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CASE REPORT

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Case report: heart failure related to intravitreal injection of anti-VEGF

Yuying Sui[1,2], Yong Zhao[1,2], Nannan Zhou[1,2], Haihui Sun[1,2], Yuanyuan Sun[1,2], Junni Liu[1,2], Zunzhe Wang[1,2] and Jianchun Wang[1,2*]

Abstract

Background Intravitreal injection of anti-vascular endothelial growth factor is considered the first-line treatment for polypoidal choroidal vasculopathy. It has potential risks for circulatory system, which should be particularly carefully evaluated in older patients. In this case study, we aim to discuss the potential impact of this treatment regimen on cardiac health.

Case presentation This case report describes an elderly patient with no prior history of heart disease who exhibited unexpected heart enlargement and dysfunction. Throughout the patient's hospital stay, various potential causes were investigated, leading to the hypothesis that a 10-year history of intravitreal injections of anti-vascular endothelial growth factor could be related to the observed clinical manifestations. The patient was advised to discontinue this treatment, and after a 2-month follow-up period, there was a gradual improvement in the patient's cardiac structure and function.

Conclusion This manuscript highlights the importance of conducting cardiac examinations before and after anti-vascular endothelial growth factor treatment, especially for individuals at risk of heart diseases like the elderly. It emphasizes the need to carefully weigh the benefits and risks of treatment regimens to ensure optimal therapeutic outcomes.

Keywords Heart failure, Anti-vascular endothelial growth factor, Intravitreal injection, Heart enlargement

Background

Regular intravitreal injection (IVT) of anti-vascular endothelial growth factor (anti-VEGF) is the recommended initial treatment for polypoidal choroidal vasculopathy (PCV) and is commonly administered to elderly patients [1, 2]. However, it is important to be aware of potential risks to the circulatory system, including hypertension, systemic VEGF depletion, and thrombotic microangiopathy [3, 4]. Clinicians should carefully consider these side effects when prescribing anti-VEGF IVT to older individuals. In this case study, we aim to explore the potential impact of anti-VEGF IVT on cardiac health.

Case report

An 80-year-old man was admitted to the hospital on January 17th, 2022, presenting with worsening dyspnea and fatigue for 2 months following a cold. His medical history included chronic bronchitis, occasional atrial premature contraction, Grade I hypertension, optic nerve atrophy in the left eye, and PCV in the right. He had a

*Correspondence:
Jianchun Wang
wangjianchun@sdfmu.edu.cn
[1]Department of Geriatrics, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, Shandong, China
[2]Department of Geriatric Cardiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, Shandong, China

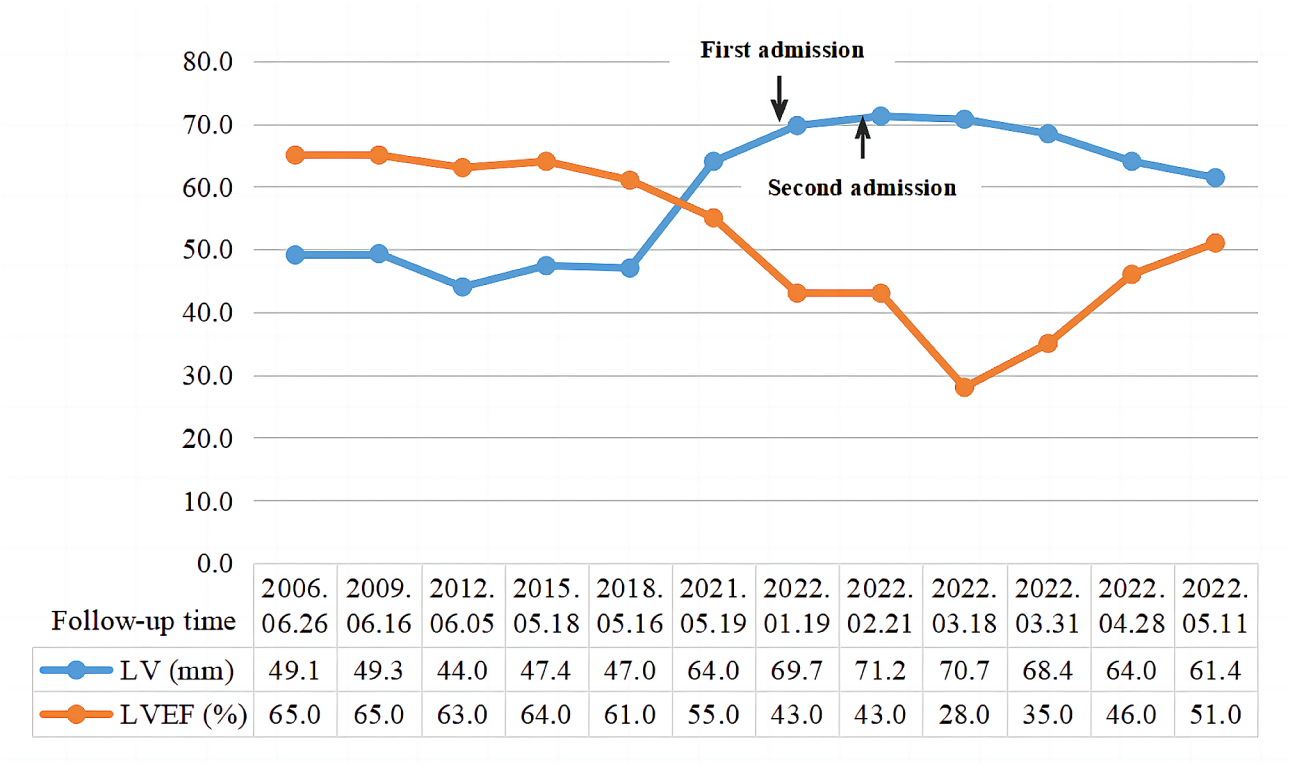
Table 1 The patient's basic laboratory tests in his admissions

Items	1st admission	2nd admission	Normal range	Units
HS-TnT	48↑	52.6↑	0–14	ng/L
WBC	6.17	10.65↑	3.5–9.5	10^9/L
Neutrophil (%)	4.59 (74.3)	9.27(87.0) ↑	1.80–6.30 (40–75)	10^9/L
CRP	0.84	31.74↑	0–10	mg/L
NT-ProBNP	3984↑	14,396↑	0-125	ng/L

Abbreviations: CKMB-M, Creatine kinase-MB Mass; AST, Aspertate aminotransferase; HS-TnI, High-sensitivity troponin I; CK, Creatine kinase; HS-TnT, High-sensitivity troponin T; MYO, Myoglobin; WBC, White blood cell; CRP, C-reactive protein; CHOL, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol

smoking history of 20 cigarettes per day for 30 years but had quit 17 years before. He denied alcohol consumption and had no family history of heart disease. Upon physical examination, the patient's vital signs were normal except for mild pitted edema in both legs. Initial laboratory tests showed an elevated N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (HS-TnT) (Table 1). Electrocardiograph (ECG) revealed atrial premature contractions, while ultrasonic cardiogram (UCG) unexpectedly showed heart enlargement (Left atrium (LA) 48.0 mm, left ventricle (LV) 69.7 mm, right atrium (RA) 48.9 mm) and reduced left ventricular ejection fraction (LVEF, 43%) without significant valvular lesions. The primary diagnosis was heart failure for this admission. Upon reviewing his previous UCG, it was noted that his LV and LVEF were normal until six months prior (from 2021.05 to 2022.01, Fig. 1). The reason for the sudden heart enlargement within this short timeframe remains unclear.

Further examinations were conducted to investigate the patient's condition. Based on the patient's symptoms and the results of coronary computerized tomography angiography (CTA, Fig. 2), ischemic cardiomyopathy was essentially ruled out. On the one hand, the patient had not reported any chest pain or other symptoms of myocardial ischemia clinically; on the other hand, the coronary CTA revealed no significant stenosis: left main trunk (LM): 20% (degree of stenosis, so as below); left anterior descending branch (LAD): 50%; left circumflex branch (LCX): 30–50%; right coronary artery (RCX): 30%. Despite considering potential causes such as myocarditis, valvular heart disease, cardiac amyloidosis, and Takotsuba syndrome, cardiac magnetic resonance (CMR, Fig. 3) did not provide conclusive evidence. The CMR findings indicated enlargement of the left ventricle and bilateral atria, diffuse thinning of the left ventricular myocardium, particularly in the anterior and lateral walls near the middle, and a diffuse decrease in myocardial contraction and diastole amplitudes. Regurgitation



Follow-up time	2006.06.26	2009.06.16	2012.06.05	2015.05.18	2018.05.16	2021.05.19	2022.01.19	2022.02.21	2022.03.18	2022.03.31	2022.04.28	2022.05.11
LV (mm)	49.1	49.3	44.0	47.4	47.0	64.0	69.7	71.2	70.7	68.4	64.0	61.4
LVEF (%)	65.0	65.0	63.0	64.0	61.0	55.0	43.0	43.0	28.0	35.0	46.0	51.0

Fig. 1 The patient's LV and LVEF changes. The figure shows the patient's LV(mm) and LVEF(%) changes during follow-up. The arrows in the figure mark the times of his first and second admission, respectively

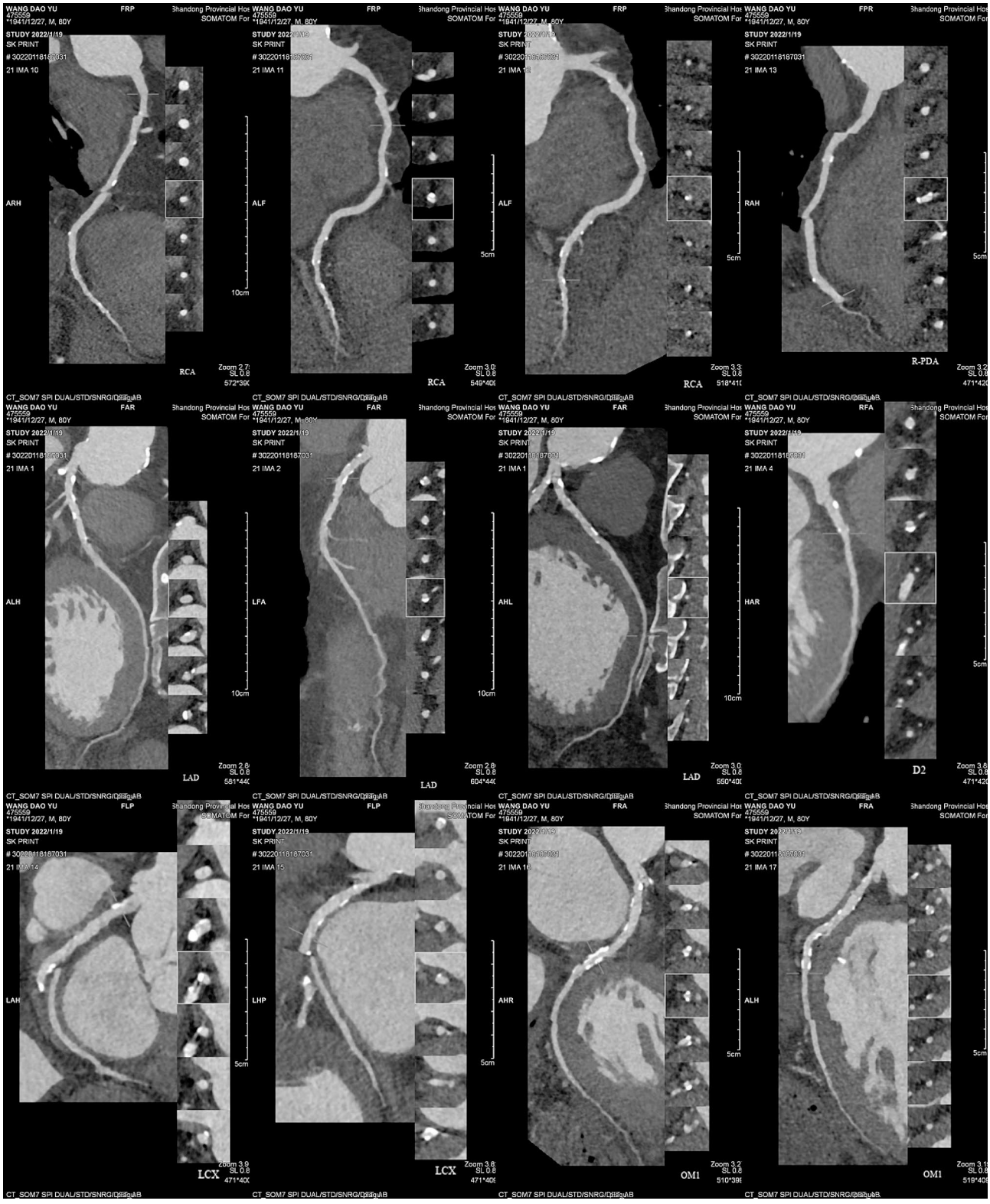


Fig. 2 The patient's coronary computerized tomography angiography images

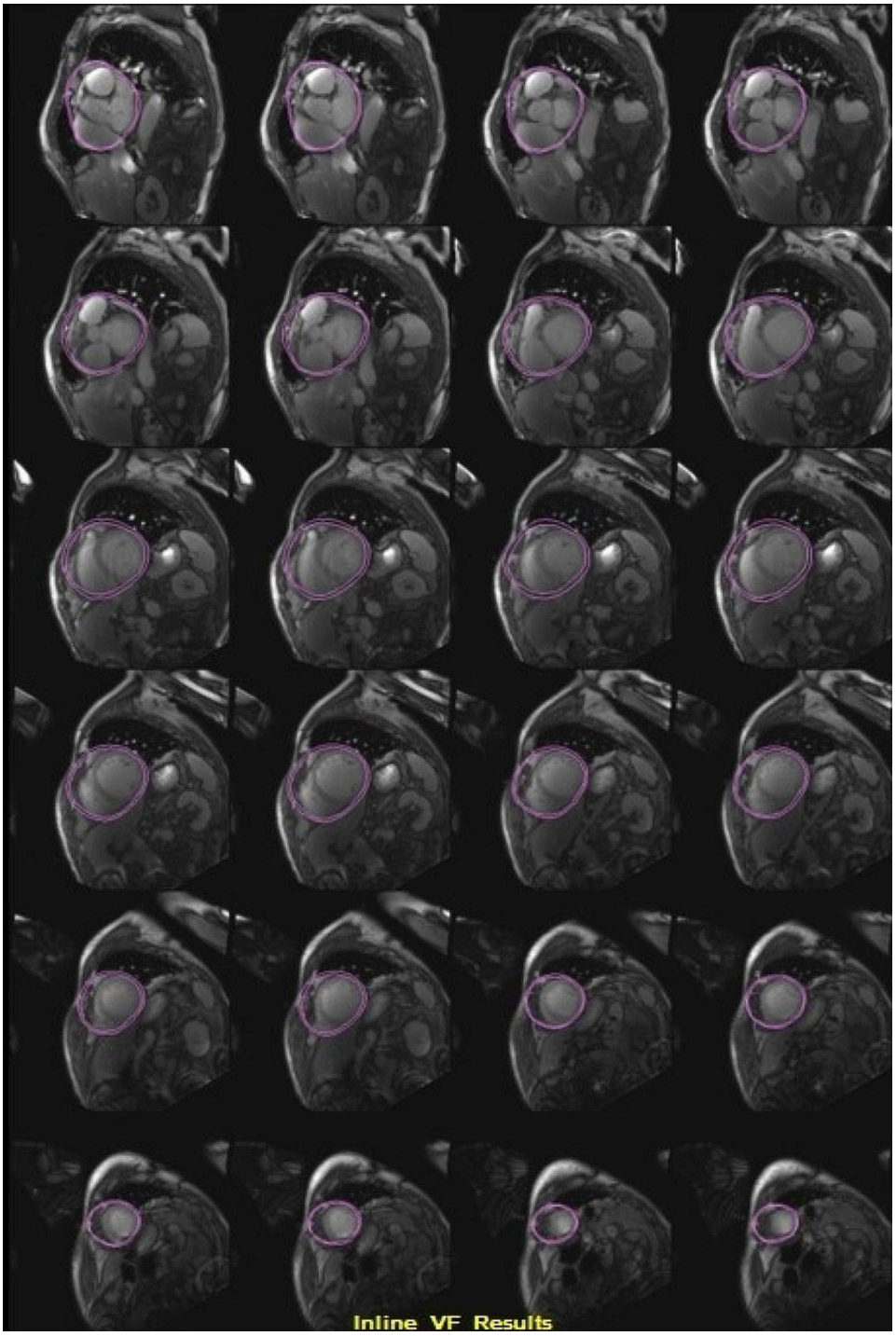


Fig. 3 The patient's cardiac magnetic resonance images

signal shadows were noted in the mitral valve area during left ventricular systolic period, with a few were observed in the aortic valve area during left ventricular diastolic period. No abnormal blood flow signal was detected in the tricuspid valve area. Additionally, myocardial resting perfusion scan showed no significant perfusion delay or defects in any myocardial segment. Measurements from the CMR showed left ventricular end-diastolic dimension (LVEDD) of 7.8 cm, right ventricular end-diastolic dimension (RVEDD) of 3.9 cm, LA of 4.3 cm, RA of 4.5 cm, interventricular septal (IVS) of 0.8 cm, left ventricular posterior wall (LVPW) thickness of 0.6 cm, left ventricular inferior wall (LVIW) thickness of 0.7 cm, LVEF of 19%, end diastolic volume (EDV) of 361 ml, end

systolic volume (ESV) of 292 ml, cardiac output (CO) of 5.2 L/min, and left ventricular mass of 225.4 g. Connective tissue disease-related cardiomyopathy was ruled out as serum protein (free) light chain and autoimmunity indicators were normal. Hypertensive heart disease was unlikely since the patient's Grade I hypertension was well controlled by basal dose medication (irbesartan 0.15 g qd). Idiopathic dilated cardiomyopathy and alcoholic cardiomyopathy were also excluded based on history and previous tests. The cause of cardiac enlargement remained unclear. Anyway, since 24-hour Holter monitoring presented frequent atrial premature beats and paroxysmal atrial fibrillation, we performed standard treatment, focusing on promoting heart function and controlling arrhythmia. Following a week of treatment, symptoms improved significantly, and the proportion of atrial premature beats on 24-hour Holter monitoring decreased from 25.01% to 13.18%. The patient was discharged on January 27th, 2022. Before discharge, the patient was prescribed Edoxaban Tosilate Tablets (30 mg qd), Rosuvastatin Calcium Tablets (10 mg qn), Amiodarone Hydrochloride Tablets (0.2 g qd), Sacubitril Valsartan Sodium Tablets (50 mg bid), Furosemide Tablets (20 mg qd), and Spironolactone Tablets (20 mg qd). The patient diligently followed this regimen until their subsequent admission.

On February 19th, 2022, the patient was readmitted due to weakness and fatigue. This time, orthopnoea and more severe peripheral edema were observed, along with an increase in NT-proBNP levels to 14,396 ng/L. The LV size had increased to 71.2 mm (Fig. 1) with minimal 24-hour atrial premature beats (1,631; 1.30%) and no atrial fibrillation detected, indicating arrhythmia was not the cause of the cardiac enlargement. Heart failure symptoms improved with timely guideline-directed medical therapy [5], but the underlying cause needed to be identified. Upon reviewing the patient's medical history, it was noted that he had been receiving a regular anti-VEGF IVT for almost 10 years (2012.11-2018.01, Ranibizumab; 2018.02-2018.10, Conbercept; 2018.11-2021.10, Aflibercept) to manage PCV. Anti-VEGF agents inhibit angiogenesis and vascular leakage from newly formed vascular networks in the choriocapillaris, which contributes to the progression of PCV [1]. However, it also poses risks for the circulatory system, including hypertension, cardiac insufficiency and myocardial ischemia. The patient was advised to discontinue anti-VEGF therapy. After a 2-month withdrawal period, there was a gradual improvement in LV and LVEF as shown in Fig. 1. The patient was discharged on May 27th, 2022, and has not experienced dyspnea or edema ever since.

Discussion

In this report, the focus was on the reason-finding process. Reviewing this case, we speculated that the prolonged frequent use of anti-VEGF might have contributed to the gradual decline in cardiac structure and function over time. As the patient aged with weaker health status, his heart might have been silently enlarging. The patient reported limited daily activity demand due to vision loss. In addition, the patient had a comfortable lifestyle with good living conditions and family support. That is, although the patient's heart function was suboptimal, he was able to maintain a tolerable quality of life with proper care. However, this delicate balance was easily disrupted, which means once there was a stressful challenge without timely relief, the superficial balance could be easily smashed. In our case, the cold, as "the last straw", might have destabilized the patient's borderline cardiac function and triggered a cascade leading to heart failure. While there was no direct evidence linking anti-VEGF IVT to the cardiac event, there were indications supporting this hypothesis. During the patient's hospitalization, other potential causes for cardiac enlargement were ruled out, and his heart function improved after discontinuation of anti-VEGF treatment.

Previous studies have shown that local administration of anti-VEGF IVT can lead to increased anti-VEGF and decreased VEGF concentration in the blood stream [6, 7]. These changes tend to accumulate over time [8, 9]. Typically, anti-VEGF is administered monthly for the first 3 months, known as a "high-frequency" regimen. Subsequently, the intervals between injections may be extended to three months or even longer ("low-frequency "or "treatment-as-needed" regimens) [10, 11]. It is uncommon in clinical practice to continue high-frequency anti-VEGF IVT for as long as 10 years. Anti-VEGF IVT could cause some circulatory issues, such as various systematic thrombosis and hypertensive cerebral hemorrhage [3, 4]. Besides, it is now known that VEGF plays a crucial role in maintaining endothelium fenestrations and organ function [12]. VEGF has been shown to enhance myocardial perfusion and function in ischemic myocardium by promoting collateral revascularization [13]. In contrary, a long-term low-dose VEGF blockade can lead to loss of fenestrations, affecting permeability and causing significant vascular regression in normally fenestrated capillaries [14]. These changes have been observed in various organs, including the brain, eye choriocapillaris, choroid plexus, thyroid, hepatic sinusoid, spleen, pancreatic islets, adrenal glands, kidneys, bone marrow and some others [14–17]. The potential impact of VEGF blockade on myocardial capillaries, especially in adults, remains poorly understood. One study conducted at Stanford suggested that abnormal development of myocardial capillaries in children could contribute to

the development of cardiomyopathy [18]. Interestingly, in normal adult microvasculature, fenestrated capillaries are VEGF-dependant. Upon removal of VEGF inhibition and restoration of VEGF levels, fenestrations and related functions can be restored [19]. In our case, the patient's heart function improved after the cessation of anti-VEGF IVT. There seemed to be some similarities that might support our hypothesis. Furthermore, the patient's UCG worsened coincidentally after switching from ranibizumab to conbercept and aflibercept successively. Whether the drug heterogeneity influenced the patient's heart also remains a question. However, to our knowledge, this case is the first one reporting long-term high-frequency anti-VEGF IVT. Previous evidence mainly comes from a few case reports and small scale clinical trials. In recent meta-analysis, no significant difference was observed in adverse reactions of cardiovascular system [20–22]. However, these analyses focused on severe thrombotic events or death rather than cardiac deformation risks. Two latest meta-analysis systemically reviewed relevant randomized controlled trials and concluded that anti-VEGF IVT did not significantly impact systemic adverse events including heart failure [23, 24]. However, these studies did not include case reports, and did not consider sequential mixed anti-VEGF treatments or the effects on elderly patients in the long term. It could not be ignored that the patient in this case is quite old, while age itself is a risk factor of some cardiovascular diseases [25]. As a result, we infer that the long-term high-frequency anti-VEGF IVT could be related to the patient's heart enlargement and subsequent heart failure. Without direct scientific evidence or re-medication trials, only a potential association, not causation, can be inferred. In spite of uncertainties, we still feel the necessity to report this case to raise awareness among clinicians. It is crucial for doctors to balance life expectancy and prognosis of specialized diseases when treating elderly patients.

Conclusion

This case study highlights a situation where an elderly patient experienced heart failure possibly linked to anti-VEGF IVT therapy. Now anti-VEGF IVT is the first-line treatment for PCV [1, 2], which is commonly used in older patients. Unfortunately, advanced age is often associated with weaker heart function. This manuscript emphasizes the importance of clinicians conducting ECG and UCG evaluations before and after anti-VEGF IVT treatment, especially in patients vulnerable to heart conditions like the elderly. It also underscores the significance of carefully balancing the benefits and risks of regimens to ensure optimal therapy outcomes.

Abbreviations

IVT	Intravitreal injection
anti-VEGF	Anti-vascular endothelial growth factor
PCV	Polypoidal choroidal vasculopathy
NT-ProBNP	N-terminal pro-brain-type natriuretic peptide
HS-TnT	High-sensitivity troponin T
ECG	Electrocardiograph
UCG	Ultrasonic cardiogram
LA	Left atrium
LV	Left ventricle
RA	Right atrium
LVEF	Left ventricular ejection fraction
CTA	Computerized tomography angiography
LM	Left main trunk
LAD	Left anterior descending branch
LCX	Left circumflex branch
RCX	Right coronary artery
CMR	Cardiac magnetic resonance
LVEDD	Left ventricular end-diastolic dimension
RVEDD	Right ventricular end-diastolic dimension
IVS	Interventricular septal
LVPW	Left ventricular posterior wall
LVIW	Left ventricular inferior wall
EDV	End diastolic velocity
ESV	End systolic volume
CO	Cardiac output
WBC	White blood cell

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Author contributions

Y.S. (Yuying Sui) and J.W. were responsible for the conception, drafting, and critical revision of the manuscript. N.Z. contributed to the retrieval and review of relevant literature. H.S. and Y.S. (Yuanyuan Sun) collected and assembled clinical information. J.L. conducted the follow-up. Z.W. analyzed and interpreted the data. All authors have read the manuscript and approved it for publication.

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Data availability

All relevant data supporting the conclusions of this article are included within the article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University. Written informed consent was also obtained from the patient for the publication of any potentially identifiable images or data included this case report.

Consent for publication

The patient has provided informed consent for publication of the case.

Competing interests

The authors declare no competing interests.

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