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• Review Article •

A man with asymmetric bilateral choroidal melanocytosis: a case report and literature review

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HIGHLIGHTS

- This case report presents a rare, bilateral, and asymmetrical presentation of isolated choroidal melanocytosis (ICM) utilizing multimodal imaging techniques. Importantly, it summarizes the differential diagnosis between ICM and other fundus pigmentary lesions, while highlighting ICM's established association with an increased lifetime risk of uveal melanoma.
- The report highlights the diagnostic efficacy of multimodal imaging, particularly spectral-domain optical coherence tomography (SD-OCT) and Near-Infrared Reflectance (NIR), in characterizing ICM. SD-OCT ruled out mass elevation and showed choroidal thickening, while NIR superiorly delineated the geographic borders of the pigmented lesions, providing a non-invasive method to differentiate the pigmentary fundus lesions.
- Future application involves utilizing this multimodal imaging protocol for the accurate diagnosis and longitudinal monitoring of pigmentary fundus lesions. Research directions should focus on elucidating the pathogenesis of ICM and identifying molecular biomarkers to stratify the risk of malignant transformation into choroidal melanoma, thereby guiding personalized management strategies.

Abstract: **Objectives:** The study aimed to report the distinctive fundus appearance of bilateral asymmetric choroidal melanocytosis and reviewed the clinical and multimodal imaging characteristics to differentiate choroidal melanocytosis from malignant pigmented retinal lesions. **Methods:** An observational case report and literature review. **Results:** A 60-year-old patient underwent comprehensive ophthalmologic examinations. Under funduscopy examination, bilateral choroidal melanocytosis with asymmetric choroidal pigmentation change was observed. In the right eye, there was diffuse darker coloration extending from posterior pole to the mid-peripheral retina. In the left eye, flat patches of choroidal hyperpigmentation were present, involving superior and inferior

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Full Text

hemisphere region, while other regions were depigmented. Spectral-domain optical coherence tomography revealed that the layers of retina and choroid were basically normal, with no elevation of the retinal pigment epithelium. Near infrared reflectance images provided a clearer view of mottled focal hyperpigmentation area, which corresponded to the choroidal hyperpigmentation.

Conclusions: This case highlights the effectiveness of multimodal imaging in distinguishing choroidal melanocytosis from malignant entities. It emphasizes the crucial role of multimodal imaging in guiding clinical management to prevent vision-threatening complications and monitor potential malignant transformation.

Keywords: choroidal melanocytosis; spectral-domain optical coherence tomography (SD-OCT); pigmentary fundus lesions; multimodal imaging

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Pigmentary ocular fundus lesions usually involved in retinal pigment epithelial (RPE) and the choroid. It's crucial to differentiate between various pigmented fundus lesions, as their nature ranges from benign to malignant and requires different clinical management strategies.^[1]

Isolated choroidal melanocytosis (ICM) is a rare condition characterized by the flat, discrete, patch choroidal melanotic hyperpigmentation, without ipsilateral iridic or anterior scleral melanocytosis.^[2-5] Although choroidal melanocytosis was usually considered a benign condition, several studies have found a close relationship between choroidal melanocytosis and choroidal melanoma.^[2,4,6-8] Therefore, an accurate diagnosis of choroidal melanocytosis and its differentiation from other pigmented fundus lesions are essential aspects of clinical practice to mitigate vision-threatening complications and ensure early intervention for potential malignant progression.

In this case, we presented unusual manifestations of bilateral choroidal melanocytosis, along with its defining characteristics through multimodal imaging. To differentiate pigmentary ocular fundus lesions, we summarized the clinical and multimodal imaging features of various diseases.

CASE PRESENTATION

A 60-year-old man of Asian descent presented for regular medical examinations. His best corrected visual acuity was 20/25 OD and 20/25 OS. Slit-lamp examination revealed mild nuclear and cortical

cataracts as well as slightly vitreous opacities. The anterior segments shown no other features of ocular melanocytosis. During fundusoscopic examination, bilateral choroidal melanocytosis with an asymmetry choroidal pigmentation changes was observed. In the right eye, there was diffuse darker coloration from posterior pole to the mid-peripheral retina (Figure 1-A). In the left eye, flat patches of choroidal hyperpigmentation were present, involving the superior and inferior hemisphere regions, while other regions was depigmented (Figure 1-B). The margin of hyperpigmentation area on the fundus were indicated by arrow heads in Figure 1. Spectral-domain optical coherence tomography (SD-OCT) revealed normal retinal layers with slightly increased choroidal thickening (Figure 1-C, D). There is no elevation of the retinal pigment epithelium (RPE) or any choroidal mass. Changes in choroidal pigmentation (either an increase or a decrease) led to alterations in OCT findings. Figure 1-D clearly shown an indistinct Sattler's layer and Haller's layer at the area of hypopigmentation (red arrow) and slightly thickened choroid with a distinct structure in the area of hyperpigmentation (yellow arrow). Near infrared reflectance (NIR) images provide a clearer view of mottled focal hyperpigmentation corresponding to the choroidal hyperpigmentation (Figure 1-C, D). The patient denied any ocular history, especially past episodes of uveitis. Additionally, the patient had no other systemic diseases, including dermatological disease such as vitiligo. After a physical examination, no other skin melanocytosis, cutaneous hypopigmentation, or white forelock was found. Based on the medical history,

systemic examination, and fundus multimodal imaging, the patient was diagnosed with choroidal melanocytosis with asymmetric fundus manifestations. Although choroidal melanocytosis is typically benign, several studies have identified a potential association between choroidal melanocytosis and choroidal melanoma.^[4,6-7] Therefore, the patients require lifelong follow-up.

DISCUSSION

A comprehensive search of the PubMed platform was conducted up to December 20, 2024, using the search terms “choroidal melanocytosis”. The search yielded 15 articles, as shown in Table 1. To date, a total of 100 cases of isolated choroidal melanocytosis have been reported. Although, according to Augsburger et al., most

cases of ICM were unilateral,^[9] 31 cases of bilateral ICM have been documented. In contrast to our case, these cases with bilateral involvement exhibit symmetrical lesions of ICM.^[5,10-14]

In this case, we present unusual manifestations of bilateral choroidal melanocytosis. Choroidal melanocytosis was previously considered part of ocular (dermal) melanocytosis (ODM), a congenital disorder characterized by increased pigmentation involving the periorbital area, episclera, sclera, and choroid.^[15-16] Ausburger et al. first defined choroidal melanocytosis as a distinct clinical entity in 2006 to distinguish clinical characteristics,^[2] but it is still poorly recognized and reported. Isolated choroidal melanocytosis presents as sector or partial hyperpigmentation of the choroid, without associated iris or scleral

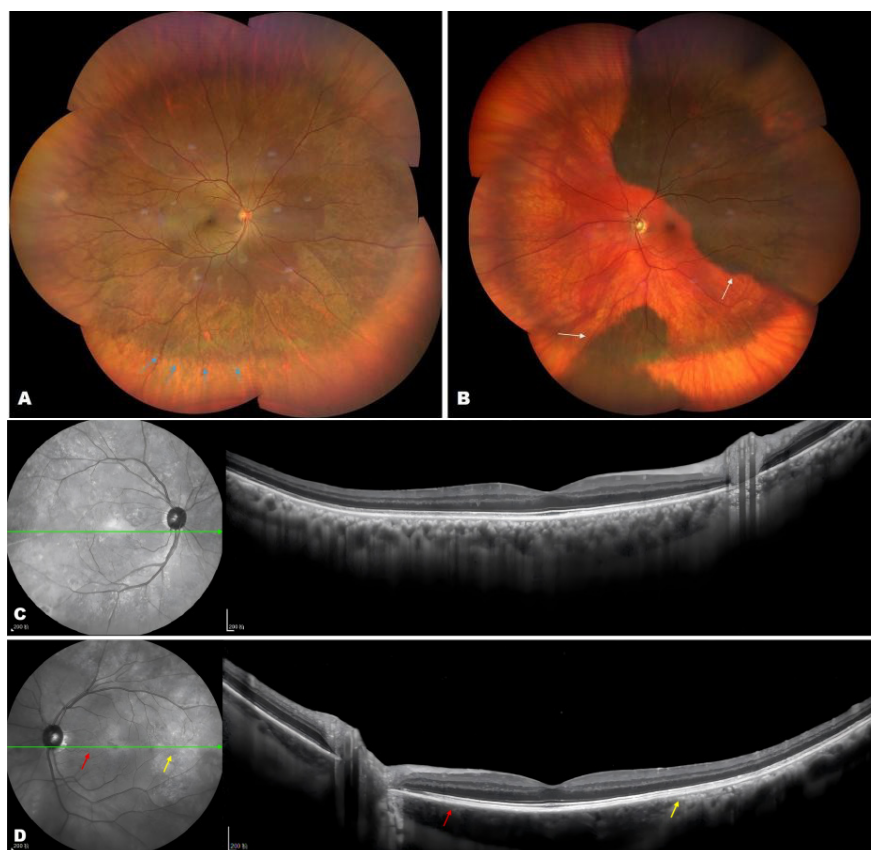


Figure 1 Multimodal imaging demonstrated bilateral choroidal melanocytosis with asymmetric pigmentation patterns

On wide-field fundus photography, the right eye displays diffuse posterior-to-midperipheral choroidal hyperpigmentation (A, indicated by the blue arrowhead), while the left eye shows patchy hyperpigmentation in the superior hemisphere and inferior midzone (B, indicated by the white arrowhead). Near-infrared reflectance imaging reveals slight mottled focal hyperreflective area in the right eye (C) and patchy hyperreflective areas with clear borders in the left eye that correspond to the choroidal hyperpigmentation (D). The SD-OCT findings for both eyes show no elevation of the RPE or choroid. Figure D clearly illustrates the indistinct Sattlers layer and Haller's layer in the area of hypopigmentation (red arrow), along with slight thickening of the choroid and well-defined choroidal structure in the area of hyperpigmentation (yellow arrow).

Table 1 Synopsis of cases of isolated choroidal melanocytosis published in Pubmed, 1974–2024

No./Author	Country/ Year	Number of patients	Gender	Age	Race	Laterality	Multimodal imaging findings	Complications	Intervention
1. Pamela Martin, et al. ^[5]	USA/ 2022	1	Female	40	Asia	Bilateral	FP: Extensive bilateral choroidal melanosis	-	Long-term follow-up
2. Arun D Singh, et al. ^[30]	Australia/ 2021	22	15 males/ 7 females	-	Middle Eastern/ Asian: 8 cases (36%)	3 unilateral/ 19 bilateral	FP: Sectoral and temporal CM	-	Long-term follow-up
3. Maura Di Nicola, et al. ^[8]	USA/ 2020	3	-	-	White	Unilateral	FP: Darkly pigmented choroidal tumor with prominent overlying lipofuscin and a large associated area of choroidal melanocytosis; AF: Prominent lipofuscin pigment along the posterior margin of the lesion; A-scan and B-scan ultrasonography demonstrated nodular choroidal tumor with low internal reflectivity.	Developed multifocal uveal melanoma	Plaque brachytherapy
4. James J Augsburger, et al. ^[4]	USA/ 2020	37	15 males / 22 females	Mean age: 31.5 years old	-	Unilateral in 36 cases; 1 bilateral case with partial iris melanocytosis in the fellow eye	FP: Homogeneous, flat choroidal hyperpigmentation. B-scan ultrasonography: Flat lesions with no measurable thickness compared to adjacent choroid. Absence of acoustic shadowing or intrinsic vascularity. AF: Absence of lipofuscin/drusen overlying ICM (except in melanoma-associated cases)	3/37 (8.1%) developed melanoma within ICM; 1/37 (2.7%) had melanoma in the fellow eye	Plaque radiotherapy
5. Jae Kyoung Lee, et al. ^[16]	India/ 2020	1	-	-	Asians	Bilateral	FP: Central hyperpigmentation with peripheral choroidal hyperpigmentation around the 360° field in both eyes FFA/AF/OCT: NAD	-	Long-term follow-up
6. Amador-Patarroyo et al. ^[11]	USA/ 2019	1	Female	50	Latin-American	Bilateral	FP: Extensive, diffuse, midperipheral hyperpigmentation in an annular pattern, sparing the macula and optic nerve OCT: NAD	-	Long-term follow-up
7. Samuel J Fallon, et al. ^[21]	USA/ 2019	1	Female	48	Caucasian	Bilateral	FP: Diffuse bilateral scleral pigmentation and choroidal darkening	Developed multifocal choroidal melanoma	Enucleation

Table 1 (continued)

No./Author	Country/ Year	Number of patients	Gender	Age	Race	Laterality	Multimodal imaging findings	Complications	Intervention
8. Kevin D. Heinze, et al. ^[10]	USA/ 2019	1	Female	44	American Indian	Bilateral	FP: Bilateral 360° confluent annular pattern of isolated choroidal melanocytosis. OCT/AF/ B-scan ultrasonography: NAD	-	Long-term follow-up
9. Patricia Hrynchak, et al. ^[31]	Canada/ 2018	1	Male	34	Greece	Bilateral	FP: Large area of flat, confluent choroidal hyperpigmentation with feathered borders OCT/AF: NAD	-	Long-term follow-up
10. Lauren B Mason, et al. ^[32]	USA/ 2016	1	Female	24	African American	Bilateral	OCT: Remarkable for increased choroidal thickness with a normal inner and outer retina.	-	Long-term follow-up
11. Marco Pellegrini, et al. ^[17]	USA/ 2014	15	9 males / 6 females	Mean age 28 years old			EDI-OCT: Choroidal melanocytosis shows increased subfoveal choroidal thickness with an apparent increase in the choroidal perivascular stromal tissue and minimal effect on the overlying retina.	-	Long-term follow-up
12. Juan P. Velazquez-Martin, et al. ^[12]	Canada/ 2013	2	-	-	White	Bilateral	FP: Flat choroidal pigmented lesions FFA/OCT: NAD	-	Long-term follow-up
13. Howard F Fine, et al. ^[14]	USA/ 2009	1	Female	43	White	Bilateral	FP: Diffuse patchy melanocytic choroidal hyperpigmentation B-scan ultrasonography: NAD	-	Long-term follow-up
14. T A Kooroor, et al. ^[13]	USA/ 2008	1	Female	40	Indian	Bilateral	FP: An area of flat choroidal hyperpigmentation with indistinct margins involving most of the posterior pole FFA: NAD	-	Long-term follow-up
15. James J Augsburg, et al. ^[2]	UK/ 2006	11	3 males/ 7 females	Median age: 17 years old	Caucasian	Unilateral	FP: An area of flat choroidal hyperpigmentation	-	Long-term follow-up

ICM = Isolated Choroidal Melanocytosis, NAD=No Abnormality Detected, FP=Fundus Photography, AF= Fundus Autofluorescence ;FFA= Fluorescein Fundus Angiograph, OCT= Optical Coherence Tomography

melanocytosis.^[2,16] In choroidal melanocytosis, the homogeneously melanotic, completely flat lesions usually located posterior to the equator area.^[4,18] According to the study with the largest sample size of choroidal melanocytosis, most cases are considered unilateral.^[2] Only a few cases have reported bilateral choroidal melanocytosis and the pigmentary lesions in both eyes were symmetrical.^[5,18] Bilateral oculodermal melanocytosis is recognized as a risk factor for primary uveal melanoma.^[7] Therefore, for bilateral choroidal melanocytosis with asymmetric pigmentary lesions, we should utilize multimodal imaging techniques to identify the lesions and avoid misdiagnoses. According to previous studies, racial disparities exist in the phenotypic expression of choroidal melanocytosis, particularly regarding variations in choroidal pigmentation and melanoma incidence across ethnic groups. Jae Kyoung Lee et al., reported a case of ICM with coexistence of choroidal hyperpigmentation and hypopigmentation. They pointed out that there is a higher prevalence of hypopigmented fundi and choroidal melanoma in Caucasian populations compared to Asian demographics, and Asian ICM patients may exhibit phenotypic characteristics analogous to Caucasian pigmentary patterns, suggesting the potential pathological coexistence of choroidal hyperpigmentation and hypopigmentation within individual patients.^[18] Fundus photography, SD-OCT and NIR are non-invasive techniques suitable for evaluating pigmentary lesions of the retina and choroid. Ultra-widefield fundus photography provides details of peripheral lesions. OCT documents layer-by-layer lesion localization and thickness measurement of choroidal lesions. Shields et al summarized the OCT findings of choroidal melanocytosis, which are characterized by increased subfoveal choroidal thickness, primarily due to thickening of the choroidal perivascular stromal tissue, with minimal impact on the overlying retina.^[17] These OCT findings will assist clinicians in distinguishing choroidal melanocytosis from other pigmented choroidal masses with associated elevation, such as choroidal melanocytoma and RPE adenocarcinoma.^[1,18] Near-infrared reflectance uses light in the near-infrared spectrum, which allows deeper penetration and better visualization of subretinal structures.^[19] Therefore, NIR enables the detection of outer retinal/choroidal

pathologies, especially pigmented lesions.^[3,20] In our case, although the OCT findings of the hyperpigmented area were not very pronounced, NIR imaging was able to clearly delineate the boundaries of the pigment lesions. Other multimodal imaging techniques include fundus autofluorescence(AF), B ultrasonography, fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA) and OCT angiography (OCTA). We summarized the multimodal findings of different pigmentary ocular fundus lesions in Table 2. Recent advancements in the diagnosis and management of choroidal melanocytosis highlight its reliance on multimodal imaging for accurate identification. Key diagnostic modalities include color fundus photography, OCT, and B-scan ultrasonography, which reveal characteristic features such as flat choroidal hyperpigmentation, absence of lipofuscin (in benign cases), and normal retina and choroid layers. While most cases remain asymptomatic and stable, studies report rare malignant transformation (e.g., 8.1% in Augsburger et al., 2020),^[4,8,23] necessitating vigilant monitoring. Interventions like plaque brachytherapy are reserved for its most common complication--uveal melanoma. Pathologically, choroidal melanocytosis involves benign proliferation of melanocytes. Current studies advocate for longitudinal surveillance via non-invasive imaging to detect early malignant changes, while molecular research aims to identify biomarkers for risk stratification.

Choroidal melanocytosis should be differentiated from other melanotic retinochoroidal diseases, including: benign and malignant pigmented neoplasms of the retinal pigment epithelium, such as RPE adenoma or adenocarcinoma; benign and malignant pigmented neoplasms of choroid, such as choroidal nevus and melanoma, freckle, and focal aggregates of normal or near-normal uveal melanocytes (FANNUMs); combined hamartoma of the retina and RPE(CHRRPE), congenital hypertrophy of the RPE(CHRPE), RPE hyperplasia, and acquired bilateral patchy-streaky choroidal melanocytic fundopathy associated with cutaneous vitiligo or therapeutic agents.^[1,4-5,22] Multimodal imaging can provide essential clues for clinicians to make a diagnosis, as shown in Table 2. There are multiple types of discrete melanocytic choroidal lesions, including choroidal nevus, melanoma, FANNUMs, and choroidal melanocytosis.

Table 2 Clinical and multimodal imaging features of pigmentary fundus lesions

Disease	The nature of the lesion	Pathology	Clinical Feature	Multimodal imaging features					Management
				Fundus photography	OCT	AF	FFA/ICGA	Ultrasound	
Choroidal Freckle (FANNUM)	Benign	Focal aggregate of normal choroidal melanocytes	Asymptomatic, middle age or older adulthood	Flat, discrete melanotic choroidal lesion	Hyper-reflective, posterior shadowing; no elevation	IsoAF	-	Non-elevated	None
Choroidal nevus	Benign to Suspect	Benign uveal melanocytes (nevus cells)	Asymptomatic	Pigmented lesion with/without RPE changes / amelanotic; drusen	Thickened choroid; drusen, retinal pigment epithelium detachment, subretinal fluid(SRF)	HypoAF (orange pigment hyperAF)	Hypofluorescent	<2 mm thick; high/low reflectivity	Monitoring follow-up
Choroidal Melanoma	Malignant	Anaplastic uveal melanocytes (uveal malignant melanoma cells)	The most common adult primary intraocular malignancy with vision loss, field defects, high metastatic risk	Well demarcated, orange pigment, subretinal fluid, or serous retinal detachment	Thickened choroid, shaggy photoreceptors, SRF; compressed choriocapillaris	HyperAF (orange pigment)	Mottled hyperfluorescence; "hot spots"; hypocyanescent	Dome/ mushroom shape; acoustically hollow	Plaque brachytherapy; enucleation, sclerouvectomy, immunotherapy
Choroidal melanocytosis	Benign	Congenital diffuse proliferation of choroidal melanocytes	Asymptomatic, associated with iris/skin hyper pigmentation	Flat, patchy melanotic lesion located at posterior to the equator	Slightly Choroidal thickening	IsoAF	-	Non-elevated	Monitoring follow-up
RPE adenoma	Benign to Suspect	Neoplastic proliferation of rpe cells forming cords or tubules	Generally diagnosed, more common in female, no predilection for race	Deeply pigmented, unilateral, abruptly elevated or dome shaped, with associated feeder arterioles, exudation, and ocular inflammation	Hyperreflective RPE elevation	IsoAF	Hypofluorescence with late staining	High reflectivity with solid mass	Partial lamellar sclerouvectomy or plaque radiotherapy
CHRPE	Benign	Hypertrophic RPE with melanosomes, Photoreceptor atrophy	Asymptomatic	Flat, black plaque with lacunae/halo, usually located at midperipheral fundus	Retinal thinning, subretinal cleft	Hypoautofluorescent	-	Non-elevated	None
CHRRPE	Benign	Gliosis and RPE proliferation Vascular and glial hyperplasia	Gray retinal mass with traction	Gray retinal mass with traction, uxtapapillary/macular - Retinal vessel tortuosity	Retinal folds, vitreoretinal traction	IsoAF	Late staining on FFA	Non-elevated or slightly elevated	Vitreotomy for traction

FANNUMs are usually discrete, small, and flat lesions without RPE changes, whereas choroidal nevus usually has distinct or feathery margins with RPE changes, such as atrophy, RPE hyperplasia, and RPE fibrous metaplasia.^[16,23-24] Multimodal imaging features also provide clues for the transformation of choroidal nevi into melanoma.^[25-26] Shields proposed the mnemonic “To Find Small Ocular Melanoma Doing Imaging” to describe risk factors for the transformation of choroidal nevus into melanoma: thickness > 2 mm on ultrasound, subretinal fluid on OCT, symptoms (visual acuity 20/50 or worse), orange pigment on AF, acoustic hollowness on ultrasound, and tumor diameter > 5 mm on fundus photography.^[27] Melanocytoma, melanoma, and RPE adenocarcinoma are solid masses with RPE or choroidal elevation, which can be detected by OCT and ultrasound. Choroidal melanoma, the most common primary intraocular malignancy in adults, appears as pigmented or amelanotic lesions with characteristic orange pigment, subretinal fluid, and serous retinal detachment.^[18] Key imaging findings of choroidal melanoma include acoustic hollowness on ultrasonography, choroidal thickening with shaggy photoreceptors on OCT, and mottled hyperfluorescence with hypocyanescence on angiography (FA/ICGA).^[18] RPE adenoma shares similar clinical features with melanoma and is usually difficult to diagnose from suspected choroidal melanoma. RPE adenoma usually grows very slowly and invades the overlying retina layers; thus, it often acquires a retinal feeding artery and draining vein.^[28] CHRPE is hypertrophic RPE with melanosomes and photoreceptor atrophy. It shows thinning of the overlying retina, loss of photoreceptors, and moderate relative shadowing of the underlying choroid on OCT.^[23] CHRRPE appears as gray retinal mass with traction and retinal vessel tortuosity.^[29] Choroidal vitiligo can appear as asymmetric bilateral choroidal hypopigmentation, which is similar to our case, but dermatologic examination can often reveal cutaneous vitiligo or white forelock among these patients. In our case, the patient has no history of intraocular inflammation, trauma, dermatological disease, or any systemic illnesses. Except for the fundus pigmented lesions, there were no other ocular abnormality. Therefore, the diagnosis of choroidal melanocytosis was made.

CONCLUSION

We presented a rare case characterized by bilateral melanocytic hyperpigmentation with different manifestations, which is prone to be misdiagnosis. Although choroidal melanocytosis usually presents asymptotically, several studies found a close relationship between choroidal melanocytosis and choroidal melanoma.^[2] Therefore, the patients with this disorder require lifelong follow-up due to its association with the development of choroidal melanoma.^[2,30]

Correction Notice

None

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Author Contributions

(I) Conception and design: Xiaolai Zhou, Yuhong Gan

(II) Administrative support: Feng Wen

(III) Provision of study materials or patients: Xiaolai Zhou

(IV) Collection and assembly of data: Yuhong Gan

(V) Data analysis and interpretation: Yuhong Gan

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

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Conflict of Interests

None of the authors has any conflicts of interest to disclose. All authors have declared in the completed the ICMJE uniform disclosure form.

Patient Consent for Publication

None

Ethical Statement

None

Provenance and Peer Review

This article was a standard submission to our journal. The article has undergone peer review with our anonymous review system.

Data Sharing Statement

None

Open Access Statement

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