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Rapidly progressive central retinal pigmented epithelium atrophy after Ivospemin (SBP-101) treatment for pancreatic adenocarcinoma

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ABSTRACT

Purpose: We report a case of retinal toxicity induced by SBP-101, a polyamine inhibitor for the treatment of metastatic pancreatic adenocarcinoma, presenting as rapidly progressive bilateral central retinal pigmented epithelium (RPE) atrophy in a patient with a silent ocular history.

Observations: A 69-year-old female patient with a metastatic pancreatic adenocarcinoma visited our retina clinic referring a 6-months history of blurred vision and progressive visual field loss. One year before, she started administration of SBP-101 combined with nab-paclitaxel and gemcitabine to treat her malignancy. Baseline ophthalmological examination showed bilateral healthy retina an 20/20 visual acuity (VA). After the second monthly cycle of SBP-101, the patient experienced significant visual loss in both eyes, with VA decreasing to 20/50 in right eye (RE) and to 20/40 in left eye (LE). In the suspect of a cancer associated retinopathy (CAR), the patient underwent bilateral injection of intravitreal slow-releasing dexamethasone, with poor clinical outcomes. Concomitant testing for anti-enolase and anti-recoverin antibodies gave negative results, while electroretinography showed borderline but within the limit values in both eyes. At 6 months, VA was 20/5000 in RE and 20/4000 in LE and the patient referred significant limitations in everyday life. Ultra-wide field fundus photography showed a bilateral, roundish area of irregular pigment loss involving the entire macula and extending beyond the arcades. Ultra-wide autofluorescence showed a central area of hypo-autofluorescence surrounded by a ring of alternating hyper- and hypo-autofluorescence areas. Optical coherence tomography showed bilateral atrophy of the subfoveal RPE and disruption of the ellipsoid zone. Optic disc examination was within the limits. No treatment was possible.

Conclusion and Importance: In conclusion, ophthalmologists should be aware of the existence of a sight-threatening side effect of SPB-101 administration, since we highlighted a massive bilateral RPE atrophy rapidly developing after the second drug injection.

1. Introduction

In several reports, metastatic pancreatic ductal adenocarcinoma (PDAC) was associated with the risk of a Purtscher-like retinopathy, either as a paraneoplastic syndrome or as an adverse effect of chemotherapy with gemcitabine.[1–3]

SBP-101 (Ivospemin), also known as diethyl dihydroxyhomospermine, is a polyamine analogue designed to induce polyamine metabolic inhibition (PMI) with high affinity to PDAC, delivered by subcutaneous injections. Essential for cellular growth, proliferation and survival, polyamine homeostasis is vital to the survival of the cell, being involved in DNA and RNA synthesis. A dysregulated polyamine metabolism, found in several subtypes of cancer cells, is associated with unstoppable proliferation.[4] In order to be effective, polyamine analogues must compete with natural polyamines, causing a negative feedback inhibition: the primary amine group of spermine alkylation, including SBP-101, is one of the major classes of analogues.[4] Although the biochemical structure of spermine analogues is well-characterized, the total effect of SBP-101 on polyamine metabolism and the underlying processes are yet to be identified.[4]

In a Phase 1A/1B trial (NTC03412799), SBP-101 demonstrated a median overall survival (OS) of 14.6 months and an objective response

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rate (ORR) of 48 %, both exceeding the standard of care in metastatic PDAC (gemcitabine + nab-paclitaxel).[5] The ongoing multicenter ASPIRE Phase 2/3 clinical trial (NCT05254171, sponsored by Panbela Therapeutics, Inc.) aims to evaluate the combination of SBP-101 with nab-paclitaxel and gemcitabine in individuals with PDAC.[6]

In the first trial, 8 cases of unspecified retinal toxicity after prolonged treatment have been reported, suggesting that SBP-101 should not be administered in patients with previous retinopathy or retinal detachment history.[5] In this study, we report a case of probable SBP-101 induced retinal toxicity, presenting as rapidly progressive bilateral central retinal pigmented epithelium (RPE) atrophy, in a patient with a silent ocular history.

2. Case description

A 69-year-old female patient with a medical background of a PDAC with peritoneal and hepatic metastasis visited our retina clinic, referring a 6-months history of blurred vision and progressive visual field loss. She had no history of diabetes or arterial hypertension. One year before, she had been included in a clinical trial for the administration of SBP-101 combined with nab-paclitaxel and gemcitabine. At the moment of clinical trial inclusion, ophthalmological examination showed an healthy retina, with normal optic nerve and posterior pole, and normal macular structure at optical coherence tomography (OCT) analysis. Bilateral visual acuity (VA) was 20/20 and intraocular pressure was within the limits.

After the second monthly cycle of SBP-101, the patient experienced significant visual loss in both eyes, with VA decreasing to 20/50 in right eye (RE) and to 20/40 in left eye (LE). Fundus examination showed pigmentary changes in the macular area, corresponding to a punctate hypo- and hyperautofluorescent pattern at blue-autofluorescence (BAF). OCT scan showed the presence of ellipsoid zone (EZ) damage and hyperreflective material between the Bruch membrane and the RPE in both eyes. At this moment, in the suspect of a CAR, the patient suspended SBP-101 treatment and underwent bilateral injection of intravitreal slow-releasing dexamethasone, with poor clinical outcomes.

In fact, after one month, the patient presented with a VA of 20/50 and 20/32 in RE and LE, respectively. Electroretinography (ERG) showed normal scotopic responses, while photopic amplitudes were at the lower limit of normal in both eyes. The patient underwent serum analysis to assess for anti-recoverin and anti-enolase autoantibodies (CORE Lab, SYNLAB, Barcelona, in accordance with the UNE-EN ISO15189 standard), which were reported to be within normal limits, thus making CAR diagnosis unlikely.

A progressive reduction of VA was reported in the following months, leading to a VA of 20/5000 in RE and 20/4000 in LE 6 months after therapy initiation. The patient referred significant limitations in everyday life, photopsias and extremely blurred vision. Ultra-wide field fundus photography showed a bilateral, roundish area of irregular pigment loss involving the entire macula and extending beyond the arcades, associated with sporadic dot-blot hemorrhages along the course of the vessels. In the ultra-widefield BAF, the roundish area seen at fundus photography showed significant autofluorescence changes: the central area was characterized by irregular hypo-autofluorescence,

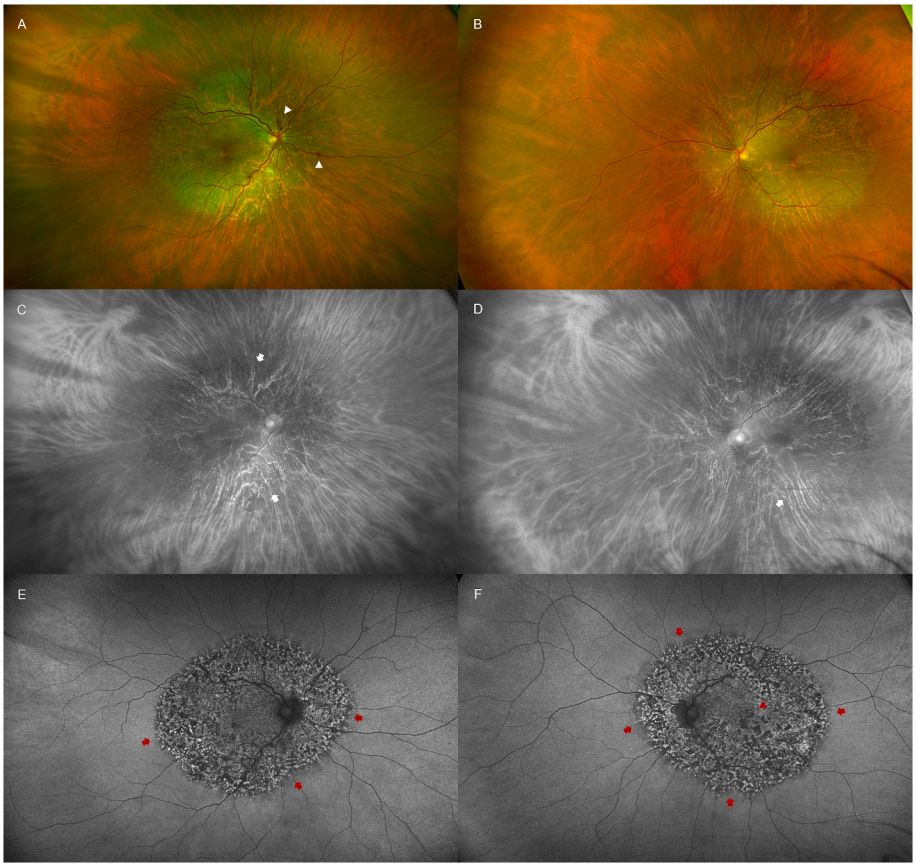

Fig. 1. Optomap ultra-wide color fundus photography (A and B), red separation image (C and D) and blue-autofluorescence (E and F) of both eyes, showing a roundish hypopigmentation lesion involving the entire macular area, extending beyond the arcades. In right eye photography (A), some dot-blot hemorrhages are visible over the course of vessels. (*white arrowheads*) The lesion appear darker in the red channel images (C and D), with sharper visualization of the underlying choroidal vessels. (*white arrows*) Autofluorescence images highlight significant hypo-autofluorescence in the foveal and parafoveal area, with confluent areas of atrophy visible in the left eye (F, *red arrowhead*). Surrounding this area, a ring of irregular hypo- and hyperautofluorescent dots is visible (E and F, *red arrows*) suggesting ongoing damage to the retinal pigmented epithelium (RPE).

surrounded by a ring of alternating hyper- and hypo-autofluorescence areas, suggesting an ongoing sufferance of the EPR in the peripheral zones of the lesions [Fig. 1].

OCT examination showed bilateral incomplete retinal pigment epithelial and outer retinal atrophy (iRORA): atrophy of the subfoveal RPE with signal hypertransmission in the choroid, disruption of the EZ and difficult visualization of the external limiting membrane (ELM). Temporal perifoveal area showed the presence of hyperreflective drusen-like deposits beneath the RPE. Moreover, subfoveal choroidal thickness (CT) was 174 μm in RE and 191 μm in LE. The analysis of the optic disc and retinal nerve fiber layer (RNFL) thickness showed normal values in both eyes [Fig. 2]. Visual field analysis (SITA-Fast) showed a central bilateral relative scotoma and a visual field index (VFI) of 26 % in RE and 31 % in LE. Finally, ERG examination, performed following the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol,[7] showed preserved responses at the dark-adapted (DA) 0.01 cd-s-m2 and at the mixed 3.0 cd-s-m2 rod-cone response. Conversely, light adapted (LA) 3.0 cd-s-m2 single flash showed a relatively preserved a-wave, while 30Hz flicker amplitudes were reduced with slightly prolonged a-wave implicit times, indicating a localized loss of function [Fig. 3].

Due to the lack of current treatment for this condition, the patient was referred to the low-vision center to receive magnifying lenses.

3. Discussion

The retinopathy and neuropathy resulting from chemotherapy-induced ocular toxicity is often bilateral and permanent.[8] In this report, we described a case of rapidly progressive RPE atrophy which developed within a few months after treatment of a metastatic PDAC with SBP-101 combined with Nab-Paclitaxel and Gemcitabine, and detrimentally affected visual function, leading to the inability to continue normal daily activities 6 months after treatment initiation.

Previously, other chemotherapeutics employed in the treatment of PDAC have been associated with ocular side effects. Cisplatin showed significant retinal toxicity, leading to bilateral central scotomas. According to Katz et al. cisplatin induces a dose-dependent damage photoreceptor cells, presenting in the form of cone malfunction, macular pigmentary changes and minor retinal ischemia changes (such as hemorrhages and cotton-wool patches), which are important components of Purtscher-like retinopathy.[9] Similarly, Kwan et al. showed that cisplatin may result in neovascularization and ischemic retinopathy, most likely due to a vaso-occlusive mechanism.[10] Similar to cisplatin, gemcitabine, despite being a well-tolerated medication, showed several possible adverse effects, including vascular toxicity and bilateral vision loss from Purtscher-like retinopathy, which seemed to be associated with a clinical history of diabetes and hypertension.[11]

Finally, nab-paclitaxel, an anti-microtubule agent mostly used in the treatment schemes of PDAC, has been recently linked to the risk of severe ischemic retinopathy and refractory cystoid macular edema.[12,13] The microtubule disassembly prevention induced paclitaxel may interfere with microtubule-dependent RPE processes, leading to macular fluid accumulation.[12] Nevertheless, in our case, no ophthalmoscopic signs of Purtscher-like retinopathy, nor cystoid macular edema were reported, even if the presence of dot-blot hemorrhages could suggest the presence of vascular wall impairment.

In this case, further differential diagnosis could be CAR, which was primarily linked to small-cell lung carcinoma, colonic tumors, and gynecological tumors. In the initial phases, CAR shows a normal fundus examination, but successively retinal atrophy, vascular narrowing, or

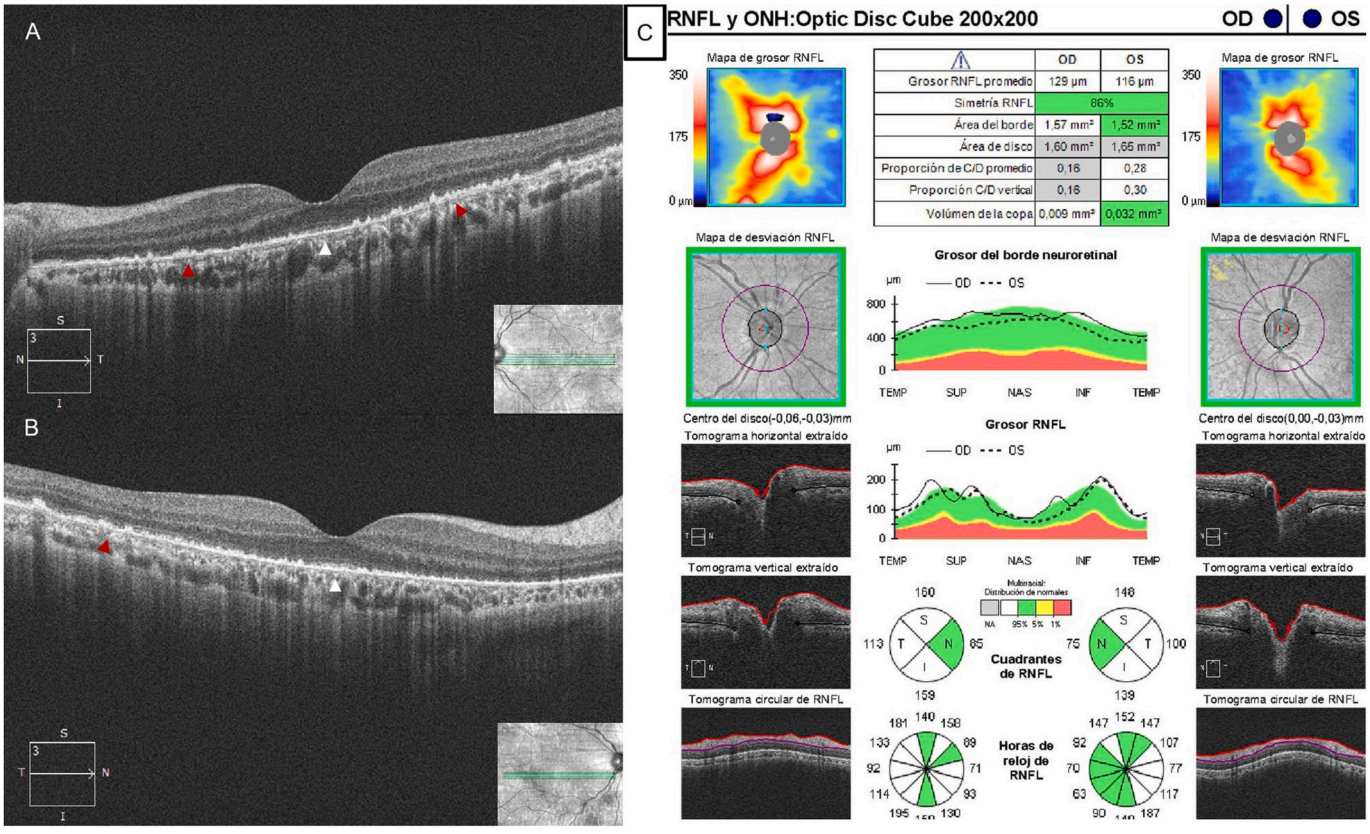

Fig. 2. Optical coherence tomography of the macular area of both eyes (A and B), showing atrophy of the retinal pigmented epithelium (RPE) in the foveal and parafoveal area (*red arrowheads*), with disrupted ellipsoid zone (EZ) and signal hypertransmission to the choroid, which appear thinned. In the perifoveal area, hyperreflective drusen-like deposits are visible beneath the RPE (*white arrowheads*). Optic disc and retinal nerve fiber layer (RNFL) analysis (C) showed normal values in both eyes.

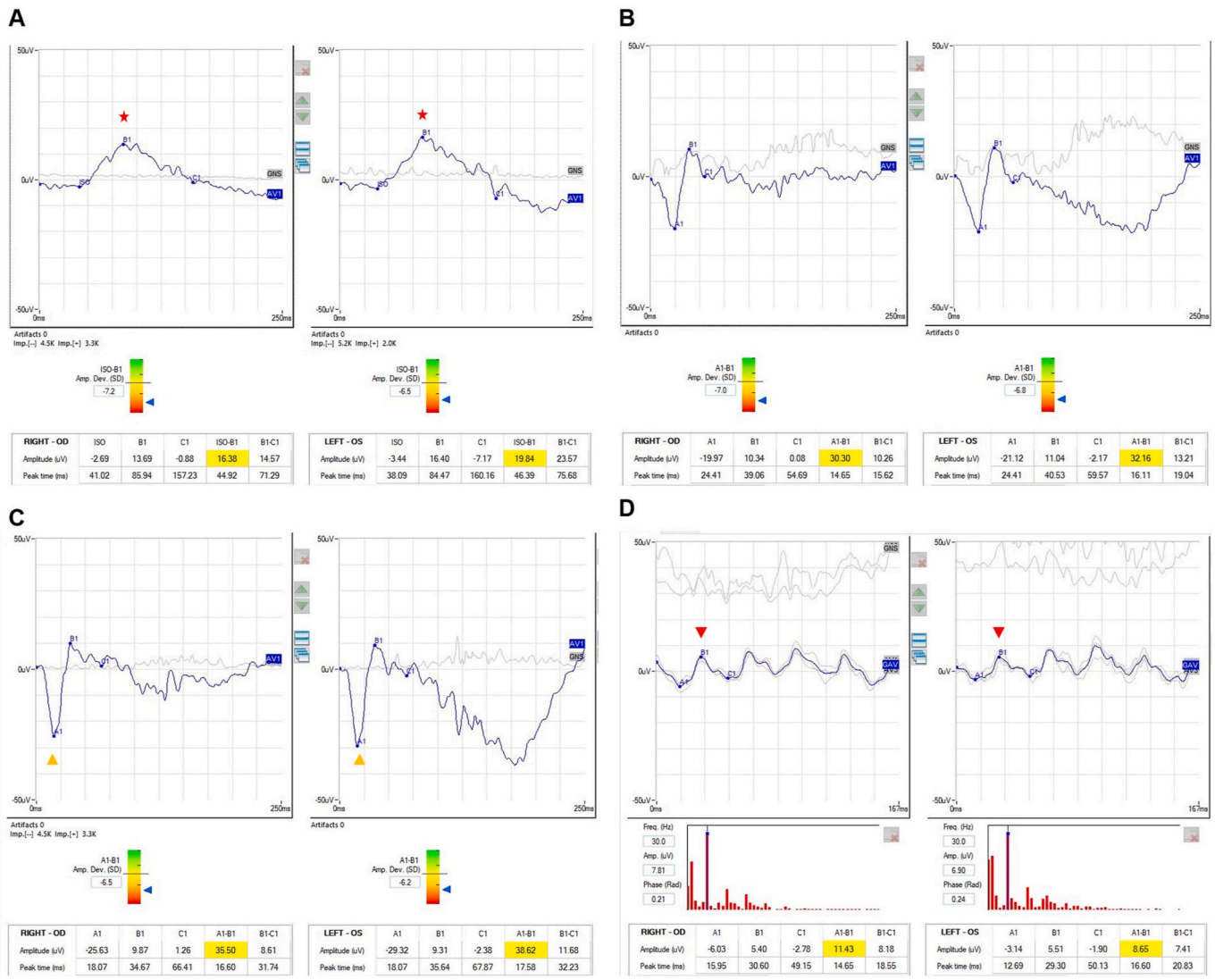

Fig. 3. Full-field electroretinograms of both eyes performed following ISCEV standard. A) Dark-adapted (DA) 0.01 cd-s-m2 response were preserved (*red stars*), as well as B) DA 3.0 cd-s-m2 (mixed rod–cone response). Conversely, while C) light adapted (LA) 3.0 cd-s-m2 photopic single flash showed relatively preserved a-waves (*orange arrowheads*), the D) LA 30Hz flicker showed reduced amplitudes (*red arrowheads*) and slightly prolonged a-wave implicit times, indicating a restricted loss of function.

advanced optic nerve paleness may appear.[14] However, none of these ophthalmoscopic findings were consistent with our case.

Moreover, the diagnosis of CAR relies heavily on ERG, which detects aberrant retinograms during both light and dark adaptations, while our patient showed scotopic responses within the limits during the follow-up, while photopic amplitudes and implicit times were initially sub-normal but significantly impaired at the last visit, suggesting progressive photoreceptor damage in the area of RPE atrophy. Finally, CAR has been associated with several circulating AAbs directed with tumor antigens which cross-react with retinal tissue, such as α-enolase, transducing, carbonic anhydrase, and recoverin.[15] In this report, serum test revealed values of anti-enolase and anti-recoverin within the limits, thus increasing the suspicion of a SPB-101 induced retinal toxicity.

Even though retinal toxicity was already highlighted in the Phase 1A/1B trial, it was referred to be limited to patients with previous retinopathy or a history of retinal detachment.[5] In our case, we highlighted a massive bilateral RPE atrophy rapidly developing in a patient with a previous healthy retina, and apparently progressing following a centrifugal pattern starting from the macular area. Since previous reports demonstrated that polyamines are essential for the proliferation of cultured bovine RPE cells,[16] we hypothesized that the SBP-101 induced blockage of polyamine metabolism may affect DNA synthesis in these cells and determine progressive cellular death. These mechanism may lead to progressive atrophy of the RPE, principally affecting those areas with higher metabolic demands, such as the posterior pole.

We suggest that ophthalmologists should be aware of the possible existence of retinal toxicity associated with SBP-101 treatment even in cases without ocular disorders history. Moreover, patients should promptly refer any symptoms to their oncologists for rapid referral to the ophthalmologist and consideration of medication stopping.

4. Conclusion

In conclusion, we presented a case report giving light to a sight-threatening complication of Ivospemin (SBP-101) administration in metastatic PDAC management. In fact, this polyamine inhibitor may induce a rapidly progressive RPE atrophy involving the entire posterior pole, already manifesting after the second subcutaneous injection in a patient with a silent ophthalmological history.

CRediT authorship contribution statement

Matteo Mario Carlà: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos Mateo:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Patient consent

We ensure that a statement of consent to publish these findings and images was gathered from the patient.

Authorship

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

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Declaration of competing interest

The authors declare no conflict of interests.

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