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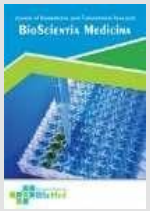

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Is It a Tumor or Not? A Case of Focal Segmental Glomerulosclerosis Secondary to Type 2 Diabetes with a Concomitant Renal Pseudotumor

Rery TF Yuniarti[1*], Ian Effendi[2], Zulkhair Ali[2], Novadian[2], Suprapti[2], Elfiani[1], Novandra AP[1], Dila Siti Hamidah[3], Fadil Pramudhya Husein[4], Ika Kartika Edi P[5]

[1]Subspecialized Residency Training Student of Nephrology, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[2]Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[3]Department of Radiology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[4]Department of Urology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[5]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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***Corresponding author:**
Rery TF Yuniarti

E-mail address:
rerysppd@gmail.com

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A B S T R A C T

Background: Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of glomerular injury that can be primary or secondary to various conditions, including obesity, diabetes, and hypertension. Renal masses, often detected incidentally, can be benign or malignant, with renal cell carcinoma (RCC) being the most common. This case report presents a patient with FSGS secondary to type 2 diabetes and a concomitant renal pseudotumor, initially suspected to be RCC. **Case presentation:** A 60-year-old woman presented with weakness, fever, and weight loss. Imaging revealed a renal mass, initially suspected to be RCC. A kidney biopsy revealed FSGS, and further evaluation confirmed type 2 diabetes. After controlling her diabetes and hypertension, the renal mass regressed, suggesting a pseudotumor. **Conclusion:** This case highlights the importance of considering pseudotumors in the differential diagnosis of renal masses, especially in patients with comorbidities such as diabetes. A kidney biopsy can help avoid unnecessary invasive procedures like nephrectomy.

1. Introduction

Focal segmental glomerulosclerosis (FSGS) is a pathological condition characterized by scarring or sclerosis affecting a portion (segmental) of some (focal) glomeruli within the kidney. It is not a singular disease entity but rather a histologic pattern of glomerular injury, representing a spectrum of clinicopathologic entities with diverse etiologies. The hallmark of FSGS is the injury to podocytes, the specialized cells lining the glomerular capillaries, which leads to the characteristic sclerotic lesions. The clinical presentation of FSGS can vary, ranging from

asymptomatic proteinuria to full-blown nephrotic syndrome, characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The progression of FSGS can lead to end-stage renal disease (ESRD), necessitating dialysis or kidney transplantation. FSGS is classified into primary (idiopathic), secondary, genetic, and unclassified forms. Primary FSGS, often presenting with nephrotic syndrome, is thought to be caused by circulating permeability factors that play a central role in the effacement of podocyte foot processes. Secondary FSGS encompasses a range of conditions, including; Maladaptive FSGS: Secondary to glomerular hyperfiltration, as seen in obesity, diabetic nephropathy, and hypertension; Virus-associated FSGS: Associated with viral infections, such as HIV and hepatitis B and C; Drug-induced FSGS: Resulting from certain medications, such as pamidronate and interferon. Genetic FSGS is caused by mutations in genes encoding proteins expressed in podocytes and the slit diaphragm. The overlapping clinicopathologic features of these various forms often pose diagnostic challenges.[1,2]

The incidence and prevalence of FSGS are difficult to ascertain due to geographical and racial disparities. Estimates of FSGS incidence range from 1.4 to 21 cases per million population. FSGS can occur at any age, affecting approximately 7-10% of children and 20-30% of adults with nephrotic syndrome. In adults, FSGS is more prevalent in males, with a 1.5 to 2-fold higher incidence compared to females. The incidence of FSGS is about 5 times higher in black patients compared to white patients, with annual incidences of 24 cases and 5 cases per million population in the United States, respectively. Renal masses, whether cystic or solid, are often detected incidentally during imaging studies. Computed tomography (CT) scans with contrast enhancement are the preferred imaging modality for characterizing renal masses. Hematuria can serve as a warning sign, prompting further evaluation and imaging, leading to diagnosis and treatment planning. The most common primary renal tumor is renal cell carcinoma (RCC), accounting for 80-90% of cases. RCC is the most lethal of the common urologic cancers, with a high mortality rate. Despite advances in diagnosis and treatment, the prognosis for patients with metastatic RCC remains poor.[3,4]

The pathogenesis of FSGS, particularly in the context of malignancy, is complex and not fully elucidated. Several mechanisms have been proposed, including; Circulating permeability factors: Primary FSGS is thought to be mediated by circulating permeability factors that lead to podocyte injury and proteinuria; Glomerular hyperfiltration: In secondary FSGS, glomerular hyperfiltration, as seen in obesity, diabetes, and hypertension, can lead to podocyte damage and sclerosis; Genetic mutations: Genetic mutations affecting podocyte proteins can disrupt the glomerular filtration barrier, resulting in FSGS; Immune dysregulation: In some cases, FSGS may be associated with immune dysregulation, as evidenced by the presence of glomerular immune deposits.[5,6] The management of FSGS depends on the underlying etiology and the severity of the disease. Treatment options include; Blood pressure control: Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are commonly used to control blood pressure and reduce proteinuria; Immunosuppression: Corticosteroids and other immunosuppressive agents may be used in primary FSGS and some secondary forms; Dietary modifications: Sodium restriction and protein intake control may be recommended; Renal replacement therapy: In cases of ESRD, dialysis or kidney transplantation may be necessary.[7,8]

The prognosis of FSGS varies depending on the underlying cause, the severity of the disease, and the response to treatment. Primary FSGS often has a poor prognosis, with a high risk of progression to ESRD. Secondary FSGS may have a better prognosis if the underlying condition can be effectively managed.[9,10] This case report presents a unique scenario of a patient with FSGS secondary to type 2 diabetes and a concomitant renal pseudotumor, initially suspected to be RCC. The patient's clinical presentation, imaging

findings, and histopathological evaluation are discussed, highlighting the diagnostic challenges and the importance of considering pseudotumors in the differential diagnosis of renal masses. The successful management of the patient's diabetes and hypertension led to the regression of the pseudotumor, underscoring the importance of addressing underlying comorbidities in the treatment of FSGS.

2. Case Presentation

A 60-year-old female, Mrs. S, presented to the Internal Medicine Clinic on October 30th, 2022, referred from the Urology Surgery Clinic with a primary complaint of a request for a kidney biopsy. The patient, a married Muslim woman with a Bachelor's degree and currently employed as a teacher, resides in Plaju Palembang. The patient's primary concern was the need for a kidney biopsy, as advised by her previous physician. She also reported experiencing increasing weakness over the past month, accompanied by intermittent fever. Approximately one month prior to her presentation (around September 2022), Mrs. S began experiencing nocturnal fevers, typically occurring in the evenings. She reported feeling well during the daytime. Additionally, she complained of difficulty sleeping, characterized by waking up at 2 am and subsequently staying awake until noon, engaging in various activities. She also noted a decline in appetite and a resultant weight loss. She reported having been heavier in the past, weighing approximately 90 kg when her husband was alive (he passed away in 2017). Her current weight was between 72-73 kg. Mrs. S denied any increased frequency of urination at night, excessive thirst, or increased appetite. She also denied any history of non-healing wounds, cough, shortness of breath, yellowing of the eyes (jaundice), or swelling around the eyes, particularly upon waking in the morning. The patient primarily complained of generalized weakness, which tended to improve with rest. The weakness was not associated with any specific posture or activity and was not accompanied by shortness of breath. She denied any pain in her right lower back and reported normal bowel and bladder habits.

One day prior to her presentation at the clinic, Mrs. S experienced cold sweats and shivering, prompting her to seek immediate medical attention at a private hospital. During her hospitalization, she underwent blood tests, an ultrasound, and an abdominal CT scan. The attending physician informed her of a suspected kidney tumor and diabetes. After five days of treatment, her condition improved, and she was discharged with instructions to enroll in the BPJS (Indonesian National Health Insurance Program) and follow up with a urology surgeon. She was also advised to start insulin therapy but declined, opting for oral medication only, including glimepiride 1x2mg, metformin 2x500mg, and vitamins. Mrs. S was referred to the urology clinic at Siloam Hospital and subsequently to the urology surgery clinic at RSMH (Dr. Mohammad Hoesin General Hospital) Palembang. The urology surgery clinic then referred her to the Hypertension Kidney Clinic at RSMH for a kidney biopsy. She was admitted under the care of a nephrologist for the biopsy procedure and discharged home while awaiting the results. The kidney biopsy revealed Focal Segmental Glomerulosclerosis (FSGS). Mrs. S was then transferred from the urology surgery clinic to the Hypertension Kidney Clinic for further management of FSGS. She was prescribed methyl prednisolone 1x4mg, myfortic 180mg 2x2 tablets, candesartan 1x4mg, glimepiride 1x2mg, and metformin 2x500mg.

On March 27th, 2023, Mrs. S returned to the Hypertension Kidney Clinic for a follow-up evaluation of her diabetes and the suspected kidney tumor. She reported following advice she found on YouTube from a Dr. ZA, suggesting that tumors or cancer could be cured by fasting and consuming alkaline drinks. She had been fasting daily and drinking Zam-zam water. She also admitted to discontinuing her metformin medication for approximately one month. Mrs. S had a history of hypertension since 2013 but has not been taking her medication regularly. She had been

managing her hypertension with dietary measures like consuming cucumbers, lemon juice with honey, and ginger. She denied any prior history of diabetes mellitus, kidney disease, jaundice/hepatitis, blood transfusions, blood disorders, tumors, malaria, or sore throat. Mrs. S reported no family history of tumors, hypertension, diabetes mellitus, kidney disease, jaundice/hepatitis, blood transfusions, blood disorders, malaria, or sore throat. Mrs. S is a widow with two adult children, a 33-year-old daughter, and a 28-year-old son, both of whom are married. She is the eldest of six siblings. All her siblings are currently in good health, except for the youngest, who passed away at the age of 30 due to seizures. Mrs. S reported eating three meals a day with a variety of side dishes and vegetables.

On March 27th, 2023, Mrs. S appeared moderately ill but was conscious and alert. Her blood pressure was 130/80 mmHg, pulse rate was 78 beats/minute with adequate and regular tension, respiratory rate was 20 breaths/minute, and axillary temperature was 36.8°C. Anthropometric measurements revealed a height of 159 cm and a weight of 72 kg, resulting in a BMI of 28.5 (Obese 1). Head and neck examinations were unremarkable. Respiratory examination revealed normal breath sounds with no wheezes or rhonchi. A cardiovascular examination revealed a regular heart rate and rhythm with no murmurs or gallops. Abdominal examination revealed a soft and non-tender abdomen with no palpable masses or organomegaly. Extremities examination revealed no edema or lymphadenopathy (Table 1).

An ECG performed on the same day was normal. Ultrasound imaging from October 17th, 2022, at Charitas Hospital, revealed a heterogeneous solid mass in the right kidney, measuring approximately 5.7 x 5.4 x 6.5 cm, suspicious for malignancy. Multiple left kidney stones and a septated cyst with calcification were also noted. CT imaging with contrast from October 19th, 2023, at Charitas Hospital confirmed the presence of a solid malignant mass with cystic components in the inferior pole of the right kidney, measuring approximately 7 x 6.5 x 8.4 cm. The mass was infiltrating the gerota fascia and right perirenal fat and was attached to the right psoas muscle, transversus abdominis muscle, and right internal oblique muscle. Multiple enlarged perirenal and para-aortic lymph nodes were also observed. Ultrasound imaging from November 8th, 2022, at RSMH, revealed an inhomogeneous hypoechoic mass in the right renal cortex parenchyma, measuring approximately 5 x 4 cm. Ultrasound imaging from April 13th, 2023, at RSMH showed a reduction in the size of the mass to 2.06 x 1.36 cm. CT imaging with contrast from April 14th, 2023, at RSMH revealed multiple simple cysts in both kidneys (Bosniak 1) but no evidence of the previously observed solid mass. CT imaging from May 3rd, 2023, confirmed the presence of simple cysts in both kidneys (Bosniak 1).

A kidney biopsy performed on November 21st, 2022, revealed Focal Segmental Glomerulosclerosis (FSGS) with one crescent and chronic nephritis. No evidence of malignancy was found. Focal segmental glomerulosclerosis (FSGS) secondary to type 2 diabetes with a concomitant renal pseudotumor, initially suspected to be RCC. Controlled type 2 diabetes. Controlled hypertension. Obesity 1. Non-pharmacological therapy; Rest; 1700 calorie diabetic diet; Patient education. Pharmacological therapy; Methylprednisolone 1x4mg; Myfortic 180mg 2x2 tablets; Candesartan 1x8mg; Glimepiride 1x2mg; Metformin 2x500mg. Referral to Urology Clinic for continued care. Regular follow-up appointments at the Hypertension Kidney Clinic. Consultations with the Endocrine Clinic, Eye Clinic, Urology Clinic, and Nutrition Clinic. Routine blood and urine tests. Regular abdominal ultrasounds and CT scans with contrast. During the month of Ramadan, the patient's treatment plan was reevaluated, and she was advised to continue her medications with adjusted dosages during Ramadan. Mrs. S was also evaluated by an endocrinologist for further management of her diabetes. Her blood sugar levels had improved, with an HbA1c of 6.1%. She was advised to continue her oral hypoglycemic medications with adjusted dosages. An ophthalmology examination revealed mild non-

proliferative diabetic retinopathy (NPDR). She was advised to maintain good blood sugar control to prevent further progression of diabetic retinopathy. The urology team recommended continuing the treatment plan as advised by the nephrologist.

Focal segmental glomerulosclerosis (FSGS) secondary to type 2 diabetes with a concomitant renal pseudotumor, initially suspected to be RCC. Controlled type 2 diabetes. Controlled hypertension. Obesity 1. With appropriate management of her diabetes and hypertension, Mrs. S's FSGS remained stable, and the renal pseudotumor regressed, confirming its benign nature. This case highlights the importance of considering pseudotumors in the differential diagnosis of renal masses, especially in patients with comorbidities such as diabetes. A kidney biopsy can be crucial in differentiating pseudotumors from malignant lesions and avoiding unnecessary invasive procedures like nephrectomy. Comprehensive management of underlying comorbidities, such as diabetes and hypertension, is essential in the treatment of FSGS and can contribute to the resolution of associated pseudotumors (Tables 2 and 3).

Table 1. Timeline of clinical and laboratory findings.

Date	Clinical findings	Laboratory findings
September 2022	Onset of fatigue, fever, and weight loss	-
October 17th, 2022	-	Elevated blood glucose levels (random blood sugar 367 mg/dL), proteinuria (urine protein-to-creatinine ratio 3.5 g/g), and microscopic hematuria. eGFR 84 mL/min/1.73 m^2
October 30th, 2022	The patient presents to the Internal Medicine Clinic for a kidney biopsy; physical examination reveals a moderate illness, blood pressure 130/80 mmHg, pulse 78 bpm, BMI 28.5 kg/m^2	-
November 21st, 2022	-	Kidney biopsy reveals FSGS with chronic nephritis but no evidence of malignancy
March 27th, 2023	Follow-up visit shows improvement in symptoms and blood glucose control (HbA1c 6.1%)	-
April 13th, 2023	-	Repeat US at RSMH shows a suspected mass with a size of 2.06 x 1.36 cm in the right kidney
April 14th, 2023	-	Repeat contrast-enhanced CT scan of the abdomen shows complete resolution of the mass
May 3rd, 2023	-	Additional contrast-enhanced CT scan confirms the absence of the renal mass

Table 2. Timeline of USG, CT scan, and biopsy.

Date	Event
September 2022	Onset of fatigue, fever, and weight loss
October 17th, 2022	Abdominal ultrasound (US) at an outside hospital shows a heterogeneous solid mass in the right kidney, suggestive of malignancy
October 19th, 2022	Contrast-enhanced computed tomography (CT) scan of the abdomen confirms the presence of a solid mass with irregular cystic components in the inferior pole of the right kidney
October 30th, 2022	The patient presents to the Internal Medicine Clinic for a kidney biopsy
November 8th, 2022	Repeat US at RSMH shows an inhomogeneous hypoechoic mass in the right renal cortex parenchyma
November 21st, 2022	Kidney biopsy reveals FSGS with chronic nephritis but no evidence of malignancy
March 27th, 2023	Follow-up visit shows improvement in symptoms and blood glucose control; repeat imaging shows a significant reduction in the size of the renal mass
April 13th, 2023	Repeat US at RSMH shows a suspected mass with a size of 2.06 x 1.36 cm in the right kidney
April 14th, 2023	Repeat contrast-enhanced CT scan of the abdomen shows complete resolution of the mass
May 3rd, 2023	Additional contrast-enhanced CT scan confirms the absence of the renal mass

Table 3. Step by step to making a diagnosis.

Step	Treatment	Finding	Interpretation
1	Patient interview	A 60-year-old woman presents with fatigue, fever, and weight loss for 1 month; history of uncontrolled type 2 diabetes and hypertension; non-compliant with medications	Symptoms and medical history suggestive of possible renal disease
2	Physical examination	Moderately ill appearance; blood pressure 130/80 mmHg; pulse 78 bpm; BMI 28.5 kg/m^2	Physical findings consistent with obesity and possible hypertension
3	Laboratory investigations	Elevated blood glucose levels (random blood sugar 367 mg/dL, HbA1c 14.3%); proteinuria (urine protein-to-creatinine ratio 3.5 g/g); microscopic hematuria; eGFR 84 mL/min/1.73 m^2	Laboratory abnormalities indicative of diabetes, kidney dysfunction, and possible glomerular disease
4	Abdominal ultrasound	Heterogeneous solid mass in the right kidney, measuring approximately 5.7 x 5.4 x 6.5 cm	Imaging suggestive of a renal mass, raising suspicion for malignancy
5	Contrast-enhanced CT scan of the abdomen	Solid mass with irregular cystic components in the inferior pole of the right kidney, measuring 7 x 6.5 x 8.4 cm; mass infiltrating the gerota fascia and right perirenal fat; multiple enlarged perirenal and para-aortic lymph nodes	CT findings further raise concern for renal cell carcinoma (RCC)
6	Kidney biopsy	FSGS with chronic nephritis; no evidence of malignancy	Biopsy results rule out RCC and confirm the diagnosis of FSGS
7	Follow-up imaging	Significant reduction in the size of the renal mass on repeat ultrasound; complete resolution of the mass on repeat CT scan	Regression of the mass confirms the diagnosis of a renal pseudotumor
8	Clinical assessment	Improvement in symptoms and blood glucose control	Clinical improvement supports the diagnosis of FSGS and the successful management of diabetes

3. Discussion

Focal segmental glomerulosclerosis (FSGS) is a complex kidney disease characterized by a specific pattern of injury to the glomeruli, the intricate network of blood vessels responsible for filtering waste products from the bloodstream. Focal term signifies that the damage is not uniformly distributed across all glomeruli within the kidney. Instead, it affects only a subset or a portion of these filtering units. This focal nature distinguishes FSGS from other glomerular diseases where damage is more widespread. The segmental term highlights that the scarring, or sclerosis, within each affected glomerulus, is localized to a particular segment or portion of the glomerulus. It is not a diffuse, global scarring of the entire glomerulus. Glomerulosclerosis refers to the actual scarring process, where the normal glomerular structure is replaced by fibrous tissue, rendering the affected segment incapable of performing its filtration function. The hallmark of FSGS lies in its unique histopathological presentation, which can be observed through microscopic examination of kidney tissue obtained via a biopsy. The defining characteristic is the presence of sclerosis or scarring in a segment of the affected glomerulus. This sclerosis appears as an increase in the extracellular matrix, deposition of collagen fibers, and obliteration of the normal glomerular capillary loops. Hyalinosis, a form of degeneration, may be observed in some sclerotic segments, appearing as a homogenous, glassy material within the affected areas. Podocytes, the specialized cells lining the glomerular capillaries, play a crucial role in maintaining the filtration barrier. In FSGS, podocytes often exhibit foot process effacement, where the normally interdigitating foot processes become flattened and fused, disrupting the filtration barrier. In some cases, inflammatory cells, such as lymphocytes and macrophages, may infiltrate the glomeruli, contributing to ongoing injury and scarring. The light microscopy technique allows for the

visualization of segmental sclerosis, hyalinosis, and inflammatory cell infiltration. It provides an overview of the extent and pattern of glomerular damage. The immunofluorescence microscopy technique uses fluorescently labeled antibodies to detect the presence of immune deposits within the glomeruli. While primary FSGS is typically characterized by the absence of significant immune deposits, secondary FSGS may exhibit immune deposits depending on the underlying cause. Electron Microscopy is a high-resolution technique that allows for detailed visualization of the podocytes and their foot processes. It can reveal subtle changes in podocyte structure, such as foot process effacement and microvillous transformation, which are crucial in the pathogenesis of FSGS. It provides definitive evidence of the characteristic segmental sclerosis, confirming the diagnosis of FSGS. It helps differentiate between primary, secondary, and genetic FSGS based on the presence or absence of immune deposits, associated histologic features, and ultrastructural findings. The histopathological findings can influence treatment decisions, as the therapeutic approach may differ depending on the underlying cause and the severity of the damage. The extent of sclerosis and the degree of podocyte injury can provide insights into the likely prognosis and the risk of progression to end-stage renal disease.[11,12]

Focal segmental glomerulosclerosis (FSGS) is not a single disease entity but rather a syndrome with a diverse array of etiologies. This heterogeneity reflects the complexity of the disease and the various pathways that can lead to the characteristic pattern of glomerular injury. Understanding the underlying causes of FSGS is crucial for accurate diagnosis, appropriate treatment, and prognostication. Primary FSGS also known as idiopathic FSGS, this form accounts for approximately 80% of FSGS cases in adults. The term "idiopathic" signifies that there is no identifiable underlying cause for the glomerular injury. However, it is believed that circulating permeability factors, yet to be fully characterized, play a central role in the pathogenesis of primary FSGS. These factors are thought to disrupt the structure and function of podocytes, specialized cells lining the glomerular capillaries, leading to proteinuria and glomerulosclerosis. Primary FSGS often presents with nephrotic syndrome, a constellation of clinical findings including heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The response to treatment is variable, and a significant proportion of patients with primary FSGS progress to end-stage renal disease (ESRD). Secondary FSGS arises as a consequence of various underlying conditions that indirectly lead to glomerular injury. Obesity, diabetes mellitus, and metabolic syndrome are increasingly recognized as important risk factors for secondary FSGS. These conditions can lead to glomerular hyperfiltration, an increased workload on the glomeruli, which can cause mechanical stress and injury to podocytes. Both essential and secondary hypertension can contribute to the development of FSGS. Hypertension can lead to glomerular hypertension, further exacerbating the mechanical stress on podocytes and promoting glomerulosclerosis. Certain viral infections, such as HIV, hepatitis B, and hepatitis C, have been associated with the development of FSGS. These viruses can directly or indirectly damage podocytes, leading to proteinuria and glomerulosclerosis. Certain medications, such as pamidronate, interferon, and anabolic steroids, have been implicated in the development of FSGS. These drugs can directly injure podocytes or induce immune-mediated damage to the glomeruli. Conditions that lead to a decrease in the number of functioning nephrons, such as congenital anomalies, reflux nephropathy, and prior kidney surgery, can also result in secondary FSGS. The remaining nephrons undergo compensatory hyperfiltration, which can lead to podocyte injury and glomerulosclerosis. Genetic FSGS is caused by mutations in genes encoding proteins crucial for podocyte function and the integrity of the glomerular filtration barrier. These mutations can disrupt the structural integrity of podocytes, impair their ability to maintain the filtration barrier and lead to proteinuria.

NPHS1 Encodes nephrin, a key component of the slit diaphragm, a specialized intercellular junction between podocytes. NPHS2 Encodes podocin, another crucial protein of the slit diaphragm. WT1 Encodes a transcription factor involved in podocyte development and function. ACTN4 Encodes alpha-actinin-4, a cytoskeletal protein important for podocyte structure. TRPC6 Encodes a transient receptor potential cation channel, involved in podocyte calcium signaling. Genetic FSGS typically presents in childhood or adolescence and often has a progressive course, leading to ESRD. However, the rate of progression can vary depending on the specific genetic mutation involved. This category encompasses cases of FSGS that do not fit into the primary, secondary, or genetic categories. These cases may represent a heterogeneous group of disorders with yet-to-be-identified etiologies or may be variants of primary or secondary FSGS with atypical features.[13,14]

The common denominator in the pathogenesis of all forms of focal segmental glomerulosclerosis (FSGS) is injury to the podocytes, highly specialized cells that form a crucial component of the glomerular filtration barrier. These intricate cells, with their interdigitating foot processes, act as a selective sieve, regulating the passage of molecules from the bloodstream into the urine. Injury to podocytes disrupts this delicate filtration barrier, leading to proteinuria, the hallmark of FSGS. In primary FSGS, where no identifiable underlying cause is evident, circulating permeability factors are believed to be the primary instigators of podocyte injury. These elusive factors, yet to be fully characterized, are thought to be soluble mediators that alter the structure and function of podocytes, leading to foot process effacement and protein leakage. Cardiotrophin-like cytokine-1 (CLC-1) is a cytokine that has been shown to induce proteinuria and glomerulosclerosis in animal models. Soluble urokinase plasminogen activator receptor (suPAR) is a circulating protein that has been associated with an increased risk of FSGS and recurrence after kidney transplantation. Anti-CD40 antibodies have been detected in some patients with FSGS and may contribute to podocyte injury. However, the exact identity and mechanisms of action of these circulating permeability factors remain an active area of research. In secondary FSGS, the mechanisms of podocyte injury are diverse and depend on the underlying cause. In conditions such as obesity, diabetes, and hypertension, glomerular hyperfiltration, an increased workload on the glomeruli, is thought to play a significant role in podocyte injury. This increased pressure and flow through the glomerular capillaries can lead to mechanical stress, stretching, and detachment of podocytes, disrupting the filtration barrier. In addition to mechanical stress, hemodynamic and metabolic factors associated with obesity, diabetes, and hypertension can also contribute to podocyte injury. Angiotensin II is a hormone that can promote inflammation and fibrosis in the glomeruli. Hyperglycemia is a high blood sugar level that can directly damage podocytes and promote the production of reactive oxygen species, leading to oxidative stress. Insulin resistance can disrupt podocyte metabolism and function. Dyslipidemia elevated levels of cholesterol and triglycerides can contribute to glomerular injury. Viral infections and certain medications can directly or indirectly damage podocytes, leading to FSGS. Viruses can infect podocytes directly, causing cell death or dysfunction. Medications can induce podocyte injury through various mechanisms, including direct toxicity, immune-mediated damage, and alterations in glomerular hemodynamics. In conditions leading to a reduced nephron mass, such as congenital anomalies, reflux nephropathy, and prior kidney surgery, the remaining nephrons undergo compensatory hyperfiltration to maintain overall kidney function. However, this adaptive response can lead to increased glomerular pressure and flow, resulting in mechanical stress and injury to podocytes, eventually contributing to FSGS. Genetic FSGS arises from mutations in genes encoding proteins essential for podocyte function and the integrity of the slit diaphragm, a specialized intercellular junction between podocytes. These mutations can disrupt the structural integrity of

podocytes, impair their ability to maintain the filtration barrier and lead to proteinuria. The specific mechanisms by which these genetic mutations lead to podocyte injury and FSGS vary depending on the affected protein. For example, nephrin is a mutation in the NPHS1 gene, which encodes nephrin, a key component of the slit diaphragm, and can disrupt the structural integrity of the slit diaphragm, leading to increased permeability and proteinuria. Podocin is a mutation in the NPHS2 gene, which encodes podocin, another crucial protein of the slit diaphragm, and can impair the proper formation and function of the slit diaphragm, also resulting in increased permeability and proteinuria. Mutations in the WT1 gene, which encodes a transcription factor involved in podocyte development and function, can disrupt the regulation of podocyte-specific genes, leading to podocyte dysfunction and FSGS. Alpha-actinin-4 is a mutation in the ACTN4 gene, which encodes alpha-actinin-4, a cytoskeletal protein important for podocyte structure, which can alter the cytoskeletal architecture of podocytes, impairing their ability to withstand mechanical stress and maintain the filtration barrier. Mutations in the TRPC6 gene, which encodes a transient receptor potential cation channel, involved in podocyte calcium signaling, can disrupt intracellular calcium homeostasis, leading to podocyte injury and FSGS.[15,16]

The clinical presentation of focal segmental glomerulosclerosis (FSGS) is remarkably diverse, spanning a spectrum from asymptomatic proteinuria to full-blown nephrotic syndrome. This variability is influenced by several factors, including the underlying cause of FSGS, the severity of the disease, and the individual patient's characteristics. In some cases, FSGS may be clinically silent, with no overt symptoms or signs. The only indication of the underlying glomerular injury may be the detection of proteinuria, the presence of excess protein in the urine, during routine urinalysis. This asymptomatic presentation highlights the importance of regular checkups and urine screening, especially in individuals with risk factors for FSGS, such as obesity, diabetes, and hypertension. At the other end of the spectrum, FSGS can manifest as nephrotic syndrome, a constellation of clinical findings resulting from significant glomerular damage and heavy proteinuria. The loss of substantial amounts of protein in the urine, exceeding grams per day, is the defining characteristic of nephrotic syndrome. This excessive protein loss disrupts the delicate balance of proteins in the bloodstream, leading to various complications. Albumin, a protein produced by the liver, plays a crucial role in maintaining the oncotic pressure of the blood, preventing fluid from leaking out of the blood vessels into the tissues. In nephrotic syndrome, the heavy proteinuria leads to a significant loss of albumin in the urine, resulting in hypoalbuminemia, or low levels of albumin in the blood. The hypoalbuminemia disrupts the oncotic pressure balance, causing fluid to shift from the bloodstream into the tissues, leading to edema, or swelling. Edema can manifest in various parts of the body, including the legs, ankles, feet, face, and hands. In severe cases, fluid may accumulate in the abdomen (ascites) or the lungs (pleural effusion), causing shortness of breath and other complications. The liver, in an attempt to compensate for the loss of albumin, increases the production of various proteins, including lipoproteins, which transport cholesterol and triglycerides in the blood. This compensatory response, coupled with the impaired lipid metabolism associated with nephrotic syndrome, leads to hyperlipidemia, or elevated levels of cholesterol and triglycerides in the blood. Hyperlipidemia can contribute to the development of atherosclerosis and increase the risk of cardiovascular disease. Generalized tiredness and weakness are common complaints in patients with FSGS, often attributed to underlying kidney disease, anemia, and the metabolic disturbances associated with nephrotic syndrome. The presence of excess protein in the urine can cause it to appear foamy or bubbly. This is often one of the first signs noticed by patients, prompting them to seek medical attention. Fluid retention due to edema can lead to weight gain, which may be gradual or sudden depending on the severity of the edema. If fluid

accumulates in the lungs (pleural effusion), patients may experience shortness of breath, especially during exertion or when lying down. Some patients may experience a decreased appetite, which can contribute to malnutrition and weight loss. These symptoms may occur due to uremia, the buildup of waste products in the blood, or as side effects of medications used to treat FSGS. The clinical course of FSGS is variable and depends on several factors, including the underlying cause, the severity of the disease, and the response to treatment. Some patients may experience a relatively indolent course with minimal symptoms, while others may progress rapidly to end-stage renal disease (ESRD). Complications of FSGS can arise from the underlying kidney disease, the nephrotic syndrome, or the treatments used to manage the condition. A sudden decline in kidney function, can be triggered by infections, dehydration, or certain medications. Gradual loss of kidney function over time, eventually leading to ESRD. Increased risk of heart attacks, strokes, and other cardiovascular events due to hyperlipidemia, hypertension, and other metabolic disturbances. Increased susceptibility to infections due to protein loss and impaired immune function. Increased risk of blood clots due to alterations in blood clotting factors and the loss of antithrombin III in the urine. Decreased production of red blood cells due to impaired erythropoietin production by the kidneys. Protein loss and decreased appetite can lead to malnutrition, which can further compromise immune function and overall health. The medications used to treat FSGS, such as corticosteroids and immunosuppressants, can have significant side effects, including weight gain, mood changes, increased risk of infections, and bone loss.[17,18]

Mrs. S, a 60-year-old woman, presented to the Internal Medicine Clinic with a constellation of symptoms that raised significant concerns. Her primary complaint was a request for a kidney biopsy, a diagnostic procedure that is not typically sought without a strong suspicion of underlying kidney disease. This, coupled with her reported symptoms of increasing weakness and intermittent fever, painted a picture of potential systemic illness. The initial focus of the investigation centered on the possibility of a renal malignancy, particularly renal cell carcinoma (RCC), a common and potentially life-threatening kidney cancer. This suspicion was fueled by the imaging findings, which revealed a heterogeneous solid mass with cystic components in her right kidney. The presence of such a mass, especially in an individual presenting with systemic symptoms, naturally raised alarm bells. However, the results of the kidney biopsy threw a curveball into the diagnostic process. The biopsy, performed to assess the nature of the renal mass, unexpectedly revealed focal segmental glomerulosclerosis (FSGS) with no evidence of malignancy. This surprising finding shifted the focus of the investigation from a potential oncological emergency to a complex glomerular disease. The diagnosis of FSGS, while unexpected, provided a crucial clue in understanding Mrs. S's condition. FSGS is a pattern of glomerular injury that can arise from various etiologies, broadly categorized as primary (idiopathic), secondary, genetic, and unclassified forms. In Mrs. S's case, the absence of any prior kidney disease or family history pointed away from a genetic or long-standing primary FSGS. The focus then shifted towards identifying a potential secondary cause. A thorough review of her medical history revealed uncontrolled type 2 diabetes, a well-established risk factor for secondary FSGS. The presence of obesity further compounded her risk, as obesity is known to contribute to both diabetes and FSGS. The diagnosis of FSGS secondary to type 2 diabetes provided a plausible explanation for the observed glomerular injury. Diabetes can lead to various microvascular complications, including diabetic nephropathy, a leading cause of chronic kidney disease. In diabetic nephropathy, the glomeruli are particularly vulnerable to damage due to hyperglycemia, inflammation, and hemodynamic alterations. The interplay between diabetes, obesity, and FSGS is complex and multifaceted. Obesity is a major risk factor for the development of type 2 diabetes, and both conditions contribute to the

pathogenesis of FSGS. Obesity can lead to glomerular hyperfiltration, an increased workload on the glomeruli, which can cause mechanical stress and injury to podocytes, the specialized cells crucial for maintaining the glomerular filtration barrier. Hyperglycemia, or high blood sugar levels, can directly damage podocytes and promote the production of reactive oxygen species, leading to oxidative stress and inflammation. Insulin resistance, a hallmark of type 2 diabetes, can also disrupt podocyte metabolism and function. In Mrs. S's case, the combination of uncontrolled diabetes and obesity likely created a milieu that promoted the development of FSGS. The chronic hyperglycemia and insulin resistance, coupled with the mechanical stress of glomerular hyperfiltration, likely contributed to podocyte injury and the subsequent glomerulosclerosis. The diagnosis of FSGS in Mrs. S was a turning point in her clinical course. It not only provided an explanation for her presenting symptoms but also guided the subsequent management decisions. The focus shifted from investigating a potential malignancy to addressing the underlying cause of FSGS, namely her uncontrolled diabetes and obesity. The successful management of her diabetes and hypertension, through lifestyle modifications and pharmacological interventions, led to a remarkable improvement in her condition. The regression of the renal mass, initially suspected to be RCC, further confirmed the diagnosis of FSGS and highlighted the importance of addressing underlying comorbidities in the treatment of this complex glomerular disease. One of the most intriguing aspects of Mrs. S's case was the unexpected regression of the renal mass following the successful management of her diabetes and hypertension. This observation challenged the initial suspicion of a renal malignancy, particularly renal cell carcinoma (RCC), and led to the consideration of a more benign entity: a renal pseudotumor. Pseudotumors, also known as renal pseudotumors or great imitators, are a diverse group of non-neoplastic lesions that can mimic renal malignancies on imaging studies. These lesions, while benign, can present a diagnostic challenge, as they often share radiological features with malignant tumors, leading to anxiety and potentially unnecessary invasive procedures. Congenital pseudotumors arise from variations in normal renal anatomy and are present from birth. The kidneys typically develop with lobulations that usually disappear by childhood. However, in some individuals, these lobulations persist, creating a lumpy appearance that can mimic a tumor. The columns of Bertin are bands of cortical tissue that extend into the renal medulla. Occasionally, a column of Bertin may be prominent or hypertrophied, creating a mass-like appearance on imaging. A dromedary hump is a bulge on the lateral border of the kidney, usually the left kidney, caused by an impression from the spleen. This bulge can mimic a renal mass. Inflammatory/Infectious pseudotumors result from localized inflammation or infection within the kidney. A localized bacterial infection of the kidney can cause inflammation and scarring, leading to a mass-like appearance on imaging. A chronic inflammatory process characterized by the accumulation of lipid-laden macrophages, which can form a mass that mimics a tumor. A collection of pus within the kidney, usually caused by a bacterial infection, can also mimic a renal mass. Vascular pseudotumors arise from abnormalities in the renal blood vessels. An abnormal connection between an artery and a vein can create a tangle of blood vessels that mimics a tumor. A localized dilation or ballooning of a blood vessel can also mimic a renal mass. A collection of blood within the kidney, usually caused by trauma or bleeding disorders, can appear as a mass on imaging. Localized scarring within the kidney, often resulting from prior injury or inflammation, can also mimic a tumor. In individuals with a single kidney or with one kidney functioning poorly, the remaining kidney may undergo compensatory hypertrophy, an enlargement to compensate for the reduced kidney function. This enlargement can mimic a renal mass. In Mrs. S's case, the exact etiology of the pseudotumor remains unclear. However, her uncontrolled diabetes may have played a significant role in its development. Diabetes

can promote chronic inflammation and microvascular changes within the kidney, which could have contributed to the formation of the pseudotumor. The regression of the pseudotumor following the successful management of her diabetes and hypertension further supports this notion. By controlling her blood sugar levels and blood pressure, the inflammatory and hemodynamic stresses on the kidney were reduced, allowing the pseudotumor to regress. The recognition of pseudotumors is crucial to avoid unnecessary anxiety, invasive procedures, and overtreatment. Misinterpretation of a pseudotumor as a malignancy can lead to inappropriate biopsies, surgeries, or even nephrectomy, the removal of the kidney. In Mrs. S's case, the initial suspicion of RCC, fueled by the imaging findings, could have led to more aggressive interventions if the kidney biopsy had not been performed. The biopsy, while intended to assess the nature of the renal mass, unexpectedly revealed FSGS, prompting a reevaluation of the case and ultimately leading to the correct diagnosis of a pseudotumor.[19,20]

4. Conclusion

This case underscores the crucial importance of considering pseudotumors as a differential diagnosis for renal masses, particularly in patients with comorbidities like diabetes. The implementation of a kidney biopsy can effectively prevent unnecessary invasive procedures such as nephrectomy. This case study emphasizes the critical need for healthcare professionals to maintain a comprehensive approach when diagnosing and managing complex cases that may involve pseudotumors.

5. References

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