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PROGNOSIS OF HYPERREFLECTIVE FOCI (DOTS) ON OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH DIABETIC MACULAR EDEMA: ABOUT 30 CASES

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INTRODUCTION

Diabetic macular edema (DME) is a thickening of the macular retina secondary to a rupture of the internal blood-retinal barrier. It is the leading cause of low vision in diabetic patients.[1] The functional prognosis depends on several anatomical factors. The spectral domain optical coherence tomography (SD-OCT) is an important tool for the diagnosis, therapeutic indication and monitoring of diabetic macular edema.

The aim of our study is firstly to assess the correlation between the number of intra-retinal hyper-reflective points (DOTS or FOCI) and the central thickness of the retina (CRT) and secondly to study the dynamics of DOTS during treatment by anti-VEGF.

PATIENTS AND METHODS

We reviewed the medical files of patients with DME who were treated with intravitreal injections of bevacizumab at the department of Ophthalmology of the Cheikh Khalifa Ibn Zaid University Hospital in Casablanca, between January 2018 and December 2019.

All patients were followed for diabetic macular edema confirmed by follow-up OCT b scan and treated with IVT of Bevacizumab according to the Trait and Extend protocol.

The inclusion criteria are
- diabetic macular edema
- Treatment of 3 injections of anti-VEGF (Bevacizumab at a dose of 1.25 mg / IVT) with 4 week intervals
- Baseline and monitoring data available over 3 months.

The exclusion criteria are
- Previous treatment with focal laser or PPR
- Tractional retinal detachment or intravitreal hemorrhage
- Presence of other vascular pathologies (eg: OVR)

The Variables studied before and after treatment are
- Corrected visual acuity
- Central retinal thickness (CRT)
- Number of intra-retinal hyper-reflective points (DOTS) and their distribution in the retinal layers

The statistical study was carried out with SPSS version 20 software.

RESULTS

The average age was 61, with extremes ranging from 55 to 76. The sex ratio was 1.3 (17 men and 13 women). The average duration of diabetes was 8 years.

The number of DOTS before treatment was 20.86 +/- 7.41 and after treatment 11. 85+/- 6 ,76.

2/3 of DOTS (68.33%) were located in the inner retinal layers. Their number significantly decreased after treatment at the level of the internal layers, going from 14.24 ± 5.01 to 8.86 ± 4.66 after treatment ($p < 0.001$) .

1/3 of DOTS (31.67%) were located in the outer retinal layers, their number significantly decreased after treatment in the outer layers from 6.6 ± 3.28 to 3.05 ± 2.10 after treatment ($p < 0.001$).Central retinal thickness (CRT) increased from 461.91 ± 82.22 µm to 348.39 ± 73.44 µm after treatment ($p < 0.001$). (table 1)

There is a significant correlation between the number of DOTS and the ECM. The correlation factor is 0.456 ($p < 0.001$) (figure 1)

The corrected visual acuity improved significantly after treatment, it went from 0.3 +/- 0.14 to 0.4 +/- 0.13 ($p < 0.001$) (table 1).

Table 1: Differences between before and after treatment with anti-VEGF : Mean changes in central retinal thickness, visual acuity and number of hyperreflective foci at baseline and after 3 injections with anti-VEGF.

	Before treatment with anti-VEGF	After treatment with anti-VEGF
Number of DOTS	20,86 +/-7,41	11,85+/- 6 ,76
Number of DOTS in inner layers	14,24±5,01	8,86±4,66
Number of DOTS in outer layers	6,6±3,28	3,05 ±2,10
Central Retinal Thickness (CRT)	461,91 ±82.22 µm	348,39 ±73.44 µm
Corrected visual acuity	0.3 +/- 0.14	0.4+/- 0.13

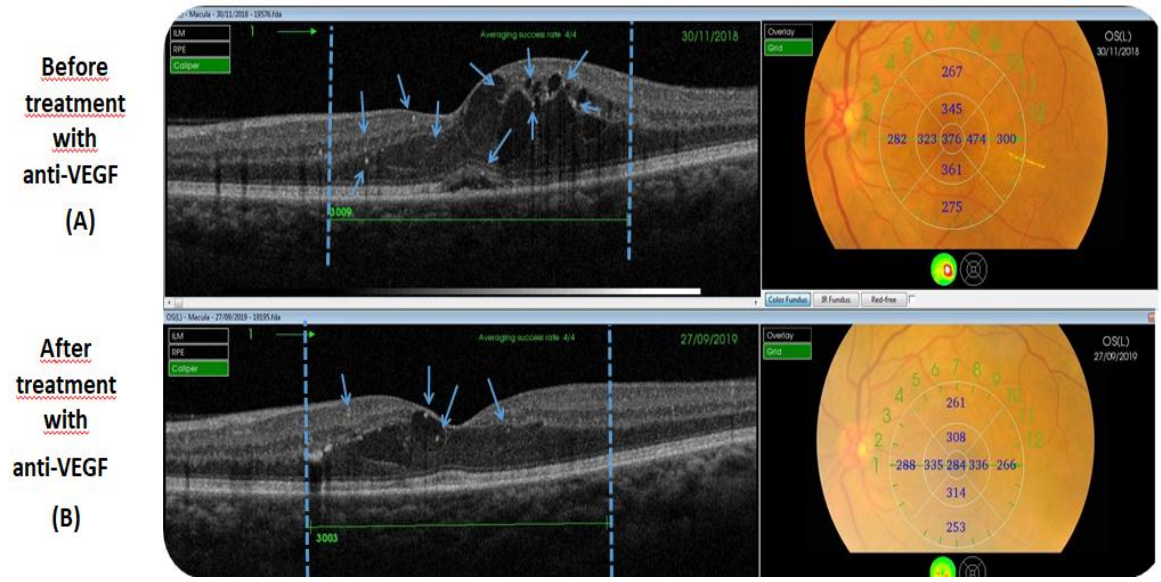

Figure 2: OCT B scan before (A) and after 3 months of IVT treatment of Bevacizumab centered on the fovea (B) showing the presence of DOTS in the central 3000 µm around the fovea.

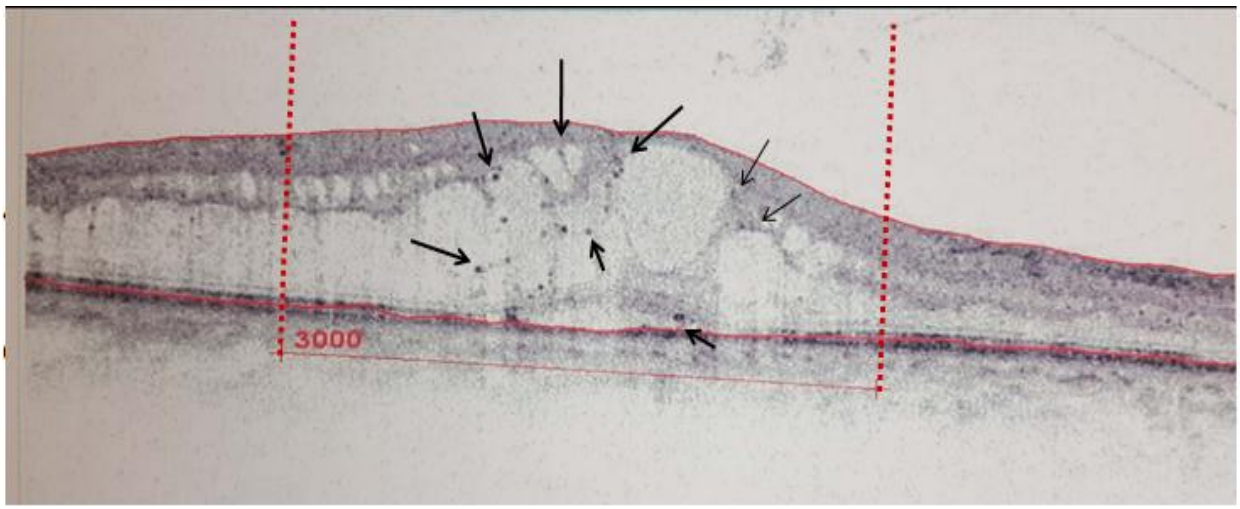

Figure 3: Foveal centered spectral domain optical coherence tomography (SD-OCT) B-scan image of a patient with DME. Black arrows indicate hyperreflective foci, within 3000 µm of the fovea (dashed bars).

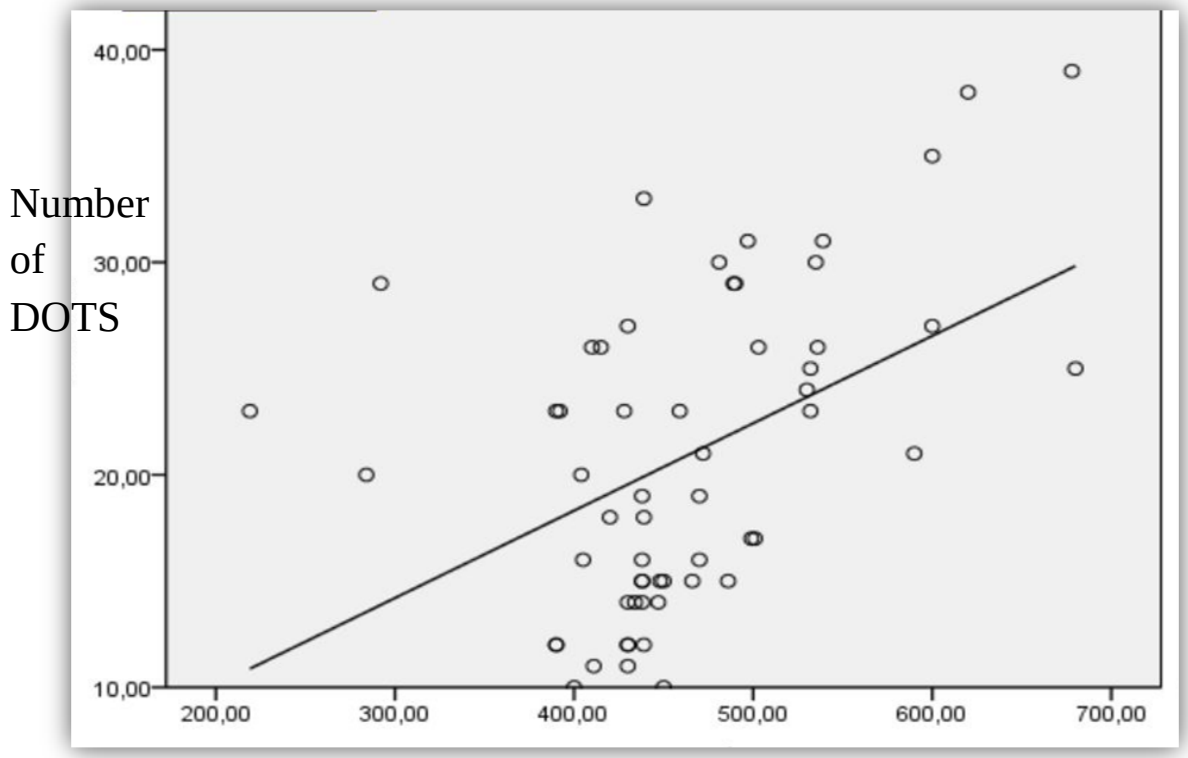

FIGURE 1: Table showing a significant correlation between the number of DOTS and the ECM. The correlation factor is 0.456.

DISCUSSION

Hyper-Reflective Points (DOTS) are small, dense, well-circumscribed round or oval particles less than 100 µm in size.[2] Their reflectivity to OCT is higher than that of pigment epithelium. They can be present throughout the retinal thickness, in the walls of intra-retinal cubicles and at the edge of a serous retinal detachment.[3]

They are seen in diabetic retinopathy, AMD; OVRs; central serous chorioretinitis; retinal dystrophies and retinal detachment.[4]

Many authors have speculated on the pathophysiology and origin of hyper-reflective points. They can be either precursor of exudates, or secondary to a migration of the cells of the pigment epithelium, or correspond to degenerated Müller cells or else to the aggregation of activated immune cells such as microgliocytes.[5]

Several studies[6] have reported the predominance of hyper-reflective points (DOTS) at the level of the inner layers of the retina (80%) compared to the outer layers. This result matches that of our study with a percentage of 68.33 percent at the level of the internal layers and 31.67 percent at the level of the external layers.

Hwang et al. Have[7] studied dots whose reflectivity is equal to that of EP, while we have used a reflectivity higher than the surrounding tissue, which, in our experience, results in a more reliable detection of DOTS. In addition, proliferative diabetic retinopathy is associated with an exuberant increase and activation of microglia, and we therefore hypothesize that neovascularization could influence the number of HF.[8] For this reason, we excluded patients with neovascularization.

In addition, different treatment response criteria were used by different study groups: Kang et al.[9] chose a definition of response to treatment of CRT <300 µm or a reduction of more than 50 µm, while Vujosevic et al. defined it by the continuous variables: improvement in VA and reduction in CRT, respectively.[10, 11, 12, 13] As in the case of our study, we have an average decrease in ECM of 113 µm after treatment with IVT of bevacizumab Hwang et al. Recently reported that a decrease in the number of FOCI was associated with a good ECM response after 3 months of treatment with bevacizumab.[14] The reason for this link is not clear, although there are substantial differences in the design of the study.

Our work shows that DOTS responds decrease after treatment to anti-VEGF (figure 2) and reside mainly in the inner layers of the retina, which is consistent with the behavior of microglial cells.[15] In addition, the decrease in the number of DOTS after 3 months of bevacizumab mainly concerned the inner retinal layers, which supports the hypothesis that DOTS in these layers corresponds to

activated microglia, and that DOTS in the outer retinal layers. may represent a different entity.[16, 17]

The hypothesis that DOTS are precursors of hard exudates is all the more possible given the equal reflectivity on OCT but also their situation in general at the level of the outer plexiform layer. Unlike microglial cells, which are not subject to rapid regression after only 3 months of treatment, although these dynamics are unknown for hard exudate precursors.[18, 19]

CONCLUSION

In DME, Intra-retinal hyper-reflective DOTS are sensitive to anti-VEGF treatment. Their initial number correlates with the response to anti-VEGF treatment in terms of reduction of central retinal thickness and improvement of visual acuity. Therefore, they are a good predictor of the evolution of diabetic macular edema Further studies are needed to analyze the evolution of DOTS in the retinal periphery.

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