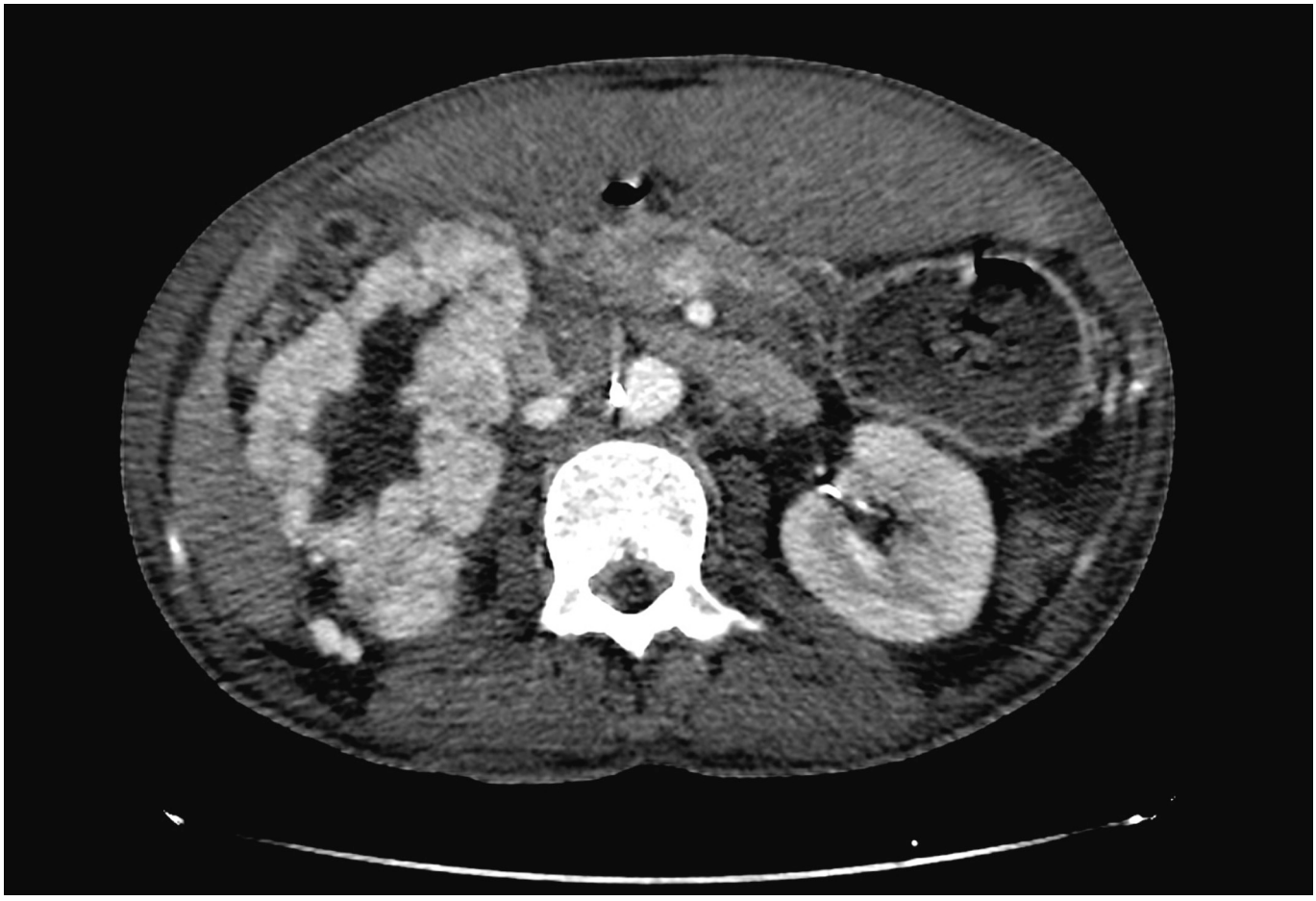

Fig. 1. CT scan axial view showing the right adrenal tumor with central necrosis and peripheral contrast uptake.

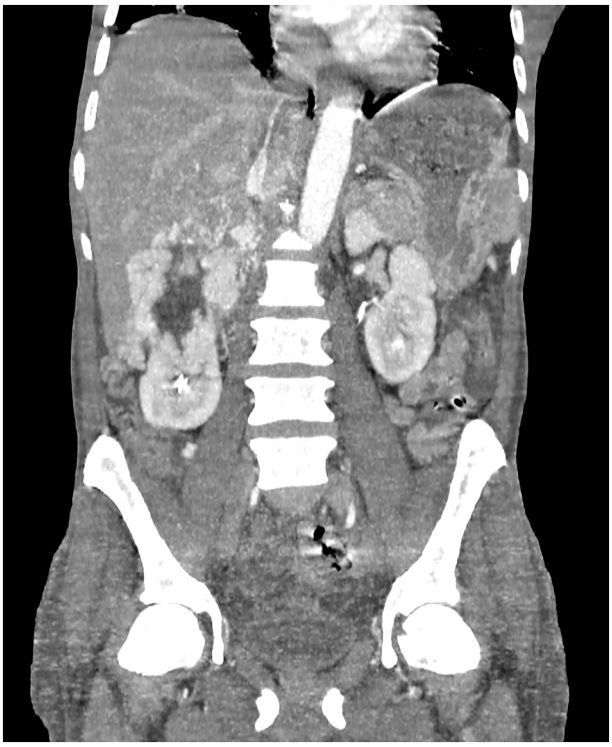

Fig. 2. CT scan, coronal view showing the invasion of the upper pole of the right kidney.

pheochromocytoma include pharmacological control of hormone mediated symptoms, surgical excision of the lesion, external irradiation and systemic chemotherapy. Surgical resection is the primary treatment for localized tumors; however, in cases of advanced disease, as seen here, surgical options may be limited. The aim of surgical debulking is to reduce and control catecholamine-related symptoms. A publication by Ellis et al. showed that the majority of the 30 patients included in their retrospective analysis experienced biochemical recurrence within the first year after surgery [7]. Moreover, the presence of residual disease at the end of surgery resulted in poor and short-lasting biochemical control. This suggests that this surgery should only be considered for patients whose tumors can be completely resected with clear margins. Preoperative management focuses on controlling hypertension and other symptoms associated with catecholamine release. Alpha-blockers are often administered 7 to 14 days prior to surgery to mitigate the risks associated with catecholamine surges during surgical intervention. The preoperative management of hypertension control, alpha blockade, and appropriate fluid resuscitation are key elements to successful perioperative surgical outcomes.

For unresectable cases, systemic therapies such as chemotherapy may be considered. The CVD regimen, which includes cyclophosphamide, vincristine, and dacarbazine, has been utilized in the treatment of metastatic pheochromocytoma [8], although the response rates can be variable with survival benefit ranging from 1 to 4 years. This regimen is associated with potential adverse effects, including myelosuppression, which may lead to neutropenia, anemia, and thrombocytopenia; peripheral neuropathy, particularly from vincristine; hepatotoxicity from dacarbazine; and risks such as nausea, vomiting, and alopecia. Additionally, cyclophosphamide carries a risk of hemorrhagic cystitis, particularly in patients with known bladder disorders such as chronic cystitis or interstitial cystitis. The CVD regimen is contraindicated in patients with severe bone marrow suppression, significant hepatic or renal impairment, severe peripheral neuropathy, or a known hypersensitivity to any of the regimen's drugs.

External beam radiation therapy directed at bone metastases, as well as other targeted techniques like radiofrequency ablation, cryoablation, chemoembolization, cyber/gamma knife, and arterial embolization, can be employed to manage local tumor-related complications. However, these methods are primarily utilized for palliative purposes, either to alleviate symptoms or to reduce overall tumor burden, rather than as curative treatments.

In summary, current treatment options for malignant and metastatic pheochromocytoma include cytotoxic chemotherapy, surgical interventions, and emerging therapies. These approaches vary in efficacy and outcomes, reflecting the complexity of these rare tumors:

- The CVD regimen has shown a disease control rate of 81 % and a biochemical response rate of 91 % in a study involving 16 patients [9]. The median overall survival was reported at 4.4 years, with a 5-year survival rate of 50 % [9].
- Surgery remains a potentially curative option, particularly for localized tumors. However, metastatic spread often limits the feasibility of complete resection [10].
- Radiolabeled MIBG therapy has gained attention, with recent FDA approval of Iobenguane I 131 for specific patient groups: adult and pediatric patients 12 years and older with iobenguane scan-positive, unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. However, this treatment comes with significant side effects that patients need to be aware of, including myelosuppression, secondary myelodysplastic syndrome, leukemia or other malignancies, hypothyroidism, elevation of blood pressure, renal toxicity, and pneumonitis.

  More recently, in march 2024, FDA approved the use of lutetium Lu 177 dotatate in the treatment of adult and pediatric patients 12 years and older with metastatic SSTR-positive pheochromocytoma/paraganglioma. This treatment is indicated when other options available have failed or are not suitable.
- Sunitinib has been tested for progressive or metastatic pheochromocytoma or paraganglioma and has shown promising results. In the FIRSTMAPPP trial, a randomised, placebo-controlled, double-blind, phase 2 trial, the 12-month progression free survival of the sunitinib group was 36 % [90 % CI 23–50] compared to 19 % in the placebo group [90 % CI 11–31]. The main grade 3 and 4 reported side effects were asthenia, hypertension and bone pain [11]
- Other investigational treatments include immunotherapy and targeted therapies (Lenvatinib, Temozolomide, Olaparib, Belzutifan), although their efficacy is still under evaluation in clinical trials.
- The National Comprehensive Cancer Network recommends including these patients with symptomatic and unresectable tumors in clinical trials.

Despite these options, the prognosis for malignant pheochromocytoma remains challenging, with 5-year survival rates ranging from 34 % to 74 % depending on various factors [10]. Further research is essential to optimize treatment strategies and improve outcomes.

Prognostic factors for malignant pheochromocytomas include tumor size, the presence of visceral metastases, and SDHB gene mutations [12]. A retrospective and prospective analysis of 491 cases conducted by Su et al. showed that the loss of SDHB expression in immunohistochemistry of pheochromocytoma and paraganglioma surgical specimens is associated with poorer prognosis [13].

Surveillance of patients with locally unresectabale or metastatic pheochromocytoma is recommended every 12 weeks (or earlier in new symptoms show up) for 12 months and is based on:

- Physical examination, blood pressure control, markers
- Thoraco-abdomino-pelvic CT scan with contrast or MIBG SPECT/CT (if previous MIBG-positive or concern for disease progression and prior to considering radionuclide therapy) or FDG-PET/CT for bone dominant disease. Somatostatin Receptor based imaging can also be

considered if previous SSTR-positive or concern for disease progression and prior to considering radionuclide therapy.

Recent studies emphasize the need for a multidisciplinary approach in managing malignant pheochromocytomas. The complexity of these tumors necessitates collaboration among endocrinologists, surgeons, and oncologists to optimize patient outcomes. Furthermore, ongoing research into the genetic basis of pheochromocytomas may yield insights into targeted therapies and improved diagnostic criteria.

This article has been reported in line with the SCARE criteria [14].

4. Conclusion

This case highlights the importance of considering malignant pheochromocytoma in patients presenting with classic symptoms of catecholamine excess. Early diagnosis through appropriate imaging is crucial for determining the extent of disease and guiding therapeutic decisions. In this case, imaging helped confirm the metastatic nature of the tumor, allowing for a more informed discussion of treatment options. The patient's decision to pursue palliative care underscores the need for a patient-centered approach, especially when the prognosis is poor and the risks of aggressive therapies may outweigh the benefits. This case emphasizes the value of multidisciplinary collaboration in managing complex cases, ensuring that treatment aligns with the patient's values and goals for quality of life.

Guarantor

Youssef Zaoui

CRediT authorship contribution statement

Youssef ZAOUI: Urology resident: First author and corresponding author has contributed in the writing and correction of this case report.

Salim OUSKRI: Urology Resident: second author has contributed in the writing of this the case report.

Ahmed IBRAHIMI: Urology assistant Professor: has contributed in the writing of this the case report.

Imad BOUALAOUI: Urology assistant Professor: has contributed in the writing of this the case report.

Hachem EL SAYEGH: Urology Professor: has contributed in the writing of this the case report.

Yassine NOUINI: Urology Professor: has contributed in the writing and correction of this the case report.

Consent

Written informed consent was obtained from the patient to publish 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 on request.

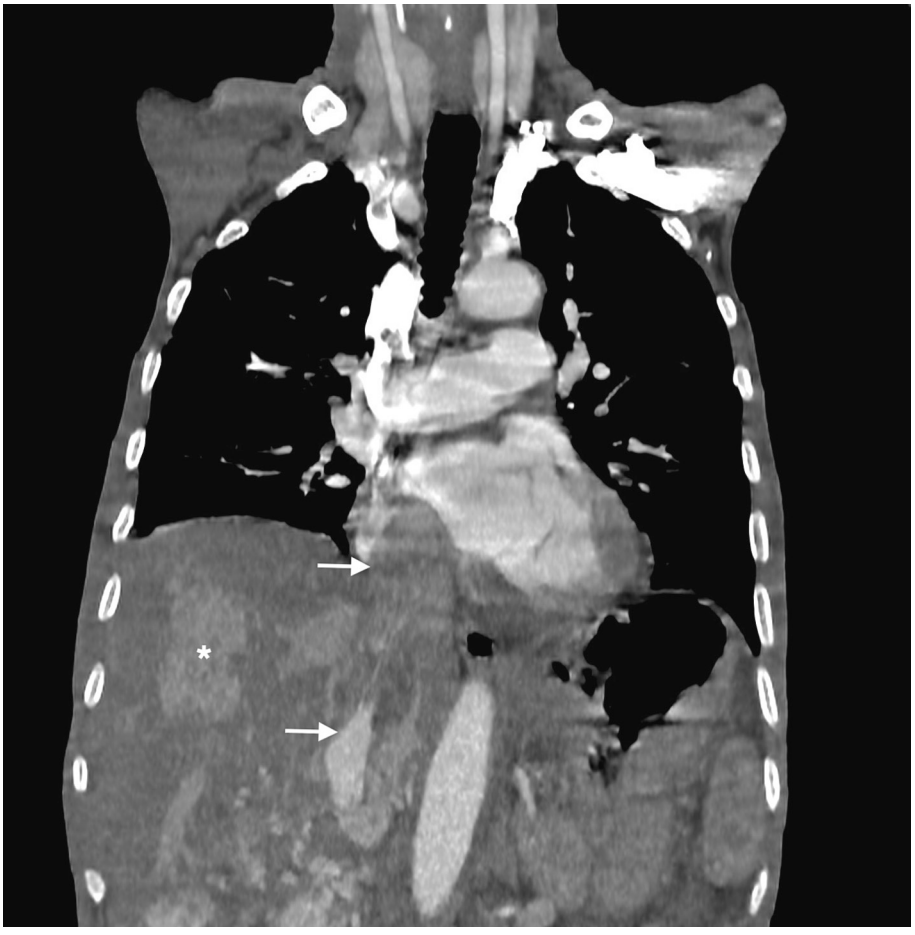

Fig. 3. CT scan, coronal view showing extension of the tumor to the inferior vena cava and right atrium (arrows: tumoral and cruoric thrombus) and a liver metastasis (asterisk).

Ethical approval

Ethical approval for this study was provided by the Ethical Committee.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors have no conflict of interest to declare.

References

[1] R.E. Goldstein, O'neill J.A., Jr., Holcomb G.W., Clinical experience over 48 years with pheochromocytoma, Ann. Surg. 229 (1999) 755–766, https://doi.org/10.1097/00000658-199906000-00001.

[2] Michael H. Johnson, Jaime A. Cavallo, R. Sherburne Figenshau, Malignant and metastatic Pheochromocytoma: Case Report and Review of the Literature, Urology Case Reports, Volume 2, Issue 4, 2014, Pages 139–141, ISSN 2214-4420, DOI:https://doi.org/10.1016/j.eucr.2014.05.001.

[3] Pacak K., Eisenhofer G., Ahlman H., Bornstein S.R., Gimenez-Roqueplo A.P., Grossman A.B. International symposium on pheochromocytoma. Pheochromocytoma: recommendations for clinical practice from the First International Symposium,. October 2005. Nat. Clin. Pract. Endocrinol. Metab. 2007;3:92–102. DOI:https://doi.org/10.1038/ncpendmet0396.

[4] L. Brunt, J. Moley, Diseases of the adrenal medulla, in: C. Townsend, R. Beauchamp, B. Evers, et al. (Eds.), Sabiston Textbook of Surgery, Elsevier, Philadelphia, PA, 2004, pp. 1052–1056.

[5] P. Legmann, F. Charleux, B. Dessout-Monsoro, H. Bahurel, H. Gouya, O. Vignaux, A. Oudjit, J. Augui, Imagerie des surrénales, EMC, endocrinologie nutrition. 10-014-D-10 (2003) 15p.

[6] G.M. Portela-Gomes, M. Stridsberg, L. Grimelius, et al., Expression of chromogranins A, B, and C (secretogranin II) in human adrenal medulla and in benign and malignant pheochromocytomas. An immunohistochemical study with region-specific antibodies, APMIS 112 (2004) 663–673, https://doi.org/10.1111/j.1600-0463.2004.t01-1-apm1121003.x.

[7] R.J. Ellis, D. Patel, T. Prodanov, et al., Response after surgical resection of metastatic pheochromocytoma and paraganglioma: can postoperative biochemical remission be predicted? J. Am. Coll. Surg. 217 (3) (2013) 489–496.

[8] M. Nakane, S. Takahashi, I. Sekine, et al., Successful treatment of malignant pheochromocytoma with combination chemotherapy containing anthracycline, Ann. Oncol. 14 (2003) 1449–1451, https://doi.org/10.1093/annonc/mdg358.

[9] Yu, Fujiwara., Yu, Fujiwara., Akihiro, Ohmoto., Naoki, Fukuda., Xiaofei, Wang., Tetsuya, Urasaki., Naomi, Hayashi., Yasuyoshi, Sato., Kenji, Nakano., Mayu, Yunokawa., Makiko, Ono., Junichi, Tomomatsu., Takeshi, Yuasa., Junji, Yonese., Shunji, Takahashi. 1. Clinical features and outcomes of metastatic pheochromocytoma treated by cytotoxic chemotherapy Endocr. J. (2021) https://doi.org/10.1507/ENDOCRJ.EJ20-0762.

[10] Maran, Ilanchezhian., Abhishek, Jha., Karel, Pacak., Jaydira, Del, Rivero. 3. Emerging treatments for advanced/metastatic Pheochromocytoma and Paraganglioma Curr. Treat. Options Oncol. (2020) https://doi.org/10.1007/S11864-020-00787-Z.

[11] -Baudin E, Goichot B, Berruti A & al., Sunitinib for metastatic progressive phaeochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet, Volume 403, Issue 10431, 1061–1070, https://doi.org/10.1016/S0140-6736(23)02554-0.

[12] E. Baudin, M.A. Habra, F. Deschamps, G. Cote, F. Dumont, M. Cabanillas, Therapy of endocrine disease: treatment of malignant pheochromocytoma and paraganglioma, Eur. J. Endocrinol. 171 (2014) R111–R122, https://doi.org/10.1530/EJE-14-0113.

[13] T. Su, Y. Yang, L. Jiang, J. Xie, X. Zhong, L. Wu, Y. Jiang, C. Zhang, W. Zhou, L. Ye, G. Ning, W. Wang, SDHB immunohistochemistry for prognosis of pheochromocytoma and paraganglioma: A retrospective and prospective analysis, Front Endocrinol (Lausanne). 16 (14) (2023 Mar) 1121397, https://doi.org/10.3389/fendo.2023.1121397.

[14] C. Sohrabi, G. Mathew, N. Maria, A. Kerwan, T. Franchi, R.A. Agha, The SCARE 2023 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int J Surg Lond Engl. 109 (5) (2023) 1136.