Dear Reviewers and editors,

Thank you for your valuable comments regarding our manuscript, titled 'Imaging features of retinal hemangioblastoma: case report and literature review', which we submitted to World Journal of Clinical Cases. We appreciate the reviewers taking the time to evaluate our manuscript, and providing helpful comments to strengthen it.

We are pleased to enclose an updated version of our manuscript, which we have revised after taking into careful consideration all the comments of the reviewers. All revisions to the manuscript have been made using the revision tool in Microsoft Word. Below, we enclose point-by-point responses to all the comments of the reviewers. Please note that we have also made some minor grammatical improvements to the manuscript (these are also shown using the revision tool).

We very much hope that our manuscript will now be considered suitable for publication and look forward to contributing to World Journal of Clinical Cases.

Yours sincerely,

Xin Tang, Zhongxiang Ding

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Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have described the imaging features of retinal hemangioma from a perspective of radiologist. Retinal hemangiomas can usually be observed directly and diagnosed by eye fundus examination. I suggest that this is included in the introduction, since this is the main reason why radiologists do not often perform diagnostics of retinal hemangiomas. Physical examination needs an improvement in english ophtahlmological terminology. Few examples: What is meant by "naked eye"? Perhaps: visual acuity without correction? "External eyes of both eyes"? Probably: periocular? The term "hematocele in the anterior chamber" is not correct, it should be "hyphema"

Q1:The authors have described the imaging features of retinal hemangioma from a perspective of radiologist. Retinal hemangiomas can usually be observed directly and diagnosed by eye fundus examination. I suggest that this is included in the introduction, since this is the main reason why radiologists do not often perform diagnostics of retinal hemangiomas.

Response: Many thanks for the reviewer's affirmation and comments. We have added it to the manuscript in introduction section according to your guildness as follows: " Its diagnosis is mainly based on clinical suspicion and confirmation by molecular testing and imaging techniques[2-4]. Moreover, retinal hemangiomas can be usually observed directly and diagnosed by eye fundus examination, which may be the main reason why radiologists infrequently perform RCH diagnosis. We retrospectively analyzed the relevant literature and found that the imaging features of RCH are rarely reported[1-11]."

Q2:Physical examination needs an improvement in english ophtahlmological terminology. Few examples: What is meant by "naked eye"? Perhaps: visual acuity without correction? "External eyes of both eyes"? Probably: periocular? The term "hematocele in the anterior chamber" is not correct, it should be "hyphema"

Response: Many thanks for the reviewer's affirmation and comments. We have modified it as follows:" Ophthalmological examination showed that visio oculus dexter (VOD) was 0.8 and Visus Oculi Sinistri (VOS) was sensitive to light (mainly contains distorted light that is located above and below the nose). Noncontact tonometer (NCT) showed that R/L = 16.3/Tn + 3 mmHg. There was no hyperemia of right bulbar conjunctiva. The cornea was clear and the depth of anterior chamber was satisfactory. Pupils were round in shape and reactive to light while light was mixed in the lens of right eye, optic disc boundary was clear and flat, while omentum was located in the fundus, mixed congestion in the conjunctiva of left eye and corneal edema were also noted. There was mild swelling in one-third of the anterior chamber, pupil was round in shape and not reactive to light and it was not extending to posterior chamber of eye, while the other details were unclear. "

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1 Title. Appropriate 2 Abstract. Appropriate 3 Key Words. Keywords should be different from the title. 4 Background. Appropriate 5 Methods. Appropriate 6 Results. Appropriate 7 Discussion. Differential diagnosis of retinal hemangioblastoma should be added. Key features to differentiate from other masses must be emphasized. 8 Illustrations and tables. The figure descriptions are careless, should be rewritten. MRI images were presented in a confusing manner. They should begin with T2 WI, after that precontrast T1WI, after that enhanced images

should be presented. Are there any DWI, if present it should be given. 9 Biostatistics. N/A 10 Units. Appropriate 11 References. Appropriate 12 Quality of manuscript organization and presentation. Average, can be upgraded. 13 Research methods and reporting. Appropriate 14 Ethics statements. No information was given, were patient's consent taken?

Response: Many thanks for the reviewer's affirmation and comments.

Q1:Keywords should be different from the title.

Response: Many thanks for the reviewer's guildness. We have made modifications on keywords as follows:"**Keywords:** Ultrasound; Computed tomography; Magnetic Resonance Imaging; Positron emission tomography/computed tomography; Case report".

Q2: Discussion. Differential diagnosis of retinal hemangioblastoma should be added. Key features to differentiate from other masses must be emphasized.

Response: Many thanks for the reviewer's guildness. We have added relevant differential diagnoses to the discussion section as follows:"According to the location and imaging characteristics of the lesion, hemangioblastomas also need to be differentiated from the following diseases. Choroidal melanoma: It is the most common ocular malignancy in adults, wherein CT shows a localized well-defined mass isodense to the extraocular muscles, generally without calcification. MRI shows hyperintense signal on T1-weighted images and hypointense signal on T2-weighted images, which is the characteristic feature, because the tumor contains paramagnetic melanin material. It also shows mild to moderate enhancement after contrast enhancement. PET metabolism indicated that glucose uptake was often increased in choroidal melanoma, and its SUVmax was >10[18-19]. Therefore it is not difficult to differentiate from this case of retinal hemangioblastoma. Choroidal hemangioma: CT shows local thickening of eyeball wall. It shows progressive significant enhancement after contrast enhancement. MRI shows higher signal than vitreous on T1-weighted images and lower than vitreous on T2-weighted images, but isointense signal compared with optic nerve and extraocular muscles on T2-weighted images, 90% of patients have concomitant mild retinal detachment. It shows progressive significant enhancement after contrast enhancement. PET metabolism suggests that choroidal hemangioma usually has no change in glucose uptake[20-21]. Therefore, enhanced dynamic

delayed scanning is of great significance in the diagnosis and differentiation of choroidal hemangioma. Retinoblastoma: It occurs in children within 5 years of age and presents with localized thickening or heterogeneous mass shadows of the eye ring on CT, more than 90% of which are mixed with dot-like calcifications. Typical MRI imaging features of retinoblastoma include a slightly higher signal on T1-weighted images and low signal on T2-weighted images, with contrast enhancement and diffusion restriction. PET metabolism mostly shows a slight increase in glucose uptake in retinoblastoma[22-23]. Thus, it is not difficult to differentiate from this case."

Q3: Illustrations and tables. The figure descriptions are careless, should be rewritten. MRI images were presented in a confusing manner. They should begin with T2 WI, after that precontrast T1WI, after that enhanced images should be presented. Are there any DWI, if present it should be given.

Response: Many thanks for the reviewer's guildness. We have modified figure descriptions as follows:

Figure 1. Ultrasound images of left retinal hemangioblastoma. A: Ultrasound showed an irregular isoechoic mass of about 6.3×7.4 mm in front of the left optic nerve head. B: Color Doppler flow imaging (CDFI) showed abundant blood flow signals in the lesion.

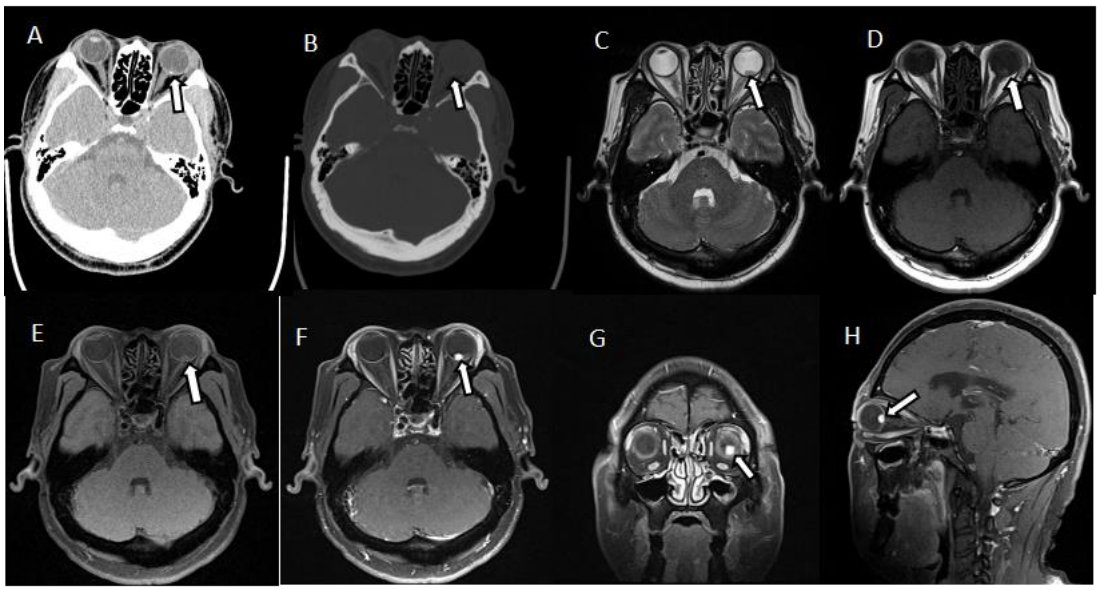
Figure 2. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of left retinal hemangioblastoma. A: CT transverse soft tissue window of orbit showed punctate calcification on the posterior wall of the left eye ring and small patchy soft tissue density in the posterior part of the eyeball. The lesion measured about 5 mm × 8 mm, with an ill-defined border. B: CT transverse bone window of orbital showed no obvious abnormal change of orbital bone. C: The lesion was hypointense on transaxial T2-weighted sequence. D-E: The lesion was slightly hyperintense on transaxial T1-weighted images (D) and transaxial T1-weighted + fat-suppression images (E). F-H: Left posterior para-bulbar lesions were significantly enhanced on gadolinium-enhanced T1-weighted + fat-suppression images [mainly included transverse (F), coronal (G), and sagittal sequences (H)] (White arrows represent lesion

Figure 3. Transaxial CT image, transaxial and coronal positron emission tomography (PET) metabolograms, color fusion map of positron emission tomography/computed tomography

(PET/CT) images at the orbital level. The transaxial CT image at the orbital level showed a patchy slightly hyperdense lesion. The transaxial PET metabologram, coronal PET metabologram and PET/CT color fusion map at the orbital level showed no metabolic changes, and its SUVmax was 50.9.

Figure 4. Postoperative histopathological and immunohistological images of left retinal hemangioblastoma. A-D: The left eyeball lesions were mainly composed of two components, capillaries and interstitial cells surrounded by vacuolated or eosinophilic cytoplasm, which showed epithelioid stromal cells and staghorn dilated thin-walled vessels in capillaries.

We also revised the MRI images as follows,but the MRI enhanced scans of routine orbital in our hospital do not contain DWI sequences.



Q4: Ethics statements. No information was given, were patient's consent taken?

Response: Many thanks for the reviewer's reminder. we obtained the patient 's consent.The patient signed a written informed consent form before the examination. This retrospective study involving human participants was reviewed and approved by Medical Ethics Committee of Hangzhou First People's Hospital, Zhejiang University School of Medicine (No. 2022-007-01).

对患者的影像资料进行全面评估，对患者的临床诊治具有重要价值，有利于患者的预后。

五、替代治疗：（*描述除了本研究的治疗方法，临床上还有的常见的其他治疗方法，需包含以下内容。如只涉及血液、尿液、标本采集和流行病学调查等，这部分可删除*）参加本研究可能改善或不能改善您的健康状况，您可以选择：

1. 不参加本研究，继续您的常规治疗。常规治疗方式有以下几种：（*常规治疗方法的具体描述*）
2. 参加别的研究。
3. 不接受任何治疗。

请与您的医生协商您的决定。

六、免费治疗：（*根据法规要求，受试者参与研究，研究者不得向其收取任何研究行为下产生的费用，因此，需写明：研究过程中，受试者不需要支付任何费用，包括研究者利用常规诊疗替代研究所需的检查等产生的费用。研究者将负责您的所有费用。*）

检查费免除。

七、赔偿：（*若有保险，可在此节提及；若无保险则需写明，若发生与研究相关的损害时，研究者将如何赔偿受试者。*）

无特殊补偿。

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在必要情况下，研究者、研究主管部门、伦理委员会及上级核查部门将在签署保密协议的前提下被允许查阅您的医疗记录及相关信息。当您签署了这份知情同意书，代表您同意您的个人和医疗信息被用于上述所指述的场合。

九、自愿性：您可以选择不参加本项研究，或者在任何时候退知研究者要求退出研究，您的数据将不纳入研究结果，您的任何医疗待遇与权益不会因此而受到影响。

如果您需要其它治疗，或者您没有遵守研究计划，或考发生了与研究相关的损伤或者有任何其它原因，研究医师可以终止您继续参与本项研究。

十、受试者义务：作为研究受试者，您有以下职责：如实提供有关自身病史和当前身体状况的真实情况；告诉研究医生自己在本次研究期间所出现的任何不适；不得服用受限制的药物、食物等（*需详细列出受限制的药物和食物名称*）；告诉研究医生自己在最近是否曾参与其他研究，或目前正参与其他研究。

十一、联系方式：您可随时了解与本研究有关的信息资料和研究进展，若发生与本研究相关的安全性新信息，我们也会及时通知您。如果您有与本研究有关的问题，或您在研究过程中发生了任何不适与损伤，或有关于本项研究参加者权益方面的问题您可以通过 13819194695（*电话号码*）与丁忠祥（*研究者或有关人员姓名*）联系。

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浙江大学医学院附属杭州市第一人民医院
浙江大学医学院附属杭州市第一人民医院
Hangzhou First People's Hospital, Zhejiang University School of Medicine

知情同意书模版

（括号内斜体字部分需根据课题不同情况自行填写）

项目名称：眼眶病变影像学新技术研究

尊敬的受试者：

我们邀请您参加浙江大学医学院附属杭州市第一人民医院医院批准开展的（眼眶病变影像学新技术）研究。本研究将在（浙江大学医学院附属杭州市第一人民医院）开展，预计将有（120）名受试者自愿参加。本研究已经得到浙江大学医学院附属杭州市第一人民医院伦理委员会的审查和批准。

本须知将提供给您一些信息以帮助您决定是否参加此项临床研究，您是否参加本项研究完全是自愿的，且您的决定将不会影响到您在本院的正常诊疗权益和待遇。若您选择参加本研究，我们研究团队将在研究过程中尽力保证您的安全和权益！

本须知提供给您一些信息以帮助您决定是否参加此项临床研究。请您仔细阅读，如有任何疑问请负责该项研究的研究者提出。

一、研究目的：背景意义（*包括国内、国外研究进展*）——*语言要求简要、通俗易懂。*

眼眶病变是临床常见、多发病，如何应用影像学新技术对眼眶患者术前精确定位和诊断非常有价值。

二、研究过程：（*包括主要研究内容、预期参加的受试者人数、过程与期限、随访的次数、需何种检查操作、告知受试者可能被分配到研究的不同组别等——语言要求通俗易懂*）。（例如：如果您同意参与这项研究，我们将对您进行编号，建立病历档案。在研究过程中我们需要采集一些您的标本，将由专业人员为您取样，例如从您的静脉上抽取静脉血5ml，或留取尿液5毫升，共两次。您的样品仅用于研究。）

（1）在依托单位浙江大学医学院附属杭州市第一人民医院采集120例健康志愿者3D-T1-MPRAGE序列、DTI 扫描的数据收集。我们对正常志愿者脑皮层、白纸纤维束进行提取分析，同时对正常志愿者数据进行影像组学分析。

（2）在依托单位浙江大学医学院附属杭州市第一人民医院收集较大样本量（120人）的眼眶患者治疗前后采集3D-T1-MPRAGE序列、DTI 数据。我们对这些数据进行提取分析。

三、可能的风险与不适：（*描述研究存在风险及可能带给受试者的不适，尽量详细*）。（例如：对于您来说，所有的信息将是保密的。您的样本采集将严格按照无菌要求操作，标本的采集可能会有一些非常小的风险，包括短暂的疼痛、局部青紫，少数人会有轻度头晕，或极为罕见的针头感染。）

本研究所进行的检查和随访均为临床常规检查项目，无额外风险及不适。

四、预期获益：（*描述受试者参与该研究后会获得好处*）（例如：通过对您的标本进行检测将有助于对疾病作出诊断，为您的治疗提供必要的建议，或为疾病的研究提供有益的信息。）

如果您对参与本研究的权益和健康有任何问题或诉求，您可以联系浙江大学医学院附属杭州市第一人民医院伦理委员会，联系电话：0571-85893643。

知情同意书签字页

我已经阅读了本知情同意书。

我有机会提问而且所有问题均已得到解答。

我理解参加本项研究是自愿的。

我可以选择不参加本项研究，或者在任何时候退知研究者后退出而不会遭到歧视或报复，我的任何医疗待遇与权益不会因此而受到影响。

如果我需要其它治疗，或者我没有遵守研究计划，或者发生了与研究相关的损伤或者有任何其它原因，研究医师可以终止我继续参与本项研究。

我将收到一份签过字的"知情同意书"副本。

受试者姓名：王有利

受试者签名：王有利

日期：2022年2月28日

我已准确地将这份文件告知受试者，他/她在确切了这份知情同意书，并有机会提出问题。

研究者姓名：丁忠祥

研究者签名：丁忠祥

日期：2022年2月28日

（注：如果受试者不识字尚需见证人签名，如果受试者无行为能力时则需代理人签名）