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## Syndecan-1 (CD138) immunohistochemical expression patterns in lupus nephritis; reflections on different clinicopathological parameters

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### ABSTRACT

**Introduction:** Syndecan 1 (SCD1) is a lectin expressed at the surface of renal tubular epithelial cells and plasma cells. In epithelial cells, cell surface syndecan1 is cleaved by inflammation-induced proteases (eg, ADAMTS, MMP), since loss of cell surface syndecan1 is associated with higher susceptibility to cell damage.

**Objectives:** To explore a potential additional value of SCD1 immunohistochemical expression in lupus nephritis specimens of different ISN/RPS classes and NIH activity and chronicity indices.

**Patients and Methods:** This retrospective study included 50 renal biopsy specimens diagnosed as lupus nephritis at the pathology laboratory, and electron microscopy (EM) laboratory of Ain-Shams University specialized hospitals. Data were collected from records as personal data, medical history and laboratory results including serum creatinine and proteinuria. Immunohistochemical expression of syndecan-1 was evaluated in renal tubular epithelial cells (TECs) followed by correlation with different clinicopathological parameters.

**Results:** Fifty renal biopsy specimens with lupus nephritis including 14 cases of class II, 4 cases of class III, 20 cases of class IV and 12 cases of class V were re-evaluated. The mean serum creatinine was  $1.57 \pm 0.67$  mg/dL. Nine cases (18%) were negative for proteinuria, while 41 cases (82%) were presented with proteinuria with a mean of  $1.5 \pm 0.9$  g/24 h. There was no statistically significant difference in the percentage of SCD-1 expression with different lupus classes. Serum creatinine and albumin showed a statistically significantly different correlation with semiquantitative score of SCD-1 expression. The highest value of creatinine detected with score 1 of SCD-1 expression ( $P=0.038$ ) and the highest value of urinary albumin was recorded with score 1 of SCD-1 expression. Accordingly, the lowest mean of urinary albumin recorded in SCD-1 score 3 ( $P<0.001$ ). There was a weakly negative association between loss of SCD-1 expression and increased NIH activity and chronicity indices.

**Conclusion:** Loss of syndecan immunohistochemical expression in renal TECs in lupus nephritis is highly associated with proteinuria and elevated serum creatinine and can be used as a predictive marker for disease severity and progression.

### *Implication for health policy/practice/research/medical education:*

Syndecan-1 (SCD-1) has been recently identified as a marker of renal tubular stress. The present work highlights the association between loss of SCD-1 expression on renal TECs in cases of lupus nephritis with elevated serum creatinine and the level of proteinuria. On the histopathological level, no association between ISN/RPS classes of lupus nephritis and loss of SCD-1 expression was found, however there was a weakly negative association between loss of SCD-1 and increased NIH activity and chronicity indices of lupus nephritis. We assumed that SCD-1 can be used as a predictive marker for progression of renal disease in SLE.

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### Introduction

Lupus nephritis (LN) represents a severe manifestation of systemic lupus erythematosus (SLE) initiated by deposition of anti-double stranded DNA (anti-dsDNA) autoantibodies in glomerular basement membranes (1-

3). In the last few years, it was hypothesized that lupus nephritis has local renal immune mechanisms rather than a systemic activity (4,5).

Several studies have been conducted for early detection of lupus nephritis activity before the progression to end-

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stage renal disease (ESRD). These studies reported a strong association between low glomerular filtration rate (GFR), high chronicity indices and poor renal outcome (6-11). Tubulointerstitial lesions in the form of interstitial inflammation and fibrosis, and tubular atrophy were known as one of the prognostic markers in lupus nephritis (12). Several underlying mechanisms for tubulointerstitial lesions include proteinuria, immune complex deposition in the interstitium, and rupture of the Bowman's capsule and induction of pro-inflammatory molecules at the surface of renal tubular cells (13-15).

Previous studies showed that changes in heparan sulfate proteoglycans (HSPGs) affect renal inflammatory responses as observed in experimental renal IRI (ischemia reperfusion injury) and primary human kidney disease (16,17). HSPGs were proved to be involved in angiogenesis, wound healing, tumor progression and inflammation through binding and presenting growth factors, chemokines and cytokines, as well as facilitating inflammatory cells adhesion by binding to the leukocyte adhesion molecule L-selectin (16,18-22).

Syndecan-1 (SCD1) is a transmembrane HSPG involved in epithelial differentiation and re-epithelialization during wound healing and inflammation (18,23-25). There are four members of syndecans. SCD1, known as CD138, is expressed on the surface of plasma, endothelial and epithelial cells (18). During tissue injury, the SCD1 shedding is accelerated through the release of different proteases and growth factors, thus it can be detected in inflammatory fluids. Epithelial cell surface SCD1 is cleaved by inflammation-induced proteases (ADAMTS and MMP) (26).

Additionally, shed/desquamated soluble syndecan-1 was found in sepsis (27), graft versus host disease (28), multiple myeloma and acute myeloid leukemia (29,30).

Few studies have assessed the role of serum SCD1 in lupus nephritis. Serum syndecan-1 was found to be significantly high in active lupus nephritis patients and correlated with disease activity. It was also significantly related to the presence of musculoskeletal manifestations and serositis which give a promising role in prediction of disease activity (31,32). Moreover, loss of cell surface SCD1 is associated with higher susceptibility to cell damage, in gastroenterological and renal disorders, and it has been recently identified as a marker of renal tubular stress (33-36).

To date, SCD1 expression in lupus nephritis has scarcely been studied. Even in these few studies, the focus was directed on its expression in plasma cells regardless of its assessment in renal tubular epithelial cells (TECs). In these studies, SCD1 stained plasma cells were not seen in glomeruli even in proliferative glomerulonephritis and they were mostly seen as scattered single cells in the

interstitium of the cortex and outer medulla. Additionally, the average medullary plasma cell SCD1 expression was found to be associated with higher disease activity and chronicity as well as all lupus nephritis classes except class II (37).

Accordingly, the study by Pamfil et al (36) showed the link between renal TEC damage (indicated by lost SCD1 expression) and poorer renal outcome in LN, which was assessed by lower GFR (36). Therefore, we sought to explore the patterns of SCD1 TEC expression in lupus nephritis patients and test potential reflections of such patterns on the prognostic indices of lupus nephritis. The role played by SCD1 in inflammation/re-epithelialization sequel has given us insights to test its expression in TEC in lupus nephritis patients to find if there is a link with different clinicopathologic parameters.

## Objectives

The aim of the present study is to evaluate SCD1 immunohistochemical expression in renal TECs in lupus nephritis in correlation with various clinicopathological parameters.

## Patients and Methods

### *Study population*

This retrospective study included 50 renal biopsy specimens diagnosed as lupus nephritis at the pathology laboratory, and electron microscopy (EM) laboratory of Ain-Shams University specialized hospitals. Data were collected from records as personal data, medical history and laboratory results including serum creatinine and proteinuria. Cases with adequate paraffin tissue blocks for immunostaining were enrolled in the study. All renal biopsy specimens were graded according to the 2003 international society of nephrology/renal pathology society (ISN/RPS) classification system (38) and national institutes of health (NIH) activity and chronicity indices (39,40). The renal specimens were re-evaluated by light microscopy (LM) and immunohistochemical staining using (syndecan-1).

### *Light microscopy*

Formalin-fixed, paraffin-embedded tissues from all cases were retrieved from the archive of the pathology laboratory. Slides were re-evaluated by two pathologists using LM (Olympus BX31) according to the histopathological guidelines for the evaluation and scoring of lupus nephritis (38-40). The pathologists were blinded to the clinical parameters of the patients.

### *Immunohistochemical staining method*

Tissue sections were deparaffinized, rehydrated, and the endogenous peroxidase activity was quenched by

10-minute incubation in 3% hydrogen peroxide in methanol. After antigen retrieval and protein block, the primary antibody (mouse monoclonal anti-human syndecan-1 antibody; sc-390791, Santa Cruz) was supplied with dilution (1:50). The secondary antibody (supersensitive immunodetection system (Biogenex, catalog No: AD000-SL) was then applied followed by peroxidase labeled streptavidin. Slides were incubated for 10 minutes with substrate chromogen (DAB) mixture. Finally, the slides were counterstained and mounted with Canada balsam.

Any staining detected in membranes of TECs is considered positive.

### *Evaluation of immunostaining*

Two scoring methods for SCD-1 expression in renal tubular epithelium were used as follows:

(a) Quantitative score; by evaluation of the percentage of SCD-1 positive TECs to the whole area of renal cortical tubules in the examined specimen (typically 5–10 visual fields per biopsy) (41).

(b) Semiquantitative score;

- Score 0; cortical renal tubules are negative for SCD-1
- Score 1; positive membranous SCD-1 in <30% of renal cortical tubules
- Score 2; positive membranous SCD-1 in 30-60% of renal cortical tubules
- Score 3; positive membranous SCD-1 in >60% of renal cortical tubules

The intensity of immunostaining was graded into weak, moderate, strong.

### *Ethical issues*

This investigation was in accordance with the Declaration of Helsinki. This investigation was conducted retrospectively on paraffin embedded blocks of kidney biopsies to test SCD-1 immunohistochemical expression in renal TECs. The study was approved by the ethical board committee of Faculty of Medicine, Ain Shams University.

### *Statistical methods*

Data was revised for its completeness and consistency. Double data entry on SPSS program version 16 was done. Quantitative data were summarized by mean along with standard deviation while qualitative data were summarized by frequencies and percentages. Analysis of variance, chi-square test and Spearman's correlation coefficient test were used for the analysis of significant differences or associations.

## **Results**

Fifty renal biopsy specimens with lupus nephritis were re-evaluated including (14 cases of class II, 4 cases of class

III, 20 cases of class IV and 12 cases of class V). Forty-two cases (84%) were females and eight (16%) were males, with mean age of  $27.96 \pm 12.9$  years.

The mean serum creatinine was  $1.57 \pm 0.67$  mg/dL. Nine cases (18%) were negative for proteinuria, while 41 cases (82%) were presented with proteinuria with a mean of  $1.5 \pm 0.9$  g/24h.

NIH activity index was ranging from 1/24 to 18/24 with a mean value  $6.24 \pm 4.3$ . NIH chronicity index was ranging from 0/12 to 8/12 with a mean value  $2.18/12 \pm 2.22$ .

Regarding comparison of different variables based on ISN/ RPS class; no statistically significant difference in percentage of SCD-1 expression and the lupus classes was detected. We found a significantly higher mean age in class III ( $P=0.011$ ). Moreover, serum creatinine showed a significant difference between groups, with the highest value in class IV, followed by class III ( $P<0.001$ ). Accordingly, proteinuria showed a significant difference between groups, with the highest value in class V, and the lowest mean in class II ( $P<0.001$ ; Table 1).

Serum creatinine and albumin showed a statistically significantly different correlation with semiquantitative score of SCD-1 expression based on percentage of stained cells, with the highest value of creatinine which was detected with score 1 of SCD-1 expression ( $P=0.038$ ). Additionally, the highest value of urinary albumin was detected with score 1 of SCD-1 expression (Figures 1A and 1B), while the lowest mean of urinary albumin recorded in SCD-1 score 3 ( $P<0.001$ ; Table 2; Figures 2A and 2B).

Regarding staining intensity, a statistically significant positive correlation between moderate intensity of SCD-1 expression and both serum creatinine ( $P=0.043$ ), and urinary albumin ( $P<0.001$ ) was found (Table 3; Figure 3).

Correlation between SCD-1 expression and NIH activity and chronicity indices was not significant. However a negative association between SCD-1 percentage and SCD-1 score and also intensity with increased NIH activity and chronicity indexes was noted, nonetheless, such association didn't mount to statistical significance (Table 4).

## **Discussion**

SCD-1 is one of the four transmembrane HSPGs of the syndecan's family. All family members contain a transmembrane core protein to which glycosaminoglycan side chains are extracellularly attached (42). In adults, SCD-1 is mainly expressed by hepatocytes (43), epithelial cells (44) and plasma cells (45).

The role of SCD-1 in re-epithelialization during wound healing and its role in restoration of TEC damage after ischemia reperfusion injury was established (18,23-25,41).

**Table 1.** Comparison between different variables based on ISN/RPS classes (ANOVA test)

Variable	Class	Number	Mean	SD	95% CI for Mean		P value
					Lower bound	Upper bound	
Age	Class II	14	25.07 <sup>b</sup>	13.96	17.01	33.13	0.011*
	Class III	4	42.75 <sup>a</sup>	12.84	22.32	63.18	
	Class IV	20	27.00 <sup>b</sup>	13.18	20.83	33.17	
	Class V	12	28.00 <sup>b</sup>	9.32	22.08	33.92	
	Total	50	27.96	13.01	24.26	31.66	
Creatinine (mg/dL)	Class II	14	1.16 <sup>c</sup>	0.23	1.02	1.29	<0.001*
	Class III	4	1.78 <sup>b</sup>	0.74	0.60	2.95	
	Class IV	20	2.05 <sup>a</sup>	0.72	1.71	2.39	
	Class V	12	1.18 <sup>c</sup>	0.24	1.03	1.34	
	Total	50	1.57	0.67	1.38	1.76	
Albumin (g/24 h)	Class II	14	.64 <sup>c</sup>	0.74	0.21	1.07	<0.001*
	Class III	4	1.50 <sup>b</sup>	1.00	-.09	3.09	
	Class IV	20	1.60 <sup>b</sup>	0.75	1.25	1.95	
	Class V	12	2.33 <sup>a</sup>	0.49	2.02	2.65	
	Total	50	1.50	0.93	1.24	1.76	
Percentage of SCD1 expression	Class II	14	39.79	35.65	19.20	60.37	0.357ns
	Class III	4	28.00	41.51	-38.04	94.04	
	Class IV	20	43.65	32.85	28.28	59.02	
	Class V	12	22.67	30.15	3.51	41.82	
	Total	50	36.28	33.79	26.68	45.88	

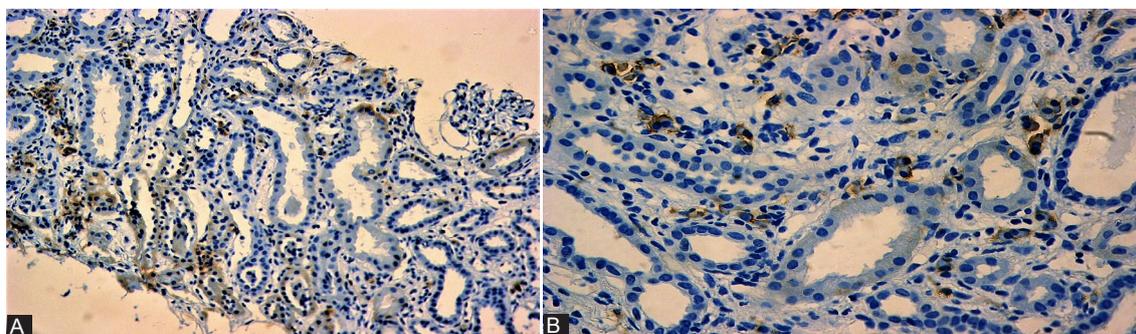
Significance level  $P \leq 0.05$ , \*Significant, ns =non-significant.

Tukey's post hoc test: Within the same comparison, means sharing the same superscript letter is not significantly different.

In the present work, evaluation of tissue SCD-1 immunohistochemical expression in renal TEC in lupus nephritis patients and its correlation with various clinicopathological parameters was our main concern.

We found a statistically significant inverse relationship between the loss of SCD-1 expression and increased proteinuria and serum creatinine. Our results were concordant with the study by Salam et al (32) who

investigated the role of serum SCD-1 in lupus nephritis and revealed a significantly higher SCD-1 in patients with active lupus nephritis compared to those with extra-renal flare and inactive disease ( $P < 0.001$  and  $P < 0.001$  respectively). They found a highly statistically significant correlation between serum SCD-1 and 24h urinary proteinuria, decreased serum complement as well as SLEDAI (systemic lupus erythematosus disease activity



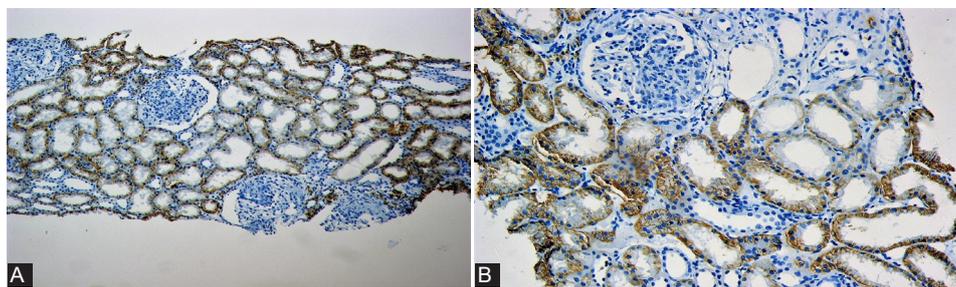
**Figure 1.** (A) Lupus nephritis class IV presented with elevated serum creatinine (2 mg/dL) and proteinuria (2.5 g/24 h) with mild SCD-1 staining in 5% of cortical renal tubules (score 1), there is focal tubular atrophy and mononuclear interstitial inflammatory cell infiltrate (SCD-1×200). (B) Lupus nephritis class V presented with heavy proteinuria (3 g/24 h) with negative SCD-1 staining in cortical renal tubules (score 1). There is occasional SCD-1 positive plasma cell infiltrate in interstitial tissue and tubular atrophy. (SCD-1×400).

**Table 2.** Creatinine and albumin level according to semiquantitative score of SCD-1 expression (ANOVA test)

	Semi-quantitative score of SCD-1	N	Mean	SD	95% CI for Mean		P
					Lower bound	Upper bound	
Creatinine	1	25	1.81 <sup>a</sup>	0.78	1.48	2.13	0.038*
	2	10	1.33 <sup>b</sup>	0.53	0.95	1.71	
	3	15	1.33 <sup>c</sup>	0.35	1.14	1.53	
Albumin	1	25	2.00 <sup>a</sup>	0.71	1.71	2.29	<0.001*
	2	10	1.40 <sup>a</sup>	0.97	.71	2.09	
	3	15	0.73 <sup>b</sup>	0.70	.34	1.12	

Significance level  $P \leq 0.05$ , \*Significant, ns =non-significant.

Tukey's post hoc test: Within the same comparison, means sharing the same superscript letter is not significantly different.



**Figure 2.** (A) a case of Lupus nephritis ISN/RPS class III with minimal proteinuria and serum creatinine 0.8 mg/dL showing moderate to strong positive SCD-1 in 80% of cortical renal tubules (score 3) (SCD-1  $\times 100$ ). (B) Lupus nephritis class IV presented with minimal proteinuria and serum creatinine 1.7 mg/dL with moderate positive SCD-1 in 70% of cortical renal tubules (score 3) (SCD-1  $\times 200$ ).

index) score indicating its potential role as a predictive marker for disease activity. Same results were detected by Kim et al (34) and Minowa et al too (46).

Although there was no statistically significant correlation between loss of SCD-1 expression and increased NIH activity and chronicity indices in this study, however there was a weekly negative association between both parameters. These data may suggest that loss of SCD-1 expression might represent an early predictor of adverse clinical course and renal function deterioration before histopathological evidence manifestation.

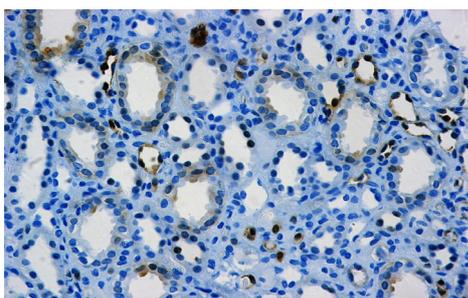
In light of the previous data in the literature and the present study, we noted that both elevated serum SCD-1 and loss of tissue SCD-1 on TEC are related to progression of lupus nephritis. This inverse relationship between serum and tissue SCD-1 could be attributed to endothelial glycocalyx loss and/or shedding from the renal epithelium. During tissue injury, SCD-1 shedding is accelerated through the release of different proteases and growth factors, thus it can be detected in inflammatory fluids (26,44). Therefore, we recommend further studies investigating both serum and tissue SCD-1 expression

**Table 3.** Creatinine and albumin level according to intensity of SCD-1 staining (ANOVA test)

		N	Mean	SD	95% CI for Mean		P
					Lower bound	Upper bound	
Creatinine (mg/dL)	0.00	2	1.20 <sup>b</sup>	0.28	-1.34	3.74	0.043*
	1.00	8	1.46 <sup>b</sup>	0.49	1.06	1.87	
	2.00	16	1.95 <sup>a</sup>	0.79	1.53	2.37	
	3.00	24	1.38 <sup>b</sup>	0.56	1.15	1.62	
Albumin (g/24 h)	0.00	2	0.50 <sup>c</sup>	0.71	-5.85	6.85	0.00*
	1.00	8	1.75 <sup>a</sup>	0.46	1.36	2.14	
	2.00	16	2.19 <sup>a</sup>	0.54	1.90	2.48	
	3.00	24	1.04 <sup>b</sup>	0.95	0.64	1.44	

Significance level  $P \leq 0.05$ , \*Significant, ns =non-significant.

Tukey's post hoc test: Within the same comparison, means sharing the same superscript letter is not significantly different.



**Figure 3.** Lupus nephritis class III with proteinuria (1 g/24 h) and serum creatinine 1.8 mg/dL showing moderate focal staining intensity (SCD-1  $\times 400$ ).

**Table 4.** Correlation between NIH activity and chronicity indices of cases presented with lupus nephritis with SCD-1 expression (Spearman's rho correlation test)

		Percentage	Semi-quantitative SCD-1 score	Score-intensity
Activity	R	-0.019	-0.038	-0.054
	P	0.893	0.792	0.709
	Sig.	Weak -ve	Weak -ve	Weak -ve
Chronicity	R	-0.150	-0.173	-0.122
	P	0.298	0.230	0.400
	Sig.	Weak -ve	Weak -ve	Weak -ve

\* Correlation is significant at the 0.05 level (2-tailed).

*Note.* -ve means there is a negative association between increased NIH activity and chronicity indices and lost syndecan expression either in percentage, score and intensity i.e., inverse relationship.

in TECs in patients with lupus nephritis to confirm this relationship and detect sensitivity of each procedure in prediction of disease activity. We also recommend investigating SCD-1 on desquamated/shed urinary TEC by flow cytometry in cases of lupus nephritis.

Supporting this hypothesis; Celie et al (41) investigated the pattern of SCD-1 expression in renal TEC in murine ischemia reperfusion injury and human renal allograft transplantation and found increased epithelial SCD-1 in allografts was correlated with low-proteinuria and serum creatinine, less interstitial inflammation, less tubular atrophy, and prolonged allograft survival. They hypothesized that SCD-1 is involved in tubular repair and survival upon renal transplantation and proposed it as a novel marker of renal allograft survival.

Additionally, Pamfil et al (36) found that SCD-1 immunohistochemical expression was significantly higher in biopsies where no tubular damage was evidenced at histological evaluation in cases of lupus nephritis.

In our study, a direct relation between tubular SCD-1 expression and different ISN/ RPS classes could not

be detected. Classification of lupus nephritis classes varies according to site of immune complex deposition. Immune complexes deposit in the mesangium or the subendothelial and subepithelial spaces or in peritubular capillaries depending on the quality of the autoantibodies, the duration, and severity of lupus nephritis (47). This finding implies that immune complex formation in the mesangium causes class I and II lesions, subendothelial immune complex formation in class III and IV, and subepithelial immune complexes in class V (38). In the present work, we did not demonstrate SCD-1 expression in renal glomeruli in all classes, thus correlating a link between glomerular SCD-1 expression as a pathogenic factor determining the site of immune complex deposition couldn't be established. From the fore-mentioned results, the role of TEC-SCD-1 involvement in disease progression was highlighted while its role in disease initiation needs to be further investigated in larger studies.

### Conclusion

In this study we revealed a clear statistically significant predictive role of TEC-SCD-1 immunohistochemical expression as an adverse predictive marker of disease progression and tubular damage in lupus nephritis patients regardless of their class. Accordingly, we propose SCD-1 immunohistochemical testing as a helpful adjunct tool to histopathological evaluation in improving insightful tailored management plans.

### Limitations of the study

The missed relationship between loss of SCD1 expression and different ISN/RPS classes could be attributed to the limited number of cases. Hence further studies with larger sample size may reach a statistically significant value and prove the role of SCD1 in the process of disease initiation.

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### Authors' contribution

MMS: designing the idea and study plan, data collection and writing the manuscript. LSS: follow up the staining procedures, scoring of immunohistochemistry and photographing, revising and editing the manuscript. Both the authors read, revised and approved the final manuscript.

### Conflicts of interest

The authors declare no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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