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Potential role of claudin-1 immunohistochemical expression and ultrastructural changes in detecting early focal segmental glomerulosclerosis

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ABSTRACT

Background: Focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are two disease entities presented mainly by nephrotic syndrome. While 95% of MCD cases showed complete remission on steroid therapy, 50% of FSGS cases progress to end-stage renal disease (ESRD). Early sclerotic lesions in FSGS can be missed in routine H&E examination.

Objectives: To differentiate early FSGS from MCD by detection of activated parietal epithelial cells (PECs) in early glomerular sclerotic lesions using claudin-1 immunohistochemical (IHC) staining and by examining podocyte ultrastructural changes.

Patients and Methods: This retrospective study included 28 cases diagnosed as MCD and 20 cases diagnosed as early FSGS. Clinicopathologic data collection, claudin-1 IHC staining and reviewing ultrastructural changes were performed and the results were statistically analyzed.

Results: A statistically significant correlation was detected between claudin-1 expression and the initial diagnosis of the studied groups (P=0.005). Claudin-1 was expressed in a visceral location in 39.28% of the biopsies initially diagnosed as MCD thus were reevaluated as early FSGS lesions. Around 63.64% of the positive cases were presented by steroid-resistant nephrotic syndrome (SRNS) and 63.6% of which showed some ultrastructural changes of FSGS in podocytes including abnormalities in mitochondrial shapes, endoplasmic reticulum changes and a decreased number of autophagic vacuoles.

Conclusions: Claudin-1 is a novel diagnostic marker that can differentiate between confusing cases of early FSGS versus MCD. Defective autophagy plays a role in the pathogenesis of FSGS.

Implication for health policy/practice/research/medical education:
The distinction between early focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) is important as they have different prognosis and management. In early FSGS parietal epithelial cells (PECs) become activated and migrate to a visceral location secondary to podocyte injury to replace injured cells. The migrated PECs then can start in matrix deposition initiating the process of glomerulosclerosis. Early podocyte damage can be reversed, but scarring resulting from denuding the GBM cannot. Claudin -1 is a transmembrane protein that has been found to be expressed exclusively by PECs within the glomeruli, therefore, it can be used to detect early PEC invasion of the glomerular tuft and serve as an early indicator of FSGS lesions preceding overt sclerosis.

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1. Background

Primary focal and segmental glomerulosclerosis (FSGS) is responsible for approximately 10%–15% of the cases of nephrotic syndrome (NS) in children and 20%–30% in adults (1). The incidence of primary FSGS has grown and it is now the leading cause of steroid-resistant nephrotic syndrome (SRNS) in both children and adults. Primary FSGS progresses to end-stage renal disease (ESRD) in about 50% of patients within 10 years of clinical onset (2). Steroids alone are not enough for treatment; in

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addition, it needs more intense immunosuppression for its management (1). Minimal change disease (MCD) is the most common cause of idiopathic NS in children accounting for 80%–90% of cases, but in adults it represents only about 10%–15% of cases being the third cause (3). MCD cases usually do not develop chronic kidney disease; in contrast 95% of MCD patients undergo complete remission on steroid administration (1).

Because of similar clinical presentation and different management and prognosis, it is important to differentiate between FSGS and MCD, since the final diagnosis is usually made by the pathologist (4). The distinction between early FSGS versus MCD may be difficult, because of the focal and segmental nature of the disease particularly when biopsy samples contain only few glomeruli or when glomerular injury is at an early-stage or when the sample is superficial and does not involve deep cortex (5). Biopsy findings of focal tubular atrophy and interstitial fibrosis should also prompt a more exhaustive search for unsampled FSGS even with normal looking glomeruli especially in a small biopsy specimen (6).

Podocyte injury is a key step in the initiation and progression of FSGS (7,8) and podocyte electron microscopic (EM) changes can be detected prior to the development of overt sclerosis (9). Podocyte injury with production of oxidants, extracellular matrix (ECM) proteins and proteinases can alter the glomerular basement membrane (GBM) matrix constituents limiting its ability to anchor podocytes and this eventually leads to podocyte detachment, apoptosis and loss (10). Defective autophagy in kidney epithelium has been accused of podocyte injury (11).

Recent studies have documented that in FSGS parietal epithelial cells (PECs) activation and migration to a visceral location occurs secondary to podocyte injury to replace injured cells. This can serve as a double edged sword as activated PECs can start in matrix deposition initiating the process of glomerulosclerosis (12). Claudin-1 is a 23-kDa transmembrane protein widely expressed in liver and kidney tissue. It is expressed exclusively by PECs within the glomeruli, therefore, it can be used to detect PEC invasion of the glomerular tuft. Normal glomeruli show claudin-1 immunostaining, exclusively at the Bowman's capsule. In contrast, in FSGS lesions migrated PECs will be stained in a visceral location, such aberrant staining could be an early indicator of FSGS lesions preceding overt sclerosis detectable by light microscopy (13).

2. Objectives

The objective of this study was to detect early FSGS changes by examining claudin-1 immunohistochemical (IHC) expression on PECs and by reviewing ultrastructural changes in podocytes in MCD and FSGS cases.

3. Patients and Methods

3.1. Patients and study design

This retrospective cohort study included 48 cases; 28cases diagnosed as MCD and 20 cases diagnosed as early FSGS collected from electron microscopy (EM) unit and pathology laboratory at Ain Shams University Specialized hospital in Cairo, during the period from 2011-2016. All patients who participated in this study signed a written, informed consent before biopsy procedure.

Collected information from the archival files of the patients included patients' age, gender, and any available clinical data regarding symptoms, laboratory findings and response to steroid therapy. Cases with early focal and segmental glomerulosclerosis were included in the study while cases exhibiting advanced sclerotic lesions or cases with secondary FSGS were excluded.

Hematoxylin and eosin (H&E) stained slides together with periodic acid-Schiff (PAS) and Masson's trichrome stained slides were re-examined for evaluation of presence of any glomerular sclerotic segments, glomerular hypercellularity, interstitial inflammation or fibrosis. Immunofluorescence and electron microscopic results were also obtained from archival files and reevaluated.

Representative H&E slides were selected and the corresponding paraffin blocks were sectioned at 5µm thick sections and immunostained using rabbit polyclonal prediluted antibody which is ready to use against claudin-1 from Thermo fisher scientific company, USA (catalog number: RB-9209-R7) according to the manufacturer's protocol.

3.2. Interpretation of claudin-1 immunohistochemical expression

In normal glomeruli without glomerulosclerosis, immunostaining for claudin-1 stained exclusively along Bowman's capsule but within sclerotic lesions, claudin-1 was also expressed by the invading PECs and was therefore found in a visceral location. Brownish membranous and/or cytoplasmic staining was considered positive.

3.2. Ethical approval

The research followed the tenets of the Declaration of Helsinki. In this research, we followed all the ethical considerations related to research on patients' clinical samples. The study was approved by the Research Committee and the Ethical Committee of Faculty of Medicine Ain Shams University.

3.3. Statistical analysis

The data collected were analyzed using a computer software program named SPSS (Statistical Package for Social Sciences) version 17, evaluation of relationship between claudin-1 expression and clinicopathologic

parameters was done using chi-square test and analysis of variance (ANOVA) test. Determining the probability factor (*P* value) assessed the significance of results. *P* value of 0.05 was chosen as the cut off for significance, $P > 0.05$: non-significant. $P < 0.05$: significant. $P < 0.001$: highly significant.

4. Results

The present study included 48 cases, of which 28 cases were diagnosed as MCD representing (58.33%) and 20 cases were diagnosed as early FSGS representing (41.67%). The patient's age ranged from 3-48 years with a mean of 17.6 years for MCD cases, and from 3-50 years with a mean of 22.2 years for FSGS cases. The male to female ratio was (1.3:1) in MCD and (1:1.2) in FSGS. No statistically significant correlation was detected between claudin-1 expression and either the age or the gender of the patient.

The clinical presentation at time of biopsy in MCD and FSGS cases fluctuated between classic nephrotic syndrome, steroid-resistant nephrotic syndrome (SRNS), steroid-dependent nephrotic syndrome (SDNS), relapsing nephrotic syndrome and nephrotic range proteinuria. Hypertension with decreased kidney function was the presentation in one FSGS case. A statistically significant correlation was detected between claudin-1 expression and the main clinical presentation for MCD at time of biopsy since 63.64% of positive MCD cases were presented by SRNS ($P = 0.036$; Table 1).

According to Columbia classification (14), FSGS cases were sub-classified into; collapsing lesions, tip lesions, cellular lesions, perihilar lesions and FSGS NOS (FSGS not otherwise specified) variant. There was no statistically significant correlation between claudin-1 expression and different FSGS variants ($P=0.504$; Table 2). MCD cases were also subdivided into histological groups according to the International Study of Kidney Disease in Children (3). The classification included focal glomerular obsolescence, mild mesangial thickening, focal tubular changes, mild mesangial hypercellularity and diffuse mesangial hypercellularity. No statistically significant correlation was detected between claudin-1 expression and different MCD histological groups (Table 3). Four of the cases diagnosed as MCD were associated with glomerulomegaly, three of

Table 1. Main clinical presentation at time of biopsy and its correlation with claudin-1 expression

Diagnosis	Symptoms	Claudin-1 expression						Chi-Square	
		Negative		Positive		Total			
		No.	%	No.	%	No.	%	χ^2	*P* value
MCD	Classic nephrotic syndrome	3	17.65	0	0.00	3	10.71	11.923	0.036*
	Steroid resistant nephrotic syndrome	3	17.65	7	63.64	10	35.71		
	Steroid dependent nephrotic syndrome	4	23.53	3	27.27	7	25.00		
	Relapsing nephrotic syndrome	2	11.76	1	9.09	3	10.71		
	Proteinuria	4	23.53	0	0.00	4	14.29		
	No available data	1	5.88	0	0.00	1	3.57		
FSGS	Nephrotic syndrome	1	25.00	5	31.25	6	30.00	1.696	0.945
	Steroid resistant nephrotic syndrome	2	50.00	5	31.25	7	35.00		
	Steroid dependant nephrotic syndrome	0	0.00	1	6.25	1	5.00		
	Relapsing nephrotic syndrome	0	0.00	1	6.25	1	5.00		
	Proteinuria	1	25.00	2	12.50	3	15.00		
	Hypertension/increase kidney function	0	0.00	1	6.25	1	5.00		
	No available data	0	0.00	1	6.25	1	5.00		

Table 2. FSGS variants and its correlation with claudin-1 expression.

FSGS variants	Claudin-1 expression						Chi-Square	
	Negative		Positive		Total			
	No.	%	No.	%	No.	%	χ^2	*P* value
Collapsing	0	0.00	1	6.25	1	5.00	3.333	0.504
Tip	0	0.00	4	25.00	4	20.00		
Cellular	0	0.00	1	6.25	1	5.00		
Perihilar	0	0.00	2	12.50	2	10.00		
NOS	4	100.00	8	50.00	12	60.00		
Total	4	100.00	16	100.00	20	100.00		

Table 3. MCD histological groups between studied MCD cases and its correlation with claudin-1 expression

MCD Histologic groups		Claudin-1 expression						Chi-square	
		Negative		Positive		Total			
		No.	%	No.	%	No.	%	χ^2	*P* value
MCD without either glomerular or tubular abnormality	Negative	12	70.59	10	90.91	22	78.57	1.638	0.201
	Positive	5	29.41	1	9.09	6	21.43		
MCD with focal glomerular obsolescence	Negative	12	70.59	9	81.82	21	75.00	0.449	0.503
	Positive	5	29.41	2	18.18	7	25.00		
MCD with mild mesangial thickening	Negative	13	76.47	8	72.73	21	75.00	0.050	0.823
	Positive	4	23.53	3	27.27	7	25.00		
MCD with focal tubular changes	Negative	13	76.47	7	63.64	20	71.43	0.539	0.463
	Positive	4	23.53	4	36.36	8	28.57		
MCD with mild mesangial hypercellularity	Negative	12	70.59	8	72.73	20	71.43	0.015	0.903
	Positive	5	29.41	3	27.27	8	28.57		
MCD with diffuse mesangial hypercellularity	Negative	17	100.00	10	90.91	27	96.43	1.603	0.206
	Positive	0	0.00	1	9.09	1	3.57		

which showed positive claudin-1 immunostaining results representing (27.27%) but with no statistically significant correlation.

Seventeen out of 28 MCD biopsies (60.71%) showed no visceral glomerular expression of claudin-1 which is consistent with the original diagnosis of MCD (Figure 1E), while 11 out of the 28 biopsies (39.28%) showed claudin-1 expression in glomerular visceral location denoting that these biopsies are early FSGS lesions that were missed in the initial diagnosis (Figure 1C & D). Claudin-1 expression also confirmed the presence of glomerulosclerosis in 16 out of the 20 FSGS biopsies (80%) (Figure 1A & B), while 4 out of 20 biopsies did not show positive claudin-1 results (20%) denoting the absence of FSGS in these sections**.** A statistically significant correlation could be detected between claudin-1 expression and the initial diagnosis of the studied groups ($P = 0.005$; Table 4).

4.1. Electron microscopic (EM) reevaluation

4.1.1. Minimal change disease cases

Electron microscopy revealed widespread effacement of podocytes foot processes, with microvillous transformation. An increased number of autophagic vacuoles was noted in the cytoplasm of podocytes (Figure 2). Interestingly seven out of the eleven cases of MCD that showed claudin-1 staining in a visceral location (63.6%) revealed some ultrastructural changes of FSGS especially podocyte hypertrophy, cytoplasmic overload, and detachment from GBM.

4.1.2. Focal segmental glomerulosclerosis cases

Widespread effacement of podocytes foot processes, with microvillous transformation were also seen in FSGS. In addition, visceral epithelial cells (podocytes) showed detachment from the underlying GBM, hypertrophy with overload of the cytoplasm by organelles. Abnormal mitochondria and abnormal profiles of rough endoplasmic reticulum (ER) were also seen since there was a decrease in

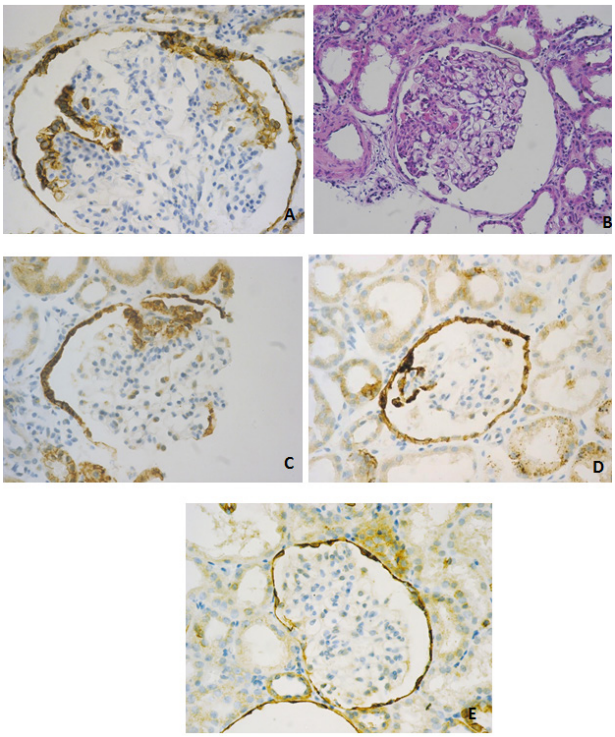

Figure 1. Claudin -1 IHC staining: (A)&(B) FSGS case: **A;** Positive Claudin-1IHC staining highlighting PECs invading glomerular tuft in a visceral location (x40). **B;** Corresponding H&E stained section, note segmental lesions in the same location as stained positively by claudin-1 IHC (x40). **(C&D)** FSGS lesions detected in biopsy initially diagnosed as MCD, note positive Claudin-1 IHC staining in visceral location highlighting PECs invading glomerular tuft (x40). **(E)** MCD case: claudin-1 IHC staining limited to PECs lining Bowman's capsule (x40).

Table 4. Confirmation of initial diagnosis of MCD and FSGS using claudin-1 immunostaining

Diagnosis	Claudin-1 expression						Chi-square	
	Negative		Positive		Total			
	No.	%	No.	%	No.	%	χ^2	*P* value
MCD	17	80.95	11	40.74	28	58.33		
FSGS	4	19.05	16	59.26	20	41.67	7.859	0.005*
Total	21	100.00	27	100.00	48	100.00		

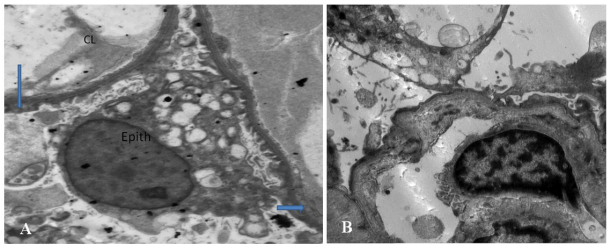

Figure 2. An electron micrograph of MCD: A; Autophagic vacuoles in the cytoplasm of visceral epithelial cells (epith), CL (capillary lumen). Arrows point to effacement of epithelial foot process **B;** Diffuse effacement of epithelial foot processes and an increased number of autophagic vacuoles.

the number of autophagic vacuoles (Figure 3).

The initial histopathologic diagnoses of MCD and FSGS were reevaluated after claudin-1 staining and ultrastructural verification and the 11 MCD cases that stained for claudin-1 in a visceral location were considered as early FSGS cases. This was further supported by the presence of some FSGS ultrastructural changes in seven out of these cases (Figure 4).

5. Discussion

The detection of early presclerotic stages of glomerular injury is of special importance. Podocyte damage and ultrastructural changes have been found to be the first detected morphologic characteristic of FSGS while it is seen prior to the development of overt sclerosis (15). Early podocyte damage can be reversed, but scarring resulting from denuding the GBM cannot (16). PECs activation and invasion of the glomerular tuft have been found to be a secondary event to podocyte damage since recent studies have documented that they play a central role in the development of FSGS (17). A subset of PECs has been found to express stem cell markers and may represent a renal stem cell niche that can replace injured cells. Upon podocyte injury the activated PECs proliferate and migrate to visceral location trying to replenish injured cells (18), yet deleterious consequences and matrix deposition by activated PECs can contribute to the initiation of scarring (19). We, therefore, designed our study comparing MCD and FSGS cases to detect early migrated PECs in visceral location of the glomerular tuft using claudin-1 IHC staining and to assess ultrastructural podocyte changes in early sclerotic stages.

Our results indicate a statistically significant correlation between claudin-1 expression and the initial diagnosis of the lesion as well as with the detection of small glomerular segmental sclerotic lesions in MCD and FSGS ($P = 0.005$). This has been concluded since claudin-1 expression on (60.71%) of cases diagnosed originally as MCD showed no visceral glomerular expression which is consistent with their initial diagnosis as MCD, while (39.28%) of these cases showed positive claudin-1 expression in glomerular visceral location indicating that these biopsies were missed FSGS in the first examination. Our results come in agreement with Smeets et al, who found that (75%) of MCD cases showed no visceral glomerular expression of claudin-1 and (25%) of cases showed positive claudin-1 expression in glomerular visceral location (5). Of interest, our study showed slight increase in number of missed FSGS cases, this is maybe owed to the large number (10 cases = 35.71 %) of our MCD cases presented by SRNS of

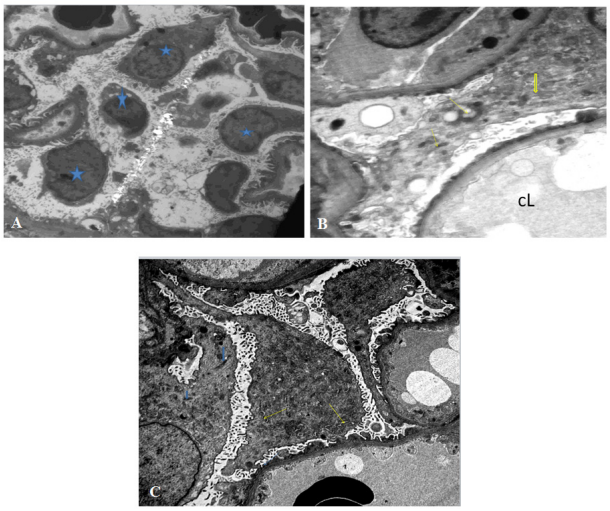

Figure 3. An electron micrograph of FSGS: A; detachment of visceral epithelial cells (stars). **B;** diffuse effacement of foot processes of epithelial cells with hypertrophy, abnormal mitochondria (thin arrows) and abnormal endoplasmic reticulum (thick arrow). **C;** Overload of the cytoplasm of podocytes, lack of autophagic vacuoles and abnormal profiles of endoplasmic reticulum are seen (arrows).

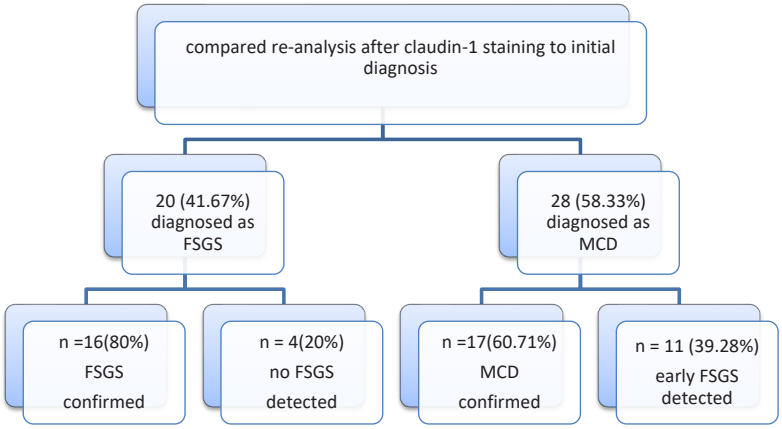

Figure 4. Summary of re-evaluation of MCD and FSGS studied cases after claudin-1 staining as compared with their original diagnoses

which seven cases (63.64%) stained positive for claudin-1. These small newly detected sclerotic lesions were not detectable in available H&E and PAS stained sections.

Analysis of claudin-1 expression on biopsies diagnosed originally as FSGS revealed positive expression in visceral location in (80%) of these cases confirming their diagnosis and negative expression in (20%) of cases. This comes in agreement with Smeets et al who found that (87%) of their cases stained positive for claudin-1 expression confirming the diagnosis of FSGS and (13%) of cases showed negative expression (5). These negative results may be explained by the focal and segmental nature of FSGS, where the original diagnosis was made on other sections of the same biopsy. Sclerotic lesions may be disappeared with further serialling especially with these early sclerotic lesions that are only found in few numbers of glomeruli.

Statistically significant correlation could be detected between claudin-1 expression and the main presenting symptom for MCD at time of presentation (P = 0.036), since, 63.64% of positive cases were presented mainly by SRNS ,this comes in agreement with the studies of Mason and also Maas et al, who reported that FSGS cases which are missed in the original biopsy are often steroid resistant (2,4), however no statistically significant correlation could be detected between claudin-1 expression and main presenting symptoms for FSGS at time of presentation (P = 0.945) or between claudin-1 expression and FSGS variants (P = 0.504).

Generally no significant correlation could be detected between claudin-1 expression and histological groups of MCD (P > 0.05), however ,we found that 4 out of seven cases that showed focal tubular changes showed positive claudin-1 expression representing 36.36% of positive MCD cases which come in agreement with Mason (2), D'Agati and Stokes (14), Vivarelli et al (6), and Kambham (1), who reported that biopsy findings of focal tubular atrophy and interstitial fibrosis should prompt a more exhaustive search for unsampled FSGS even with normal looking glomeruli especially with a small biopsy specimen hence these findings suggest the possibility of presence of a glomerulus with a segmental lesion in the tissue near the biopsy.

In the current study 4 cases diagnosed as MCD were associated with glomerulomegaly three of which showed positive claudin-1 immunostaining results representing (27.27%) of positive cases, these results come in agreement with Fogo et al, who reported that 33.3% of patients originally diagnosed as MCD with increased glomerular area up to 1.75 time more than normal glomerular area and 100% of MCD patients with glomerular area greater than 1.75 time than normal glomerular area, both proved to be FSGS cases in the subsequent biopsies done (20), yet our results do not reach statistical significance (P = 0.114) most probably because of the few number of MCD cases with glomerular hypertrophy included in our study. No statistically significant correlation could be detected between claudin-1 expression and patient's age (P = 0.209 for MCD and P = 0.587 for FSGS) or patient's gender (P = 0.315 for MCD and P = 0.369 for FSGS) which also comes in agreement with previous studies (21, 22).

Reviewing the EM changes of our FSGS cases revealed widespread effacement of podocytes foot processes, microvillus transformation, podocyte detachment from the underlying GBM. This was in accordance with the study of Fatima et al (17). Podocytes also showed hypertrophy with overload of the cytoplasm by organelles, abnormal mitochondria, abnormal profiles of rough endoplasmic reticulum and a decrease in the number of autophagic vacuoles. Moreover 7 out of 11 MCD cases that were reevaluated as FSGS due to the presence of claudin-1 staining in a visceral location revealed some ultrastructural changes of FSGS in the form of podocyte

detachment from GBM, hypertrophy and cytoplasmic overload with organelles. Ultrastructural changes of FSGS in our study were similar to those of Kawakami et al, who demonstrated cytoplasmic vacuolation and abnormalities in podocyte ER and mitochondria which showed increased diameter, dysmorphic shapes, reduced length and focal loss of cristae. The mitochondrial and ER changes have been attributed to defective autophagy in kidney epithelium (11). The autophagic degradation pathway is important for cell homeostasis and responses to environmental stress. Macroautophagy is a process by which organelles are turned over and disposed of and their building blocks recycled. When autophagy is disrupted in kidney epithelium, failure to remove aged mitochondria by "mitophagy" appears to be a central problem. Aged mitochondria persist and, instead of generating ATP efficiently, they produce injurious oxygen radicals in excess with limited ATP production (23). Reactive oxygen species (ROS) generation can also result from persistence of misfolded proteins with the development of stressed ER and activation of the cell stress signaling pathways. In absence of autophagy stressed ER persist with processing of abnormal proteins leading to generation of pathologic signals. Thus defective autophagy in kidney epithelium with its consequences can provide new insights in the pathogenesis of FSGS and further studies highlighting this process are recommended (11).

6. Conclusions

We concluded that IHC detection of the PEC marker claudin-1 can be used to detect early FSGS lesions that can be missed on routine H&E sections thus it can be used as a diagnostic marker to differentiate between confusing cases of MCD and early FSGS. Claudin-1 staining is also recommended in cases of MCD presented clinically with steroid resistance or showing glomerulomegaly on histologic examination. Further studies concerning the role of autophagy in the pathogenesis of FSGS are specially recommended.

Limitations of the study

The limitations of the current study were the few number of cases included and the unavailability of some clinical and laboratory data in some cases.

Authors' contribution

NGE and EAM designed the study. EAM collected the data and followed the IHC staining. NGE revised the IHC staining and ultrastructural results. NMAR revised the IHC staining, drafted and wrote the paper. WAAEM collected clinical and laboratory data. OHN revised the methods and results. All authors edited and revised the final manuscript and accepted its publication.

Conflicts of interest

Authors declare no conflicts of interest.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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