

## Single Case

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# IgA Nephropathy in a Patient Treated with Adalimumab

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## Keywords

IgA nephropathy · Adalimumab · Crohn's disease · Glucocorticoids · Vedolizumab

## Abstract

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common glomerulonephritis worldwide, characterized by IgA deposits in the glomerular mesangium. It has a progressive nature and can eventually lead to end-stage kidney failure. It can occur as a potential side effect of treatment with tumor necrosis factor alpha antagonist that has been used for numerous chronic inflammatory conditions, such as Crohn's disease. In this study, the case of a 33-year-old man with renal dysfunction, nephrotic proteinuria, and erythrocyturia is described. He had had a history of Crohn's disease for 8 years and had been treated with adalimumab for the past 7 years. The diagnosis of IgAN was confirmed by kidney biopsy. After discontinuance of adalimumab and the induction of corticosteroid therapy, he made a remarkable recovery. Four years after the first presentation of IgAN and discontinuation of adalimumab, his renal function was normal with no proteinuria and only mild erythrocyturia.

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## Background

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common glomerulonephritis (GN) worldwide [1]. It is characterized by IgA deposit in the glomerular mesangium. Patients with IgAN present with overproduction of an aberrantly glycosylated form of IgA1 that forms immune complexes with glycan-specific immunoglobulin G (IgG) and IgA antibodies.

These antibodies often obtain reactivity against antigens from extrinsic microorganisms after repetitive mucosal infections. The overproduction of the aberrantly glycosylated IgA1 is purported to be a genetic trait [2]. The immune complexes that are formed contribute to glomerular inflammation and mesangial proliferation.

Further glomerulosclerosis and tubulointerstitial fibrosis lead to loss of renal function [1]. IgAN has a higher prevalence in younger Caucasian or East Asian male individuals and often presents with macroscopic hematuria during an upper respiratory or gastrointestinal illness [3]. However, the clinical manifestation can vary from asymptomatic microscopic hematuria to rapidly progressive GN or nephrotic syndrome. The definitive diagnosis of IgAN requires a biopsy, which confirms characteristic IgA dominant or codominant immune deposits on immunofluorescence microscopy [3, 4] that corresponds to electron-dense mesangial and paramesangial deposits on electron microscopy.

IgAN is caused by diverse environmental and genetic factors. In most cases, the disease is idiopathic, but it can be associated with other conditions, such as Crohn's disease [5]. There are some reports that tumor necrosis factor alpha (TNF $\alpha$ ) could be the inducer of IgAN [6, 7].

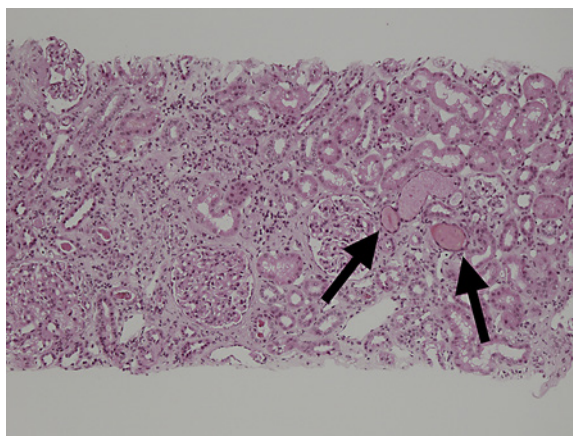
Adalimumab (Humira™) is a monoclonal antibody that binds to TNF $\alpha$  and neutralizes its biological function [8]. In previous decades, TNF $\alpha$  antagonists improved the outcomes of various chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease [9]. Adalimumab is an effective therapeutic option, administered subcutaneously, for induction of response and maintenance of remission in patients with moderate to severe Crohn's disease [10, 11]. TNF $\alpha$  antagonists are generally well tolerated. The most common side effects of adalimumab are reactions at the sites of injection, headache, and diarrhea. However, the effects of TNF $\alpha$  antagonists are not clearly defined as they show both pro-inflammatory and immunosuppressive natures [12]. Treatment with TNF $\alpha$  antagonists has been linked to immunogenicity [8] and is associated with induction of flares of autoimmune diseases [13], such as lupus-like syndrome, and demyelinating diseases [14]. The occurrence of IgG- or IgE-neutralizing antibodies against infliximab and adalimumab decreases their therapeutic effect [15]. Few case reports have described the onset of IgAN after treatment with these agents. Clinical presentation can vary significantly, with possible end-stage renal disease [6, 7, 16].

### Case Presentation

A 33-year-old man had Crohn's disease for 8 years, starting in 2008, with predominant involvement of the terminal ileum and rectum with occasional occurrence of an anal fissure. After the diagnosis, he was treated with mesalamine and methylprednisolone for 1 year followed by switching to adalimumab, after an exploratory surgery of the abdomen. He had been receiving adalimumab for 7 years up until the visit to the nephrology department.

Three weeks prior to the presentation to the nephrology department, his attending gastroenterologist for the first time noticed an increase in serum creatinine of 145  $\mu$ mol/L (reference range 44–97  $\mu$ mol/L) and serum urea of 10.9 mmol/L (reference range 2.8–7.5 mmol/L). Additionally, proteinuria and hematuria were detected (hemoglobin 3 out of 4, [reference 0] and protein 3 out of 4 [reference 0] on dipstick, and numerous erythrocytes were seen in the urine sediment). His primary disease was in remission, aside from occasional discomfort in the lower right abdominal quadrant with episodes of feeling unwell. He denied changes in his urine, changes in appetite, loss of weight, or fever.

He had no prior personal or family history of kidney disease. However, analysis of laboratory urine data at the onset of Crohn's disease showed that he already had hemoglobinuria and mild proteinuria (hemoglobin 3 and protein 1 on the dipstick). Also in the year 2007 – 1 year



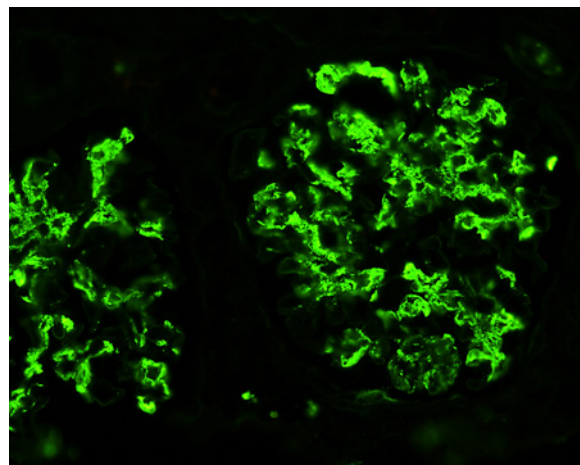
**Fig. 1.** Mesangioproliferative GN with RBC casts (arrows), tubular injury, and interstitial infiltrate (hematoxylin-eosin,  $\times 100$ ). GN, glomerulonephritis.

before the onset of Crohn's disease, erythrocytes were present in the urine sediment but with no proteinuria on the dipstick. Older urine results were not available.

At the previous checkup, 3 months prior to the visit to the nephrology department, he had normal renal function with a serum creatinine of  $91 \mu\text{mol/L}$ . He was treated with the biological drug adalimumab (Humira)  $40 \text{ mg}$  subcutaneously regularly every 14 days. Due to his anxiety, he had occasionally taken alprazolam and paracetamol for the management of pain. He had not been receiving any other immunosuppressive drugs or nonsteroidal anti-inflammatory drugs. He had allergies to mites and animal fur, which presented as allergic rhinitis. He was not a smoker and did not consume alcohol or drugs regularly.

Clinical examinations revealed a blood pressure of  $140/70 \text{ mm Hg}$ , heart rate  $89 \text{ beats per minute}$ , body weight of  $74 \text{ kg}$ , and height of  $178 \text{ cm}$ . He was cardiorespiratory compensated, eupneic, and afebrile. There were no abnormalities in his physical examination. Edema or vasculitic rash was not present. His serum creatinine was  $159 \mu\text{mol/L}$ , and his estimated glomerular filtration rate (eGFR CKD-EPI) was  $44 \text{ mL/min/1.73 m}^2$ . Urine analysis showed erythrocytes of  $895 \times 10^6/\text{L}$  (reference range up to  $10 \times 10^6/\text{L}$ ), and his urinary protein/creatinine ratio was  $302$  (reference range  $<20$ )  $\text{g/mol}$ .

The patient was admitted for further diagnostics. During hospital stay, his urinary protein/creatinine ratio was  $402.0$  (reference range  $<20$ )  $\text{g/mol}$ , and  $24 \text{ h}$  urine protein excretion was  $4.34$  (reference range  $<0.15$ )  $\text{g}$ . The IgG/creatinine ratio was  $14.44$  (reference range  $<1.13$ )  $\text{g/mol}$ , albumin/creatinine ratio  $340.63$  (reference range  $<2.26$ )  $\text{g/mol}$ , and alpha-1 microglobulin/creatinine ratio  $2.58$  (reference range  $<1.58$ )  $\text{g/mol}$ , indicating selective glomerular with mild tubular proteinuria. Urine analysis showed erythrocytes of  $980 \times 10^6/\text{L}$  and leucocytes of  $18 \times 10^6/\text{L}$ . Dysmorphic erythrocytes were present in the urine. Full blood count, hemostasis, hepatitis B and C, human immunodeficiency virus, cytomegalovirus serology, and interferon-gamma release assay were all in normal ranges. He had mild normocytic anemia (hemoglobin concentration  $123 \text{ g/L}$ ) and increased sedimentation rate ( $44 \text{ mm/h}$ ). His serum cholesterol levels ( $6.0 \text{ mmol/L}$ ) and IgA antibodies ( $1.9 \text{ g/L}$ ) were elevated. Ultrasound revealed kidneys of normal size and echogenicity. An ultrasound of the abdomen and a chest X-ray did not show any remarkable abnormalities. Kidney biopsy was performed, showing diffuse mesangioproliferative, endoproliferative, exudative, necrotizing, and extracapillary GN, evaluated as M1, E1, S1, T1, and C1 (fibrocellular crescents) according to the Oxford classification. In addition,  $40\%$  chronic tubulo-interstitial nephritis of moderate intensity was observed, accompanied by erythrocyte and hemoglobin tubular casts (Fig. 1). The immunofluorescence staining of the biopsy specimen was typical for IgAN, with strongly positive IgA and C3 deposits (Fig. 2).



**Fig. 2.** IF showing the immune deposits of IgA in the glomeruli. IgA, immunoglobulin A; IF, immunofluorescence.

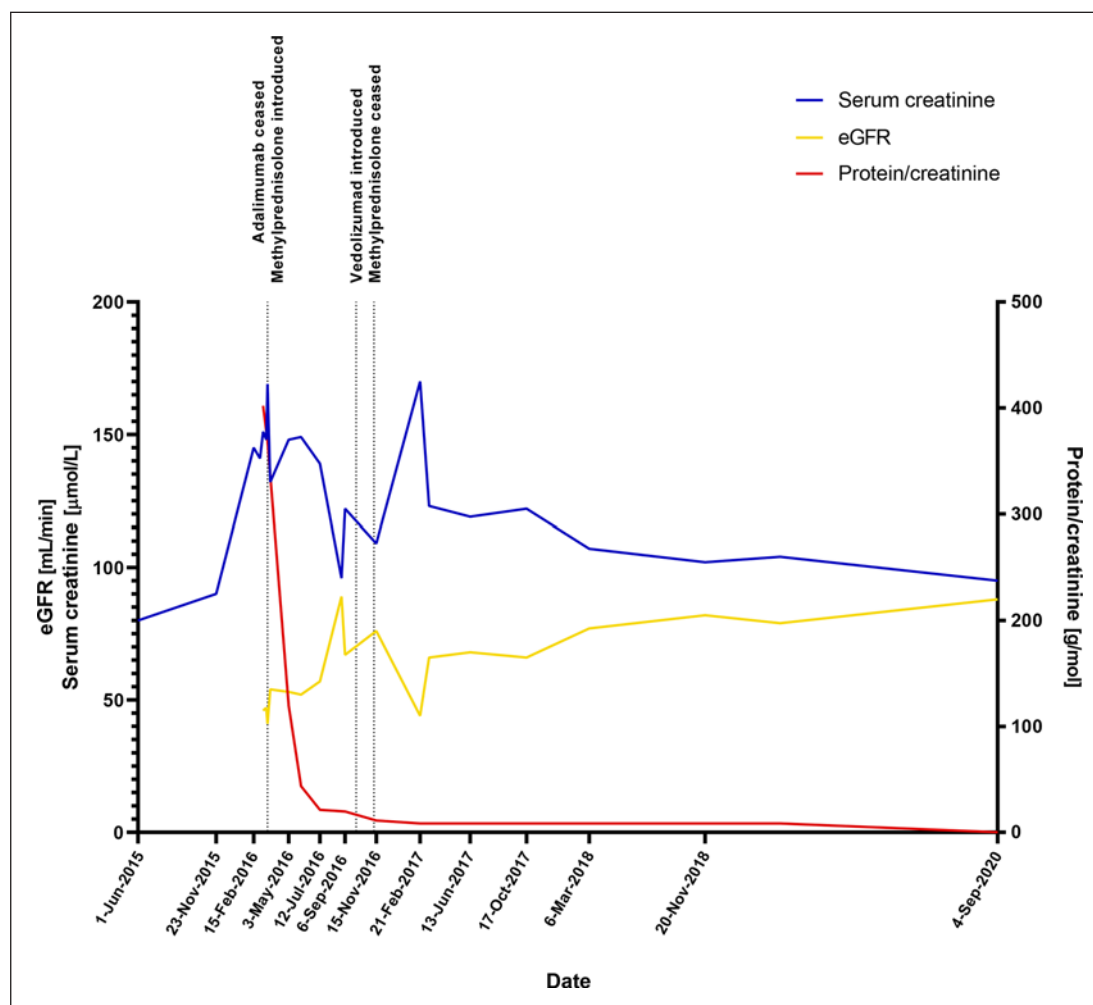
Upon the diagnosis, according to the kidney biopsy, adalimumab, as a potential inducer of IgAN, was discontinued. The patient received 3 consecutive daily pulses of methylprednisolone in a daily dose of 500 mg intravenously. Serum creatinine and proteinuria decreased after discontinuing treatment with adalimumab and the introduction of corticosteroids (Fig. 3). He was discharged and prescribed oral methylprednisolone 32 mg/day, supportive therapy, perindopril 4 mg/day, and fluvastatin 80 mg/day. Methylprednisolone was gradually decreased and subsequently stopped 8 months after the induction. At that time, serum creatinine was 109  $\mu\text{mol/L}$ , proteinuria 0.12 g per day, and erythrocyturia  $216 \times 10^6/\text{L}$ . For the control of his Crohn's disease, vedolizumab was prescribed 1 month before the cessation of corticosteroids. In the next 4 months, after the induction of the new biological drug, his renal function transiently deteriorated, with no deterioration of proteinuria, but recovered thereafter. Four years after the first presentation of IgAN and discontinuation of adalimumab, his renal function was excellent with a serum creatinine concentration of 95  $\mu\text{mol/L}$ , estimated daily proteinuria  $<0.03$  g (Fig. 3), and erythrocyturia  $15 \times 10^6/\text{L}$ .

## Discussion

Crohn's disease is an inflammatory disease that has numerous extraintestinal complications [17]. An active form of Crohn's disease is strongly associated with IgAN [18]. Altered intestinal permeability and increased production of IgA in the gastrointestinal mucosa potentially drive this complication [19]. In the present case, the patient has been in remission for years; therefore, Crohn's disease alone was presumably not the cause of IgAN.

Analysis of laboratory urine data from the past showed that he already had hemoglobinuria and mild proteinuria at the onset of Crohn's disease on the dipstick, and 1 year before the onset of Crohn's disease, erythrocytes were found in the urine sediment. Theoretically, there is a possibility that the patient may have a mild form of IgA GN present at the onset of Crohn's disease or even before, but it has significantly worsened and clinically manifested with TNF $\alpha$  antagonist treatment.

We observed a prompt response to the cessation of the adalimumab and steroid therapy, which implies its role in the pathogenesis of the GN. Corticosteroids facilitated the recovery of renal function. Stable renal function with the absence of proteinuria after discontinuation of methylprednisolone, even 4 years after the first visit to the nephrology department, with



**Fig. 3.** eGFR, serum creatinine concentration, and proteinuria at different time points. eGFR, estimated glomerular filtration rate.

no additional immunosuppression for IgAN, suggests that adalimumab could be the main factor in the occurrence or deterioration of IgAN in this patient.

Patients with adalimumab-induced IgAN present with the occurrence of aberrant IgA1 as observed in the primary IgAN [20]. As the sole presence of these antibodies is not nephritogenic, the involvement of antibodies against TNF $\alpha$  antagonist is suspected of driving the TNF $\alpha$  antagonist-induced IgAN as the biological drugs react as antigens for antibody formation. Additionally, the antibodies against glycans of the heavy chain of TNF $\alpha$  antagonists may cross-react with glycans on IgA1 molecules [20]. The other possible underlying etiopathogenic process is that aberrantly glycosylated IgA1 binds to antigenic epitopes of TNF $\alpha$  antagonists [20]. Both mechanisms lead to the formation of large immune complexes that can cross glomerular endothelial fenestrae and be deposited in the mesangium of the kidneys, thus causing renal damage. Therefore, TNF $\alpha$  antagonists may act as triggers of the disease in genetically prone individuals. The third possible mechanism may be independent of the structure of the TNF $\alpha$  antagonist molecule and may be due to the immunomodulatory effect of TNF $\alpha$  antagonists that involve cytokine imbalance. T-helper (Th) cells mainly differentiate into either Th1 or Th2 cells. Th1 cells (secreting interferon- $\gamma$ , interleukin [IL]-2L, IL-3, and



TNF $\alpha$ ) support cell-mediated immunity, whereas Th2 cells (secreting IL-4, IL-10, IL-5, IL-9, and IL-13) enhance humoral immune responses [21]. TNF $\alpha$  antagonists induce a shift from the Th1 pattern to Th2 pattern [22], promoting the development of antibody-mediated immunity. It was recently found that IgAN is characterized by a higher proportion of circulatory Th2, T follicular helper cells, Th17, Th22, and  $\gamma\delta$  T cells but lower Th1 and regulatory T cells. It was found that Th2, Th17, and T follicular helper cell-type ILs contribute to the elevated synthesis of galactose-deficient IgA1 [23], leading to IgAN.

Regarding the structure, several types of TNF $\alpha$  antagonists are known. Infliximab is a chimeric mouse/human anti-TNF $\alpha$  antibody composed of a murine variable region and a human IgG1 constant region. Adalimumab is a fully humanized anti-TNF $\alpha$  monoclonal antibody. Etanercept is a fusion protein composed of 2 extracellular portions of human TNF receptor 2 and the FC portion of human IgG1 [24]. Due to their differences in structure, they are not equally effective in different clinical settings [25, 26] and have different side effects, for example, induction of granulomatous infections [27]. Descriptions of IgAN induced by adalimumab [28], golimumab [29], or infliximab [28, 30] can be found in the literature. Etanercept has been described as a causative agent of vasculitis with renal impairment [16], crescentic necrotizing GN [31], lupus nephritis [32], and membranous GN [32, 33]. In a study by Saint-Marcoux and De Bandt [16] in which etanercept, infliximab, and adalimumab were used, in 2 of 39 patients, IgA deposition was found in the glomeruli on renal biopsy, but the description of whether these 2 patients received etanercept or another TNF $\alpha$  antagonist is lacking. There are no reports in the literature that etanercept could induce IgAN.

It was suggested that induction of IgAN is not a class effect of TNF $\alpha$  antagonists as infliximab may even reduce proteinuria and induce remission of IgAN [34] and has been used successfully as a replacement drug in a patient with CD in whom adalimumab has caused IgAN [7]. Recently published case reports reported patients in whom infliximab triggered IgAN [28, 30]. According to these recent results, it seems that there is a class effect of TNF $\alpha$  antagonists inducing IgAN, perhaps with the exception of etanercept, and it is becoming discouraging to use another TNF $\alpha$  antagonist in the case that IgAN is produced during TNF $\alpha$  antagonist treatment.

From the case reports described in the literature and from our case, we attempted to determine whether the treatment duration with TNF $\alpha$  antagonists has any effects on the histological characteristics of IgAN. According to the described cases, kidney biopsies of patients on TNF $\alpha$  antagonists uniformly displayed deposits of IgA and C3, but glomerular histopathologic changes are diverse, including segmental mesangial proliferation followed by segmental and global glomerulosclerosis and crescents, without a clear relationship to treatment duration. Chronic tubulointerstitial changes also varied from focal (<25% according to Oxford classification) to extensive, accompanying >50% of biopsy (according to Oxford classification), found mostly in patients with a long-lasting treatment period. According to the recognized (known) TNF $\alpha$  antagonist immunomodulatory effects, it may be speculated that interstitial infiltrates could be more prominent than primary IgAN, but moderate mononuclear infiltrates in the interstitium were described only in 2 of 8 cases, including our case (and a case described by Bhagat Singh et al. [7]).

The lack of correlation between the duration of TNF $\alpha$  antagonist treatment and severity of glomerular lesions might be explained by an idiosyncratic drug reaction, which may occur any time after the commencement of therapy [35]. The presence of active versus chronic lesions on kidney biopsy may depend on the time between the onset of adalimumab-related IgAN and clinical recognition of kidney disease, including kidney biopsy.

In conclusion, it is of paramount importance to assess renal function and examine urine at the start of treatment with TNF $\alpha$  antagonists to rule out possible pre-existing kidney disease and then regularly monitor renal function and urinalysis with regular determination

of proteinuria in patients treated with adalimumab and other TNF $\alpha$  antagonists. The possibility of predicting an IgAN complication by measuring the serum concentration of aberrant IgA1 after the induction of adalimumab treatment should be further addressed.

### Statement of Ethics

The patient in this study provided written informed consent for use of his clinical information for inclusion in a medical publication.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

All authors contributed to the paper. T.M. collected the data and wrote the paper, N.S. participated in the treatment of Crohn's disease and critically reviewed the paper, NK performed histopathologic analysis of renal biopsy and critically reviewed the paper, J.L. participated in the diagnosis and critically reviewed the paper, and D.K. participated in the treatment of the patient, gave the idea for the paper, and critically reviewed the paper.

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