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Case Study

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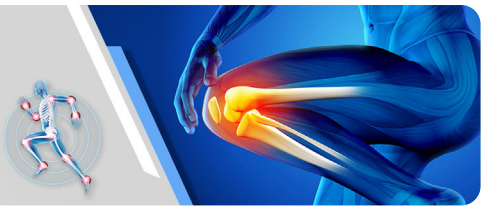

Adalimumab-Induced Minimal Change Disease

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Abstract

Tumor Necrosis Factor inhibitors are frequently used for treatment of rheumatic and other inflammatory diseases. These medications are generally well tolerated and have shown great efficacy for treatment of Rheumatoid Arthritis [1].

Though nephrotic syndrome and renal injury can occur secondary to medications, anti-TNFα agents are rarely associated with nephrotoxicity [2]. Here we report a case of a patient who presented with generalized edema and ultimately found to have adalimumab induced minimal change disease (MCD).

Keywords: Minimal change disease; Anti-TNF; Adalimumab; Rheumatoid Arthritis

Introduction

Tumor Necrosis Factor alpha (TNF-α) is a major inflammatory cytokine that plays a central role in the pathological development of inflammatory diseases [3]. It is secreted from Th1 cells and macrophages and work to active synovial fibroblasts, promote epidermal hyperplasia, and recruit inflammatory cells [4]. TNF-α inhibitors block the signaling between inflammatory cytokines and their respective receptors thereby neutralizing their proinflammatory effects.

Common TNF-α inhibitors on the market such as etanercept, infliximab, and adalimumab can be used to treat a variety of inflammatory conditions such as ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, juvenile idiopathic arthritis, ulcerative colitis, and rheumatoid arthritis [1].

Adalimumab is a human monoclonal antibody that has been employed for the treatment of rheumatoid arthritis since 2002 [5]. Most common adverse reactions are minor and do not require medication discontinuation. Very few cases in literature have linked usage of anti-TNF therapy to nephrotoxicity and even fewer for adalimumab associated kidney disease.

Case Presentation

A 63-year-old female with past medical history of seropositive erosive rheumatoid arthritis (RA), untreated hepatitis C, and osteoporosis presented to the emergency department with the chief complaint of whole-body swelling. Her RA had been well controlled over the past year on etanercept (Enbrel), methotrexate, and low dose prednisone with low disease activity.

The symptoms had started approximately one week ago following her fifth dose of adalimumab (Humira) which was recently started in outpatient rheumatology clinic per patient's request due to belief that Enbrel is contributing to hair loss. She noted a fever on the day of her most recent

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adalimumab injection and low-grade temperature the day after along with a pruritic rash all over the body involving the face, upper arms, legs, and chest. She has been urinating less and has some pain with urination over the past 5 days and has not urinated at all in the 24 hours leading up to her presentation. Since being switched to adalimumab, she has had non-bloody-non-bilious vomiting about three times a day for a week along with watery diarrhea.

A review of systems was positive for fevers, shortness of breath, and lower extremity swelling. Vitals were stable on admission with temperature of 97.8 °F, heartrate 93 beats per minute, respiratory rate 20 breaths per min, blood pressure 127/78 mmHg, and oxygen saturation 99% on room air.

Physical exam showed a pleasant woman who is alert and interactive in no acute distress. Findings were notable for 2+ pitting edema in the bilateral lower extremities associated with tenderness to palpation. Skin exam was negative for erythema, rash, lesions, and ecchymosis. Joint exam with no tenderness to palpation or synovitis. Remainder of physical exam was within normal limits.

Initial laboratory findings revealed mildly elevated BUN/creatinine ratio of 27/0.7 and elevated serum potassium 5.1 mEq/L. Albumin and total protein also significantly decreased compared to baseline. (Table 1). A bladder scan was done in the emergency room that found only 30cc of urine. Urinalysis demonstrated profoundly elevated urine protein/creatinine ratio of 3.25g along with increased white blood cells of 164 and many bacteria (Table 2). Patient received empiric treatment for urinary tract infection with ceftriaxone and was subsequently admitted to medicine for further workup.

Table 1: Initial laboratory values.

Lab	Values	Reference range
WBC	5.2 k/μL	4.0-11.0 k/μL
Hemoglobin	12.9 g/dL	12.0-16.0 g/dL
Hematocrit	0.375	36.0-48.0%
Platelets	260 k/μL	150-450 k/μL
Sodium	134 mEq/L	133-145 mEq/L
Potassium	5.1 mEq/L	3.5-4.8 mEq/L
Chloride	102 mEq/L	97-110 mEq/L
Bicarbonate	26 mEq/L	23-30 mEq/L
BUN	27 mg/dL	8-23 mg/dL
Creatinine	0.7 mg/dL	0.5-1.0 mg/dL
Albumin	1.6 g/dL	3.5-5.2 g/dL
ALP	91 U/L	35-105 U/L
AST	20 U/L	0-32 U/L
ALT	14 U/L	0-33 U/L
Total Protein	4.9 g/dL	6.0-8.3 g/dL

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; WBC, white blood cells

Chest X-ray showed mild pulmonary congestion without focal consolidations (Figure 1). CT abdomen pelvis demonstrated small pelvis and right paracolic fluid along with anasarca and bilateral small pleural effusions related to fluid overload. Nephrology was consulted and recommended renal biopsy due to concerns for membranoproliferative glomerulonephritis related to untreated hepatitis C infection. She was also started on torsemide for generalized edema.

Patient responded well to diuresis with improvements in urine output and generalized edema. Additional workups were negative for autoimmune etiologies (Table 3).

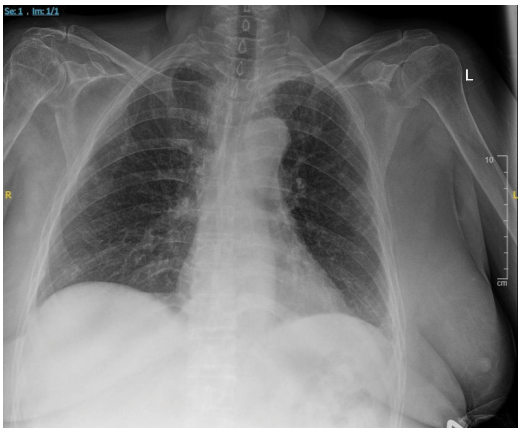

Figure 1: Chest X-ray.

Table 2: Urinalysis.

Lab	Values	Reference range
Color	Yellow	Yellow
Appearance	Cloudy	Clear
Spec Gravity	1.033	1.005-1.035
pH	5	5.0-7.0
Protein	>600 mg/dL	Negative
Creatinine	184.5 mg/dL	20-275 mg/dL
Glucose	Negative	Negative
Ketones	Negative	Negative
Bilirubin	Negative	Negative
Blood	Small	Negative
LE	Trace	Negative
Nitrite	Negative	Negative
WBC U	164	0-5 /HPF
RBC U	23	0-3 /HPF
Bacteria	Many	Absent
Hyaline Cast	>20	0-2 /LPF

LE: leukocyte esterase; WBC U: urine white blood cells; RBC U: urine red blood cells

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Patient's lipid panel results were consistent with nephrotic syndrome and she was subsequently started on a high intensity statin. 24-hour urine protein was markedly increased >3900mg. Diagnostic renal biopsy was performed demonstrating minimal glomerular alterations with marked effacement of foot processes ultrastructurally and negative immunofluorescence studies (Figure 2,3,4).

Table 3: Follow-up laboratory values.

Lab	Values	Reference range
CRP	2 mg/dL	0-5 mg/dL
ESR	104 mm/hr	0-20 mm/hr
C3	110 mg/dL	90-180 mg/dL
C4	24 mg/dL	10-40 mg/dL
ANA	Negative	Negative
C-ANCA	<1:20 titer	<1:20 titer
P-ANCA	<1:20 titer	<1:20 titer
Anti-PR3	<0.2 U	0.0-0.9 U
MPO	<0.2 U	0.0-0.9 U
ACA IgM	19 MPL U/mL (indeterminate)	<13 GPL U/mL
ACA IgG	<9 GPL U/mL	<15 GPL U/mL
IgG	410 mg/dL	700-1600 mg/dL
IgM	167 mg/dL	40-230 mg/dL
IgA	409 mg/dL	70-400 mg/dL
IgE	198 IU/mL	0-100 IU/mL

ACA, anticardiolipin antibody; ANCA, antineutrophil cytoplasmic antibody; ANA, antinuclear antibody; C3, complement component 3; C4, complement component 4; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Anti-PR3, anti-proteinase-3; MPO, myeloperoxidase

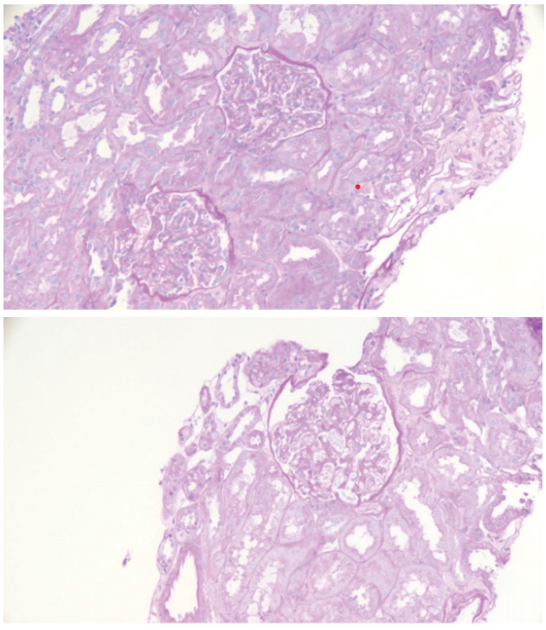

Figure 2: Light Microscopy.

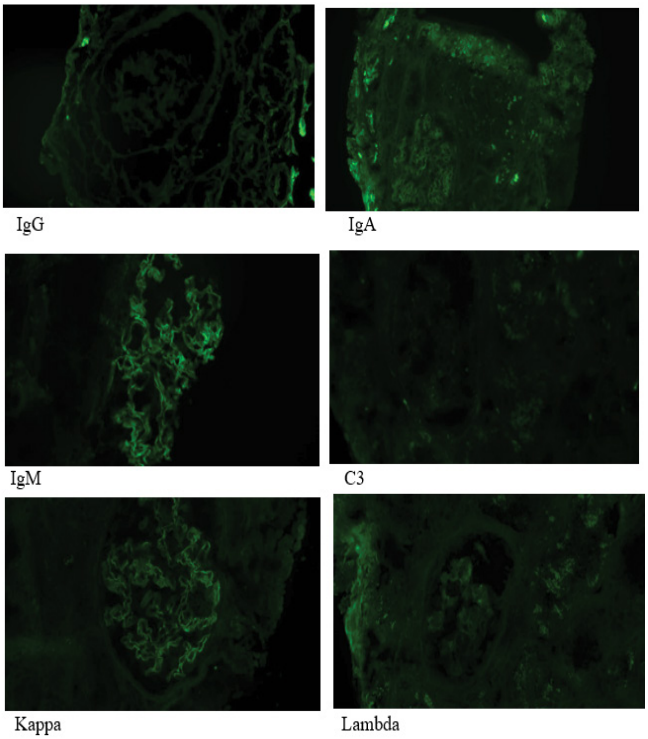

Figure 3: Immunofluorescence.

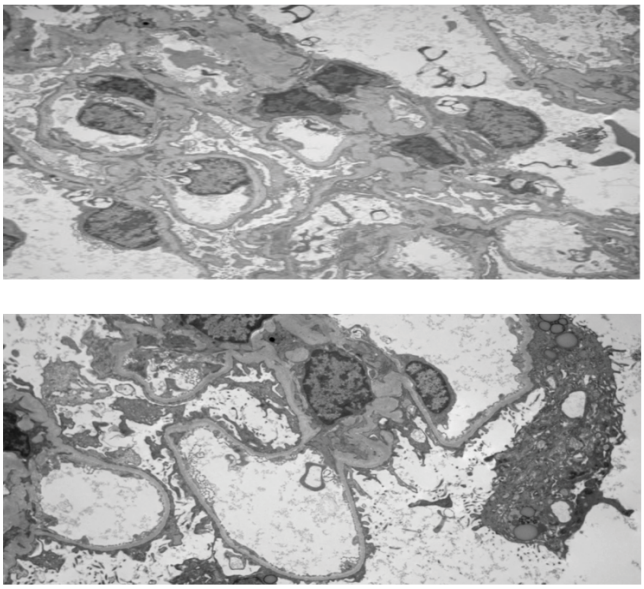

Figure 4: Electron Micropscopy.

Etiology of the significant podocytopathy and proteinuria were determined to be secondary to TNF-α inhibitor use given the time course of disease and having ruled out other processes. Adalimumab was discontinued and patient was restarted on prednisone at 1mg/kg along with trimethoprim/sulfamethoxazole for pneumocystis jirovecii prophylaxis. The patient was discharged back home with close outpatient follow-ups with both nephrology and rheumatology.

Discussion

Minimal change disease (MCD) is one of the most common causes of nephrotic syndrome. Most often seen in children, this condition accounts for approximately 70-90% of nephrotic syndrome in those under 10 years and arises from histopathologic lesions in the glomerular epithelial foot processes [6]. It is characterized by excess protein loss through the urine leading to edema and intravascular volume depletion that tends to respond rapidly to corticosteroids [7].

MCD can be idiopathic or occur secondary to other conditions such as infections, neoplasms, toxin exposure, allergies, and medications [8-10]. Drug induced MCD typically involves NSAIDs, lithium, and certain antibiotics [11]. In adults, MCD accounts for 10-15% of all nephrotic syndrome and is often less well characterized compared to children population [12].

Anti-TNF agents are generally well tolerated with common side effects being headaches, injection site reaction, rashes, infusion reactions, and upper respiratory tract infections [13,14]. More serious adverse effects that may appear several weeks to months following therapy are infections, autoimmune conditions and malignancies such as lymphoma [15].

Few cases of nephrotoxic reactions to anti-TNF therapy have been described in literature. Some of these include a case of extra capillary glomerulonephritis in a pediatric patient being treated with etanercept for juvenile psoriatic arthritis, two cases of acute kidney injury and sarcoid-like granulomatosis in patients being treated with etanercept for rheumatoid arthritis, a case of minimal change disease in a patient being treated with etanercept for psoriasis, a case of membranous glomerulonephritis in a patient being treated with etanercept for ankylosing spondylitis, and a case of crescentic glomerulonephritis in a patient treated with etanercept for rheumatoid arthritis [16-21].

TNF-α works as an immunoregulator and can play a critical role in maintaining immune homeostasis and kidney protection. In animal models as well as controlled clinical trials have shown that decreased expression of TNF alpha is linked to worsening in symptoms of autoimmune conditions such as multiple sclerosis [22,23]. Therefore, by blocking the signaling cascade, adalimumab could perhaps increase susceptibility to other autoimmune processes such as MCD.

Conclusion

Though uncommon, TNF-α inhibitors in rare circumstances can lead to glomerular disease and need to be considered in patients who develop new onset acute kidney injury or abnormal urinalysis following administration of TNF-α inhibitors. When patients on anti-TNF therapy develop nephrotic syndromes, minimal change disease should be suspected with discontinuation of offending agent and prompt initiation of corticosteroids. There is currently no data to show whether patients who developed nephrotoxicity to TNF-α inhibitors are at increased risk of recurrent episodes in the future. Thus, a joint decision between patient and physician is necessary to guide further medical therapy.

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