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Original Article

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Clinicopathological Characteristics of Anti-Glomerular Basement Membrane Disease with Atypical Features

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ABSTRACT

Objective: Anti-glomerular basement membrane (anti-GBM) disease is a rare disorder characterized by pulmonary and kidney involvement, which is a lesser-known variant of this disease with an unpredictable clinical course. The aim of this study is to present 4 cases of anti-GBM disease with atypical clinicopathological findings.
Methods: This study included patients diagnosed with atypical anti-GBM disease at Gazi University Hospital between January 2012 and December 2020.
Results: Four patients with atypical anti-GBM disease were included in this study. All the patients were male, and only 1 of them was seropositive for anti-GBM antibody, albeit at a low serum titer. Three of them had lung involvement, and all of them had hematuria with proteinuria (2 were in the nephrotic range). Kidney biopsy findings of the patients were heterogeneous and included endocapillary proliferation with crescents, nodular glomerulosclerosis with crescents, necrotizing diffuse crescentic glomerulonephritis, and mesangial and endocapillary proliferative glomerulonephritis without crescents. Only 1 case did not show glomerular necrotizing lesions. The presence of linear staining with IgG along the glomerular capillary walls was the common immunofluorescence finding for all. The clinical course of all 4 cases was different from each other, while 2 patients required permanent kidney replacement therapy, 1 patient died due to pulmonary complications, and 1 patient died because of immunosuppression-related complications.
Conclusion: Atypical anti-GBM disease is rare and may manifest itself with both intriguing clinical and pathological findings. The first step for an accurate diagnosis is to be aware of the disease.
Keywords: Atypical anti-GBM disease, acute kidney injury, Goodpasture's syndrome

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INTRODUCTION

Anti-glomerular basement membrane (anti-GBM) disease is characterized by acute clinical nephritis with necrotizing diffuse crescentic glomerulonephritis alone or combined with pulmonary hemorrhage through circulating autoantibodies. It mainly develops against the noncollagenous (NC-1) part of the type IV collagen α3 chain in both glomerular and alveolar basement membranes.[1,2] The disease usually manifests with pulmonary and/or kidney involvement in the form of rapidly progressive glomerulonephritis. It may result in mortality if aggressive treatment is not started immediately.[1] Therefore, it requires nephrological urgency.

Although the specificity and sensitivity of anti-GBM antibodies in Goodpasture's disease are high (90%-100% and 94%-100%, respectively),[3] false positive[4-6] or false negative[7,8] results can occur. Therefore, a kidney biopsy remains the gold standard and obligatory diagnostic method,[9,10] providing prognostic information for patients.[11] Its most characteristic feature is strong (at least 2+) immunofluorescence staining, showing

linear deposition with IgG along the glomerular capillary walls.[1] However, the disease can present some unexpected clinical and histopathological findings, including the absence of serum anti-GBM antibodies and mesangial and endocapillary proliferation patterns with rare or no crescents in a kidney biopsy. Furthermore, a better clinical course can occur in some patients, mostly without lung involvement, referred to as "atypical anti-GBM disease."[12,13]

Here, we will present the kidney biopsy and clinical findings from 4 cases of atypical anti-GBM disease.

METHODS

This study included patients diagnosed with atypical anti-GBM disease at Gazi University Hospital between January 2012 and December 2020.

Patients' demographic (age, gender, and smoking status) and clinical characteristics (complaints, urinalysis, BUN, blood creatinine, and C-reactive protein values) were retrieved and saved from the hospital information management system.

The hospital performs hematoxylin–eosin, Congo red, Masson's trichrome, periodic acid–Schiff (PAS), periodic acid–methenamine silver (Jones) stained sections, and direct immunofluorescence staining on cryostat sections with anti-IgG antibodies (Dako, Copenhagen, Denmark), anti-IgA (Dako, Copenhagen, Denmark), anti-IgM (Dako, Copenhagen, Denmark), complement C3 (Dako, Copenhagen, Denmark), complement C1q (Dako Agilent), kappa (Dako, Copenhagen, Denmark), and lambda light chains (Dako, Copenhagen, Denmark) for all kidney biopsies. For this study, archived sections in the pathology laboratory were reviewed light microscopically by a nephropathologist (IIG).

All patients who underwent kidney biopsy in our hospital filled in the "Informed Consent Form" in their own handwriting.

Ethical approval was obtained from the Gazi University ethics committee on May 05, 2023, with resolution number 2023-606 and session number 09.

MAIN POINTS

- Atypical anti-glomerular basement membrane (GBM) disease may present with interesting clinical and pathological findings; therefore, both the nephrologist and the nephropathologist should be aware of this disease.
- As kidney biopsy is almost the only way to diagnose the disease (especially in seronegative patients), clinicopathological communication and correlation are of great importance.
- Since there is no standardized treatment for atypical anti-GBM disease and it is a rare disease, every patient in the literature is valuable and deserves a thorough evaluation.

RESULTS

Clinical Features

Four patients with atypical anti-GBM disease were included in this study. All patients were male. The mean age of the patients was 36 (25-60) years. Three patients were smokers, and 1 patient was an ex-smoker. The patients complained about hemoptysis, darkening urine color, pretibial edema (patient 1), weakness, hemoptysis, swelling in the eyes and hands (patient 2), darkening urine color, a sore throat, a cough, and hemoptysis (patient 3). Patient 4 was admitted to the hospital during a checkup because of incidentally detected high blood creatinine (1.4 mg/dL) and microscopic hematuria (18 RBC/HPF) (Table 1). Patient 1 had a history of mild hemoptysis. None of the patients had a family history of kidney disease.

The patients were physically examined when they were admitted to the hospital. All patients had high arterial blood pressure (160/100 mm Hg) and normal vital signs (blood pressure, pulse, body temperature, and respiratory rate) apart from patient 2. Patients 1 and 2 had skin paleness and bilateral +1 pretibial edema. The initial physical examinations of patients 3 and 4 only revealed conjunctival paleness.

Laboratory investigations showed abnormalities in all 4 patients, which are summarized in Table 2. For all patients, serum antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCAs) levels were negative, and serum immunoglobulin levels and complement levels were within normal limits. Patient 2's serum anti-GBM antibody titer was low (at 1/10 dilution) but still positive. The other patients' serum anti-GBM antibodies were negative.

All patients had anemia, and their mean hemoglobin (Hb) value was 10.6 g/dL (9.6-11.2), measured by the complete blood count (CBC) of the patients. Erythrocyte sedimentation and C-reactive protein rates were high in all patients: the mean values were 47.8 mm/s and 8.5 mg/L, respectively. The mean values of blood urea nitrogen (BUN) and creatinine were 48.5 mg/L and 4.01 mg/dL, respectively. All patients had hematuria and proteinuria in urinalysis.

The patients' kidney ultrasounds were unremarkable. Posteroanterior (PA) chest x-rays revealed bilateral infiltrations in the lung parenchyma. Furthermore, a high-resolution lung computed tomography (CT) scan showed ground-glass densities, suggesting bilateral peribronchial interstitial septal thickening accompanied by alveolar hemorrhage in patient 1. Patient 2's PA chest x-ray revealed bilateral infiltrations in the lung parenchyma. Patient 3's PA chest x-ray revealed infiltrations in the basal zones of the lung, but there was no sign of alveolar hemorrhage in the high-resolution lung CT scans. Patient 4's PA chest x-ray and urinary ultrasonographic examinations revealed no abnormalities.

Table 1. Clinical Features of Patients

Patient Number	Hemoptysis	Cough	Dark Urine	Pretibial Edema	Weakness	Serum Anti-GBM Antibody	Radiological Findings
1	+	–	+	+	–	–	• Bilateral infiltrations in the lung parenchyma (PA chest x-ray) • Groundglass densities, suggesting bilateral peribronchial interstitial septal thickening accompanied by alveolar hemorrhage (CT scans)
2	+	-	-	+	+	+ (1/10 titer)	Bilateral infiltrations in the lung parenchyma (PA chest x-ray).
3	+	+	+	-	-	-	• Bilateral infiltrations in the basal zones of the lung (PA chest x-ray). • There was no sign of alveolar hemorrhage (CT scans).
4	-	-	-	-	-	-	No abnormalities in PA chest x-ray.

anti-GBM, anti-glomerular basal membrane; CT; computer tomography; PA, posteroanterior.

Table 2. Laboratory Investigations of Patients

Patient Number	Hb (g/dL)	ESR (mm/hour)	CRP (mg/L)	BUN (mg/dL)	Creatinine (mg/dL)	Spot Urine Protein–Creatinine Ratio (mg/g)	Urinalysis			Urine Protein (mg)/day
							RBC/HPF	WBC/HPF	Protein	
1	9.6	87	18	58	3.06	13200	26	2	+++	–
2	11.2	30	3	16	2.8	950	10	2	+	–
3	10.2	40	11.2	98	8.8	–	149	9	+	2020
4	10.8	34	1.62	22	1.4	1065	32	4	++	1035

BUN, blood urea nitrogen, CRPb C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HPF, high-power field; RBC, red blood cell; WBC, white blood cell.

Pathological Features

Figures 1, 2, 3, and 4 show the patients' kidney biopsies and all pathological features summarized in Table 3. In the light microscopy, the mean numbers of total glomeruli and global sclerotic glomeruli were 33.8 (17-48) and 4.5 (0-8), respectively. Patient 2's kidney biopsy included only 1 segmental sclerotic glomerulus. The mean numbers of cellular, fibrocellular, and fibrous crescents were 9.25 (0-19), 7 (0-13), and 1.5 (0-2), respectively. Nonsclerotic and noncrescentic glomeruli revealed different pathological findings in each patient. Patient 1 had endocapillary and mesangial proliferation (Figure 1A), and patient 2 had a nodular glomerulosclerosis pattern (Figure 2A and B). In patient 3's kidney biopsy, glomerular morphology was nonspecific. Patient 4's glomeruli appeared heterogeneous with segmental mesangial and endocapillary proliferative foci; 2 glomeruli had small nodule formations in the mesangium (Figure 4B). All biopsies had interstitial inflammation to varying degrees. A prominent inflammatory response with polymorphonuclear

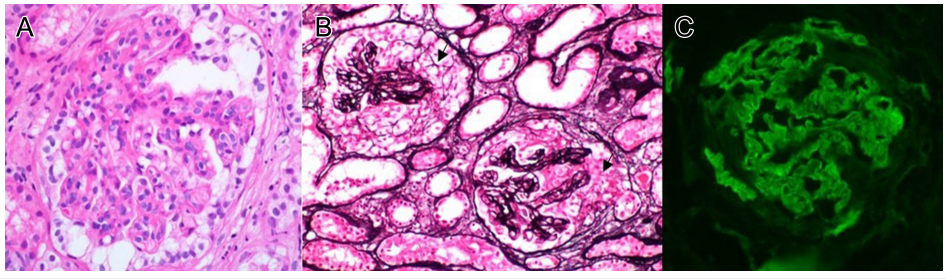

Figure 1. Kidney biopsy of patient 1. (A) Endocapillary and mesangial proliferative glomerulonephritis in a noncrescentic glomerulus (H&E ×400). (B) Cellular crescents filling the Bowman's space in 2 glomeruli (periodic acid–methenamine silver [Jones] ×200). (C) Strong linear staining of GBM for IgG by immunofluorescence. GBM, glomerular basement membrane; H&E, hematoxylin and eosin; IgG, immunoglobulin G.

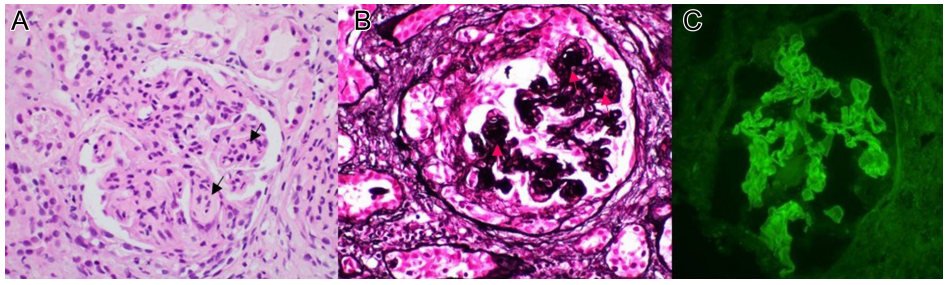

Figure 2. Kidney biopsy of patient 2. (A) Global mesangial expansion with mesangial cellularity and nodule formation (H&E ×400). (B) Accentuated mesangial nodules positive on silver stain (periodic acid–methenamine silver [Jones] ×400). (C) Strong linear staining of GBM for IgG by immunofluorescence. GBM, glomerular basement membrane; H&E, hematoxylin and eosin; IgG, immunoglobulin G.

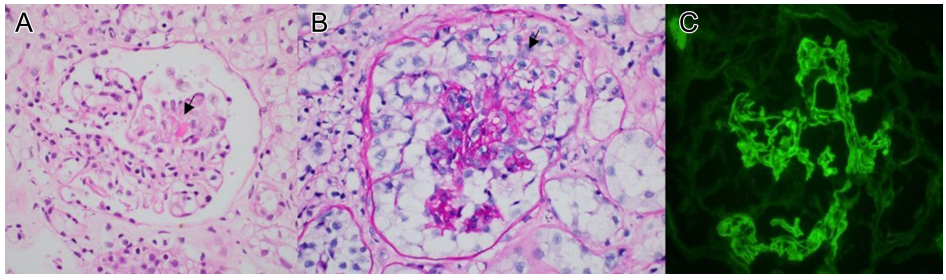

Figure 3. Kidney biopsy of patient 3. (A) Necrotizing glomerulonephritis with segmental tuft necrosis in a glomerulus (H&E ×400). (B) Cellular crescent formation with nearly collapsed glomerular tuft (PAS ×400). (C) Strong linear staining of GBM for IgG by immunofluorescence. GBM, glomerular basement membrane; H&E, hematoxylin and eosin; IgG, immunoglobulin G.

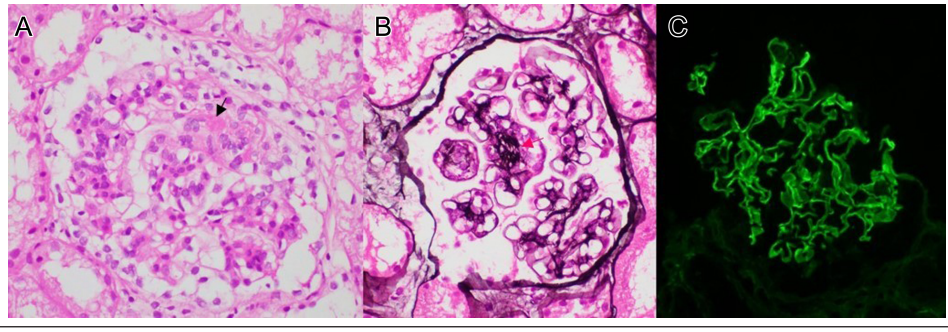

Figure 4. Kidney biopsy of patient 4. (A) A glomerulus with mesangial and endocapillary proliferation and accompanying segmental fibrinoid necrosis (H&E ×400). (B) A small, accentuated mesangial nodule formation which was silver in an otherwise unremarkable glomerulus (periodic acid–methenamine silver [Jones] ×400). (C) Strong linear staining of GBM for IgG by immunofluorescence. GBM, glomerular basement membrane; H&E, hematoxylin and eosin; IgG, immunoglobulin G.

Table 3. Pathological Features of Patients

Patient Number	Glomeruli			CC	FCC	FC	FN	Interstitial inflammation	ATI
	Total	GS	SS						
1	44	8	0	19	6	5	2	Prominent	Prominent
2	26	5	1	4	9	0	0	Mild	Mild
3	48	5	0	14	13	6	2	Prominent	Prominent
4	17	0	0	0	0	0	2	Minimal	None

ATI, acute tubular injury; CC, cellular crescent; FC, fibrous crescent; FCC, fibrocellular crescent; FN, fibrinoid necrosis; GS, global sclerosis; SS, segmental sclerosis.

leukocytes and eosinophils was observed in the interstitium in patients 1 and 3. Patient 2 had mild interstitial inflammation with sparse eosinophils in the interstitium. There was minimal mononuclear inflammation in patient 4's kidney biopsy. All patients apart from patient 4 had acute tubular injuries varying from mild to prominent. The vascular walls were nonspecific in biopsies, but patient 4's arteriolar walls revealed hyaline arteriolosclerosis and moderate arteriosclerosis.

In immunofluorescence microscopy, there was bright (intensity of 3+ [scale 0-3 +]), global, linear staining along the glomerular capillary walls with IgG (Figure 1C, 2C, 3C) in all biopsies. IgG deposition was kappa monotypic in patient 2 and lambda monotypic in patient 4. Spotty 1+ (intensity of 3+ [scale 0-3 +]) mesangial staining for C3 was present in patient 4's kidney biopsy (Figure 4C). IgM, IgA, and C1q were negative in all patients.

Clinical Follow-Ups

Each patient presented with different clinical pictures; therefore, different follow-ups and treatments were pursued.

Based on the definitive diagnosis of atypical anti-GBM disease, patient 1 was prescribed 1000 mg methylprednisolone for 3 days and 500 mg intravenous (IV) cyclophosphamide. Nine cycles of plasmapheresis were performed following pulse steroid therapy. Intravenous cyclophosphamide was continued every 2 weeks at the same dose for the following 12 weeks. As no kidney response to this treatment occurred, 2 cycles of weekly rituximab were also administered at a dose of 375 mg/m^2. The serum creatinine level was reduced to 2.3 mg/dL, and the patient was discharged. At the 2-month follow-up visit, the patient presented with pancytopenia, fever, and a urinary tract infection. *Klebsiella pneumoniae* was identified in the patient's urine culture. Intravenous 1 × 1 g ertapenem and granulocyte colony-stimulating factor were initiated. As the patient's condition deteriorated, with shortness of breath, hypoxia, severe pneumonia, and neutropenic fever, he was transported to the intensive care unit (ICU). Unfortunately, the patient died of severe acute respiratory distress syndrome and heart failure within 4 days.

A combined pulse steroid, plasmapheresis, and cyclophosphamide treatment was started for patient 2. Following the second plasmapheresis cycle, the patient was transferred to the ICU due to increased hemoptysis. The plasmapheresis was continued, and the patient's hemoptysis regressed. Intravenous immunoglobulin was administered to correct hypogammaglobulinemia. After 7 cycles of plasmapheresis, hemodialysis (HD) was initiated for metabolic acidosis and uremia. Anti-GBM antibodies were cleared by plasmapheresis. Oral steroid treatment was tapered and discontinued within 6 months because there was no kidney response. Steroids were tapered and stopped after 6 months. Patient 2 has since undergone 3 times weekly.

For patient 3, kidney replacement therapy (KRT) was started immediately due to severe uremic symptoms. Following the kidney biopsy diagnosis of anti-GBM disease, 500 mg of methylprednisolone was given to the patient for 5 days. A 10-cycle plasmapheresis treatment was started, and 500 mg of IV cyclophosphamide was administered simultaneously. During follow-up, patient 3's respiratory symptoms ceased. There was no kidney response; therefore, steroids were tapered and discontinued, and patient 3 was discharged with a maintenance HD treatment program.

As patient 4 was diagnosed with atypical anti-GBM disease, 1000 mg methylprednisolone was prescribed daily for 3 days, followed by 500 mg IV cyclophosphamide. A high-resolution CT scan of the patient's thorax did not reveal pulmonary involvement. Intravenous cyclophosphamide continued to be given every 2 weeks at the same dose. Hematuria and proteinuria were resolved. Patient 4 had a serum creatinine level of 1.2 mg/dL in the sixth month after the biopsy and did not need HD.

DISCUSSION

Anti-GBM disease is an autoimmune disorder characterized by autoantibodies targeted to the basement membranes in the walls of capillary blood vessels in the kidneys and lungs. The disease may be kidney limited or affect the lungs and kidneys. The anti-GBM disease that affects only the kidneys is called anti-GBM glomerulonephritis, while the disease form that involves both kidneys and lungs is known as Goodpasture syndrome/disease. This form constitutes 34%-62% of total anti-GBM cases.[14]

Antibodies that are most frequently formed against the target epitopes in the NC-1 area of the alpha-3 subunit of type IV collagen can be detected using different methodologies, including radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), and chemiluminescence and western blot.[7] However, in some cases, the antibody may also develop against the similar regions of α4 [α4NC1] and α5 [α5NC1] chains.[15,16] The most common type of immunoglobulin is IgG, primarily the IgG1 and IgG3 subtypes. Rarely, the disease may be triggered by IgM and IgA autoantibodies.[17] The disease often presents with a pulmonary hemorrhage and acute clinical nephritis with necrotizing crescentic glomerulonephritis. The continuous linear deposition of immunoglobulin [usually IgG] along the GBMs demonstrated by immunofluorescence microscopy is a hallmark of the disease.[1] Electron microscopy reveals no electron-dense deposits. The disease course is usually monophasic with initial severe pulmonary and kidney involvement; however, subsequent relapses occasionally occur.[9,18]

Some patients with anti-GBM disease show atypical histopathological findings and/or clinical presentation and course. These cases are called atypical anti-GBM disease.[12,13] The most striking feature is the absence of serum anti-GBM antibodies with strong linear IgG immunofluorescence staining on kidney biopsy. The

findings from the 4 patients presented in this study match this definition with some additional features.

Linear capillary wall IgG staining on a kidney biopsy may be seen in other glomerulonephritis types,[12] including fibrillary glomerulonephritis and monoclonal immunoglobulin deposition disease (MCIDD) (light and heavy chains). In addition, weak linear staining can be nonspecific in diagnosing diabetic nephropathy and smoking-associated glomerulosclerosis. It may even be seen in patients with heavy proteinuria. Therefore, all the abovementioned differential diagnoses should be ruled out individually before any patient is diagnosed with atypical anti-GBM disease.

Many speculations have been made about the absence of anti-GBM antibodies in the serum in such patients, as Glassock summarized in a recent commentary.[7] The intrinsic sensitivity of the chosen test may be insufficient. Antibodies other than those that cause the classical disease[19] or belong to the nontypical immunoglobulin subclasses may develop against the epitopes of collagen type IV and make their detection difficult.[8,19-23] Nondetection may also be caused by the low pathogenicity/affinity or concentration of the antibodies, which may even explain the relatively low severity of pulmonary and kidney involvement in some patients.[24]

Patients 1 and 4 presented a subacute disease course. The pathological diagnosis of anti-GBM disease was a surprise for their nephrologists because there were 2 atypical features found in these patients: (i) serum anti-GBM antibody was not detected by standard assays (ELISA) and (ii) neither the patients' pulmonary involvement nor the kidney biopsy findings were as severe as expected in classical anti-GBM disease. In patient 1, the pulmonary disease may have preceded kidney manifestations as the patient had experienced hemoptysis almost a year before the onset of kidney disease. However, concomitant clinically silent kidney disease cannot be excluded, as the patient did not have a kidney biopsy at the time. Patient 4 had neither pulmonary symptoms nor pulmonary involvement on thorax CT. Conversely, patient 3, with the negative serum anti-GBM antibodies, presented clinically and histopathologically with a full-blown anti-GBM disease.

Patient 2 was a young male with renopulmonary involvement. The unexpected finding in this patient was the nodular glomerulosclerosis pattern in his kidney biopsy, which may represent smoking-associated glomerulosclerosis, diabetic nephropathy, fibrillary glomerulonephritis, MCIDD, amyloidosis, membranoproliferative glomerulonephritis (MPGN), or proliferative glomerulonephritis with monoclonal immunoglobulins. Furthermore, except for the amyloidosis, MPGN, and proliferative glomerulonephritis with monoclonal immunoglobulins, smoking-associated glomerulosclerosis, diabetic nephropathy, fibrillary glomerulonephritis, and MCIDD may also show linear IgG deposition along the glomerular capillary walls, as previously mentioned. Patient 2 had no diabetes mellitus, and a negative Congo red stain ruled out amyloidosis. However, this finding could still represent smoking-associated glomerulosclerosis, fibrillary glomerulonephritis, or MCIDD.

The linear IgG staining was monotypic in 2 patients (patient 2—IgG-kappa and patient 4—IgG-lambda). Initially, the foreground differential diagnosis for these patients was MCIDD, primarily characterized by the presence of nodular glomerulosclerosis (rarely with proliferative features and/or with crescents. It is also characterized by linear staining along the glomerular and tubular basement membranes for a single light chain and a single heavy chain by IF and the specific ultrastructural features. There was no identifiable tubular basement membrane staining with IgG on IF in any patients. It would have been easy to make this distinction if an ultrastructural examination had been possible. Instead, these cases were consulted by the Hematology Clinic to identify a possible monoclonal gammopathy. A recent case presented by Turner et al was highly instructive: it demonstrated that immunoglobulins produced by myeloma cells might cross-react with commercial anti-GBM testing in a patient whose kidney biopsy shows nodular glomerulosclerosis and linear IgG staining along the tubular and glomerular basement membranes.[25] Did an undiagnosed monoclonal gammopathy cause serum anti-GBM to become positive, albeit at low titer, for patient 2, as in Turner's case? Following a detailed hematological examination and eliminating other causes of serum anti-GBM antibody false positivity, such as human immunodeficiency virus and *Pneumocystis carinii* infections,[4-6] Patient 2 was diagnosed as an atypical anti-GBM disease.

Notably, 70%-79% of polytypic atypical anti-GBM nephritis cases had crescents and/or fibrinoid necrosis in the glomeruli.[13,23] In comparison, this rate was only reported in 10% of monotypic cases.[13] Findings from patient 4, whose detailed hematological workup was negative and whose kidney biopsy showed a noncrescentic phenotype, may support these results. However, 1 case is insufficient to draw conclusions in this area.

Few case reports, or series of cases, come under the title of atypical anti-GBM in the literature.[26-30] The disease incidence was reported to be between 8% and 11.8% in 2 relatively large series, where all native kidney biopsies were retrospectively reviewed.[12,13] The patients' ages at diagnosis varied significantly (15-85 years).[12,13,23] There was a prominent male dominance in all series ;[12,13,23] however, the disease was also seen in fema les.[12,13,23,28,29] The most consistent kidney finding was the presence of microscopic hematuria.[12,13,23] In contrast, the degree of proteinuria varied between the reported series (none, up to 53% nephrotic range proteinuria, 37% nephrotic syndrome).[12,13,23] Mild impairment in kidney functions with a median serum creatinine at biopsy was 1.8 mg/dL and 1.9 mg/dL in 2 large series (0.84-9.62 mg/dL).[13,23] Pulmonary involvement occurred

in only 16% of patients in Liang's series[23] and did not occur in any patients in Nasr's series.[13] Most of the patients were seronegative for anti-GBM antibodies.[13] The overall kidney survival was generally better than in classic anti-GBM disease.[13,23] Histopathological morphology was variable with no or focal crescents, rare fibrinoid necrosis, and proliferative changes, including mesangial and/or endocapillary proliferative GN and MPGN with or without TMA features.[12,13,23] However, unlike common atypical anti-GBM nephritis, cases with diffuse crescentic glomerulonephritis were also reported, although these were rare.[23,26,27,29] The most frequently stained IgG subtypes on immunofluorescence were IgG1, followed by IgG4, IgG2, and IgG3.[13,23] Electron microscopy revealed no electron-dense deposits except for a few small mesangial, subendothelial, and subepithelial ones.[13,23] Segmental widening of the subendothelial zone and foot process effacement was present in some cases.[13,23] The inability to perform IgG subtype staining and electron microscopy were the most critical limitations in this study.

CONCLUSION

The atypical anti-GBM disease may manifest with interesting clinical and pathological findings, which may be related to the causes that initiated the disease, such as cigarette smoke or inhaled toxins, the epitope exposed, the type of the antibody formed, and the specific HLA alleles that determine the patient's genetic predisposition. The disease course may not necessarily be moderate compared to its classical form. The kidney function status at the time of presentation, lung involvement, and crescents in the kidney biopsy appear to be the significant prognostic parameters for disease outcome. As there is no standardized therapy for the atypical anti-GBM disease, treatment with a combination of plasmapheresis, steroids, and cyclophosphamide may benefit these patients. More must be discovered about the findings of these patients to better understand and treat this disease. However, its low incidence reduces the possibility of future randomized controlled trials.

Ethics Committee Approval: Ethical approval was obtained from the Gazi University ethics committee on May 05, 2023, with resolution number 2023-606 and session number 09.

Informed Consent: Informed consent for the kidney biopsy procedure was obtained from all individual patients included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Medical Practices – İ.I.G., Ö.D.; Design – İ.I.G., Ö.H., Ö.D.; Data Collection or Processing – B.Öğ., S.Y., B.Öz., O.Ö., B.K.; Analysis or Interpretation – İ.I.G.; Literature Search – İ.I.G.; Writing – İ.I.G., S.Y., B.K., B.Ö.

Declaration of Interests: The authors declare that they have no competing interest.

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