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Nodular Regenerative Hyperplasia and sinusoidal hepatic lesions in oxaliplatin based chemotherapy

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Abstract

Introduction Nodular Regenerative Hyperplasia (NRH), Sinusoidal Obstruction Syndrome (SOS) and Sinusoidal Dilatation (SD) are the most recognized patterns of drug-induced liver injury secondary to oxaliplatin based regimens in colorectal liver metastases (CRLM). The use of different combinations in chemotherapy treatments, an incidence reported for NRH that ranges between 4.8% and 15%, and a considerable variability for other vascular lesions, makes the evaluation a challenge.

Study Design A historic prospective maintained database cohort of 160 tissue samples of CRLM.

Methods The aim of this study is to evaluate the incidence of vascular hepatic lesions (SD, SOS and NRH) due to oxaliplatin based regimens. Additionally, it details a series of seven cases of NHR, its relationship with other vascular alterations, type of treatment and the presence or not of blue liver syndrome.

Results Univariate analysis showed association between preoperative use of oxaliplatin with or without biological agents and developing SD ($p<0.05$). Notably, the use of 5-FU was also found to increase the risk of SD. Multivariate analysis confirmed the association between oxaliplatin and developing SD ($p=0.021$). All seven cases of NRH (incidence of 6%) were treated with FOLFOX regimen with at least 6 cycles. These cases presented severe SD and diagnosis of SOS and represented 31.8% of all patients with SOS.

Conclusions Oxaliplatin based chemotherapies regimens are associated with SD, SOS, NRH and blue liver syndrome. These vascular alterations seem to be part of an evolutionary process. The role of 5-FU although not extensively studied, could act as a synergic factor.

Keywords Nodular Regenerative Hyperplasia, Sinusoidal Obstruction Syndrome, Sinusoidal Dilatation, Colorectal liver metastasis, oxaliplatin

Introduction

Surgical resection remains the only treatment with a curative potential for patients suffering from colorectal liver metastasis (CRLM). Preoperative chemotherapy with or without biological agents has proven beneficial for tumour downsizing, shrinking and recurrence and has allowed surgical unresectable lesions to become resectable [1, 2]. Moreover, it has been reported a longer progression free survival and overall survival [3, 4]. Preoperative chemotherapy and biological agents are also recommended for patients with resectable metastatic lesions, since it reduces relapse rate and increases the negative margin (R0) resection preserving mores liver remnant [1, 5].

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Table (1) –Clinical and Treatment Characteristics

	N (%)
Age [yr]*	64 [9.9]
Gender	
Female	44 (29.7)
Male	104 (70.3)
Primary Localization	
Colon	94 (63.5)
Rectum	54 (36.5)
Type of Metastasis	
Synchronous	91 (61.5)
Metachronous	57 (38.5)
Chemotherapy	
Oxaliplatin based	99 (67.8)
5-Fluorouracil	88 (59.5)
Capecitabine	21 (14.4)
Irinotecan	17 (11.5)
Biological agent	
Bevacizumab	39 (26.4)
Cetuximab	23 (15.5)
No treatment	32 (21.6)

** Values are mean.*

The addition of oxaliplatin, irinotecan and capecitabine to the classic chemotherapy regimens based on 5-fluorouracil (5-FU) remain the most recommended preoperative treatments in different combinations for CRLM [6, 7]. However, a negative effect of the addition of these drugs as histopathological liver lesions has been studied by de Leve et al. and Rubbia-Brandt et al. These studies focus on the repercussion on the remaining hepatic parenchyma by evaluating the integrity of the sinusoidal wall and its relationship with treatment [8, 9].

In this context, Vauthey ET. Al. described these effects as steatosis, steatohepatitis and sinusoidal injury [10]. The most important vascular lesions described within chemotherapy regimens based on oxaliplatin are Sinusoidal Dilatation (SD), the presence of perisinusoidal fibrosis in the Sinusoidal Obstruction Syndrome (SOS) and Nodular Regenerative Hyperplasia (NRH) [11–13]. Finally, the blue liver syndrome has been described as a macroscopic expression of advanced vascular lesions [14].

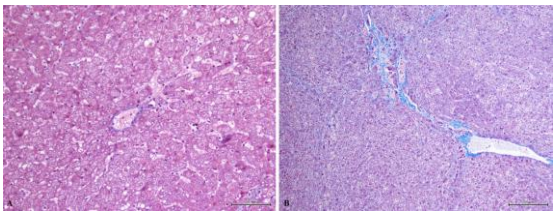

Figure 1. Masson trichrome a)Centrilobular sinusoidal dilatation X200 b)Endothelial sinusoids disruption, hepatocellular atrophy and perisinusoidal fibrosis (SOS) X200

The incidence of SD, SOS and NRH varies greatly among published series. This is probably due to a lack of standardization and heterogenic histologic description of these lesions. Nevertheless, Pathology reporting protocols clearly recommends that a histological report should include the evaluation of these alterations in the non-tumoural post-treatment liver [15,16]. Furthermore, the repercussion in morbidity mortality and the effect on outcome is still unclear [17].

Longer survival rates have been published with the use of biological agents such as bevacizumab and cetuximab in addition to standard chemotherapy regimens. A potential benefit of bevacizumab, in addition to oxaliplatin based regimens, has even been published as “protector” for developing vascular hepatic lesions [18–20]. In contrast, the histological effects in the liver of cetuximab have not been extensively studied.

Liver NRH and SOS are the most severe lesions within the spectrum of the vascular damage attributed to oxaliplatin based treatments. After the first reports alerting about these alterations, different series have established an incidence of NRH, varying from 4.8% to 15% [20–22]. Among the liver vascular lesions mentioned previously, the NRH is the least frequent and its impact is poorly known. Likewise, there is considerable variability in the incidence published when evaluating SD and SOS due to chemotherapy.

As a result, the objective of the present manuscript is to establish the incidence of

Table (2) –Association analysis between events of interest in the preoperative treatment group

		SOS Yes (%) No (%)		NRH Yes (%) No (%)	
SD	Yes	22 (46.8%) 25 (53.2%)	***P<0.001***[1]	7 (14.9%) 40 (85.1%)	***p=0.001***[1]
	No	0 (0.0%) 69 (100%)		0 (0.0%) 69 (100%)	
SOS	Yes	-	-	7 (31.8%) 15 (68.2%)	***P<0.001***[1]
	No	-		0 (0.0%) 94 (100%)	

[1] Estimated using Fisher's exact test method, two-tailed;
SD: Sinusoidal Dilatation; SOS: Sinusoidal Obstruction Syndrome; NRH: Nodular Regenerative Hyperplasia
p value considered significant when **< 0.05**

vascular hepatic lesions, namely SD, SOS and NRH, due to oxaliplatin based regimens in a cohort of 160 surgical specimens of CRLM from our hospital and to describe the occurrence of seven cases of NHR.

Patients and Methods

A historic prospective maintained database of 160 liver resections that underwent preoperative chemotherapy and surgery due to CRLM was assessed for SD, SOS and NRH. The resections, with curative intention, took place between 2007 and 2013 at the Pathology Department of the Hospital Complex of Navarra (Pamplona, Spain). All patients were revised and approved by the Multidisciplinary Committee of Digestive Tumours board.

Preoperative chemotherapy was defined as at least six cycles of any chemotherapy regimen within six months prior to surgical liver resection. Only specimens with available non-tumoural liver parenchyma >20mm away from the metastasis for histological evaluation were included. Each resection was then carefully reviewed for metastatic synchronicity or metachronicity, primary localization, type of chemotherapy regimens and biological agents, number of chemotherapy cycles and date of surgery.

Twelve (12) patients were lost either for not meeting the criteria abovementioned or insufficient pathological or clinical data during this assessment. The remaining 148 liver resections, including primary clinical characteristics, chemotherapy and type of biological agent, are described in Table 1. The series consist of 44 women and 104 men, with a median age in years of 64 (Standard Deviation 9.9). Synchronous metastases were reported in 91 cases and metachronous in 57. Thirty-two patients did not receive any preoperative treatment and acted as control group.

Ninety-nine (99) cases received oxaliplatin based regimens, eighty (80/99) were in combination with 5-FU with or without irinotecan/capecitabine. Seventeen (17) cases did not received oxaliplatin and were based in either irinotecan or capecitabine, of which eight (8/17) were in combination with 5-FU.

Within the oxaliplatin based group, fifty-one (51/99) received biological agent (34 bevacizumab and 17 cetuximab). In the group not receiving oxaliplatin, eleven (11/17) received biological agent (5 bevacizumab and 6 cetuximab).

All clinical decisions were made homogenously at Multidisciplinary Hepato-oncology board.

Table (3) –Subgroup analysis by treatment group

		SD Yes (%) No (%)		SOS Yes (%) No (%)		NRH Yes (%) No (%)	
Oxaliplatin based chemotherapy							
Other treatments	Ox	44 (44.4%) 55 (55.6%)	*p=0.059*[2]	22 (22.2%) 77 (77.8%)	***p=0.039***[2]	7 (7.1%) 92 (92.9%)	*p=0.591*[2]
	Others	3 (17.6%) 14 (82.4%)		0 (0.0%) 17 (100%)		0 (0.0%) 17 (100%)	
Bevacizumab	Ox	28 (43.1%) 37 (56.9%)	*p=0.705*[1]	16 (24.6%) 49 (75.4%)	*p=0.428*[1]	4 (6.2%) 61 (93.8%)	*p=0.689*[2]
	Ox+ Bev	16 (47.1%) 18 (52.9%)		6 (17.6%) 28 (82.4%)		3 (8.8%) 31 (91.2%)	
5-FU	Ox	6 (31.6%) 13 (68.4%)	*p=0.209*[1]	2 (10.5%) 17 (89.5%)	*p=0.229*[2]	0 (0.0%) 19 (100%)	*p=0.340*[2]
	Ox+ 5-FU	38 (47.5%) 42 (52.5%)		20 (25.0%) 60 (75.0%)		7 (8.8%) 73 (91.3%)	
No preoperative treatment group							
Oxaliplatin	None	0 (0.0%) 32 (100%)	***p<0.001***[2]	0 (0.0%) 32 (100%)	***p=0.001***[2]	0 (0.0%) 32 (100%)	*p=0.193*[2]
	Ox	44 (44.4%) 55 (55.6%)		22 (22.2%) 77 (77.8%)		7 (7.1%) 92 (92.9%)	
5-FU	None	0 (0.0%) 32 (100%)	***p<0.001***[2]	0 (0.0%) 32 (100%)	***p=0.002***[2]	0 (0.0%) 32 (100%)	*p=0.187*[2]
	5-FU	39 (44.3%) 49 (55.7%)		20 (22.7%) 68 (77.3%)		7 (8.0%) 81 (92.0%)	

[1] Estimated using Chi-squared method;

[2] Estimated using Fisher's exact test method, two-tailed;

SD: Sinusoidal Dilatation; SOS: Sinusoidal Obstruction Syndrome; NRH: Nodular Regenerative Hyperplasia; Ox: Oxaliplatin based chemotherapy; 5-FU: 5-Fluorouracil based chemotherapy; Bev: Bevacizumab

*p value considered significant when <**0.05***

Pathological Study

All tissue was formalin-fixed and paraffin-embedded. Morphological analysis was made on haematoxylin and eosin (HE), Masson's trichrome and reticulin stains. Histopathological review was made by two different expert pathologists blinded to the medical history or chemotherapy regimens. To evaluate and classify histologically the liver damage secondary to chemotherapy a protocol developed by Gómez Dorronsoro *et al*., [23] was used for our evaluation.

The slides were reviewed for histological features of SD, NRH and perisinusoidal fibrosis for SOS. These lesions were evaluated and graded according to the degree presented by Rubbia-Brandt *et al*., [20]. SD was graded 0, 1, 2 or 3: 0, absent; 1, mild (centrilobular involvement limited to one-third of the lobular surface); 2, moderate (centrilobular involvement in two-thirds of the lobular surface); and 3, severe (complete centrilobular involvement). As an evolution of SD, the presence of perisinusoidal fibrosis was used to determine histological SOS as present or absent, as is described by consensus [23] protocol as high grade sinusoidal lesions.

Finally, NRH was defined as a micronodular transformation of the liver on behalf of hepatocyte nodules delimited by atrophic trabecules in the absence of fibrous septa, which is evident with HIM in the majority of examined areas, and then confirmed with reticuline. NRH was evaluated as present or absent.

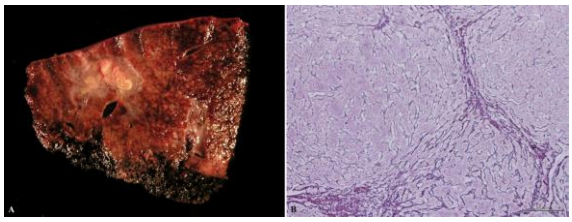

Figure 2. NRH a) Fresh cut section of a liver with micronodular transformation b) Nodular regenerative Hyperplasia. Reticulin staining X100

Further review was made for the NRH cases for clinical signs including portal hypertension, hepatic insufficiency, embolization, blue liver and type of surgery.

Statistical Analysis

For statistical analysis purposes all variables were treated as dichotomic variables except for age. SD was considered as positive if any grade 1, 2 or 3 was assessed by the expert pathologist and negative for grade 0.

Association between variables was determined using Fisher's test and χ^2 test. Univariate and multivariate analysis was made using logistic regression model. The variables used were the presence or absence between dilatation any grade, presence or absence of SOS, the use of oxaliplatin based chemotherapy, other chemotherapy used, biological agent, localization, sex and synchronous or metachronous metastasis. Statistical significance was set as two tailed p-value of <0.05.

Figure 3: Blue liver. Hepatic surface.

This study has been performed in accordance with the World Medical Association Declaration of Helsinki.

Results

Our series consisted of 148 liver resections, where 116 received preoperative chemotherapy and 32 received only surgery as treatment and acted as a control group.

Among the group treated with preoperative chemotherapy, SD was present in 47/116 specimens, of which 44/47 were treated with a regimen containing oxaliplatin and 16/47 in combination with bevacizumab. As an evolution of the previous lesion, SOS, as presence of fibrosis (Figure 1), was present in 22/116 specimens, all of them with a regimen containing oxaliplatin and only 6/22 in combination with bevacizumab. NRH was found on 7/116 specimens, all of them 7/7 treated with a FOLFOX regimen (5-FU + Leucovorin + Oxaliplatin) and 3/7 in combination with bevacizumab.

Notably, among the control group there were no findings of SD, SOS or NRH in any specimen.

The association analysis in Table 2 highlights the interrelationship between the vascular lesions. From the 47 specimens with SD, 22/47 presented SOS and 7/47 NRH. All cases of SOS presented along with SD and all cases of NRH had SOS and SD. Statistical significance was achieved between the three events of interest.

Chemotherapy subgroup analysis

A subgroup analysis was performed by treatment group (oxaliplatin and control group), the results are presented in Table 3. Oxaliplatin based chemotherapy is associated with the development SD (p=0.059) and SOS (p=0.039) when compared to other chemotherapies in independence of biologic agent used. One case

Table 4: Description of NRH cases

Age	Gender	Location	Type of metastases	Preoperative regimen	Adjuvant Agent	# of cycles	Type of Surgery	Histological findings	Clinical findings
62	Male	Rectum	Synchronous	FOLFOX	Cetuximab	6	Left hepatectomy	SD (3), SOS	Embolization Hep insuff.
67	Male	Rectum	Metachronous	FOLFOX	Bevacizumab	6	Left hepatectomy	SD (2), SOS	Blue Liver
76	Male	Rectum-Sigma	Synchronous	FOLFOX	None	12	Left hepatectomy	SD (3), SOS	Blue Liver
75	Male	Rectum	Synchronous	FOLFOX	Bevacizumab	6	Seg. V	SD (2), SOS,	-
69	Male	Colon	Synchronous	FOLFOX	Cetuximab	6	Hepatectomy of seg. II-II	SD (2), SOS	Blue Liver
50	Male	Colon	Synchronous	FOLFOX	Cetuximab	7	Hepatectomy of seg. II,	SD (2), SOS	Blue Liver
59	Male	Rectum	Synchronous	FOLFOX	Bevacizumab	6	Left hepatectomy	SD (2), SOS	Embolization

Seg: segmentomy; Hep. insuff: Hepatic insufficiency; SD (x): Sinusoidal Dilatation (grade); FOLFOX: 5-FU/Leucovorin/Oxaliplatin.

of SD was found for a patient receiving 5-FU without oxaliplatin.

When comparing oxaliplatin based chemotherapy group with the group without preoperative treatment, a statistical significant association was found on both SD and SOS (both $p<0.001$). Furthermore, when comparing the 5-FU with the control group, a statistical significant association was also found on both SD and SOS ($p=0.001$ and $p=0.002$ respectively).

Similarly, the univariate analysis showed association between preoperative use of oxaliplatin based chemotherapy with or without biological agents and developing SD ($p<0.05$). Notably, the use of 5-FU was also found to increase the risk of both liver vascular lesions, although it did not reach statistical significance ($p=0.09$). Additionally, our results did not confirm any protective effect of bevacizumab on SD ($p=0.632$), nor cetuximab ($p=0.747$).

Finally, the multivariate analysis confirmed a statistically significant association between oxaliplatin based chemotherapy and developing SD ($p=0.021$).

NRH description of cases

There were 7 cases of NRH (Figure 2) which presented morphological changes of SD and diagnosis of SOS as summarized in Table 4. These cases represent 31.8% of all patients with SOS. Notably, all NRH cases were men and were treated with FOLFOX regimens with at least 6 cycles at the moment of assessment. These patients presented a median age of 62 (range: 47-83). Two underwent embolization, one presented portal hypertension, one hepatic insufficiency and blue liver was reported in 4 patients who afterwards were diagnosed of NRH. A major or complex type of hepatectomy was seen in 6 of the 7 patients.

In our series, nine patients were reported with blue liver macroscopic appearance (Figure 3). All of them were treated with oxaliplatin based chemotherapy and diagnosed with high grade SD and SOS. In four of them NRH was present.

Discussion

The findings of this study have demonstrated an association between preoperative oxaliplatin based chemotherapy in CRLM patients and the development of histological vascular liver lesions. The use of biological agents has not proven beneficial as “protector” of the liver. Furthermore, this study has provided a detailed description of seven NRH cases and its

relationship with FOLFOX chemotherapy regimen, SD, SOS and blue liver syndrome.

Oxaliplatin based chemotherapy is the gold standard treatment for colorectal cancer especially in the metastatic setting. It has been associated with vascular liver lesions, mainly with SD, SOS and, less frequently, NRH [13, 24–26].

In our study the incidence of SD in oxaliplatin based regimens is consistent with what has been reported in literature. Such incidence varies depending on the grading and therefore definition of SD. If SD is considered only in severe dilatation (grade 2 or 3), the incidence in our series is of 26,7% while previously reported range is between 9,7% and 23% (27). However, if SD is considered as part of an evolutive process, mild dilatation (grade 1) is also comprised as presence of SD, in our series the incidence is of 40,5%. This result is slightly underrepresented compared to the incidence ranged between 52% and 56% reported in literature [27, 28] and up to 79% first described by Rubbia-Brandt *et al*., [20].

Our study has shown oxaliplatin based chemotherapy as a predictor for developing SD. In the multivariate analysis, when SD was considered as positive when graded 1, 2 or 3, showed a statistical significant (p=0.021) association with oxaliplatin based chemotherapy. Moreover, when SD was considered as positive only when graded 2 or 3, p value was in the limit for statistical significance (p=0.057). Previous results suggest the relationship of oxaliplatin with the entity of SD despite the scoring used.

There is no standard histological classification for SOS. Histopathologic vascular liver lesions, such as SD, perisinusoidal haemorrhage, fibrosis and NRH, are included together in this broad spectrum [22], resulting also in a discordance in terminology among series [28]. Recently, a more objective assessment of sinus damage is being attempted through the immunohistochemical study with CD 31/34 AML to digitally assess the endothelization of these sinusoids and establish Indices of Sinusoidal Damage [14, 16].

The findings of this study are biologically plausible since the physiological process of sinusoidal lesion usually begins as a mild dilatation (SD). As it the dilatation progresses, the sinusoidal wall could be compromised and ruptured, sometimes peliosis can be found, and finally perisinusoidal fibrosis is formed (SOS) [29]. Besides biologic processes involved in the pathogenesis of SOS [27] oxidative stress, remodelling of the extracellular matrix and the coagulation cascade, gene expression analyses have suggested angiogenic pathways [12].

NRH can also occur within this setting of toxic liver injury previously reported by Rubbia-Brant *et al*., [20], in which the macroscopic examination shows a liver with a micro-macro nodular configuration often alongside blue liver [27].

Published literature reports that incidence varies between 4.8% and 15% [21, 22, 27]. In our cohort, the 7 cases diagnosed with NRH represent 6% among the treated group and 7.1% among the ones treated with oxaliplatin, therefore greater numbers are needed to study a specific correlation with primary and/or concomitant treatment. All 7 cases of NRH, presented either SD grade 2 or 3 and diagnosis of SOS, supporting the evolutionary process hypothesis. Notably, except for one exception all cases underwent a mayor or complex hepatectomy, indicative of an already fragile patient due to surgery with the additional liver damage.

SOS and other hepatic sinusoidal abnormalities may show a characteristic macroscopic aspect called the “blue liver” or “blue liver syndrome” [8, 9, 26, and 30]. There is a relationship between blue liver and SOS and NRH since we found that out of the 9 (29%) patients were reported with blue liver, all presented SD grade

2 (33.3%) or 3 (66.6%) and all with were treated with oxaliplatin based chemotherapy. Furthermore, all 9 cases presented SOS and 4 presented the final stage of NRH, suggesting the macroscopical finding of blue liver might be indicative of advanced hepatic vascular lesions.

The effect on vascular alterations of 5FU in combination with oxaliplatin, irinotecan or capecitabine based regimens, has not been extensively studied. Although not the main object of this manuscript, this study found a possible correlation for 5-FU and the development of SOS in the multivariate analysis (p=0.067) in accordance to some publications [25, 26, 28] as a possible synergic effect.

These results should be further studied since from the 88 patients treated with 5-FU, 80 were in combination with oxaliplatin and 8 with either irinotecan or capecitabine. Additionally, we found a reduced incidence of SD in irinotecan based regimens (p=0.053), also in line with some publications [13]. However, the number of patients treated with irinotecan in our series is limited (17 patients).

Longer survival rates have been proven with the use of monoclonal antibodies in addition to oxaliplatin based regimens. It has been also published a potential benefit of the use of Bevacizumab as “protective factor” for developing sinusoidal lesions [19, 20, 31], and even with Cetuximab [32], however this was not evident in our analysis.

Out of the scope of this study are the clinical implications of our histological findings in morbidity and mortality to establish prognostic factors, a prospective study is needed. The main limitation of our study is the number of liver resections given the low incidence of previously discussed hepatic vascular alterations. With more events of interest, a more powerful subgroup analysis could be performed, especially for NRH.

Conclusions

In conclusion, sinusoidal lesions and NHR are not frequent; the incidence of these vascular lesions in our series is similar to others reported in literature. Oxaliplatin based chemotherapy regimens, have a relationship with the development of these sinusoidal lesions and with the appearance of NRH. The role of 5-FU although not extensively studied, seems to act as a synergic factor for vascular alterations. Preventive strategies such as the use of bevacizumab are still not clear. These vascular alterations are part of an evolutionary process that starts with a mild SD and may progress to fibrosis and SOS and finally NRH.

Learning Points

1. Systemic Oxaliplatin- based chemotherapies are associated with sinusoidal lesions in liver parenchyma.

2. Sinusoidal dilatation, sinusoidal obstruction syndrome and nodular regenerative hyperplasia are part of an evolutionary process.

3.5-Fluorouracil seems also to have a synergic effect on these vascular lesions when in chemotherapy combined therapies.

List of Abbreviations Used

5-FU : 5-Fluorouracil

CRLM : Colorectal Liver Metastasis

FOLFOX: Chemotherapy regimen based on 5-Fluorouracil + Leucovorin + Oxaliplatin

NRH : Nodular Regenerative Hyperplasia

SD : Sinusoidal Dilatation

SOS : Sinusoidal Obstruction Syndrome

Declaration of Interest

PA works for Institut de Recherches International Servier (I.R.I.S.) however, there were no affiliation or financial involvement with this or any other organization or entity, with financial or scientific interest, with the subject matter or materials discussed in the manuscript.

All other authors reported no conflicts of interest.

Authors' Contributions

PA designed the study, contributed with data acquisition, performed data analysis and interpretation, draft writing, review and edition of final manuscript,

MGD conceptualized the study, participated in the study design, literature search, read, revised and approved the final manuscript for submission,

MM participated in the acquisition of data, methodology and interpretation the histological slides, review and edition of the final manuscript,

IA participated in the acquisition of data, interpreted the histological slides, review and edition of the final manuscript,

AG performed the analysis and interpretation of data, software management and reviewed and edit and approved the final manuscript.

All authors have read and agreed to the published version of the manuscript.

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