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Metastatic Malignant Vagal Paraganglioma in a Young Woman: A Case Report

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Abstract **Case Report**

Background: Vagal paragangliomas (VPGL) are exceptionally rare neuroendocrine tumors, accounting for only 2–5% of head and neck paragangliomas. Although most are slow-growing and non-functional, they carry an intrinsic metastatic potential, and malignancy is established only by the presence of distant metastases in tissues devoid of paraganglia. ***Case presentation:*** We report the case of a 37-year-old woman with no significant medical or family history, who presented with chronic dysphonia and a progressively enlarging high left jugulo-carotid mass, without clinical signs of catecholamine hypersecretion. Cervical imaging showed a 7.1 × 3.1 × 2 cm lesion encasing the left carotid axes, with central necrosis, a second infrahyoid lesion, and suspicious cervical lymph nodes. Thoracic and abdominal CT revealed multiple "cannon-ball" pulmonary nodules and three hepatic lesions. Laryngoscopy confirmed left vocal cord paralysis, reflecting vagus nerve involvement. Biopsy with immunohistochemistry confirmed the diagnosis of paraganglioma, and 18F-FDG PET-CT showed intense hypermetabolism of the cervical mass and of the pulmonary and hepatic secondary sites. The patient received six cycles of CVD chemotherapy (cyclophosphamide, vincristine, dacarbazine), followed by progression according to RECIST 1.1 criteria (hepatic and cervical). She was then switched to temozolomide, which was well tolerated. After three cycles, the disease showed a mixed response, with slight pulmonary regression and stable initial cervical lesion, but a new carotid bifurcation lesion and hepatic progression. ***Conclusion:*** Metastatic malignant vagal paraganglioma is a rare entity whose management should be discussed within a dedicated multidisciplinary tumor board, following ENDOCAN-COMETE recommendations and tailored to the tumor's molecular profile, notably SDHx status. This case illustrates the sequential systemic options available (CVD, temozolomide, with sunitinib and peptide receptor radionuclide therapy as further options) and underlines the value of functional imaging (68Ga-DOTATATE PET-CT), genetic counseling, and prolonged follow-up given the unpredictable course of the disease.

Keywords: Paraganglioma; vagal paraganglioma; head and neck; metastatic; temozolomide; case report.

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INTRODUCTION

Paragangliomas (PGL) are rare neuroendocrine tumors arising from paraganglia, small clusters of cells derived from the ganglia of the autonomic nervous system. Two groups are classically distinguished according to their location and functional profile: sympathetic paraganglia, located along the para-vertebral chains and in the pelvis, most often secreting catecholamines, and parasympathetic paraganglia, predominating in the head and neck and occasionally in the thorax, usually non-functional [1].

The overall incidence of pheochromocytomas and paragangliomas is estimated at 0.4 to 0.8 per 100,000 person-years, with a metastatic rate of 10 to 20% across all locations [2]. Head and neck paragangliomas (HNPGL) alone account for 65 to 70% of all PGL but less than 0.6% of head and neck cancers, with a reported metastatic fraction of 6 to 19% in the most recent series [1,3].

Their classic sites of origin are distributed between the carotid bodies (at the bifurcation of the common carotid artery), the jugulotympanic paraganglia and the vagal paraganglia (VPGL), located along the vagus nerve. Carotid body tumors (CBT) remain the most frequently observed, whereas VPGL remain the rarest, accounting for only 2 to 5% of HNPGL [3,4].

Since the 5th edition of the WHO classification of head and neck tumors (2022), all paragangliomas are now considered to carry an intrinsic metastatic potential rather than being classified as strictly 'benign' or 'malignant', malignancy remaining defined exclusively by the occurrence of distant metastases in tissues devoid of paraganglia [4,5].

In patients with a cervical paraganglioma, the clinical picture most often manifests as a mobile, painless, sometimes pulsatile swelling. Depending on the location and tumor extension, other symptoms may appear, such as tinnitus, hearing loss, headache or dizziness. Cranial nerve involvement is also possible, manifesting notably as dysphonia, dysphagia or the onset of Claude Bernard-Horner syndrome. Finally, the largest lesions can induce non-specific compressive signs, such as local pain or a sensation of heaviness, characteristic of invasive tissue masses [1,6].

The management of metastatic paragangliomas relies, according to the recommendations of the French national ENDOCAN-COMETE network, on a multidisciplinary strategy aimed at controlling tumor progression and secretory symptoms [7]. Therapeutic options now combine targeted therapies — foremost among them sunitinib, whose efficacy was demonstrated by the randomized FIRSTMAPPP trial [8] — systemic chemotherapy and peptide receptor radionuclide therapy, while surgery and external radiotherapy remain reserved for the local management of compressive foci. This personalized approach favors preservation of quality of life in tumors that are most often slow-growing, but whose behavior remains unpredictable from one patient to another [7].

We report here a case of malignant paraganglioma of the left vagus nerve with pulmonary and hepatic metastases, highlighting the diagnostic, immunohistochemical, functional imaging and therapeutic aspects.

Case Presentation

A 37-year-old woman, married and mother of four children, with no notable personal or family medical history, presented with chronic dysphonia associated with a progressively enlarging high left jugulo-carotid swelling. This mass evolved without associated dyspnea, dizziness or peripheral facial palsy. No functional signs suggestive of catecholaminergic hypersecretion (paroxysmal hypertension, palpitations, headache) were reported. The course occurred without fever, but was marked by a deterioration in general condition.

The work-up performed in this patient was comprehensive, combining morphological and functional imaging, endoscopy and pathology.

Cervico-thoracic CT (30 May 2025) identified, at the cervical level, a left latero-cervical lesion encasing the common carotid artery and its two bifurcation branches, extending from C2 to C5 and measuring 65 x 30 x 23 mm, of heterogeneous density with a hypodense center and an enhancing peripheral rim, associated with a second left basi-cervical lesion measuring 17 x 16 mm interposed between the common carotid artery and the vertebral artery (V1). At the thoracic level, multiple 'cannon-ball' pulmonary nodules with spiculated contours were noted, together with three hepatic lesions located at the dome and in segments IV and VI.

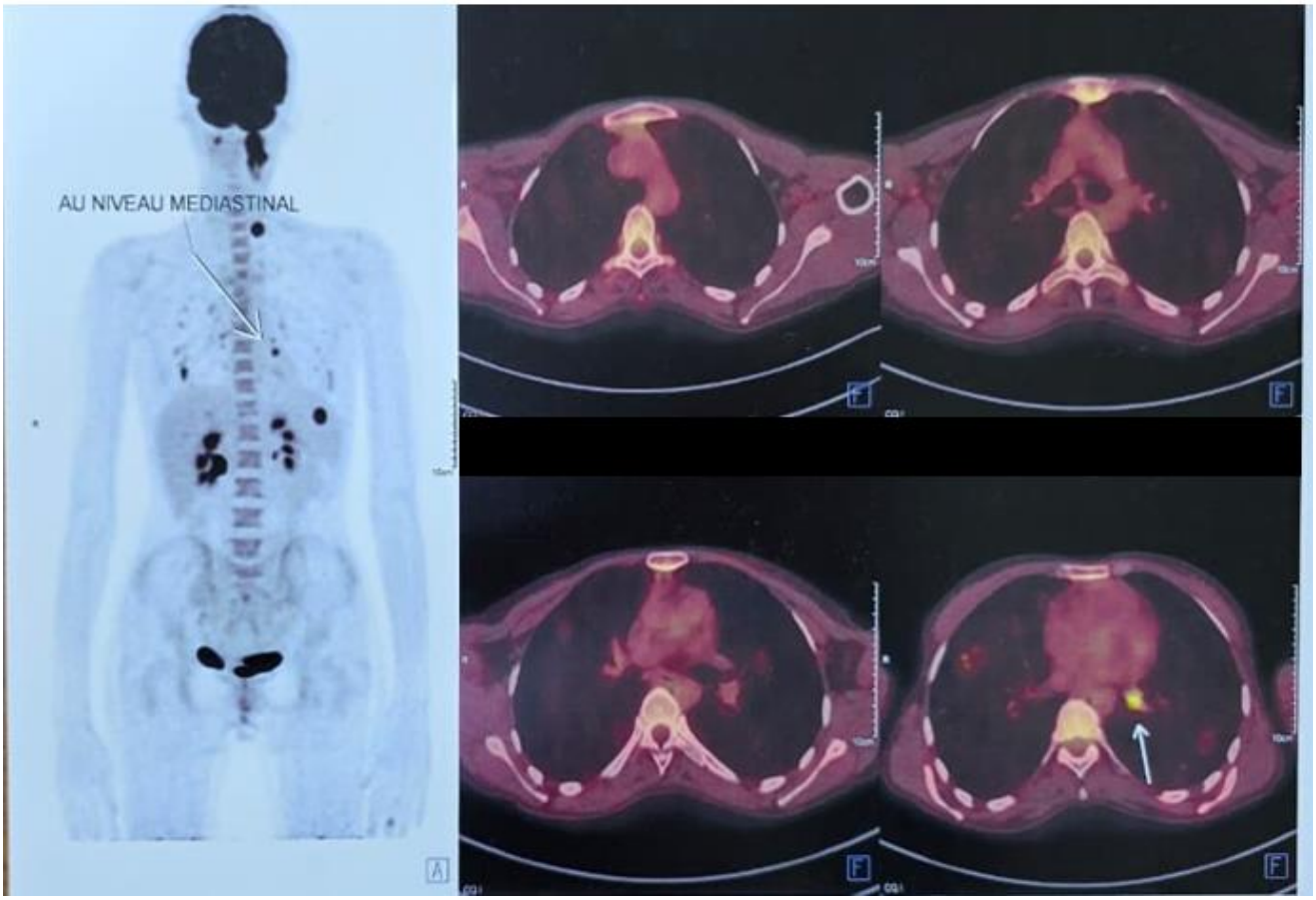
Cervical ultrasound (28 July 2025) confirmed a lesion centered on the left carotid body, hypoechoic, heterogeneous, well-defined, measuring 2.25 x 1.8 cm, circumferentially encasing the carotid arteries while these remained patent, with a second infrahyoid lesion of 1.5 x 1.5 cm and high jugulo-carotid lymphadenopathy.

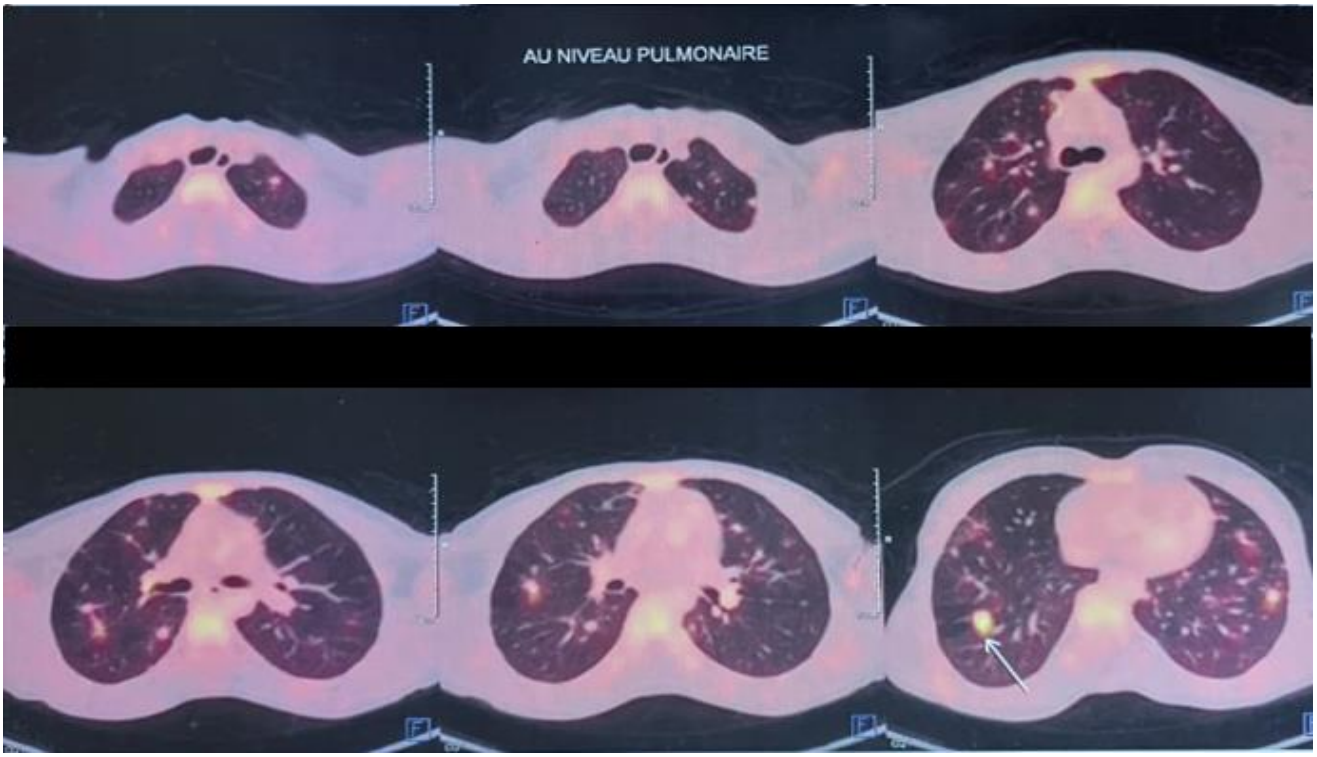
Cervical MRI (16 July 2025) further characterized a lesion centered on the left carotid body, measuring 7.1 x 3.1 x 2 cm, with heterogeneous intermediate T2 signal and diffusion restriction, showing intense peripheral enhancement and delineating central areas of necrosis. The lesion encased the left internal and external carotid arteries, compressed the ipsilateral internal jugular vein (IJV), and was in contact with several neighboring structures (parapharyngeal space, thyroid lobe, submandibular gland, sternocleidomastoid muscle). A second infrahyoid lesion with similar features was also described. Cervical lymph nodes with diffusion restriction were noted (up to 15 x 12 mm). On MR angiography, there was an absence of flow in the left IJV and a slender appearance of the left sigmoid and transverse sinuses.

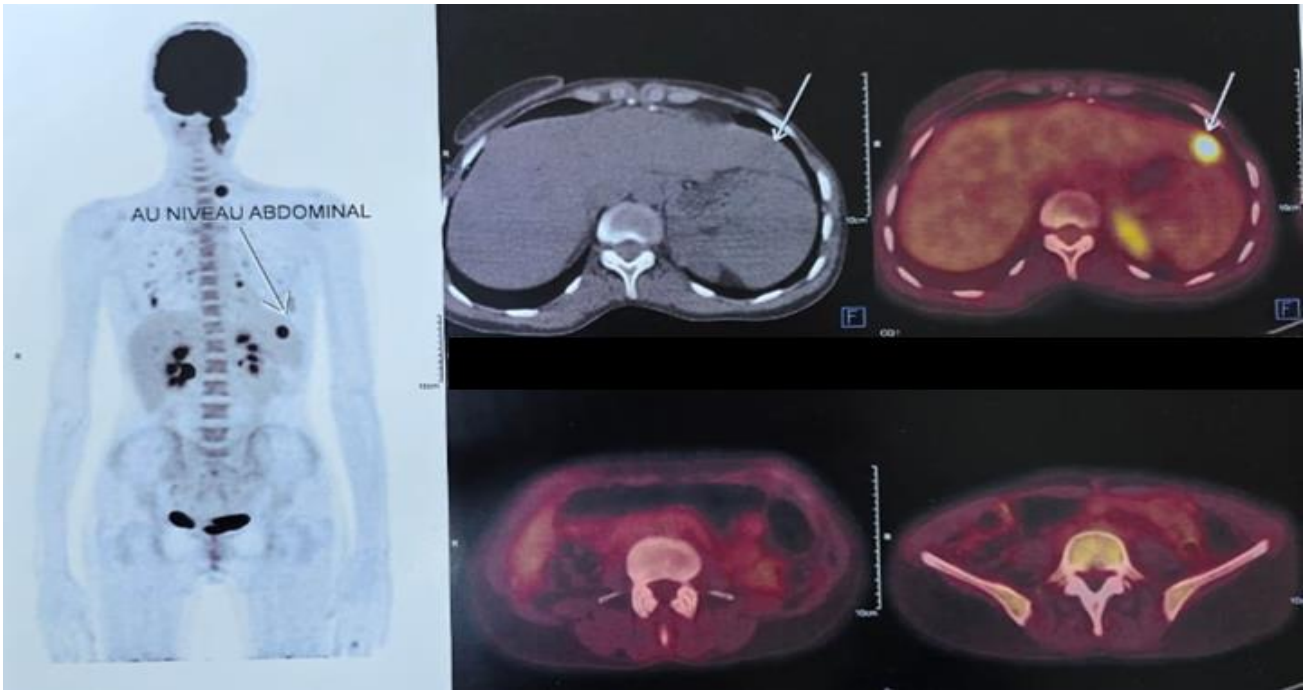
Nasal fibroscopy and bronchoscopy (23 July 2025) revealed left vocal cord paralysis with cricoarytenoid edema. Direct laryngoscopy (18 July 2025) did not identify any suspicious lesion at the various laryngeal levels or in the nasopharynx.

Biopsy of the mass (15 August 2025) revealed a tumor proliferation suggestive of paraganglioma, confirmed by immunohistochemistry (25 August 2025), which concluded to a paraganglioma.

PET-CT (10 September 2025) demonstrated intense hypermetabolism of the upper left jugulo-carotid mass, with a secondary site along the left lower jugular axis, probable involvement of the right upper jugular axis, multiple nodular pulmonary sites and a probable hypermetabolic hepatic site in segment II.


AU NIVEAU MEDIASTINAL


AU NIVEAU PULMONAIRE



Follow-up cervico-thoraco-abdomino-pelvic CT (2 February 2026), performed after 6 cycles of CVD chemotherapy (cyclophosphamide, vincristine, dacarbazine), concluded to progression according to RECIST 1.1 criteria, with an increase in number and size of the hepatic lesions (up to 20 x 21 mm in segment II), persistence of scattered bilateral pulmonary nodules, and persistence of the nodular lesion in the posterior left jugulo-carotid dihedral (17 x 16 x 15 mm).

The patient is currently on temozolomide, with good tolerance.

Follow-up cervico-thoraco-abdomino-pelvic CT (12 May 2026), performed after 3 cycles of temozolomide, showed a disease with mixed evolution, overall non-progressive but marked by elements of local progression. The initially known cervical paragangliomatous lesion remained stable, but a new paragangliomatous site appeared at the left carotid bifurcation (27 x 36 x 51 mm), constituting an element of progression. Secondary pulmonary sites showed a slight dimensional regression of the largest nodules. In contrast, secondary hepatic involvement showed progression, with an increase in the necrotic segment II lesion (29 x 20.6 mm versus 20 x 21 mm), while the segment V lesion was no longer identified. No suspicious bone lesion was detected. Overall, this work-up therefore reflects a disease that is not strictly stable, marked by the appearance of a new cervical site and hepatic progression, counterbalanced by a slight pulmonary regression.

DISCUSSION

Epidemiology, classification and genetic basis

Head and neck paragangliomas (HNPGL) are rare neuroendocrine tumors, accounting for approximately 0.6% of all head and neck cancers, with an estimated metastatic fraction of 6 to 19% in the most recent series [1]. About half of HNPGL occur in a context of hereditary predisposition, mainly related to germline pathogenic variants of the succinate dehydrogenase genes (SDHx), which constitute the main risk factor for multifocal and metastatic disease [1,5]. The 5th edition of the WHO classification of head and neck tumors (2022) now considers all paragangliomas as neoplasms with intrinsic metastatic potential rather than as strictly 'benign' or 'malignant' entities, malignancy remaining defined exclusively by the occurrence of distant metastases in tissues devoid of paraganglia [5]. The overall incidence of pheochromocytomas and paragangliomas has remained stable over time, at around 0.4 to 0.8 per 100,000 person-years, with a reported metastatic fraction of 10 to 20% across all locations [2].

Among HNPGL, vagal paragangliomas (VPGL) are extremely rare, accounting for 2 to 5% of all head and neck paragangliomas [3,4]. They occur at any age but preferentially affect adults between the 4th and 6th decades, with a clear female predominance in sporadic forms [1,3]. Their malignant potential is higher than that of carotid body tumors, the only formal proof of malignancy remaining, as for all HNPGL, the presence of nodal or distant metastases [4].

Clinical presentation

The clinical presentation of VPGL is typically insidious: a high, lateral, mobile cervical mass with slow progression, associated in large tumors with involvement of adjacent cranial nerves — the vagus nerve first and foremost (dysphonia, reflex cough on palpation), but also the accessory and hypoglossal nerves [1,4]. In our observation, the chronic dysphonia and the left jugulo-carotid swelling evolving for more than a year

correspond to the classic clinical picture of a large vagal paraganglioma. Left vocal cord paralysis reflects invasion or compression of the vagus nerve by the mass and constitutes, independently of malignancy, a sign of poor functional prognosis [1,6]. Catecholamine secretion, unlike in adrenal pheochromocytomas, remains rare in parasympathetic HNPGL and was not found in our patient; this does not, however, obviate the need for systematic measurement of plasma or urinary metanephrines and methoxytyramine at initial work-up [6].

Paraclinical findings

Imaging plays a central role in the evaluation of paragangliomas, providing three essential pieces of information: the precise location of the primary tumor, the detection of possible multifocality — which should raise suspicion of a hereditary syndromic form — and the detection of distant metastases, the only means of confirming malignancy with certainty and guiding the choice between curative-intent management and a palliative approach [6].

Cervical ultrasound remains the first-line morphological examination for any cervical mass. It typically shows a solid, hypoechoic, heterogeneous and hypervascular lesion on color Doppler, but remains insufficient to define locoregional extension or multifocality, which justifies the systematic use of cross-sectional imaging [3]. In our case, it identified two lesions of the left carotid space, hypoechoic and hypervascularized, the main one, centered on the carotid body, measuring 2.25 x 1.8 cm, associated with high jugulo-carotid lymphadenopathy, a picture consistent with paraganglioma.

On contrast-enhanced CT, paragangliomas present as solid masses with intense, early enhancement, reflecting their rich vascularization, with a sensitivity of 80 to 90% and a specificity close to 90% for positive diagnosis [3]. CT angiography further defines the relationships with the carotid axis and jugular venous return, guiding surgical or endovascular therapeutic decisions. In our patient, CT revealed two left cervical lesions with intense peripheral enhancement and a necrotic center, encasing the carotid axes, associated with secondary pulmonary 'cannon-ball' and hepatic sites, immediately signaling the malignant and metastatic nature of the disease.

MRI remains the reference examination for locoregional work-up. The heterogeneous T2 signal with areas of signal void producing the classic 'salt and pepper' appearance, related to intratumoral arterial flow, is nearly pathognomonic when present [3,6]. In our patient, MRI showed two lesions of the left carotid space with diffusion restriction and intense peripheral enhancement delineating areas of central necrosis, producing the 'lyre sign' by splaying of the carotid bifurcation, associated with suspicious cervical lymph nodes and left vocal cord paralysis reflecting vagus nerve involvement.

Functional imaging plays an increasing role in the staging of metastatic forms. 18F-FDG PET-CT, as in our patient, demonstrates intense hypermetabolism of the primary tumor and secondary sites, with high sensitivity for the detection of nodal, pulmonary and hepatic metastases. More recently, 68Ga-DOTATATE PET-CT, targeting the somatostatin receptors overexpressed by neuroendocrine cells, has established itself as the most effective functional examination for mapping HNPGL, superseding MIBG scintigraphy and FDG-PET in the detection of multifocal or metastatic forms, while also guiding eligibility for peptide receptor radionuclide therapy [9]. Its still-limited availability justifies a gradual integration into surveillance algorithms, particularly in carriers of SDHx variants [9].

Histology and immunohistochemistry

The definitive diagnosis relies on pathological examination, supplemented by immunohistochemistry: positivity for chromogranin A and synaptophysin in the chief cells, associated with characteristic staining of sustentacular cells by S100 protein [5]. No isolated histological criterion can, however, confirm malignancy; only the occurrence of distant metastases, as in our observation with pulmonary and hepatic sites, allows this to be formally established [4,5]. Constitutional genetic testing for a pathogenic variant of the SDHx genes is recommended in any patient with HNPGL, all the more so in the presence of a metastatic or multifocal form, because of its prognostic and therapeutic implications, as well as for family genetic counseling [1,5].

Management of metastatic disease

In France, the management of metastatic paragangliomas relies on a multidisciplinary evaluation within the national ENDOCAN-COMETE 'Adrenal Cancers' network, endorsed by the French National Cancer Institute, combining expert pathological review and discussion at a dedicated multidisciplinary tumor board [7]. The 2023 recommendations of this network emphasize that survival in these patients is heterogeneous, sometimes exceeding seven to ten years, which requires that any therapeutic intervention be justified in light of the disease's rate of progression, tumor burden and genetic status [7].

At the systemic level, the therapeutic strategy has been profoundly reconsidered since the 2024 publication of the randomized FIRSTMAPPP trial, conducted under the auspices of the ENDOCAN-COMETE and ENSAT networks: in patients with progressive metastatic pheochromocytoma/ paraganglioma, sunitinib doubled the one-year progression-free survival rate compared with placebo (35.9% versus 18.9%), with an even more marked benefit in patients carrying an SDHB variant (objective response rate of 50%) [8]. This is the first randomized

trial ever conducted in this ultra-rare disease, and its authors now position sunitinib as the medical option with the highest level of evidence for antitumor efficacy in progressive metastatic disease, making it, with the endorsement of the ENDOCAN-COMETE network that coordinated the trial, a first-line treatment to be discussed at a dedicated tumor board, particularly in SDHB-mutated patients [7,8]. Chemotherapy combining cyclophosphamide, vincristine and dacarbazine (CVD regimen), historically the most widely used systemic treatment in practice and still cited among first-line options in the 2023 network recommendations, retains a reported disease control rate of 48 to 100% and a progression-free survival of up to 20 to 40 months; it is, however, based on retrospective series rather than a randomized trial, unlike sunitinib [7]. Temozolomide, an oral alkylating agent related to dacarbazine, is an alternative used as monotherapy or as maintenance treatment after 6 to 9 cycles of CVD; its efficacy correlates with MGMT promoter hypermethylation, more frequent in SDHB-mutated tumors, which explains the better response observed in these patients [7]. In our patient, progression of the hepatic and cervical disease according to RECIST 1.1 after six cycles of CVD led to a switch to temozolomide, currently well tolerated; treatment with sunitinib could also be discussed in the event of further progression, in line with the most recent data.

Peptide receptor radionuclide therapy with 177Lu-DOTATATE, indicated in patients whose tumor expresses somatostatin receptors on functional imaging, is an increasingly discussed option in first or second line depending on the uptake profile, as an alternative or complement to sunitinib and CVD [7,9]. In the event of failure of previous lines, cabozantinib, another tyrosine kinase inhibitor, has recently shown promising results in a phase II trial [10]. Surgery and external radiotherapy remain reserved for the local management of compressive or symptomatic foci, in an approach favoring preservation of quality of life and cranial nerve function rather than a systematically curative intent [7].

Prognosis and follow-up

The prognosis of metastatic HNPGL remains heterogeneous and difficult to predict on the basis of isolated clinical or histological criteria alone, which justifies prolonged follow-up, combining repeated morphological and functional imaging, in all patients, including after apparent disease control [1,6]. SDHB mutational status is currently considered one of the most robust prognostic factors for metastatic risk and response to systemic treatments, whether sunitinib or temozolomide, reinforcing the value of early genetic counseling and cascade family screening [7,8].

Our observation thus illustrates the clinical presentation, imaging features and sequential therapeutic strategy of a metastatic malignant vagal paraganglioma, and underlines the value of structured multidisciplinary management, in line with the most current recommendations, combining functional imaging, genetics and evolving systemic options (sunitinib, CVD, temozolomide, peptide receptor radionuclide therapy, second-line targeted therapies) tailored to the tumor's molecular and evolutionary profile.

CONCLUSION

Malignant vagal paraganglioma is a rare entity, the diagnosis of which relies on a combination of clinical, morphological, functional and immunohistochemical findings, with certainty of malignancy provided only by the demonstration of distant secondary sites, as illustrated by our observation. Management of metastatic forms should be discussed at a dedicated multidisciplinary tumor board, drawing on the most current recommendations of the ENDOCAN-COMETE network, and tailored to the tumor's evolutionary and molecular profile, particularly its SDHx mutational status. Recent advances in functional imaging, notably 68Ga-DOTATATE PET-CT, and the expansion of the therapeutic arsenal — sunitinib, peptide receptor radionuclide therapy, second-line targeted therapies — now offer broader sequential therapeutic options, while preservation of quality of life and cranial nerve function remains the priority objective. Prolonged follow-up, combining clinical surveillance, imaging and family genetic counseling, remains essential given the unpredictable course of these tumors.

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