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Macular findings expedite accurate diagnosis of MIDD in a young female patient with newly diagnosed diabetes

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ABSTRACT

Purpose: To report a case of a 34-year-old female patient with newly diagnosed Maternally Inherited Diabetes and Deafness (MIDD) in the setting of undifferentiated macular dystrophy and newly discovered diabetes.

Observations: A 34-year-old woman presented to the retina service with new-onset diabetes and a history of hydroxychloroquine use. Ophthalmologic examination showed findings early in the patient's presentation that within the context of her recent diabetes diagnosis and family history pointed to MIDD as the specific cause of the patient's many different symptoms. This diagnosis was further supported through obtaining previous ophthalmic images of the patient's mother demonstrating circular areas of geographic atrophy seen in advanced MIDD, and the diagnosis was confirmed through genetic testing.

Conclusions and importance: As was observed in the patient discussed in this manuscript, recognition of macular dystrophy findings suggestive of MIDD can hasten a timely diagnosis for a patient with diabetes of unspecified etiology. Additionally, knowledge of the underlying cause being MIDD can optimize care for patients in terms of treatment, understanding their risk for various diabetes complications, screening for additional systemic manifestations, and initiating valuable genetic counseling for patients and their families. Given these factors and the surprisingly high prevalence of MIDD among diabetes patients, increased awareness of MIDD and its manifestations can help to optimize diagnosis and management for these patients.

1. Introduction

The clinical syndrome of Maternally Inherited Diabetes and Deafness (MIDD) is an underdiagnosed cause of diabetes that is now recognized to comprise up to 1% of all cases.[1] This syndrome is caused by a m.3243A > G pathogenic variant in the MT-TL1 mitochondrial gene that impairs oxidative phosphorylation/ATP production.[1] Notably, this pathogenic variant also causes MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) and these two syndromes are thought to exist on a spectrum of phenotypes.[2] One of the most common manifestations of MIDD is a progressive pattern-like macular dystrophy observed in 86% of patients.[3] We report a case of a 34-year-old female patient with newly diagnosed MIDD in the setting of undifferentiated macular dystrophy, progressive hearing loss, and newly discovered diabetes.

1.1. Case report

A 34-year-old female with recently diagnosed diabetes, multiple years progressive hearing loss, hydroxychloroquine use (2 years of 4.6mg/kg/day) for seronegative inflammatory arthritis, fibromyalgia, migraines, and anxiety presented to the retina service for hydroxychloroquine screen and new diabetic eye examination. This patient was diagnosed with diabetes one month prior after presenting to the emergency department with blurred vision and excessive thirst, where she was found to have a blood glucose of 605mg/dl and HbA1c of 13%. At initial presentation the endocrinology service thought that the etiology of the patient's diabetes was Maturity Onset Diabetes of the Young (MODY), a hereditary form of diabetes resulting from mutations in nuclear genes needed for pancreatic islet cell function, due to the patient's significant family history of insulin-dependent diabetes.[4]

At initial ophthalmologic visit, this patient had no prior history of pertinent ocular pathology, outside of high myopia in both eyes (BE). Her initial examination was notable for the following refraction: −9.25 + 2.25 @ 100 right eye (RE)/−9.00 + 2.25 @ 082 left eye (LE). The visual acuity was 20/20 in BE, and the intraocular pressures were within normal limits in BE. Slit lamp examination was largely unremarkable. Retinal examination revealed pigmented deposits in the macula

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(Fig. 1A). Imaging of the posterior pole showed hyperautofluoresence bilaterally in the perifoveal area and hyperreflective deposits at the level of the retinal pigment epithelium (RPE) (Fig. 1B & C).

At presentation, these lesions were thought to be caused by a type of pattern-like dystrophy, although the exact genetic etiology was not obvious. Less likely considerations included myopic degeneration (less likely due to uncharacteristic macular appearance) or lesions secondary to prior inflammatory episodes (less likely due to no previous symptoms suggestive of prior inflammatory episodes, such as photopsia or scotomas). Hydroxychloroquine toxicity was felt to be unlikely due to the patient being on a relatively low-risk dose (<5.0mg/kg/day) and the patient's macular appearance not resembling findings typically seen with hydroxychloroquine toxicity, notable for disruption in the parafoveal ellipsoid zone.[5]

Additional history revealed that the patient's mother had a diagnosis of age-related macular degeneration. On a subsequent visit with the endocrinology service, they elicited further history that the patient had multiple maternal aunts and a maternal female cousin with early-onset hearing loss (around age 30s–40s), in addition to the diabetes diagnoses that were previously known. No family member on the paternal side of the family was affected by these symptoms. Given the finding of macular pattern-like dystrophy and new details about the patient's family history

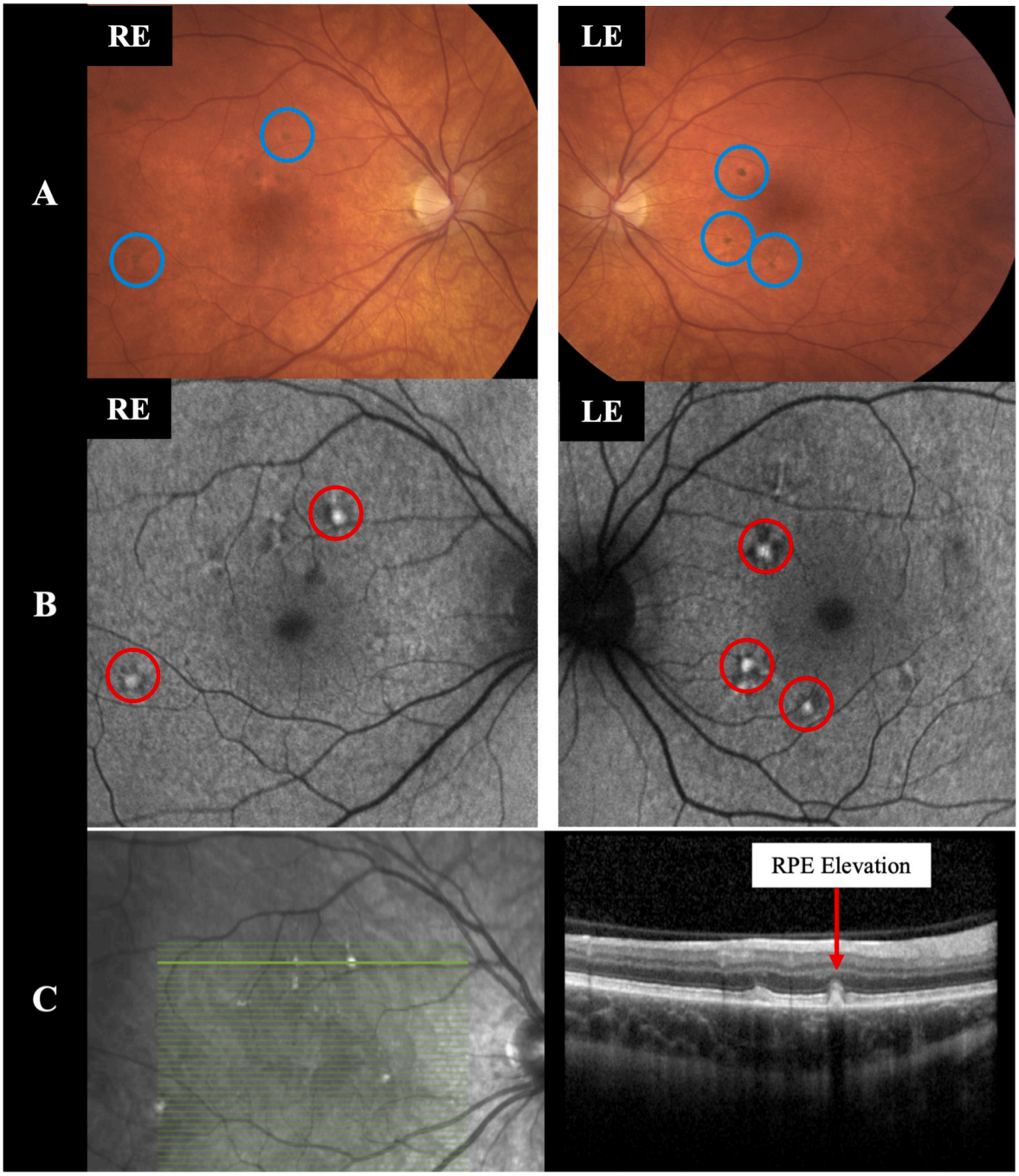

Fig. 1. Posterior pole, autofluorescence (AF), and OCT (Optical Coherence Tomography) imaging at initial presentation demonstrating early retinal changes**:** A) Color fundus photos show small hyperpigmented deposits (circled in blue) in the non-central macula of BE. B) AF reveals multiple hypo/hyperautofluorescent areas (circled in red) perifoveally and C) OCT reveals hyperreflective deposits in the retinal pigment epithelial (RPE) layer of the retina in BE corresponding to the areas of hypo/hyperautofluorescence on AF. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in the setting of the patient's own hearing loss, the patient's presumed diagnosis was changed to MIDD rather than MODY.

At this time genetic testing was not undergone due to lack of insurance coverage. The patient continued to follow with the retina service. One year after her initial presentation to the retina service, her imaging demonstrated notable progression of her maculopathy (Fig. 2). At this time, the patient was able to obtain her mother's posterior pole and autofluorescence imaging from her ophthalmologist that had recently started seeing her given the concern for MIDD (Fig. 3). These images revealed findings that supported a late stage MIDD pattern-like dystrophy including circular areas of geographic atrophy in the non-central macular and peripapillary regions. The patient subsequently obtained insurance coverage and underwent genetic testing. This revealed the presence of a heterozygous (with unknown heteroplasmy percentage) m.3243A > G pathogenic variant in the *MT-TL1* gene – the responsible pathogenic variant for MIDD.

2. Discussion

Mitochondria play an essential role in generating ATP through oxidative phosphorylation.[6] Mitochondria possess their own circular DNA, and alterations in this DNA can cause disease due to disruption of oxidative phosphorylation and the production of energy.[1,6] In contrast to nuclear DNA, mitochondrial DNA inheritance is solely maternal.[6]

MIDD is the result of an A to G base substitution at position 3243 (m.3243A > G) of the mitochondrial DNA in the MT-TL1 gene. This affects the mitochondrial $tRNA^{Leu}$ tertiary structure and promotes abnormal dimerization of the molecule, thus affecting oxidative phosphorylation and ATP production, specifically by causing deficient activity in complexes 1 and 4 of the mitochondrial respiratory chain7,8. Manifestations of MIDD are observed in organs with a high degree of metabolic activity, including the endocrine pancreas, retina, cochlea, muscle, kidney, and brain1. MIDD constitutes up to 1% of patients with diabetes but is often misdiagnosed as Type 1 or Type 2 diabetes.[1] Over 85% of patients with the m.3243A > G pathogenic variant develop diabetes, with a mean age at diabetes diagnosis of 37 years, and most MIDD patients require insulin within 2 years of their diabetes diagnosis.[1,9–11] MIDD patients appear to develop diabetes at an earlier age on average than type 2 diabetes patients, who have an average age of 46 at diabetes diagnosis.[12]

Of note, a high degree of phenotypic variability is observed in MIDD cases, even within the same lineage, which is due in part to the inter-tissue variability in mutant heteroplasmy load.[1,13] Heteroplasmy arises due to each individual cell containing thousands of mitochondria, each of which may contain mutant or wild-type mitochondrial DNA.[13] As such, individual cells (and consequently tissues) have variable proportions of mutant mitochondrial DNA. This characteristic results in variability in the number and severity of phenotypic manifestations, as was seen in one study that identified an association between higher heteroplasmy load and increased severity of MIDD-associated retinopathy.[14] The m.3243A > G pathogenic variant that causes MIDD is also associated with a variety of phenotypes spanning a broad spectrum of disease classifications, including MELAS, Myoclonic Epilepsy associated with Ragged Red Fibers (MERFF), Kearns-Sayre syndrome (KSS), Leigh syndrome, and Progressive External Ophthalmoplegia (PEO).[1,15]

In terms of ocular manifestations of MIDD, the primary feature is a macular dystrophy observed in around 86% of cases.[3] Patients may report visual loss, night blindness, scotoma, or photophobia, but these symptoms do not typically occur until there are severe changes to the RPE.[16,17] De Laat developed a grading system for MIDD macular dystrophy: extrafoveal mottling seen on autofluorescence (grade 1), sub-retinal elevations and areas of RPE/outer retinal loss (grade 2), large confluent areas of outer retinal loss with relative foveal sparing (grade 3), and atrophy affecting the fovea (grade 4).[18] While this formalized grading system exists, the natural history and rate of progression for MIDD-associated retinopathy have not been well characterized.[19] Previous studies have seen mixed results as to whether or not there is a correlation between age and severity of retinopathy, but notably these were comparisons between patients rather than following individual patients longitudinally.[18,20] Previous case reports have provided examples of the rate of decline in visual acuity, reporting on two separate patients losing between one and three Snellenlines of visual acuity over a 15 year period.[19] However, there have not been studies examining the rates of visual acuity decline within a larger and more broadly representative sample of patients. Notably, significant visual acuity loss is not commonly seen until the retinopathy has progressed to include chorioretinal atrophy of the fovea (grade 4).[19] There is currently no effective treatment for MIDD macular dystrophy, but theoretical treatment possibilities have been proposed in the areas of antioxidant therapy or sub-retinal gene therapy.[19]

It is recommended that MIDD patients undergo yearly ophthalmologic examinations, and RPE abnormalities in the setting of other findings suggestive of MIDD should prompt genetic testing for the m.3243A > G pathogenic variant in mitochondrial DNA.[1,15] Recognition of MIDD is important for early initiation of regular screening and examination of MIDD patients. In addition to yearly ophthalmologic examinations, MIDD patients should also undergo yearly neurological and cardiovascular examinations, yearly hearing tests, yearly screening for proteinuria, and possible brain MRI if any central neurological symptoms appear.[1]

Recognition of MIDD being the underlying cause of diabetes is also crucial for optimizing patients' diabetes management. Treatment of diabetes for MIDD patients differs from other types of diabetes, most notably in that metformin should be avoided due to risk of lactic acidosis.[1] There have been reports of previously undiagnosed MIDD patients being prescribed metformin and experiencing seizures.[20]

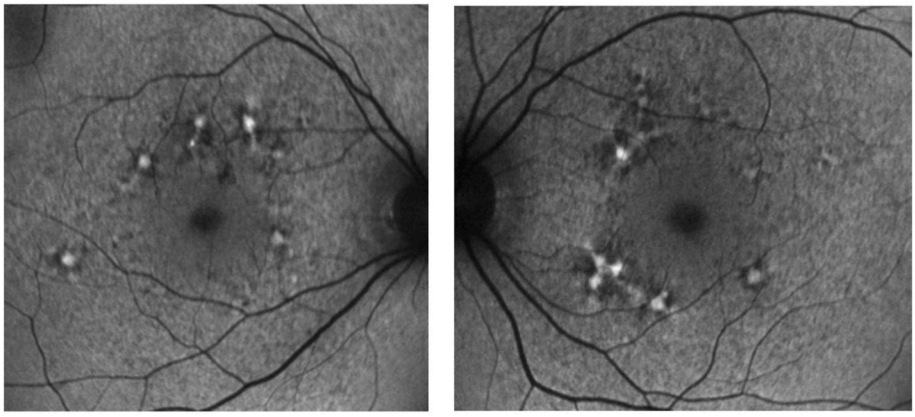

Fig. 2. AF imaging one year after presentation shows expansion of the areas of hypo/hyperautofluorescence corresponding to the deposits in the RPE on OCT.

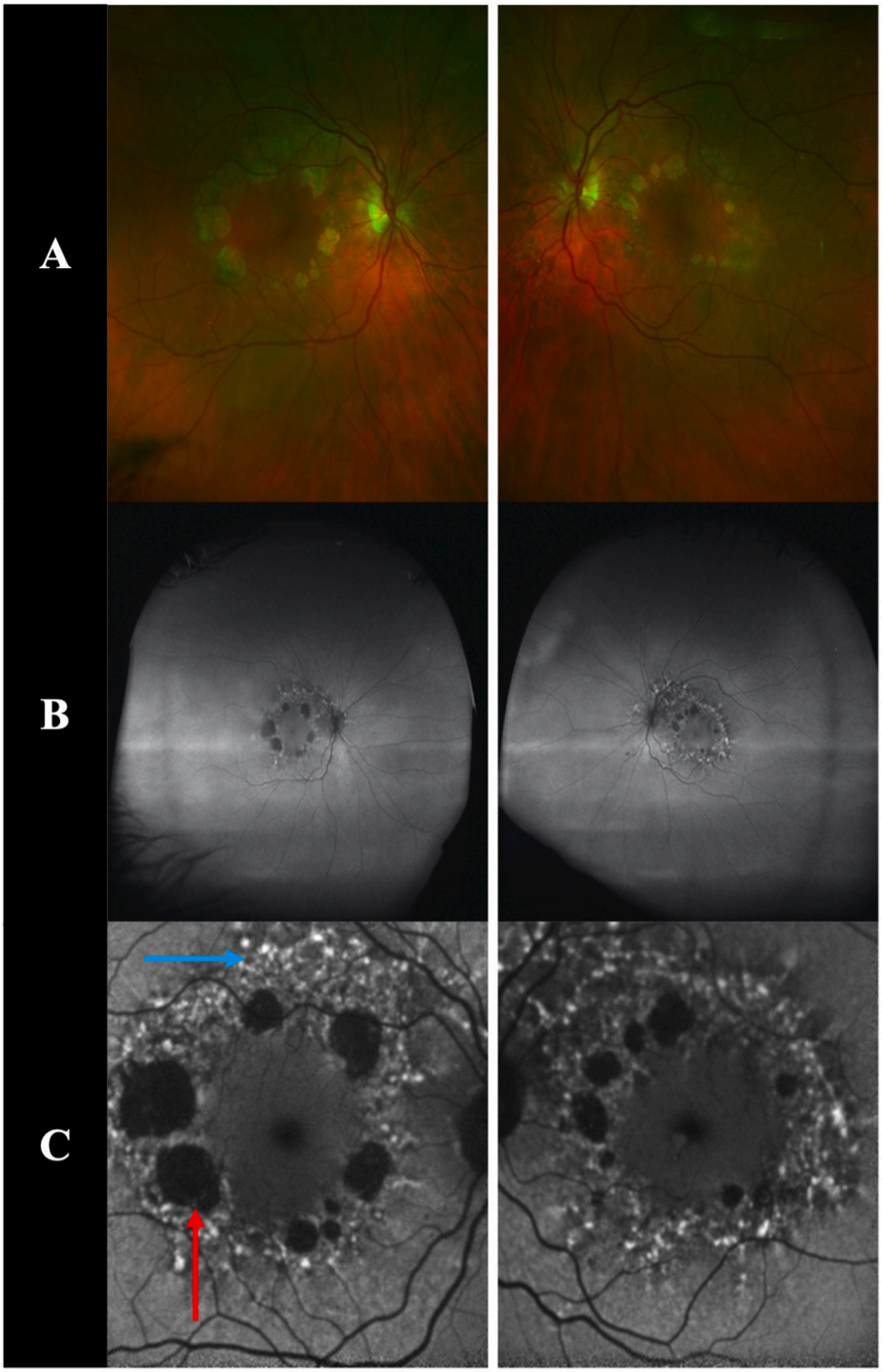

Fig. 3. The mother's fundus photography (A) and Autofluorescence (B and enlarged in C) shows circular areas of geographic atrophy (example shown by red arrow) indicating loss of RPE in the non-central macula of both eyes. The speckled areas (example shown by blue arrow) of hyperautofluorescence (C) in both eyes indicate areas of RPE dysfunction. Courtesy (Nathan Farley, MD). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Instead of metformin, MIDD patients with diabetes should be initiated on a sulfonylurea or insulin1. There are a number of other medications that should be avoided in MIDD patients, including tetracyclines, chloramphenicol, anti-epileptic drugs (valproate, phenytoin, and phenobarbitone), and nucleoside analogue reverse transcriptase inhibitors.[1]

MIDD patients also have different risk levels for various diabetes complications. Interestingly, it has been observed that MIDD patients have a 2.5 times lower incidence of diabetic retinopathy as compared to patients with type 2 diabetes.[21] This is thought to be due to a number of factors including better glycemic control, lower hypertension prevalence, and reductions in retinal metabolism, retinal blood flow, oxygen consumption, and vasoproliferative factors production.[19,21] Previous studies have identified statistically significant correlations between presence of diabetes, higher heteroplasmy levels, and severity of MIDD-associated retinopathy.[14] Knowledge of these relationships can help clinicians be more mindful of how heteroplasmy levels, MIDD-associated retinopathy, and diabetes-related complications are associated.

In the case discussed here, a 34-year-old woman presented to the retina service with new-onset diabetes and a history of hydroxychloroquine use. Ophthalmologic examination showed pigmented macular deposits, bilateral hyperautofluoresence in the perifoveal area, and hyperreflective RPE deposits, which within the context of the

patient's recent diabetes diagnosis and significant family history pointed to MIDD as the specific cause of the patient's many different symptoms. This diagnosis was further supported through obtaining previous ophthalmic images of the patient's mother demonstrating circular areas of geographic atrophy seen in advanced MIDD, and the diagnosis was confirmed through genetic testing. Overall, the clinical trajectory for this patient in arriving at the correct diagnosis underscores our observation that the ocular findings in MIDD can be critical to the diagnosis of the spectrum of these diseases, which are more common than was once thought.

3. Conclusions

MIDD is an underdiagnosed and surprisingly common cause of diabetes and pattern macular dystrophy. MIDD is caused by a pathogenic variant in mitochondrial tRNA that affects translation of proteins necessary for oxidative phosphorylation. It is part of a spectrum of diseases that share the same genotype but have a different phenotype, including MELAS, MERFF, KSS, Leigh syndrome, and forms of PEO. MIDD pattern-like dystrophy has a heterogenous presentation ranging from mild pigmentary changes to geographic atrophy of the macula. As was observed in the patient discussed in this manuscript, recognition of macular dystrophy findings suggestive of MIDD can hasten a timely diagnosis for a patient with diabetes of unspecified etiology. Additionally, knowledge of the underlying cause being MIDD can optimize care for patients in terms of treatment, screening for additional systemic manifestations, and initiating valuable genetic counseling for patients and their families. In the setting of pattern-like dystrophy it is difficult to screen for hydroxychloroquine toxicity, and for patients with MIDD it may be recommended to consider alternative immunosuppressive agents. Given these factors and the surprisingly high prevalence of MIDD among diabetes patients, increased awareness of MIDD and its manifestations can help to optimize diagnosis and management for these patients.

3.1. Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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