Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated most of the suggestions made by the reviewers. Please see below for a point-by-point response to the reviewers' comments and concerns.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

The authors present a case report of clinical interest, illustrated by interesting images. The subject falls within the scope of the journal. Some concerns should be addressed before considering the publication of this study. Several suggestions were made. Suggestions were drawn in yellow. In red questions that needed to be modified or answered. Please address each question raised and highlight the changes in the revised manuscript. INCLUDE THE FOLLOWING TOPICS AND REFERENCES : Clinically, VHL disease can be classified by clinical phenotype, each phenotype correlating with a specific genotype: type 1—low risk for pheochromocytoma but high risk for hemangioblastomas, clear cell renal carcinoma, cysts, and pancreatic neuroendocrine tumors; type 2A—high risk for pheochromocytoma but low risk for clear cell renal carcinoma; type 2B—high risk for pheochromocytoma and clear cell renal carcinoma; and

type 2C—high risk only for pheochromocytoma. Ganeshan D, Menias CO, Pickhardt PJ, *et al* Tumors in von Hippel-Lindau syndrome: from head to toe—comprehensive state-ofthe-art review. Radiographics. 2018;38:849–66. Knowledge of the main imaging findings of VHL disease can empower radiologists to establish associations in cases in which the findings are suggestive of the syndrome, allowing them to make the initial diagnosis of previously unknown cases, with an emphasis on the lower range of the age of onset of many of the associated lesions. In addition to the initial diagnosis, abdominal imaging plays an important role in the screening/early detection and followup of the lesions (some with higher risk than others), in accordance with the follow-up protocols proposed. Poulsen MML, Budtz-Jørgensen E, Bisgaard ML. Surveillance in von Hippel-Lindau disease (vHL). Clin Genet. 2010;77:49–59. Fernandes DA, Mourão JLV, Duarte JÁ, Dalaqua M, Reis F, Caserta NMG. Imaging manifestations of von Hippel-Lindau disease: an illustrated guide focusing on abdominal manifestations. Radiol Bras. 2022 Sep-Oct;55(5):317-323.

Response: We present the changed locations according to the recommendations. 'place' was removed and replaced with 'role'. The 'pathology report after biopsy' was removed and replaced with 'histopathological examination'.

The ' Before proceeding to the case report of our patient with a prediagnosis of VHL, we would like to give some more general information about VHL syndrome. VHL syndrome, as we mentioned in the above paragraph, is an autosomal dominant inherited tumor disease that occurs due to germline mutations in the VHL gene located on the short arm of chromosome 3. Patients with VHL can develop multiple benign and malignant tumor structures that can affect various organ systems at various levels. To give examples, retinal hemangioblastomas (HBs), central nervous system (CNS) HBs, endolymphatic

sac tumors, pancreatic neuroendocrine tumors, pancreatic cystadenomas, pancreatic cysts, clear cell renal cell carcinomas, renal cysts, pheochromocytomas, paragangliomas, and epididia and large ligament cystadenomas can be given as examples of many findings. One of the most important points in making a clinically meaningful diagnosis and initiating treatment is to know that VHL syndrome can be classified according to clinical phenotype. Each phenotype is associated with a particular genotype. It is basically divided into 2 types, type 1 and type 2. Type 2 is divided into 3 types as type 2A, type 2B and type 2C. If we talk about Type 1; they show a very low risk for pheochromocytoma; but it shows a high risk for clear cell renal carcinoma, hemangioblastomas, cysts and pancreatic neuroendocrine tumors. In Type 2A; contains a high risk of pheochromocytoma; but it has a low risk for clear cell renal carcinoma. In Type 2B; It has a high risk of pheochromocytoma and clear cell renal carcinoma. In Type 2C; only contains a high risk for pheochromocytoma. We have summarized the types of VHL syndrome in general[14]. VHL syndrome is a syndrome that requires lifelong prophylactic surveillance. The surveillance data we have are based on best medical judgment. However, there is no evidence of any effect[15]. VHL syndrome is a multisystem-related familial cancer syndrome with a prevalence ranging from 1 in 31,000 to 1 in 85,000[16,17]. It is autosomal dominant in inheritance type and the estimated incidence of its newly developed mutation is 1-23%[18,19]. Regarding the diagnosis point, the clinical diagnosis of VHL syndrome can be made in the following situations: 1) The presence of at least one tumor specific to this disease and in individuals with a family history of the disease (for example, retinal or CNS hemangioblastomas, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors, and endolymphatic sac tumors)); 2) In patients with two or more CNS hemangioblastomas; 3) apart from these, renal and epididymal cysts, retinal or CNS hemangioblastoma in addition to at

least one visceral tumor of the disease is considered sufficient without diagnosis in patients[2]). After the diagnosis of VHL syndrome, various surveillance begins in patients; because this syndrome affects many organs at the same time. We will now touch on these through examples. Imaging of the central nervous system begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Eye examination starts directly upon diagnosis and is repeated every 12 mo. Imaging of the abdominal region begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Neurological examination starts directly upon diagnosis and is repeated every 12 mo. A 24-hour urine test for catecholamine levels basically begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Audiometric examination begins at age 15. Since the risk of ocular and neurological findings and poor prognosis is higher, examinations are performed at more frequent intervals as the diagnosis is made[14].

We want to get started with the imaging features. Here we will relate it to the finding that it is associated with organs. Starting with the kidney first, it is seen in more than two-thirds of patients with histological subtype VHL syndrome with multicentric renal cysts and clear cell RCCs in the kidney[21]. The VHL syndrome associated with RCCs tends to develop at an earlier age than sporadic RCCs (35–40 *vs* 55–60 years) and is usually distinguished from the previous ones by being bilateral and present at multiple sites[21,22]. Cystic lesions may be due to many separate components, for example; may be a combination of simple cysts, atypical complex cysts, and cystic RCCs. In patients with VHL syndrome, all renal lesions, including simple cysts, should be monitored by imaging because of their malignant potential. There is no relationship between their size and malignant potential, which is important for prognosis. Growth rate and any sign

of transformation from cystic to solid (partitions, solid components, or increased contrast) should be carefully evaluated; because they may be important for the prognostic course of the tumor. Especially CT and MRI are two important imaging modalities that are frequently used in the evaluation of kidney lesions suspected to be BCC and in the staging of such lesions. If we look at the CT imaging features, RCCs tend to be heterogeneous or show intense early contrast enhancement and progressive washout. means and can be seen as 10 HU or more attenuation of simple renal cystic lesions in the nephrographic phase of CT imaging. Increases below 10 HU are considered within the normal range and are not categorized as increases[23]. Although visual identification of intralesional enhancement on MRI may be sufficient for its characterization, a ≥ 15% increase in signal intensity compared to non-contrast T1-weighted images should suggest RCC. Another important point to note is that even simple cystic lesions may increase in signal intensity up to 5% after contrast agent injection, possibly due to motion artifacts or partial volume losses[23]. The term "clear cell" refers to the microscopic accumulation of fat and glycogen. This microscopic fat in MRI imaging can provide a reduction in signal intensity on out-of-phase T1-weighted images. The main purpose of imaging and the therapy applied together with it, to eliminate such lesions before secondary involvement occurs. Since RCC can metastasize to the liver, lung, bone, pancreas, CNS and epididymis, it is of particular importance to make a differential diagnosis with tumors characteristic of VHL disease, such as pancreatic neuroendocrine tumors. If we look at the imaging features of the pancreas, pancreatic cyst may develop in 42% of patients in VHL syndrome, while serous cystadenoma and pancreatic neuroendocrine tumor developed in 11%, respectively[24] . Such pancreatic cysts are usually multicenter and can be seen as hypotenuated lesions without contrast enhancement. Pancreatic cysts may even be the only manifestation of VHL

disease. If we look at serous cystadenomas, they appear as septated, multiloculated cystic lesions. They are benign epithelial lesions that can form cysts (six or more) of up to 2 cm each, usually smaller than 1.0 cm. The walls are thin, their thickness is less than 2 mm, and an increase in contrast is observed. On MRI, serous cystadenomas are typically hyperintense on T2-weighted images and hypointense on T1-weighted images; however, if there is intracystic hemorrhage, an increase in signal is observed that can be hyperintense in both. When a fibrotic central scar is present, a hypointense signal is produced with delayed contrast enhancement on T1- and T2-weighted images. Although pathognomonic, a central scar is seen only in 20-30% of cases. In the absence of scar, the combination of microcystic appearance and vascular contrast enhancement may support the diagnosis. Serous cystadenomas are not associated with the pancreatic duct. Pancreatic neuroendocrine tumors can be seen in 9-17% of patients with VHL syndrome. Compared with sporadic pancreatic neuroendocrine tumors, those associated with VHL syndrome appear earlier (mean, 35 *vs* 58 years). The neuroendocrine tumors seen in VHL are typically multifocal and most commonly located in the pancreatic head section and the uncinate process. On non-contrast CT imaging, pancreatic neuroendocrine tumors are usually hypotenuated or isoattenuating. On contrast-enhanced CT and MRI examinations, these tumors show intense (homogeneous, annular, or heterogeneous) contrast enhancement in the early stages of the arterial phase, but generally exhibit the same contrast enhancement as the rest of the body. Pancreatic neuroendocrine tumors It has no direct relationship with the ductal system. In patients with VHL syndrome, pancreatic neuroendocrine tumors are usually diagnosed on imaging alone[21,24]. However, the production of catecholamines (epinephrine, norepinephrine and dopamine) in patients with pheochromocytoma or paraganglioma is highly variable.

Therefore, the clinical picture can vary widely. It is common to encounter a triad of headache, sweating and tachycardia associated with arterial hypertension in these patients. During diagnosis, evidence for the production of catecholamines and their metabolites is of great importance. To continue, it may rarely be associated with paraneoplastic syndromes (most commonly Cushing's syndrome due to ectopic production of adrenocorticotropic hormone). Pheochromocytomas are seen in 25-30% of VHL disease cases, while paragangliomas are seen in 15%[25,26]. Like its clinical presentations, imaging findings are diverse. Lesions are mostly solid and heterogeneous; but may also contain cystic areas. Although an intense enhancement can be observed after contrast application, this indicates that they are hypervascular, mainly in their solid components[21,22]. An important point to always keep in mind is that absolute or relative washout of pheochromocytomas CT may overlap with that of an adenoma or a malignant lesion; because, contrast-enhanced CT may not always facilitate diagnosis[27,28]. The high signal intensity on T2-weighted MRI scans of a pheochromocytoma - termed the bulb sign - is an important feature for diagnosis,
present in 11-65% of patients[29]. Usually isointense; but if there is bleeding it may also present with a hyperintense appearance. Although rare, intracellular fat can be seen in the lesion, and this may cause loss of signal intensity on out-of-phase T1-weighted images, as in adenomas. As a result of different degrees of pathological degeneration, pheochromocytomas may present in many different forms as imaging. This is why they are known as "chameleon tumors" among radiologists. Because of the broad spectrum of imaging manifestations, functional studies are often required to be included in the diagnosis for greater diagnostic accuracy of pheochromocytomas and paragangliomas and to detect non-adrenal or metastatic disease[30]. To sum up, in addition to the initial diagnosis, it plays an important role in the detection and follow-up of lesions in

line with the recommended follow-up protocols in abdominal imaging[31,32,33]. Radiologists, with multidisciplinary approaches and medical equipment more treatment modalities for patients with VHL syndrome They seek to improve their quality of life and aim to reduce the mortality and morbidity caused by the disease.' section has been included by referring to the references and adding 'INCLUDE THE FOLLOWING TOPICS AND REFERENCES: Clinically, VHL disease can be classified by clinical phenotype, each phenotype correlating with a specific genotype: type 1—low risk for pheochromocytoma but high risk for hemangioblastomas, clear cell renal carcinoma, cysts, and pancreatic neuroendocrine tumors; type 2A—high risk for pheochromocytoma but low risk for clear cell renal carcinoma; type 2B—high risk for pheochromocytoma and clear cell renal carcinoma; and type 2C—high risk only for pheochromocytoma. Ganeshan D, Menias CO, Pickhardt PJ, *et al* Tumors in von Hippel-Lindau syndrome: from head to toe—comprehensive state-ofthe-art review. Radiographics. 2018;38:849–66. Knowledge of the main imaging findings of VHL disease can empower radiologists to establish associations in cases in which the findings are suggestive of the syndrome, allowing them to make the initial diagnosis of previously unknown cases, with an emphasis on the lower range of the age of onset of many of the associated lesions. In addition to the initial diagnosis, abdominal imaging plays an important role in the screening/early detection and followup of the lesions (some with higher risk than others), in accordance with the follow-up protocols proposed. Poulsen MML, Budtz-Jørgensen E, Bisgaard ML. Surveillance in von Hippel-Lindau disease (vHL). Clin Genet. 2010;77:49–59. Fernandes DA, Mourão JLV, Duarte JÁ, Dalaqua M, Reis F, Caserta NMG. Imaging manifestations of von Hippel-Lindau disease: an illustrated guide focusing on abdominal anifestations. Radiol Bras. 2022 Sep-Oct;55(5):317-323.' according to the specified location.

'tumor' was removed and replaced with 'lesion'.

Upon being asked whether the figure is A or B, '[Fig. 1 b]' has been added.

The lowercase letter f in '[Fig.1]' is written in uppercase.

The words 'on T1 weighted image' were added upon suggestion.

‘(which was the contrast? Hepatocyte-specific MRI contrast agents were used?)’ questions were answered with

‘In this case from our hospital, iohexol (Opaxol 350 mg/100 mL) was used in CT and gadoxetate disodium (Primovist 0.25 mmol/mL) was used as hepatospecific agent in MR.’.

'hyperdense tumor' was removed and replaced with 'enhancing lesion'.

'showes strong' was removed and replaced with 'demonstrates intense'.

The sentence ' More studies are needed to reach the diagnosis with imaging methods without the need for biopsy. ' was removed upon the suggestion.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Interesting article to read and very well written. It is a teachable case.

Response: Thank you for taking the time to evaluate our work and for your valuable comments.

1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Response: Thank you for taking the time to evaluate our work and for your valuable comments.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the

bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: References were rearranged according to the suggestions. Thank you for taking the time to evaluate our work and for your valuable comments.