ISSN 0120-4157

Biomédica

Revista del Instituto Nacional de Salud

PUBLICACIÓN ANTICIPADA EN LINEA

El Comité Editorial de *Biomédica* ya aprobó para publicación este manuscrito, teniendo en cuenta los conceptos de los pares académicos que lo evaluaron. Se publica anticipadamente en versión pdf en forma provisional con base en la última versión electrónica del manuscrito pero sin que aún haya sido diagramado ni se le haya hecho la corrección de estilo.

Siéntase libre de descargar, usar, distribuir y citar esta versión preliminar tal y como lo indicamos pero, por favor, recuerde que la versión impresa final y en formato pdf pueden ser diferentes.

Citación provisional:

Morales JP. Stroke in a young adult associated with primary membranous nephropathy: case report. Biomédica. 2024;44 (Supl. 1).

Recibido: 07-07-23

Aceptado: 24-04-24

Publicación en línea: 25-04-24

Stroke in a young adult associated with primary membranous nephropathy: case report.

Stroke associated with membranous nephropathy

Evento cerebral isquémico en un adulto joven asociado con nefropatía membranosa primaria: reporte de caso

Juan Pablo Morales

Departamento de Medicina Interna, Universidad del Valle, Cali, Colombia

Correspondencia:

Juan Pablo Morales, Calle 11 oeste # 15-85, apartamento 201, Cali, Colombia

Teléfono: +57 3178120756

juan.morales@correounivalle.edu.co

Introduction. Stroke in young individuals is becoming increasingly prevalent worldwide. Its causes can vary widely, necessitating thorough investigation by a multidisciplinary team. Pinpointing the precise underlying pathology responsible for the stroke yields significant benefits for patients, particularly in recurrent events.

Case presentation. A 38-year-old man presented to the emergency department with symptoms suggestive of stroke, including right hemiparesis, dysarthria, ataxic gait, and right central facial palsy. Brain MRI revealed an ischemic lesion located in the left basal ganglia and near the corona radiata. Following an extensive work-up, a diagnosis of nephrotic syndrome was established. Through histopathology examination and the exclusion of secondary causes, primary membranous nephropathy was confirmed as the underlying condition.

The patient underwent treatment tailored to address the specific glomerulopathy, along with anticoagulation therapy and immunosuppression as per current guidelines. Subsequent assessments showed stabilization of renal function, resolution of edema, and the absence of new thromboembolic events during follow-up.

Conclusion. Nephrotic syndrome should be recognized as a potential underlying cause of stroke in young patients, and therefore, it should be included in the differential diagnosis during the evaluation of patients with coagulopathies. Screening for nephrotic syndrome can be facilitated by conducting a simple urinalysis, a diagnostic tool readily available in most healthcare facilities. This highlights the importance of considering renal pathology in the assessment of stroke etiologies, especially when coagulation abnormalities are present.

Keywords: cerebral infarction; stroke; young adult; nephrotic syndrome; glomerulonephritis, membranous.

Introducción. Los eventos cerebrovascular en los jóvenes son un problema creciente en todo el mundo. Sus etiologías pueden ser variadas y requieren un trabajo riguroso por parte de un equipo multidisciplinario. Identificar la patología específica que conduce al ictus tiene un impacto beneficioso en los pacientes, especialmente en los eventos recurrentes.

Presentación del caso. Se presenta el caso de un hombre de 38 años que acudió al servicio de urgencias, con hemiparesia derecha, disartria, ataxia y parálisis facial central derecha, confirmados mediante resonancia magnética cerebral una lesión isquémica localizada en los ganglios basales izquierdos y cerca de la corona radiada. Después de un estudio exhaustivo, se estableció el diagnóstico de síndrome nefrótico. Utilizando las características histopatológicas y descartando otras causas secundarias, el diagnóstico final fue nefropatía membranosa primaria. El paciente recibió tratamiento específico para su glomerulopatía, anticoagulación e inmunosupresión según las guías vigentes.

En el seguimiento posterior, se encontró estabilización de la función renal, el edema resolvió y no se identificó ningún nuevo evento tromboembólico.

Conclusión. El síndrome nefrótico es una patología para considerar entre las posibles etiologías del ictus en pacientes jóvenes y debería ser teniendo en cuenta dentro de los estudios de coagulopatías. El tamizaje de esta patología requiere únicamente un uroanálisis, el cual está disponible en la mayoría de los centros de atención de salud.

Palabras clave: infarto cerebral; accidente cerebrovascular; adulto joven; síndrome nefrótico; glomerulonefritis membranosa.

Ischemic stroke in young adults is increasingly recognized as a significant global health issue, affecting both developed and developing nations. Its impact on healthcare systems is a major concern due to the resulting disability in young people affected, many of whom are in their productive working years (1). The definition of “young adult” often varies according to different studies, generally it is considered aged 18 to 50 years. In recent years, there has been a rise in the incidence of ischemic stroke among young adults, despite some regions lacking comprehensive reporting. Currently, approximately one in ten ischemic strokes occur in this demographic (2).

While chronic diseases such as high blood pressure, diabetes, and obesity are on the rise among young people, the diagnosis of ischemic stroke in this population should prompt physicians to investigate less commonetiologies , including vascular, cardiac, hematologic, autoimmune, toxic and genetic conditions (3). Traditionally, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) has been utilized to study, categorize, and report stroke etiology. Etiology is classified as “probable” when the results align with the patient´s clinical presentation and imaging findings, and as “possible” when conclusive evidence is lacking or relevant investigations were not performed (4). However, ischemic stroke in young adults warrants heightened attention and more extensive diagnostic evaluation to rule out additional conditions, since treating the underlying condition can significantly impact the recurrence of stroke events and improved prognosis. This case report illustrates how timely identification of the underlying condition can positively influence patient outcomes.

Case presentation.

A 38-year-old male patient arrived at the emergency department complaining of a 24-hour right hemiparesis, dysarthria, and ataxic gait. He denied similar previous episodes, seizures, chest pain or loss of consciousness. In the last 9 months he had presented ankle edema and mild dyspnea on exertion. He was medicated with hydrochlorothiazide plus amiloride 50/5 mg once daily, furosemide 40 mg daily, losartan 50 mg twice daily, nifedipine 30 mg and atorvastatin 40 mg once daily to control elevated blood pressure (BP) and dyslipidemia.

In the physical examination on admission, his vital signs were BP 162/100 mmHg, heart rate 99, respiratory rate 17, temperature 36.1 Cº, weight 69 Kg and height 1,7 meters (BMI 23,8). Neurological abnormalities included right central facial nerve palsy and a tendency to fall to the right side during Romberg test. Sensitivity and musculoskeletal reflexes were normal. There was mild bilateral ankle edema, with no ascites or jugular veinengorgement. Initial tests showed anormal brain computed tomography (CT), and blood tests indicating abnormal kidney function, subclinical hypothyroidism, and mild normocytic anemia (table 1).

Considering ischemic stroke in a young adult as the initial diagnostic hypothesis, several additional tests were performed to clarify the TOAST classification, including transesophageal echocardiogram, neck and brain CT angiography and 24-hours Holter ECG. However, only brain magnetic resonance imaging showed an ischemic lesion in the left basal ganglia and near the corona radiata (figure 1). Other tests results were within normal limits. Additional blood tests included rheumatologic tests, screening for infectious diseases, lipid panel, complementary kidney function tests and serum albumin. Lab results showed massive 24 hour-

proteinuria (10 grams), severe dyslipidemia, and markedly decrease serum albumin. The estimated glomerular filtration rate was 57 mL/min/1,73 m^2 (Using CKD-EPI equation). With these results, nephrotic syndrome criteria weremet. Initial management for glomerular disease included renin-angiotensin axis inhibitors, BP control, sodium and protein intake restriction, and lipid lowering with high-intensity statins. Due to alterations in kidney function tests and the possibility of a serious complication like stroke, the nephrotic syndrome was considered severe. A kidney biopsy was proposed for a probable primary glomerulopathy with the possibility of starting immunosuppression therapy. The diagnosis of primary membranous nephropathy (MN) was established after analyzing the pathology specimen through basic stains, immunohistochemistry, and electron microscopy (figure 2). Anti-PLA2R antibodies in serum or other associated antibodies to MN were not measured. Due to low serum albumin levels and massive proteinuria, full anticoagulation therapy was started, initially with low molecular weight heparin and subsequently warfarin. According to the latest kidney disease: Improving Global Outcomes (KDIGO) guideline onglomerular disease, and the severity of this patient´s glomerular disease, immunosuppression therapy was started in a six-months scheme including cyclophosphamide at a dose of 750 mg/m^2 during months two, four, and six and methylprednisolone at a dose of 1 gr during months one, three and five; the so called Ponticelli modified scheme. The immunosuppression therapy was administered along with Trimethoprim sulfamethoxazole at a dose of 800/160 mg for *Pneumocystis jirovecii* prophylaxis every other day.

One month after of initial presentation at the emergency room, new tests were taken during the outpatient clinic follow-up. There was a significant decrease in lipid panel values, serum albumin and kidney function remained stable, and no new ischemic events were documented. The ankle edema disappeared, as did the dyspnea with exertion.

Ethical standard

The author confirms that have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Written informed consent was obtained from the patient and a witness for publication of this paper and any accompanying images or laboratory results.

Discussion

Nephrotic syndrome (NS), particularly membranous nephropathy is a complex and multifactorial hypercoagulable state. This condition arises from high urine protein excretion and significant hypoalbuminemia, which indirectly leads to a reduction in natural anticoagulant proteins such as C and S proteins, as well as antithrombin III (5). Traditionally, NS has been associated with venous thromboembolic events. The overall incidence of venous thromboembolic events in patients with nephrotic syndrome is around 25%. However, in the subgroup of patients with MN, renal vein thrombosis can be up to 37% (5). However, arterial thrombotic events may also occur in rare cases, although most of the evidence available is in the form of case reports. The current understanding of the mechanisms and pathophysiology involved remains limited. Observational studies have provided some data suggesting that platelet function may play a role in the development of arterial

thrombosis observed in NS. However, the precise alterations are not yet fully understood (6).

In this case, a case of ischemic stroke in a young man is presented. After applying the TOAST strategy, extensive studies were conducted to rule out secondary causes. Ultimately, the diagnosis of primary membranous nephropathy was confirmed through histopathology and immunofluorescence features. A significant role was attributed to anti-phospholipase A2 receptor antibodies (anti-PLA2R) that, with high sensitivity and specificity, confirmed that it was a primary membranous nephropathy subtype (7). In recent years, the significance of anti-PLA2R in MN has increased. Many cases of MN have been found to have anti-PLA2R antibodies, and the detection of these antibodies in serum has helped in diagnosing primary MN, eliminating the need for kidney biopsy. Furthermore, anti-PLA2R titers have facilitated patient follow-up and prognosis assessment (8,9).

The two most frequent complications in NS are infections and thrombotic events. While venous thromboembolic events have been extensively described, arterial thrombosis is a highly uncommon complication in patients with NS (5). In cases where arterial events do occur, the most frequent locations are the femoral and iliac arteries, as reported by Fahal *et al* (10). Nevertheless, when considering a specific group of patients with MN, this data becomes controversial since the selected group consists only of patients with MN.

In such scenarios, the most common locations for arterial thrombosis appear to vary, with a higher frequency observed in the coronary circulation, central nervous system, and peripheral arteries. These events predominantly occur during the first year of the disease when hypoalbuminemia and proteinuria are at their peak (11).

In the paper published by Roy *et al.,* there is a compilation of patients with NS and stroke. Strikingly there were few cases with MN, none of these in Latin America, probably due to underdiagnosis (12).

Once the diagnosis of MN-associated stroke has been established, the next challenge is to determine the treatment strategy. The KDIGO guideline recommends implementing general measures for MN patients, with particular emphasis on the renin-angiotensin axis inhibitors, blood pressure control, and dietary recommendations regarding sodium and protein intake. Additionally, it is crucial to determine anticoagulation therapy for these patients. In general, patients with serum albumin levels below 2.5 g/dl would benefit from receiving anticoagulation, preferably with heparin and warfarin, as long as there are no contraindications to initiating therapy. Furthermore, recent evidence suggests that patients with MN may derive benefits from antiplatelet therapy with aspirin if their serum albumin is below 3.2 g/dl, aimed at preventing thromboembolic events (6).

Another challenge to face is the initiation of immunosuppressive therapy in MN. This approach is based on assessing the patient's risk level. In this case, the patient was at a high to very high risk due to the deterioration in glomerular filtration rate, high urine protein excretion, and the occurrence of a major vascular complication, such as stroke. Considering the data and available resources, it was decided to initiate an immunosuppression regimen consisting of oral cyclophosphamide and steroids, following the traditional modified *Ponticelli protocol* (13). In some regions with different resources, a Rituximab-based protocol may be chosen (14), however, in our context, the feasibility of starting and maintaining this specific drug regimen is limited, and it cannot be guaranteed the

complete treatment for this patient. These are crucial factors to consider when contemplating long-term immunosuppression protocols. Getting oral cyclophosphamide can be difficult in some Latin American countries. Interestingly, the study published by Luzardo et al. provides some evidence regarding switching from oral cyclophosphamide to the parenteral route, demonstrating acceptable outcomes in terms of efficacy and safety (15). Nevertheless, it is important to approach this new information with caution due to the retrospective nature of the data.

Conclusions

Stroke in young individuals is a major contributor to disability. The approach should prioritize identifying the underlying etiology of stroke to effectively reduce the risk of recurrent thromboembolic events. In such cases, it is crucial to maintain a low threshold of suspicion to many low-incidence pathologies, and it is important to follow a systematic strategy like TOAST. As demonstrated in this case, certain conditions may not be included in most protocols, including nephrotic syndrome. When encountering a young patient with stroke and edema, it is essential to consider nephrotic syndrome, and a simple urinalysis can serve as an initial screening test, followed by appropriate further evaluation.

Acknowledgment.

The author would like to thank patient and his family for permission to publish this paper.

Conflicts of interest

The author declares no conflicts of interest.

Funding

The construction of this paper was accomplished with author´s own resources. There was no external funding.

References.

1. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. Lancet Neurol. 2018;17:790-801. https://doi.org/10.1016/S1474-4422(18)30233-3

2. Boot E, Ekker MS, Putaala J, Kittner S, De Leeuw F-E, Tuladhar AM. Ischaemic stroke in young adults: a global perspective. J Neurol Neurosurg Psychiatry. 2020;91:411-7. https://doi.org/10.1136/jnnp-2019-322424

3. Stack CA, Cole JW. A diagnostic approach to stroke in young adults. Curr Treat Options Cardiovasc Med. 2017;19:1-19. https://doi.org/10.1007/s11936-017-0587-6

4. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41. https://doi.org/10.1161/01.STR.24.1.35

5. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome–associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;73:513-20. https://doi.org/10.2215/CJN.10131011

6. Zou H, Li Y, Xu G. Management of anticoagulation and antiplatelet therapy in patients with primary membranous nephropathy. BMC Nephrol. 2019;20:1-11. https://doi.org/10.1186/s12882-019-1637-y

7. Francis JM, Beck Jr LH, Salant DJ. Membranous nephropathy: a journey from bench to bedside. Am J Kidney Dis. 2016;68:138-47. https://doi.org/10.1053/j.ajkd.2016.01.030

8. Alsharhan L, Beck Jr LH. Membranous Nephropathy: Core Curriculum 2021. Am J Kidney Dis. 2021. https://doi.org/10.1053/j.ajkd.2020.10.009

9. Beck Jr LH, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361:11-21. https://doi.org/10.1056/NEJMoa0810457

10. Fahal IH, McClelland P, Hay C, Bell G. Arterial thrombosis in the nephrotic syndrome. Postgrad Med J. 1994;70:905-9. https://doi.org/10.1136/pgmj.70.830.905

11. Lee T, Derebail VK, Kshirsagar AV, Chung Y, Fine JP, Mahoney S, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. Kidney Int. 2016;89:1111-8. https://doi.org/10.1016/j.kint.2015.12.041

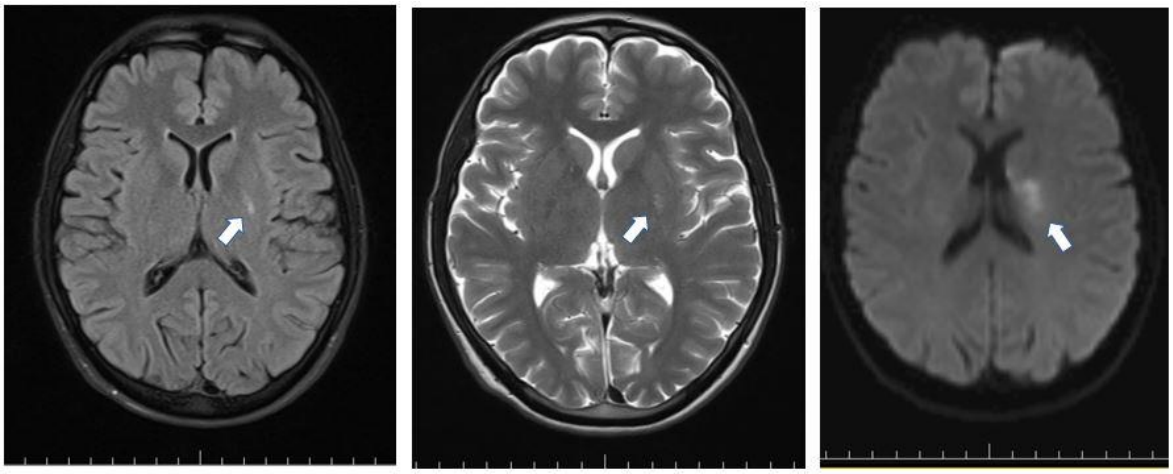
12. Roy C, Deschaintre Y, Sabbagh R, Roy D, Cardinal H, Bollée G. Ischemic stroke of possible embolic etiology associated with nephrotic syndrome. Kidney Int Rep. 2017;2:988-94. https://doi.org/10.1016/j.ekir.2017.04.004

13. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol. 1998;9:444-50. https://doi.org/10.1681/ASN.V93444

14. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med. 2019;381:36-46. https://doi.org/10.1056/NEJMoa1814427

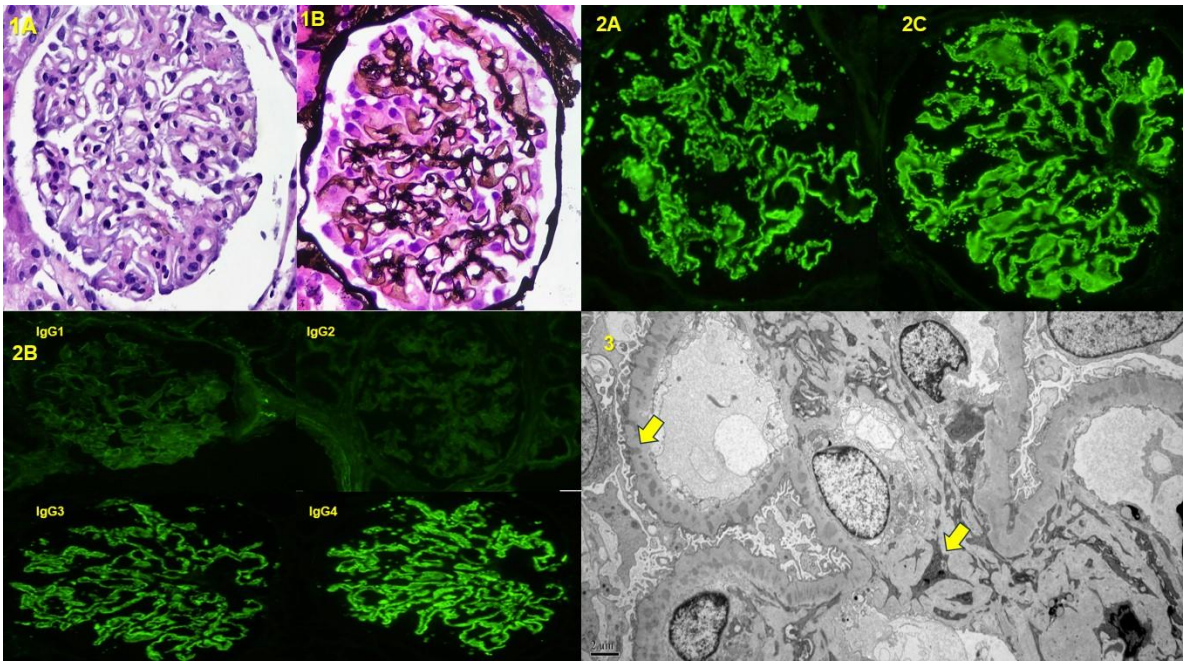
15. Luzardo L, Ottati G, Cabrera J, Trujillo H, Garau M, Bedat CG, et al. Substitution of oral for intravenous cyclophosphamide in membranous nephropathy. Kidney360. 2020;1:943-9. https://doi.org/10.34067/KID.0002802020

Figure 1. Brain magnetic resonance imaging.



Left: T1 sequence, Middle: T2 sequence, Right: Diffusion sequence. White arrows: There is a small lesion with restriction to diffusion compromising the left basal ganglia region, the caudate nucleus, and part of the corona radiata. The size of the lesion is 2.5 centimeters.

Figure 2. Renal biopsy.



The renal biopsy shows a total of 20 glomeruli, 1 of them sclerosed.
Number 1. 1A. These glomeruli showed marked podocyte activation associated with diffuse thickening of the glomerular basement membranes in the hematoxylin-eosin staining (40x), 1B. with evidence of spikes and holes in the methenamine silver stain (40x) . The interstitium shows few areas of interstitial fibrosis and tubular atrophy.
Number 2. 2A-B. With direct immunofluorescencestains, intense granular staining is observed in the basement membranes with IgG (4+), C3 (2+), kappa (4+), lambda (4+) (40x) and anti-PLA2R (2-3 +) (2C). The subclasses of IgG show a predominance of IgG4 (4+) over the other subclasses IgG3 (3+), IgG2 (1+), IgG1 (2+).
Number 3. Electron microscopy shows electron dense deposits of mesangial and intramembranous locations (arrows), some with peaks (5000x).

Table 1. Laboratory tests at admission and 1 month after discharge from hospital.

Test	Admission	1 month later	Normal range
SCr	1.57	1.4	0.7-1.2 mg/dL
BUN	37.5	43	9-20 mg/dL
Potassium	4.6		3.5-5.1 mEq/L
Sodium	135		137-145 mEq/L
Total calcium	7.49		8.4-10.2 mg/dL
Blood glucose	94		74-106 mg/dL
TSH	8.53	4.54	0.47-4.68 uUI/mL
Thyroxine	1.12		0.78-2.19 uUI/mL
AST	19		17-59 IU/L
ALT	8		0-50 IU/L
WBC	11.21		4.05-11.84 (1000/uL)
Hb	10.9		13.5-17.2 gr/dL
MCV	89.2		80-99 ft
PLT	408		150-450 (1000/uL)
RDW	12.9		11.5-14.7%
HIV	Negative		
Hepatitis B antibodies	Negative		
Hepatitis C antibodies	Negative		
Syphilis	Negative		
A1C	4.78%		0-6.5%
Antinuclear antibodies	Negative		
Antiphospholipid antibodies	Negative		
Albumin	1.6	1.4	3.5 – 5 gr/dL
Total cholesterol	310	365	0-200 mg/dL
HDL	43	66	40-60 mg/dL
LDL	190	187	< 100 mg/dL
TG	1575	408	0-150 mg/dL
Antithyroid antibodies	Negative		
PCR	9.82	9.47	mg/mg

mg: milligram, dL: deciliter, mEq: milliequivalent, L: litre, uUI: microinternational unit, IU: international unit, uL: microliter, gr: gram, ft: femtolitre, SCr: serum creatinine, BUN: blood urea nitrogen, TSH: thyroid stimulating hormone, AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBC: white blood cells, Hb: hemoglobin, MCV: mean corpuscular volume, PLT: platelets, RDW: red cell distribution width, HIV: human immunodeficiency virus, A1C: glycated hemoglobin, HDL: high density lipoproteins, LDL: low density lipoproteins, TG: triglyceride, PCR: protein-creatinine urine ratio