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CASE REPORT

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Good response to pulsed dye laser in patients with capillary malformation-arteriovenous malformation syndrome (CM-AVM)

Helena Iznardo MD[1] | Esther Roé MD[1] | Luis Puig MD, PhD[1] | Mikka Vikula MD, PhD[2] | Cristina López-Sánchez MD[1] | Eulalia Baselga MD, PhD[3]

[1]Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma, Barcelona, Spain

[2]Human Molecular Genetics, de Duve Institute, University of Louvain, Brussels, Belgium

[3]Department of Dermatology, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

Correspondence
Helena Iznardo, MD, Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Mas Casanovas 90, Barcelona 08041, Spain.
Email: hiznardo@santpau.cat

Abstract

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant disorder caused by heterozygous mutations in *RASA1* and *EPHB4*. Capillary stains in CM-AVM are compatible with Schöbinger's phase I AVMs. Vascular laser has been classically contraindicated for the treatment of AVMs, as there is a fear of accelerating their progression. In this study, we have treated capillary stains in five CM-AVM patients with pulsed dye laser, with improvement and without worsening or recurrence of the lesions after 1 year of clinical and ultrasound follow-up.

KEYWORDS

arteriovenous malformation, capillary malformation-arteriovenous malformation syndrome, capillary malformations, pulsed dye laser

1 | INTRODUCTION

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant disorder caused by heterozygous mutations in *RASA1*[1-3] and *EPHB4*.[4] The estimated incidence is about 1/10.000 in northern Europeans, although its true prevalence remains unknown, and it is probably underdiagnosed.[5] Up to a third of patients have associated fast-flow lesions such as arteriovenous malformations (AVM) and arteriovenous fistulae (AVF) that can be cutaneous, subcutaneous, intramuscular, intraosseus, intracerebral, or intraspinal. Visceral AVMs can be life-threatening, emphasizing the need for early diagnosis.

The clinical picture of CM-AVM is characterized by multiple typical appearing capillary malformations (CMs)—small, round to oval in shape, and pink-to-red patches with a peripheral white halo and random distribution—which have been named "rhodoid nevi" by Happle.[6] Multiple pinpoint telangiectasias with a white halo (Bier spots) can be seen in some patients, especially those with mutations in *EPHB4*.[4,7] This white halo together with the identification of arterial flow with Doppler ultrasound points to a steal phenomenon and suggests that these lesions are actually early or small AVMs. In this study, we sought to evaluate the response of CM in CM-AVM to pulsed dye laser (PDL), which, to our knowledge, has never been reported.

2 | MATERIAL AND METHODS

This was a retrospective study of five patients with a diagnosis of CM-AVM treated with PDL between February 2015 and December 2018 at a tertiary referral dermatology department in Barcelona, Spain. The institutional review board waived this study for review. Genetic testing and family histories were performed. Imaging techniques included cerebral and spinal magnetic resonance in all patients and cutaneous ultrasound of CMs (Esaote MyLab gamma and Esaote Mylab C) in three patients. The ultrasound was performed with a 22 mHz linear probe. The depth explored was 1.5 cm, and the PRF of Doppler mode was between 720 Hz and 1.2 kHz. Treatment of the larger and aesthetically more disfiguring lesions with the 595-nm PDL Cynergy Multiplex system (Cynosure Inc) was performed under sedation for younger patients; topical anesthesia with procaine and lidocaine was administered to older patients who required it. The procedure consisted of the application of PDL every 6 weeks using the following parameters: 7-7.5 J/cm^2 radiant exposures, 0.5 ms pulse duration, and 10 mm spot size, with a single pulse stamped technique and without overlapping. Clinical end point was moderate purpura without frosting. A continuous flow of cold air was applied during treatment (SmartCool®; Cynosure Inc).

Digital images were obtained before and after each treatment session using the Canon PowerShot G7 Mark II with fixed settings. Two dermatologists not involved in the study evaluated responses to treatment according to improvement in color: 5 (75%-100%, excellent), 4 (50%-75%, good), 3 (25%-50%, moderate), 2 (1%-25%, poor), and 1 (0%, none). All patients have been followed up until the time of writing.

3 | RESULTS

Four girls and one boy with CM-AVM, aged 5 to 19 years, were treated with PDL (Table 1). All of them had multiple rhodoid nevi with one dominant, larger lesion. Three of the patients had multiple pinpoint telangiectasias. Genetic studies performed at de Duve Institute demonstrated germline mutations in *RASA1* (2/5) or *EPHB4* (3/5). None of the patients had CNS fast-flow lesions. All had a family history of CM-AVM. The older brother of one of the patients (subject 4) died due to intracranial hemorrhage arising from an AVM.

Ultrasound imaging of CMs (treated and non-treated) in three patients (3 and 4, *RASA1*; 5, *EPHB4*) showed heteroechoic lesions within the dermis and subcutaneous tissue, with hypoechoic channels. Doppler analysis showed increased vascular flow with arterial waveforms in all the non-treated lesions. Treated lesions showed persistence of deeper vessels with a decreased density of vessels in the upper layers.

All patients were treated with 595-nm PDL. Laser sessions were repeated every 6-8 weeks until a clinically satisfactory result was obtained. Good responses were obtained after 3-6 sessions (excellent in 4/5 and moderate in 1/5) (Figures 1 and 2). Treatment was well tolerated by all. Adverse events included pain during the procedure in all patients. Crusting and blistering with residual hypopigmentation occurred in two patients (subjects 1 and 3). All patients are currently being followed up, with no evidence progression of the treated lesions after 8-36 months.

TABLE 1 Patient characteristics

	Gender, age	Genetic study	Neuroimaging	High frequency ultrasound	Parameters Spot (mm); Fluency (J/cm^2); Pulse duration (ms)	Number of sessions	Response
1	F, 15 yo	*EPHB4*	No lesion	Not performed	10; 7.5; 0.5	3	3
2	F, 15 yo	*EPHB4*	No lesion	Not performed	10; 7-7.5; 0.5	4	5
3	M, 5 yo	*RASA1*	No lesion	Yes (arterial waveforms)	10; 7.5; 0.5	8	5
4	F, 13 yo	*RASA1*	No lesion	Yes (arterial waveforms)	10; 7.5-9; 0.5	4	5
5	F, 19 yo	*EPHB4*	No lesion	Yes (arterial waveforms)	10; 7; 0.5	3	5

Note: Response was evaluated according to improvement in color: 5 (75%-100%, excellent), 4 (50%-75%, good), 3 (25%-50%, moderate), 2 (1%-25%, poor), and 1 (0%, none).

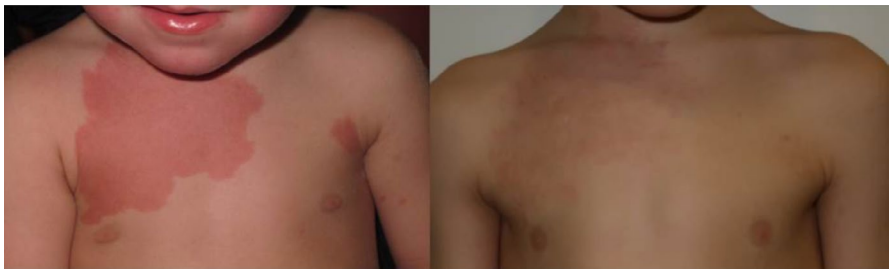

FIGURE 1 Good response after PDL treatment. Patient 3 shows an excellent response after 8 PDL sessions

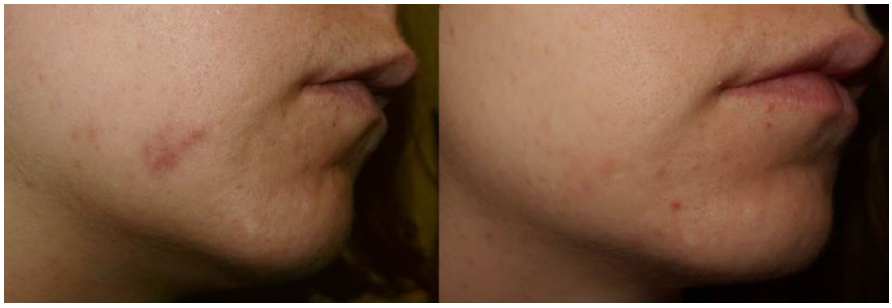

FIGURE 2 Good response after PDL treatment. Patient 5 shows an excellent response after 3 PDL sessions

4 | DISCUSSION

Capillary malformation-arteriovenous malformation syndrome is an underdiagnosed disorder that requires early recognition to avoid life-threatening complications. Therefore, most studies have focused on management of fast-flow lesions, with no mention to the treatment of rhodoid nevi. Even though they are usually small in size, they tend to be multiple and often there are one or two larger dominant patches that can cause aesthetic concerns.

Pulsed dye laser, the standard treatment for CMs, allows selective photothermolysis of vessels by means of its target chromophore, hemoglobin. AVMs are fast-flow lesions composed of an artery and a vein without a capillary network. Their evolution is classified according to the Schöbinger stages (phase I—quiescent; phase II—expansion; phase III—destruction; phase IV—decompensating). Rhodoid nevus features are compatible with Schöbinger's phase I AVMs, namely pink macules with arteriovenous shunts detected by Doppler ultrasound. Furthermore, AVM development on a CM has also been described: In a recent study of 31 patients with nodular lesions that appeared on CMs, AVMs were identified in 32.3% and a combination of pyogenic granuloma and AVM in 16%.[7]

The use of vascular laser for fast-flow lesions has been classically contraindicated as there is a fear of accelerating the progression of the AVM, especially if residual vessels are left untreated. However, there are recent reports of good response to laser treatment in selected patients with Schöbinger stage I AVMs.[8,9] Both Nd:YAG laser alone and a combination of PDL at 595 nm with Nd-YAG at 1064 nm (Multiplex system, Cynosure Inc) have been used with up to 90% response rates and no recurrence in acquired digital AVMs.[9] To our knowledge, PDL monotherapy has not been previously reported. Lapresta and co-workers suggested that this superficial laser cannot treat the deepest part of the lesion and would not prevent the possible progression of the malformation.[10] In the case of rhodoid nevus, the results of our study suggest otherwise, as we did not observe precipitation to Schöbinger stage II. This may be due to the fact that rhodoid nevi may represent a *forme fustre* of AVMs, as progression to full AVMs has not been described. Our patients were closely monitored, and ultrasound imaging with Doppler studies was performed to identify possible residual vessels. Even though we only found a decreased density of vessels in the upper dermis, we have not observed progression or recurrences after at least 8 months of follow-up.

In conclusion, this is the first study on treatment of rhodoid nevi in patients with CM-AVM. Treated lesions improved and did not recur after 8-36 months of follow-up. These good results support the use of PDL for treatment of CMs in CM-AVM for aesthetic reasons. The limitations of our study include its retrospective nature, the small number of patients, and the lack of Doppler examination in some patients. Further studies are needed to confirm that treatment of capillary stains in patients with CM-AVM is both safe and effective.

ORCID

Helena Iznardo https://orcid.org/0000-0002-0710-5521

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