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Therapeutic potential of lorlatinib in ALK-mutated metastatic paraganglioma: Insights from clinical case report and literature review

Maria Concetta Nigro [a,*], Giacomo Corradi [b], Margherita Nannini [a,b], Guido Di Dalmazi [b,c], Lorenzo Tucci [b,c], Giorgio Tolento [d], Cristina Nanni [e], Arber Golemi [e], Antonio De Leo [b,f], Dario De Biase [f,g], Cristina Mosconi [b,h], Caterina Balacchi [h], Valentina Vicennati [b,c], Maria Abbondanza Pantaleo [a,b]

[a] Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[b] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna 40138, Italy
[c] Division of Endocrinology and Diabetes Prevention and Care, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy
[d] Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[e] Nuclear Medicine, IRCCS, Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy
[f] Solid Tumor Molecular Pathology Laboratory, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy
[g] Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy
[h] Department of Radiology, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna 40138, Italy

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ABSTRACT

Paragangliomas (PGLs) are rare neuroendocrine tumours that may display metastatic potential and have limited treatment options once advanced. The aim of this paper was to review the literature data available on the treatment of metastatic PGL, focusing on targeted therapy with anaplastic lymphoma kinase (ALK) inhibitor. In this scenario, we report a case of a 16-year-old boy with metastatic PGL, initially presenting back pain and substantial disease involvement in the thoracic spine, abdominal organs, and skeletal system. After failure of standard treatments, molecular profiling was conducted on tumour samples. The presence of a pathogenic ALK point mutation, specifically F1174L, led to off-label therapy with the ALK inhibitor lorlatinib. After starting treatment, the patient experienced rapid overall improvement, including complete resolution of pain, decreased plasma catecholamine levels, and stabilization of disease, with excellent treatment tolerance. After 12 months of therapy, imaging revealed reduced tumour burden, particularly in the thoraco-lumbar region. This case represents the first report of a PGL harbouring ALK F1174L mutation, successfully treated with lorlatinib. It underscores the utility of molecular profiling in rare cancers and the potential for targeted therapy to provide durable responses and improve outcomes where traditional treatments fail. As literature on the treatment of metastatic PGL is poor and largely based on retrospective studies, case series and case reports, and few clinical trials are available, our experience contributes valuable clinical insight and suggests that genetic testing and personalized treatment strategies, including ALK inhibitors, may offer new hope for patients with metastatic PGLs.

1. Background

Paraganglioma (PGL) is a rare neuroendocrine tumor arising from the sympathetic or parasympathetic extra-adrenal paraganglia, differing from pheocromocytoma (PCC) that originates from the adrenal medulla. Together, they are identified by the combined term PPGLs (paraganglioma and pheochromocytoma). PGLs are characterized by their ability to secrete catecholamines, leading to symptoms such as hypertension, palpitations, and anxiety, but in most cases, they are asymptomatic and diagnosed accidentally during routine examinations

* Corresponding author.
E-mail addresses: mariaconcetta.nigro2@unibo.it (M.C. Nigro), giacomo.corradi@studio.unibo.it (G. Corradi), margherita.nannini@unibo.it (M. Nannini), guido.didalmazi@unibo.it (G. Di Dalmazi), lorenzo.tucci5@unibo.it (L. Tucci), giorgio.tolento@aosp.bo.it (G. Tolento), cristina.nanni@aosp.bo.it (C. Nanni), arber.golemi@aosp.bo.it (A. Golemi), antonio.deleo@unibo.it (A. De Leo), dario.debiase@unibo.it (D. De Biase), cristina.mosconi@aosp.bo.it (C. Mosconi), caterina.balacchi@aosp.bo.it (C. Balacchi), valentina.vicennati@aosp.bo.it (V. Vicennati), maria.pantaleo@unibo.it (M.A. Pantaleo).

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(Neumann et al., 2019; Lam, 2017).

PGLs which originate from parasympathetic system are mainly located in the head and neck, while sympathetic ones may mainly originate in the chest, abdomen and pelvis (Lam, 2017).

The majority of PGLs present a benign behavior. However, there are a limited number of cases that first present as metastatic, involving lymph nodes, skeletal tissue, lungs, and liver, characterized by an incidence of one per million people annually, a 5-year survival rate of about 40–77 % and a progression-free survival (PFS) that varies among clinical trials from 4 to 36 months (Hescot et al., 2019).

The etiology of these tumors is complex, with genetic predispositions playing a significant role in up to 40 % of cases (Favier et al., 2015; Dahia, 2017; Crona et al., 2019). Advances in imaging techniques and molecular diagnostics have improved our understanding of paragangliomas, paving the way for targeted therapeutic strategies (Lenders et al., 2020; Antonio et al., 2020; Jimenez et al., 2020; Nasca et al., 2024).

Due to the rarity of PGLs, centralized management of these cases at specialized referral centers is of utmost importance. To provide the patient with the best possible care, a multidisciplinary approach based on shared decision is mandatory. Oncologists, radiotherapists, endocrinologists, radiologists, nuclear medicine physician, pathologists and surgeons specialized in this type of tumor must actively collaborate with one another. In fact, surgery by specialists with adequate expertise is the treatment of choice, when it is feasible (Lenders et al., 2014). Systemic strategies are limited and the management of metastatic PGLs depends on their biochemical and molecular phenotype (Nölting et al., 2022; Fishbein et al., 2021; Fassnacht et al., 2023). The first purpose is to manage the catecholamines secretion. Treatment options range from the use of alpha blocker to manage hypertension, to metabolic radiotherapy, systemic chemotherapy and target therapies (Fassnacht et al., 2023). Locoregional therapies can be used for antalgic-palliative purposes.

About half of patients are eligible for $^{1\ 31}$I-MIBG therapy, on the base of high uptake from specific diagnostic scan (Gonias et al., 2009; Pryma et al., 2019). In addition, other targeted therapy as yttrium 90-labelled [^{90}Y] DOTATOC (N-(4,7,10-(tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetyl-D-Phe-c[Cys-D-Tyr-Trp-Lys-Thr-Cys]-Thr(ol))), lutetium-177-labelled [^{177}Lu] DOTATATE (N-4,7,10-(tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetyl-D-Phe-c [Cys-D-Tyr-Trp-Lys-Thr-Cys]-Thr) or somatostatin analogues (SSA) should be considered, based on imaging scans with ^{68}Gallium (^{68}Ga)-DOTA-SSA positron emission tomography/computed tomography (PET/CT) (Lenders et al., 2020; Vyakaranam et al., 2019; Han et al., 2019). In metastatic PGLs with no significant radiotracers uptake, chemotherapy is the recommended strategy. Regimens based on cyclophosphamide and dacarbazine in combination with vincristine (CVD) and/or doxorubicin (CVDD or CDD) are the current standard of care (Fassnacht et al., 2023; Niemeijer et al., 2014). Other options, including temozolomide (Hadoux et al., 2014; Tena et al., 2018) alone or in combination with capecitabine and tyrosine kinase inhibitors (TKIs), like sunitinib and pazopanib, resulted to be effective in second line setting (Nasca et al., 2024; Tena et al., 2018; Nölting et al., 2019; Favier et al., 2012; Ayala-Ramirez et al., 2012; Jasim et al., (2017)). Lastly, also inhibitors of the DNA repairing enzyme Poly (ADP-ribose) polymerase (PARP) (especially in combination with temozolomide), immunotherapy and radio-immunotherapy showed potentially interesting results deserving to be further explored in the next future (Nölting et al., 2022, 2019; Pang et al., 2019; Caisova et al., 2019). Treatment with bisphosphonate and denosumab is recommended in case of bone metastases.

Given the limited therapeutic options for metastatic PGLs, there is an urgent need for novel treatment approaches. Recent years have witnessed an increase in personalized and molecular target therapies, with the aim to prolong the survival of these patients, also improving their quality of life by reducing the disease burden (Wang et al., 2022). However, these tumors only rarely present molecular alterations that can be specifically targeted by medical therapies. For this, the tumor genomic profiling is not standard in the management of patients with these tumors.

The aim of this paper was to review the literature data available on the treatment of metastatic PGL, focusing on targeted therapy with anaplastic lymphoma kinase (ALK) inhibitor, and to report the results of targeted therapy in a young patient affected by metastatic paraganglioma with *ALK* point mutation, specifically F1174L, after failure of standard treatments.

2. Main text

2.1. Case presentation

Since January 2023, a 16-year-old boy reported the onset of back pain unresponsive to analgesic therapy, leading to a magnetic resonance imaging (MRI) of the cervical-thoracic spine which revealed a large mixed composition mass, mostly solid, located in the posterior thoracic region, with an intradural extra-medullary development extending longitudinally for 53 mm, involving the pleural sheets on the right. A follow-up CT scan of the chest and abdomen additionally showed involvement of the lumbar spine with bulging of the posterior somatic wall and involvement of the left neural foramina at L1-L2 and L2-L3. There was solid tissue in front of the left psoas muscle (maximum diameter approximately 56 ×40 mm) and an area measuring about 70x40x60 mm in the left flank in the mesenteric fan, enveloping the inferior mesenteric artery and without cleavage plane with the adjacent intestinal loops. In addition, normetanephrine and 3-methoxytyramine resulted above the upper limit on blood test (normetanephrine 55700 pmol/L [normal value 730 pmol/L], 3-methoxytyramine 1810 pmol/L [normal value 180 pmol/L]).

In March 2023, the patient underwent urgent stabilization and decompression surgery from T2 to T6, preceded by selective arterial embolization. Histopathological examination of the trabecular and medullary bone tissue, skeletal muscle tissue, and fibrocartilaginous tissue revealed a localization of a paraganglioma with focal nuclear pleomorphism, focal tumor necrosis, a mitotic index of 3/10 HPF, a GAPP score of 8, negative expression of somatostatin receptor 2 A (SSTR2A), no alteration in SDH complex, and Ki-67 30 %.

The subsequent ^{18}F-fluorodeoxyglucose-labeled (FDG) PET scan confirmed mild radiotracer uptake in the noted thoraco-lumbar locations (SUVmax 3.5). Additionally, the Ga-DOTANOC PET scan showed a slight uptake of the radiopharmaceutical between C1 and the left occipital clivus (SUVmax 4.2). For diagnostic and therapeutic purposes, in April 2023, a total body scintigraphy with ^{123}I- MIBG was performed, showing pathological uptake in the paravertebral tissue at the level of L2. Additional multiple areas of radio-pharmaceutical uptake were observed at the level of the skeleton, mediastinum, and abdomen.

Therefore, considering the extent of the disease and persistent spinal pain, surgery was excluded and systemic therapy with Temozolomide 200 mg/m^2 die 1–5, q 28 (a total of 2 cycles completed) was initiated in May 2023, with moderate tolerance except for Grade 1 nausea/vomiting, according to Common Terminology Criteria for Adverse Events version 5 (CTCAE v.5), in combination with 4 mg intravenous (IV) zoledronic acid (q28). Subsequently, in July 2023, the patient underwent treatment with ^{131}I-MIBG for cytoreductive purposes with an activity of 7857 MBq (212.4 mCi), with good tolerance. The subsequent CT scan of the chest, abdomen, and pelvis showed substantial disease stability. Afterwards, he also received radiation treatment for cytoreductive/pain-relief purposes at the spinal level (L2).

Due the absence of a satisfactory clinical response and reduction of disease after these treatments, molecular analysis was performed using an NGS multigene panel Oncomine on the operative histological material, which showed the presence of a pathogenic nucleotide substitution in the *ALK* gene, p.Phe1174Leu (F1174L). In view of this finding, also considering the persistence of pain, predominantly in the thoraco-

lumbar region, and the progressive disease shown in the next CT scan, (Fig. 1 **A,B and C**), following the acquisition of favorable opinion from the territorial drug regulatory authority, therapy with an ALK inhibitor, lorlatinib 100 mg/day orally, for off-label use was started in November 2023. The treatment with 4 mg zoledronic acid IV every 28 days was maintained.

The first re-evaluation CT scan showed substantial stability of the disease, with a slight reduction of the pathological tissue enveloping the lumbar spine. In subsequent evaluations, there was a reduction in contrast enhancement alongside substantial dimensional stability of the major lesions. Clinically, there was a complete resolution of the pain symptoms, with simultaneous discontinuation of pain relief therapy by the patient. Additionally, there was a progressive reduction of normetanephrine and 3-methoxytyramine (Table 1**,** Fig. 2).

More than a year after starting treatment with lorlatinib, the patient is in excellent clinical condition. He performs normal daily activities and regular moderate physical exercise without pain. He showed excellent tolerance to the treatment, except for grade 1 hypertriglyceridemia, hypercholesterolemia and fluctuant mood alterations, according to CTCAE v.5. The latest CT scan (March 2025) showed substantial stability of the disease, with a reduction in some of the noted paravertebral lesions and stability of the others (Fig. 3 **A, B and C**).

We summarize the key time points of the clinical case in Fig. 4.

2.2. Literature review

This report describes the case of a young male patient affected by metastatic PGL, successfully treated with lorlatinib in view of the identification of a pathogenic point mutation in *ALK* (F1174L). To our knowledge, this is the first case described in literature of PGL characterized by this rare alteration. The *ALK* gene encodes a receptor tyrosine kinase involved in the development of the central and peripheral nervous system (Armstrong et al., 2011; Hallberg and Palmer, 2016; Janoueix-Lerosey et al., 2018). *ALK* was initially identified as a fusion partner in anaplastic large cell lymphoma (ALCL) (Zhang et al., 2022). However, it is implicated in several solid tumors, notably non-small cell lung cancer (NSCLC) where the *EML4-ALK* fusion is prevalent, inflammatory myofibroblastic tumors, and neuroblastoma. In fact, *ALK* activates multiple downstream signaling pathways (PI3K-Akt, RAS-MAPK, JAK-STAT etc.), influencing various cellular processes and gene expression (Hallberg and Palmer, 2016). Various *ALK* inhibitors have demonstrated efficacy and safety in patients affected by NSCLC with *ALK* rearrangements. Crizotinib was the first approved, followed by ceritinib, alectinib, brigatinib, and lorlatinib (Cooper et al., 2022). Lorlatinib is the most potent and selective approved third-generation *ALK* inhibitor, developed to deal with acquired resistance to previous-generation TKIs, presenting efficacy against a large spectrum of *ALK* kinase domain resistance mutations (Zou et al., 2015; Johnson et al., 2014; Shaw et al., 2017; Solomon et al., 2018). Currently, it represents the standard of care in first line setting for advanced/metastatic *ALK*-rearranged NSCLC patients, with a reduction of 72 % in the risk of disease progression, compared to crizotinib (Shaw et al., 2020).

Differently, point *ALK* mutations have been described in a limited number of solid tumors, including neuroblastoma (NB), in which *ALK* synergizes with *MYCN* in driving tumor development (Mossé et al., 2008; Higashi et al., 2019), anaplastic thyroid carcinoma, glioblastoma multiforme, rhabdomyosarcoma, and NSCLC (Murugan and Xing, 2011; Grzelinski et al., 2009; van Gaal et al., 2012; Choi et al., 2010; Amin et al., 2016). In the latter case, the specific alteration F1174L has been identified as a resistance mutation in *ALK* fusion-positive NSCLC previously treated with *ALK* inhibitors (Elshatlawy et al., 2023; Mizuta et al., 2021; Kodama et al., 2014). In detail, the F1174L mutation replaces a phenylalanine with leucine within a hydrophobic cluster near the DFG motif, a conserved amino acid sequence—Aspartate (D), Phenylalanine (F), Glycine (G)—located at the start of the activation loop of ALK's kinase domain. This disrupts auto-inhibitory interactions, favoring an active kinase conformation, and leads to autophosphorylation and basal signaling even in absence of ligand (Jiang et al., 2018). Constitutive activation of ALK F1174L drives sustained downstream pathways, notably PI3K/AKT/mTOR and MAPK/ERK, promoting cell proliferation, survival, and transformation (Sasaki et al., 2010).

In contrast, a singular case of *ALK*-mutated PGLs has been described in literature (Heregger et al., 2021), and no case of PGLs harboring F1174L *ALK* mutation has been reported. Heregger R. et al., described a sustained response to brigatinib in an adult patient with R1192P *ALK* mutated PGL, pre-treated with alectinib and cyclophosphamide (Heregger et al., 2021). The patient achieved a partial response for about 10 months after starting 3rd-line brigatinib, demonstrating a different efficacy of the two second-generation *ALK* inhibitors (Amin et al., 2016). Authors showed for the first time that the use of *ALK* inhibitors in *ALK*-mutated PGL may be a successful therapy in addition to standard treatments (Heregger et al., 2021).

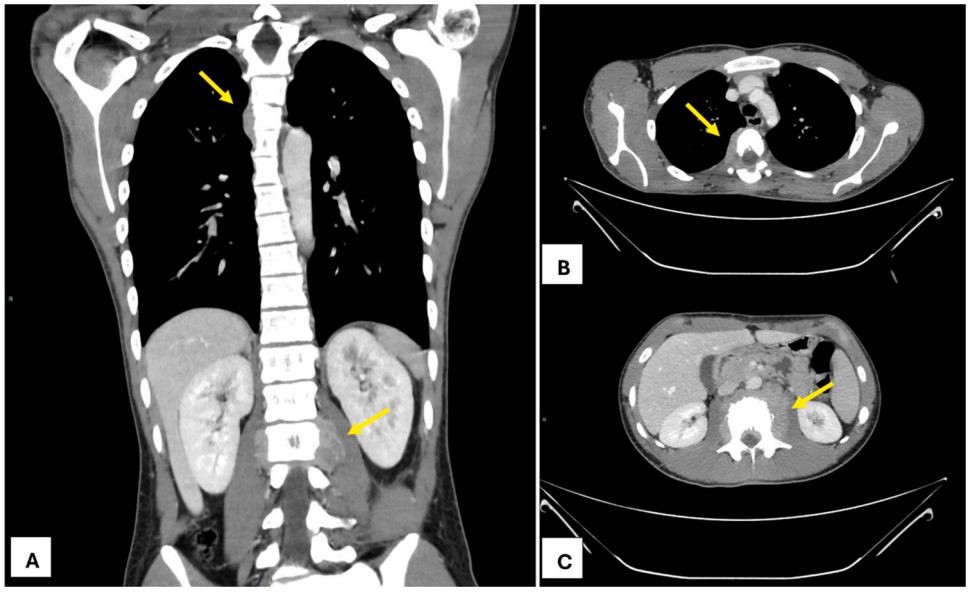

Fig. 1. Baseline CT scan performed prior to initiating treatment with lorlatinib revealed clear evidence of disease progression, with the most significant tumor burden localized in the thoracic (A, B) and lumbar (A, C) spinal regions, indicated by yellow arrows.

Table 1
Blood exam dosing metanephrine, normetanephrine and 3-methoxytyramine from starting treatment to 12-months follow-up.

	T0 (pmol/L)	After 6 months of lorlatinib (pmol/L)	After 12 months of lorlatinib (pmol/L)	Reference values (pmol/L)
Metanephrine	144	162	140	**450**
Normetanephrine	55700	3290	2600	**730**
3-Methoxytyramine	1810	65	82	**180**

pmol/L=picomole per liter; T0 = time zero.

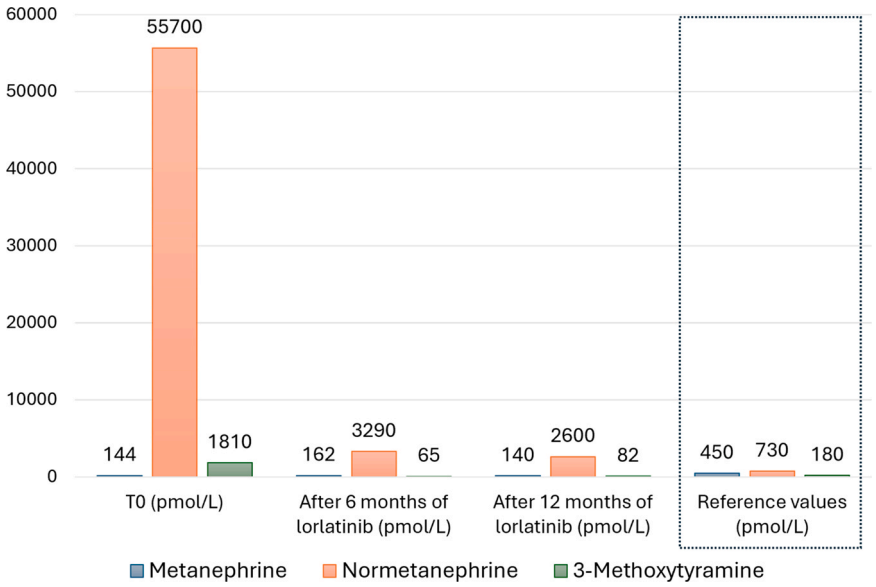

Fig. 2. Serial measurements of plasma metanephrine, normetanephrine, and 3-methoxytyramine levels from the initiation of lorlatinib treatment (time 0, T0) through 12 months of follow-up. Hormone concentrations are plotted over time, with the reference upper limits of normal indicated by the shaded (boxed) area for comparison. These biomarkers were used to monitor biochemical response to therapy.

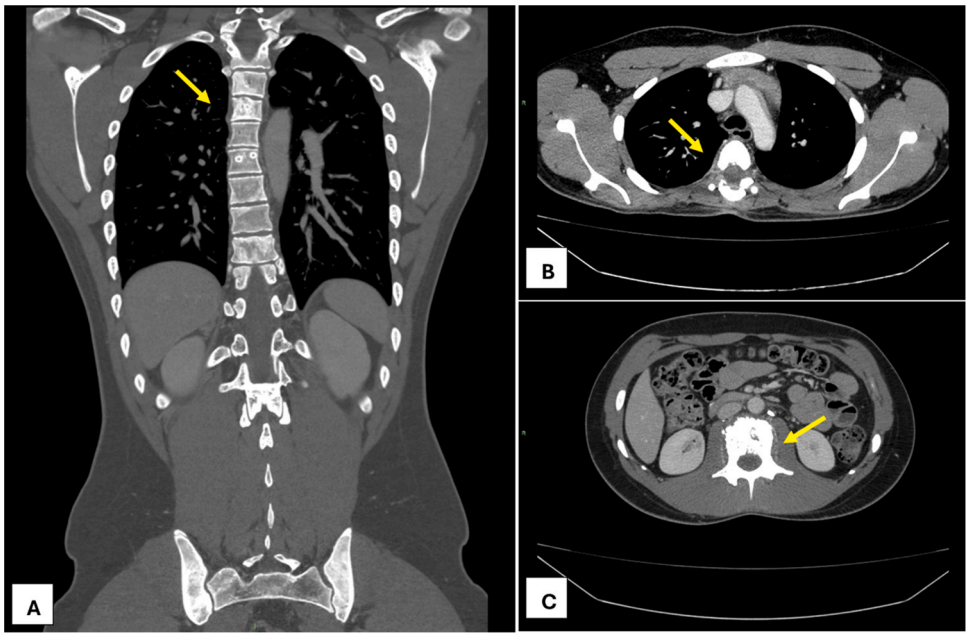

Fig. 3. CT scan performed more than one year after the initiation of lorlatinib treatment demonstrated a partial radiological response, with a dimensional reduction of more than 30 % compared to baseline. The most notable decrease in tumour burden was observed in the thoracic (A, B) and lumbar (C) spine lesions, indicated by yellow arrows. These findings are consistent with a sustained therapeutic effect in areas previously affected by progressive disease.

Whereas more data are available regarding NB and NSCLC.

NB, the most common pediatric solid tumor accounting for approximately the 15 % of cancer related mortality in children, share several features with paraganglioma, including likely the etiopathogenesis (Mossé et al., 2008; Higashi et al., 2019; Tonini and Capasso, 2020; Zafar et al., 2021). Like PGL, NB derives from the cells of sympathetic nervous

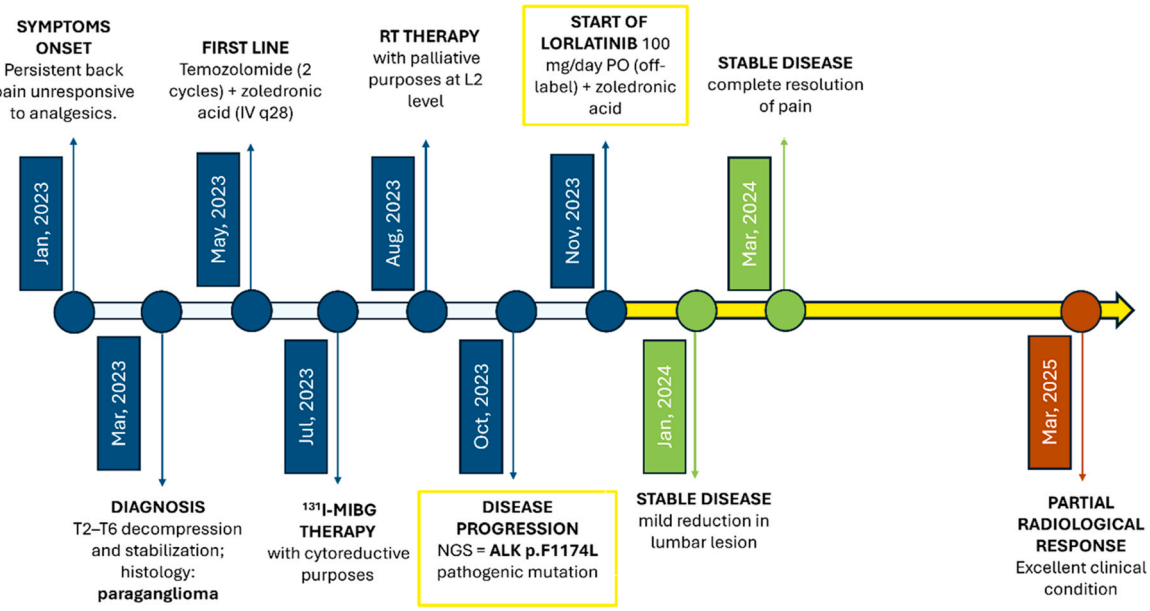

Fig. 4. Concise and structured summary timeline capturing the key clinical events, treatments, molecular findings, and outcomes of the case. Treatment with lorlatinib, started on Novembre 2023, is represented by the yellow timeline.

system, particularly sympathoadrenal progenitor stem cells, which can differentiate into adrenal chromaffin cells and sympathetic ganglion cells, and can exhibit catecholamine synthesis (Matthay et al., 2016; Brodeur, 2003). Both NB and PGL are associated with genetic alterations, including mutations in genes related to the neurofibromatosis type 1 (*NF1*) and other tumor suppressor genes (Knudson and Amromin, 1966; Farma et al., 2022; Martínez de Lapiscina et al., 2024). Several molecular pathways are involved in NB pathogenesis and *ALK* is recognized as an oncogenic driver (Zafar et al., 2021; Pacenta and Macy, 2018). Increased *ALK* mRNA expression in NB correlates with poor prognostic factors such as metastatic disease, *MYCN* amplification, and decreased survival. Germline *ALK* mutations are reported in 50 % of hereditary NB cases and point *ALK* alteration may be identified in both familial and sporadic NB (Zafar et al., 2021). Otherwise, about 30 % of PGLs present germline alteration in other genes, including *VHL*, *RET*, *NF1*, *MAX*, *TMEM127* and *SDH* complex (Gimenez-Roqueplo et al., 2008). The specific F1174L *ALK* mutation is a frequent somatic alteration in NB, acting as both TKi resistance and activating mutation (Mossé et al., 2008; Chen et al., 2008; George et al., 2008; Janoueix-Lerosey et al., 2008; Bresler et al., 2014, 2011; Pastorino et al., 2023; Bobin et al., 2024). In fact, this point mutation causes a change in the structure of the *ALK* protein at the site where the inhibitor would normally bind. This alteration can either directly affect the binding pocket, making it less compatible with the TKi, or induce conformational changes that stabilize the active form of *ALK*, further reducing the efficacy of the inhibitor. As a result, cancer cells with the F1174L mutation can continue to proliferate, presenting resistance to first- and second-generation ALK inhibitors, such as crizotinib, alectinib and ceritinib (Amin et al., 2016; Heuckmann et al., 2011). Differently, lorlatinib demonstrated, both in vitro and in vivo, a considerable efficacy across acquired *ALK*-activating mutations, including F1174L (Bobin et al., 2024; Yoda et al., 2018)]. Liu T. et al., described an exceptional complete response to lorlatinib in a child with relapsed, refractory, metastatic neuroblastoma harboring an *ALK* F1174L mutation, progressing to crizotinib combined with cyclophosphamide, highlighting the varying sensitivity of *ALK* mutations to different inhibitors (Liu et al., 2021). An additional single-center retrospective review evaluated the use of *ALK* inhibitors in adult patients with *ALK*-mutated neuroblastoma, including *ALK* F1174 mutation (Stiefel et al., 2023). This work reported an excellent overall response to lorlatinib in most patients, while no response was observed in patients treated with other *ALK* inhibitors, such as crizotinib, ceritinib, alectinib or brigatinib (Stiefel et al., 2023). Moreover, results from an ongoing phase I trial (NCT03107988) investigating lorlatinib in *ALK*-altered NB, including F1174L mutation, are eagerly awaited (Goldsmith et al., 2023).

Although ALK F1174L is a well-characterized oncogenic driver in neuroblastoma, its functional role in paraganglioma is still unclear and remains to be fully elucidated. While biological extrapolation may be plausible due to certain similarities between NB e PGL, potential lineage-specific differences must be considered, along with the current lack of mechanistic validation in paraganglioma models.

3. Discussion

Our case supports the use of lorlatinib against *ALK* mutations, particularly F1174L, in the context of PGLs, a rare neoplasia characterized by limited therapeutic options. Historically, treatment for PGLs has been confined to surgical interventions, when feasible, and conventional chemotherapy regimens, which frequently yield suboptimal results and unacceptable side effects. This case highlights the importance of performing molecular analyses at least after failing the first line medical therapy to identify therapeutic targets, that may potentially provide prolonged benefits to patients (as in our case), when treated with specific compounds. Moreover, the targeted treatments can be well tolerated and may impact patient's quality of life less than standard chemotherapy. In our case, this young patient did not experience significant toxicity, allowing him to carry out his daily activities without impairing. Clearly, the identification of these mutations is uncommon and due to the rarity of these tumors their frequency in paragangliomas is not well understood. Rare tumors typically represent the conditions that should be discussed among the molecular tumor board in order to offer additional opportunity of treatments outside the context of standard recommendation. Therefore, it is crucial to centralize these patients into referral centers and to report to the scientific community also single cases to share knowledge about this peculiar entity, helping the physicians in the management of these diseases. In the next future, an urgent need is the design of specific prospective trials for paragangliomas, although this may be challenging given their low incidence as well as for all rare tumors.

This case report is of fundamental importance because it

demonstrates the potential utility of genomic profiling even in this type of tumor, paving the way for a more personalized and multidisciplinary management, and therapeutic approach for these patients.

4. Conclusion

Literature data of treatment of metastatic PGL arise mainly from retrospective studies, case series, case reports, and few clinical trials are available in this rare tumour. In our experience of multidisciplinary approach of rare tumours, the case reported a young patient affected by advanced paraganglioma, who had singular *ALK* mutation, progressed to standard treatment. A targeted therapy with lorlatinib was administered, with a remarkable and durable response, both clinical and radiological. This report was the first case of *ALK* F1174L-mutated paraganglioma and showed the potential utility of molecular analysis in this rare solid tumor. Given the rarity and aggressive clinical course of metastatic paraganglioma, earlier implementation of genomic testing - particularly in younger patients or those presenting with high-risk features – may facilitate the identification of actionable mutations, guide targeted treatment decisions, and ultimately improve patient outcomes. In addition, this case underscores the growing relevance of tumor-agnostic precision oncology, where treatment is guided by actionable molecular alterations rather than tumor histology, reflecting an evolving regulatory landscape and expanding therapeutic opportunities.

Significant advancements are occurring in the understanding and treatment of metastatic PGLs. While progress has been made, a multidisciplinary approach incorporating genetic testing, advanced imaging, and participation in clinical trials remains essential for optimal management. Future research focuses on personalized medicine approaches and improved combination therapies to enhance outcomes for patients with these rare and challenging tumors.

Authors' contributions

Conception and design: MCN, GC, MN, GDD, VV, MAP. Writing, review and editing, Data curation: All authors; Provision of study materials or patient: All Authors; Final approval of manuscript: All authors.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Policlinico Sant'Orsola Malpighi, Bologna, Italy (approval number: 95/2013/U/Tess).

Consent for publication

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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Declaration of Competing interest

The authors declare no conflict of interest.

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Maria Concetta Nigro (MCN): MD. Oncologist with clinical and research experience in soft tissue sarcomas, thyroid and adrenal cancer. PhD student at the University of Bologna.

Giacomo Corradi (GC): MD. Oncology resident, with clinical expertise in gastrointestinal and rare cancer.

Margherita Nannini (MN): MD. Oncologist with clinical and research experience in soft tissue sarcomas, thyroid and adrenal cancer. Professor at the University of Bologna.

Guido Di Dalmazi (GDD): MD. Endocrinologist with clinical and research expertise in adrenal disease. Professor at the University of Bologna.

Lorenzo Tucci (LT): MD. Endocrinologist with clinical and research expertise in adrenal disease.

Giorgio Tolento (GT): MD. Radiotherapist at IRCCS Azienda Ospedaliero-Universitaria di Bologna with clinical and research activity expertise in gynaecological and adrenal malignancies and brachytherapy.

Cristina Nanni (CN): MD. Nuclear medicine physician and radiologist with particular experience in clinical applications of PET/CT with FDG and novel tracers in various fields of oncology and onco-hematology, PET/CT with multiphase total body CT, LAFOV PET.

Arber Golemi (AG): MD. Nuclear physician with clinical and research expertise in thyroid cancer, PET scan and radiometabolica therapy. MD at IRCCS Policlinico Sant'Orsola Bologna.

Antonio De Leo (ADL): MD. PhD Pathologist with clinical and research experience in oncologic pathology, with expertise in molecular pathology. Researcher at the University of Bologna.

Dario De Biase (DDB): Associate Professor of General Pathology University of Bologna. Molecular pathologist at the Solid Tumor Molecular Pathology Laboratory in Bologna, involved in the molecular characterization of various solid tumors - including lung, brain, thyroid, ovarian, and breast cancers - through the application of next-generation sequencing (NGS) technologies.

Cristina Mosconi (CM): MD. Radiologist specialised in adrenal and hepato-biliary imaging and interventional radiology. Professor at the University of Bologna.

Caterina Balacchi (CB): MD. Radiologist specialised in adrenal and hepato-biliary imaging. Consultant at IRCCS Azienda Ospedaliero-Universitaria di Bologna.

Valentina Vicennati (VV): MD. Endocrinologist with clinical and research expertise in thyroid cancer and adrenal disease. Professor at the University of Bologna.

Maria A. Pantaleo (MAP): MD and PhD. Oncologist with clinical and research experience in soft tissue sarcomas, thyroid and adrenal cancer. Professor at the University of Bologna.