Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Case Reporte

doi: 10.31450/ukrjnd.1(85).2025.01

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Concurrent hepatitis B infection and IgA nephropathy in a patient with a history of malignant melanoma

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Citation: Terzioğlu GC, Alp A, Sönmez MGO, Sarı FB, Genek DG, Huddam B. Concurrent hepatitis B infection and IgA nephropathy in a patient with a history of malignant melanoma. Ukr J Nephrol Dialys. 2025;1(85): 3-9. doi: 10.31450/ukrjnd.1(85).2025.01.

Abstract. *IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis characterized by the deposition of IgA-dominant immune complexes in the mesangium, leading to mesangial proliferation and subsequent renal injury. Clinically, IgAN often manifests as episodic macroscopic hematuria following upper respiratory tract or gastrointestinal infections. Disease progression is variable, with 20–50% of patients advancing to end-stage renal disease within 10–20 years of diagnosis.*

Although IgAN is primarily idiopathic, it may also occur secondary to systemic conditions such as Henoch-Schönlein purpura, HIV infection, toxoplasmosis, ankylosing spondylitis, and liver cirrhosis. Less commonly, IgAN can be associated with hepatitis B virus (HBV) infection or manifest as a paraneoplastic phenomenon.

Here, we report a unique case of clinical presentation and successful treatment of concurrent HBV infection and IgAN in a patient with a history of malignant melanoma. To our knowledge, this is the first documented case in which these three conditions (IgAN, HBV infection, and malignant melanoma) coexist in a single patient.

Key words: *IgA nephropathy, HBV infection, malignant melanoma, paraneoplastic syndrome, immunotherapy, end-stage renal disease, renal pathology.*

Article history:
Received October 25, 2024
Received in revised form November 29, 2024
Accepted December 03, 2024

Conflict of interest. The authors declare no conflict of interest.

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УДК: 616-006.81:[616.36-002+616.611-002]-036

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Конкомітантний перебіг гепатиту В та IgA-нефропатії у пацієнта з анамнезом злоякісної меланоми

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Резюме. *IgA-нефропатія (IgAN) — це імунокомплексний гломерулонефрит, який характеризується відкладенням імунних комплексів з переважанням IgA у мезангії, що спричиняє мезангіальну проліферацію та прогресуюче ураження нирок. Клінічно захворювання часто проявляється епізодичною макрогематурією після перенесених інфекцій верхніх дихальних шляхів або шлунково-кишкового тракту. Перебіг хвороби варіабельний, проте у 20–50% пацієнтів протягом 10–20 років від моменту встановлення діагнозу розвивається термінальна стадія хронічної хвороби нирок.*

Хоча IgA-нефропатія найчастіше має ідіопатичне походження, вона також може бути вторинною до системних захворювань, таких як пурпура Геноха-Шенляйна, ВІЛ-інфекція, токсоплазмоз, анкілозуючий спондиліт і цироз печінки. Рідше IgAN може асоціюватися з HBV інфекцією або проявлятися як паранеопластичний синдром.

У цій статті представлено унікальний випадок клінічної картини та успішного лікування конкомінантного перебігу вірусного гепатиту В та IgAN у пацієнта зі злоякісною меланомою в анамнезі. Наскільки нам відомо, це перший задокументований випадок, коли ці три захворювання (IgAN, HBV інфекція і злоякісна меланома) співіснують в одного пацієнта.

Ключові слова: *IgA-нефропатія, вірусний гепатит В, злоякісна меланома, паранеопластичний синдром, імунотерапія, термінальна стадія хронічної хвороби нирок, патологія нирок.*

Introduction. IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide [1, 2]. Compared to the general population, patients with IgAN have a reduced life expectancy and an increased risk of mortality [3]. Renal biopsy findings such as crescent formation, mesangial hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis are considered risk factors for progression to renal failure [3].

IgAN can occur in isolation or in association with other diseases such as chronic liver disease, celiac disease, HIV infection, group A streptococcal infection, malignancies, granulomatosis with polyangiitis and minimal change disease, and it has been reported that regions where IgAN is endemic also have a high prevalence of HBV infection [2]. Antigenemia is likely to cause the accumulation of circulating immune complexes in the mesangial and subendothelial areas, and imaging techniques can identify these deposition sites, supporting this mechanism [4]. Conversely, some studies have suggested that HBs antigenemia does not have a high incidence in IgAN, thus questioning the association of HBV infection with the aetiology and pathogenesis of IgAN [2]. Therefore, the role of HBV antigenemia in IgAN remains controversial.

A review of the literature shows that although the coexistence of the three pathologies can be observed separately, the occurrence of all three clinical conditions together in a single case is unique. We also aimed to speculate that paraneoplastic glomerulonephritis may occur many years later in a patient with malignant melanoma.

Case. A 40-year-old male patient presented to the nephrology clinic with a complaint of dark urine of several weeks' duration.He had no additional symptoms. He had a history of resection of a malignant melanoma of the back approximately 9 years ago. The patient reported that he had received no specific treatment after diagnosis and was considered cured after successful surgery. There was no recent history of strenuous exercise, trauma, or recent medical treatment. Arterial blood pressure was 130/87 mmHg, heart rate was 89/ minute and no significant findings were noted on physical examination. Laboratory tests on admission are shown in Table 1.

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Table 1

Laboratory findings of the patient on admission

Parameter	Result	Reference Range	Parameter	Result	Reference Range
WBC ($x10^3/\mu L$)	8.76	4.23–9.07	**Magnesium** (mg/dL)	1.99	1.5–2.5
HGB (g/dL)	15.3	12–16	**CRP** (mg/L)	1.35	0–5
HCT (%)	43.6	40.1–51	**Calcium** (mg/dL)	9.08	8.6–10.6
MCV (fL)	85.7	79–92.2	**C3** (g/L)	0.21	0.1–0.4
PLT ($x10^3/\mu L$)	207	160–340	**C4** (g/L)	1.01	0.9–1.8
Urea (mg/dL)	53	16.6–48.5	**Potassium** (mmol/L)	4.78	3.5–5.1
Creatinine (mg/dL)	1.27	0.65–1.20	**Spot urine alb/creat** (mg/g)	1674	0–30
eGFR (ml/min/1.73 m^2)	70	-	**Spot urine prot/creat** (mg/g)	1774	0–200
Total protein (g/L)	61.8	64–83	**Phosphorus** (mg/dL)	3.6	2.5–4.5
Albumin (g/L)	42.2	35–52	**Sedimentation** (mm/h)	12	-
Uric Acid (mg/dL)	6.0	3.4–7.0	**ANA**	Positive (+), fine granular	-
Sodium (mmol/L)	139.5	136–145	**Urine test (TIT)**	Protein (+), leukocyte (-), erythrocyte (+3)	-
Anti-HIV	Negative	-	**HBeAg**	Negative	-
Anti-HBc IgG	Positive	-	**Anti-HBe**	Positive	-
Anti-HBc IgM	Negative	-	**HCV**	Negative	-
HBsAg	Positive	-	**HBV-DNA** (IU/mL)	290,000	-
Anti-HBs	Negative	-	-	-	-

Abbreviations: *ANA – Antinuclear Antibody; Anti-HBc IgG – Hepatitis B Core Antibody, IgG; Anti-HBc IgM – Hepatitis B Core Antibody, IgM; Anti-HBe – Hepatitis B e-Antibody; Anti-HBs – Hepatitis B Surface Antibody; Anti-HIV – Antibody test for Human Immunodeficiency Virus; Ca – Calcium; C3 – Complement component 3; C4 – Complement component 4; CRP – C-Reactive Protein; eGFR – Estimated Glomerular Filtration Rate; ESR – Erythrocyte Sedimentation Rate; HBeAg – Hepatitis B e-Antigen; HBsAg – Hepatitis B Surface Antigen; HBV-DNA – Hepatitis B Viral DNA (viral load); HCV – Hepatitis C Virus; HCT – Hematocrit; HGB – Hemoglobin; K – Potassium; MCV – Mean Corpuscular Volume; Mg – Magnesium; Na – Sodium; P – Phosphorus; PLT – Platelet count; TIT – Urine Test (Test-Indicator Tape); Total protein – Total serum protein level; UA – Uric Acid; Urea – Blood Urea Nitrogen; WBC – White Blood Cell count.*

Abdominopelvic ultrasonography showed bilateral normal renal size, parenchyma, and echogenicity. Renal biopsy was planned due to haematuria, proteinuria, and decreased GFR. The renal biopsy specimen showed; 39 glomeruli of which 13 had global sclerosis, 6 had segmental sclerosis and 1 glomerulus had fibrous crescent. The glomeruli also showed mesangial expansion, increased cellularity, thickening of the basement membranes, focal tubular atrophy, interstitial fibrosis, and chronic inflammation in the tubulointerstitial area. Immunofluorescence staining was significant for IgA (+4) and C3 deposition in the mesangial area. These findings were consistent with IgAN (Fig. 1).

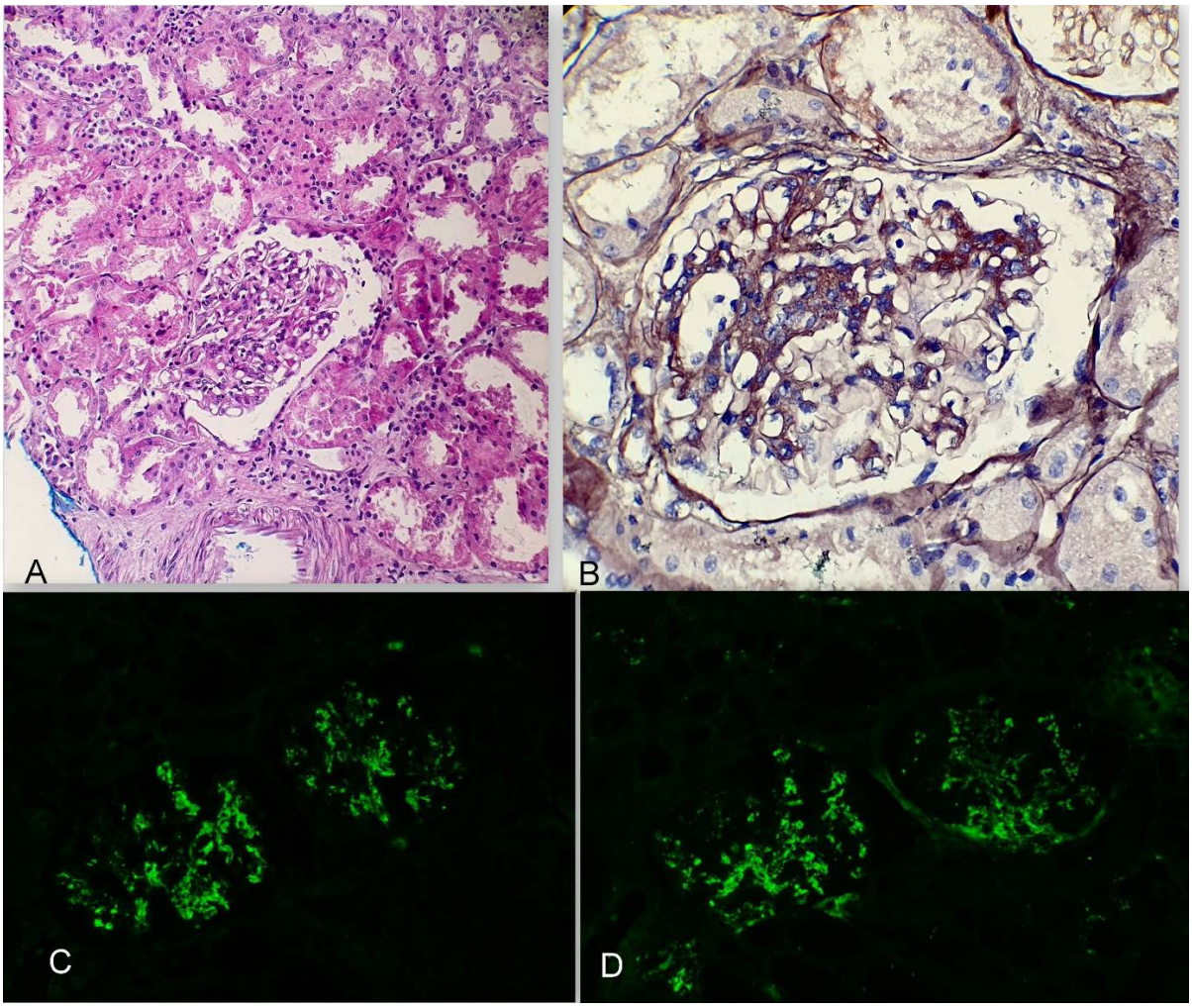

Fig. 1. Histopathological and immunofluorescence findings in IgA nephropathy. (A) Increased mesangial cellularity and matrix expansion (mesangial expansion), H&E staining, ×200 magnification. (B) Mesangial expansion and hypercellularity, Jones histochemical staining, ×400 magnification. (C) Mesangial IgA deposits, direct immunofluorescence (DIF), ×200 magnification. (D) Mesangial C3 deposits, DIF, ×200 magnification.

At the same time, routine investigations revealed concurrent HBsAg positivity and an HBV DNA viral load of 290,000 IU/ml. Entecavir was ordered at a dose of 0.5 mg per day. At the same time, the patient was started on low-dose ramipril, and the dose was titrated to 10 mg/day. During follow-up, the patient experienced an increase in proteinuria despite ramipril treatment. Twelve months after starting ramipril, the patient developed swelling of the eyes and pretibial edema. At the same time, a creatinine level of 1.4 mg/dL and a 24-hour protein level of 1.7 grams were observed, indicating progression. After consultation with the oncology and gastroenterology clinics, methylprednisolone 60 mg/day was started; at the 1-month follow-up, the protein level was 939 mg; at the 2-month and 3-month follow-ups with the same corticosteroid dose, the urine protein levels were 849 mg and 317 mg, respectively; because of the proximal myopathy-like complaints, the corticosteroid dose was gradually reduced; with the dose reduction, the protein level continued to decrease at the 1-month follow-up (Fig. 2).

The patient's current treatment regimen continues in our clinic as ramipril+entekavir (due to persistent HbsAg(+)), with the most recent proteinuria level of 397 mg/day, albuminuria of 247 mg/day and serum creatinine of 1.74 mg/dl.

Discussion. Hepatitis B virus is widespread worldwide, with approximately 2 billion people infected. Of these patients, approximately 35 million develop chronic HBV infection, making it one of the most common diseases worldwide. The incidence of persistent HBV infection varies by geographical region. In China, Southeast Asia, and sub-Saharan Africa, HBV infection is observed in 8-15% of the total population, whereas in Europe and the USA, this rate is around 2% [5].

In the United States, HBV infection is estimated to be prevalent in 10% of the population. HBV infection can lead to a variety of extrahepatic clinical manifestations, including rash, bone marrow involvement, arthralgia, and nephropathy. One of the most common extrahepatic findings is nephropathy, which is observed in individuals chronically infected with the hepatitis B

virus. During HBV infection, secondary glomerulonephritides such as membranoproliferative glomerulonephritis (MPGN), membranous glomerulonephritis (MGN), mesangial glomerulonephritis, IgAN, focal segmental glomerulosclerosis (FSGS) and minimal change disease may occur. A review of the literature reveals a lack of numerous clinical studies investigating the frequency of HBV and nephropathy. In a study analyzing the association between hepatitis B and glomerulonephritides, it was shown that IgA nephropathy is more common in adults, whereas MGN is more common in children [6].

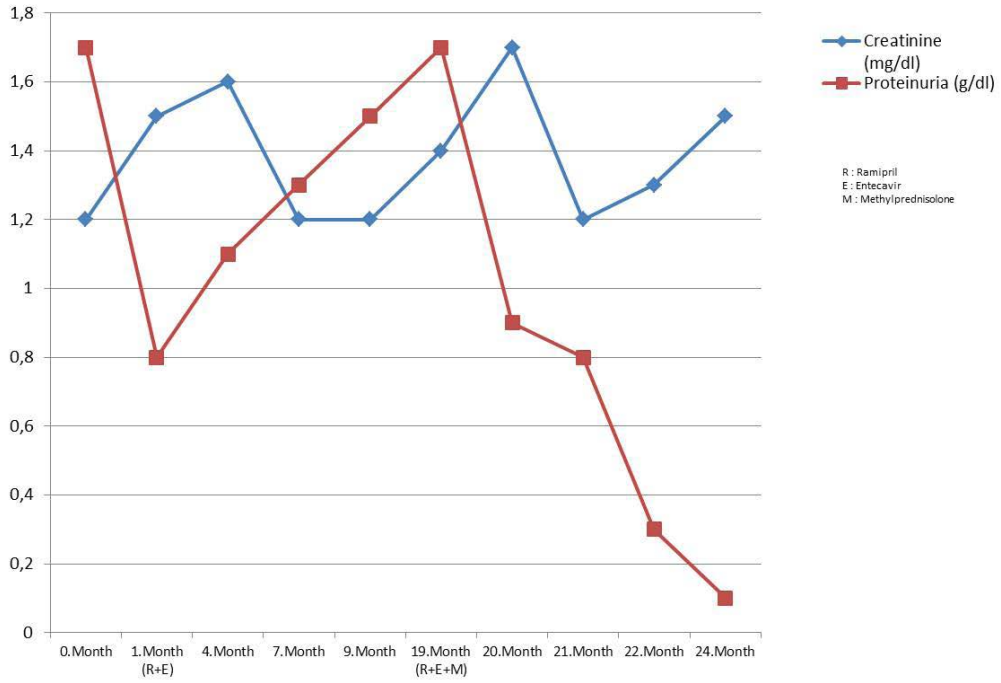

Fig. 2. Changes in creatinine and proteinuria levels over the course of treatment.

Glomerulonephritis may occur as a paraneoplastic syndrome in association with various cancers; cancer-associated glomerulonephritis is predominantly membranous glomerulonephritis and, although its pathogenesis is not fully understood, it has been associated with the accumulation of tumor antigens or immune complexes in the glomerular basement membrane [7].

Nephrotoxicity associated with malignancy may be paraneoplastic, but may also result from the agents used to treat the primary disease. Renal injury is a serious complication that can result from the progression of the neoplastic disease as well as from the treatment methods used. Over the years, the spectrum of renal disease in cancer patients has evolved, mainly due to changes in chemotherapy regimens and the introduction of immunotherapy. Antineoplastic drugs can cause damage to the renal tubules, glomeruli, parenchyma, and blood vessels, leading to a wide range of complications, from mild, asymptomatic increases in serum creatinine to hemodialysis requiring acute kidney injury (AKI) [8].

Immunotherapy is considered a key component in the treatment of cancer patients. Today, immunotherapy is used in the treatment of several malignancies, particularly melanoma. Nivolumab is a PD-1 monoclonal antibody used in the treatment of malignant melanoma. A review of the literature shows cases of glomerulonephritis and vasculitis associated with nivolumab [9].

Paraneoplastic glomerulonephritis is a rare secondary cause of glomerulonephritis. Altered immune responses appear to play a role in the pathogenesis of paraneoplastic glomerulonephritis. A study in Buffalo/Mna timomal rats showed that tumor cells induce polarisation of the immune response towards T-helper-2 (TH2) or cause overexpression of the TH2 cytokine interleukin 13, leading to the development of glomerulonephritis [10].

The relationship between the malignant process and the accumulation of immune complexes in glomerulonephritis is not clearly understood yet. It is thought that the accumulation of tumor antigens or immune complexes in the glomerular basement membrane may be the cause. Studies have suggested aetiological mechanisms such as tumor antibody production against tumor antigens, circulating factors secreted by T lymphocytes, B cell production and the M component of cryoglobulins, and circulating Ig-A to cause glomerulonephritis. Antibodies to exogenous or endogenous antigens in cancer patients may cause immune complex nephritis in susceptible groups. It is not known how these immunological mechanisms affect the time interval between cancer and GN formation [11]. The aetiological role of HBV antigenemia and HBV antigen accumulation in IgA nephropathy remains controversial. The nephropathy is thought to

be caused by an accumulation of circulating immune complexes in the mesangial and subendothelial areas, and studies have supported this accumulation mechanism. Many studies have demonstrated deposition of HBsAg, HBcAg, and HBeAg along with immunoglobulins and complement in the glomeruli. While some chronic HBsAg carriers develop IgA nephropathy, others may develop MPGN or MGN. This variation may be related to the size and loading characteristics of the HBV antigens, as well as the relationship between these antigens and their antibodies. These differences may explain the occurrence of different renal pathologies. HBeAg has the smallest molecular weight, which allows it to pass through the glomerular basement membrane more easily and causes subepithelial dense deposits visible under the microscope. This is a well-known characteristic morphological feature of MGN and the localised formation of antigen-antibody complexes induces the characteristic proteinuria and subepithelial immunodeposits seen in MGN. Therefore, HBeAg is considered a nephrogenic antigen for MGN. In contrast, HBsAg, which is larger in size, is thought to play a role in the formation of mesangial HBsAg-anti-HBsAg complexes in HBV-associated IgAN [5].

A study by Lai et al. investigated the relationship between HBV infection and IgA nephropathy and reported a positive correlation between the prevalence of IgAN and HBV. It was observed that in individuals with IgAN, HBsAg, HBcAg and corresponding immune complexes accumulate in the mesangial and subendothelial areas of the glomeruli [12].

The basic principles in the treatment of HBV-associated glomerulonephritis include reducing proteinuria, treating and preventing recurrence, preserving renal function and preventing progression to end-stage renal disease. Entecavir is the first-line treatment option due to its low resistance and antiviral efficacy [13].

Blood pressure, proteinuria and serum creatinine levels are considered to be the most robust and reliable indicators of clinical prognosis in IgAN. Treatment focuses on maintaining optimal blood pressure levels, controlling proteinuria through renin-angiotensin system inhibition, and implementing dietary and lifestyle modifications. Immunosuppressive therapy is usually preferred in patients at high risk of progression to end-stage renal disease [13].

In inactive HBV carriers, corticosteroid therapy has been shown to achieve both partial and complete remission of IgAN. In addition, it has been observed that there is no significant difference in the reduction of proteinuria levels between corticosteroid monotherapy and a combination of corticosteroid and antiviral treatment [14].

Due to the lack of genetic analysis data on malignant melanoma and the lack of long-term follow-up of the case, a clear distinction between primary and secondary IgA nephropathy cannot be made. This is a limiting factor in our case.

Conclusions. The relationship between HBV infection and IgAN remains unclear. Although the coexistence of HBV infection and IgAN is not common in clinical practice, it is interesting that both conditions are associated with the deposition of immune complexes in the mesangial and subendothelial areas of the glomeruli. At the same time, a review of the literature showed that there are not many studies evaluating the relationship between IgAN and HBV infection. The unique aspect of our case is the coincidence of malignant melanoma, HBV infection and IgAN in the same patient. We observed a significant regression of proteinuria and successful treatment when corticosteroid and antiviral therapies were combined. To our knowledge, this is the first reported case in the literature demonstrating the coexistence of these 3 clinical entities.

The treatment of paraneoplastic glomerulonephritis is aimed at treating the primary disease and requires a multidisciplinary targeting of both the tumor and the glomerular lesions. The identification of biomarkers from blood, urine, or kidney biopsy samples that would confirm the diagnosis of paraneoplastic glomerulonephritis will facilitate the diagnosis of the primary disease. Another important point is that patients with a history of malignancy should have their kidney function monitored regularly for the possibility of new glomerular pathology.

Informed consent statement. Written informed consent was obtained from the patient.

Conflicts of interest statement. The authors have no competing interests to declare.

Funding source. The authors declare that there is no funding source.

Author contributions:

Gülsüm Ceren Terzioğlu: Conceptualization, investigation, original draft preparation, and data analysis of the patient's clinical condition.

Alper Alp: Conceptualization, investigation, patient management, original draft preparation, and analysis of the patient's diagnostic data.

Mürşide Gülay Örgün Sönmez: Conceptualization, patient diagnosis, and data collection and analysis.

Ferda Bacaksızlar Sarı: Conceptualization and oversight of patient data investigation.

Dilek Gibyeli Genek: Conceptualization, review and editing, and analysis of the patient's clinical outcomes.

Bülent Huddam: Conceptualization, review and editing, and supervision of data analysis.

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