

CASE REPORT

크론병 환자에서 인플릭시맵과 메살라진 치료 후 발생한 지연발생 급성 세뇨관간질 신염 증례

유양재, 정상윤, 구대희, 고강지, 표희정, 권영주, 박영태, 원남희¹
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A Case of Late Onset-Acute Tubulointerstitial Nephritis with Infliximab and Mesalazine Treatment in a Patient with Crohn's Disease

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Infliximab is a chimeric anti-tumor necrosis factor-alpha monoclonal antibody. Infusion related reactions and infection are well known side effects of infliximab; however, renal complications have not been well recognized. We report on a patient with late onset-acute tubulointerstitial nephritis (ATIN) after treatment with infliximab and mesalazine for Crohn's disease. A 25-year-old woman was admitted with a purpuric rash on both lower extremities and arthralgia. She had been diagnosed with Crohn's disease 5.6 years previously and had been treated with mesalazine and infliximab. Serum creatinine level, last measured one year ago, was elevated from 0.6 mg/dL to 1.9 mg/dL. Results of urinalysis, ultrasound, and serologic examinations were normal. With a tentative diagnosis of Henoch-Schönlein purpura, oral prednisolone was given, and serum creatinine decreased to 1.46 mg/dL, but was elevated to 2.6 mg/dL again at two months after discontinuation of prednisolone. Renal biopsy indicated that ATIN was probably induced by drug, considering significant infiltration of eosinophils. Concomitant use of infliximab with mesalazine was supposed to trigger ATIN. Oral prednisolone was administered, and serum creatinine level showed partial recovery. Thus, ATIN should be suspected as a cause of renal impairment in Crohn's disease even after a long period of maintenance treatment with infliximab and mesalazine. (*Korean J Gastroenterol* 2014;63:308-312)

Key Words: Acute tubulointerstitial nephritis; Acute kidney injury; Crohn disease; Infliximab

INTRODUCTION

Acute tubulointerstitial nephritis (ATIN) is a disorder that manifests as acute kidney injury (AKI) with interstitial inflammation, edema, and tubulitis, which is usually related to drug or infection.¹ Renal dysfunction of ATIN is assumed to be reversible in most cases, and drug related ATIN should resolve with discontinuation of the responsible drug. However, one recent study showed that despite appropriate treatment,

a significant proportion of ATIN cases progress to chronic kidney injury.²

Although ATIN can be idiopathic, drug-induced ATIN is more prevalent. In an analysis of pooled data from three large studies reported in 2004, drug-induced ATIN accounted for 91 of the 128 cases (71.1%). Almost every drug is capable of inducing ATIN, and the clinical presentation and laboratory findings vary according to the class of drug involved (i.e., NSAIDs-related ATIN versus other types of drug-induced

Received August 28, 2013. Revised September 16, 2013. Accepted October 2, 2013.

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Financial support: None. Conflict of interest: None.

ATIN).^{3,4} Induction of ATIN is characterized by infiltration of various inflammatory cells into the interstitium, such as lymphocytes and monocytes, eosinophils, plasma cells, neutrophils, and histiocytes. A higher proportion of eosinophil infiltrates can also indicate drug-induced ATIN, except NSAIDs-related ATIN, which often does not cause eosinophil infiltration.⁴

Infliximab, a chimeric tumor necrosis factor-alpha (TNF- α) monoclonal antibody, has been used in treatment of patients with inflammatory bowel disease and rheumatoid arthritis. TNF- α monoclonal antibody treatment along with mesalazine has been established for remission of Crohn's disease, and is considered the most potent treatment available at present.^{5,6} Infusion related reaction and infection are well known side effects of infliximab treatment⁷; however, renal complications, particularly in cases of prolonged concomitant use with mesalazine have not been well recognized.

Here, we report on a patient who presented with delayed onset ATIN after a prolonged period of maintenance treatment with infliximab and mesalazine for Crohn's disease.

CASE REPORT

A 25-year-old woman was admitted with a purpuric rash on both upper and lower extremities and arthralgia of both ankle joints. She had been diagnosed with Crohn's disease 5.6 years previously and was treated with 3.0 g/day of mesalazine. Infliximab was added to her treatment protocol after 3.5 years of mesalazine treatment because she had experienced multiple relapses and a fistula was identified at the distal ileum. She had been stable since the start of infliximab

administration. The 19th infliximab infusion had been administered one month prior to admission.

On admission, BUN and creatinine were elevated to 26 and 1.9 mg/dL from her baseline level of 11.0 and 0.6 mg/dL from one year previously. Urinalysis showed no abnormal findings, such as hematuria, pyuria, or proteinuria. Proteinuria of 209 mg was detected in 24-hour urine collection. Kidney size and echogenicity was preserved within the normal range on ultrasonography, and serologic examinations showed no significant abnormalities. Ten milligram of oral prednisolone was given for control of purpura and arthralgia with the impression of Henoch-Schönlein purpura, although vasculitis was not confirmed with skin biopsy because the skin lesion lasted for a relatively short period of time. After administration of prednisolone and hydration, the purpura and arthralgia resolved, and her creatinine decreased to 1.46 mg/dL, although it did not reach the baseline level in the serial follow-up.

Prednisolone was discontinued after two months of treatment, and regular infliximab infusion had been continued every other month. Creatinine increased again, up to 2.6 mg/dL, five months after discontinuation of prednisolone (Fig. 1). Renal biopsy revealed ATIN with interstitial inflammation. Drug induced interstitial nephritis was suspected due to infiltration of various inflammatory cells in the tubules, especially eosinophils. Included glomeruli had a normal appearance, and immunofluorescence study for all immunoglobulins and complements showed negative results. Chronic exposure to causative drugs was also suspected because acute inflammatory cell infiltration and edema was also seen along with signs of chronic tubulointerstitial nephritis

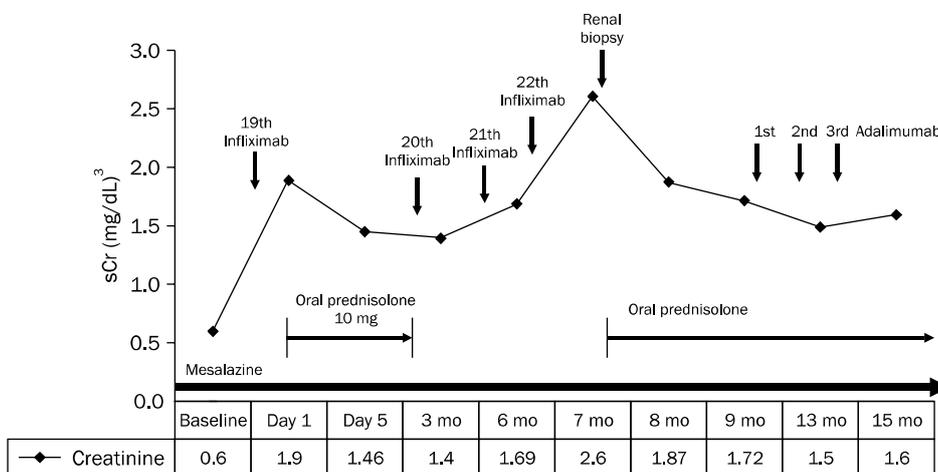


Fig. 1. Changes of serum creatinine levels. Creatinine level showed a slight decrease after initial administration of oral prednisolone. However, it increased again when the steroid was discontinued according to infliximab treatment. Oral prednisolone (0.5 mg/kg) was reintroduced, and the serum creatinine level remained nearly stable after adalimumab treatment.

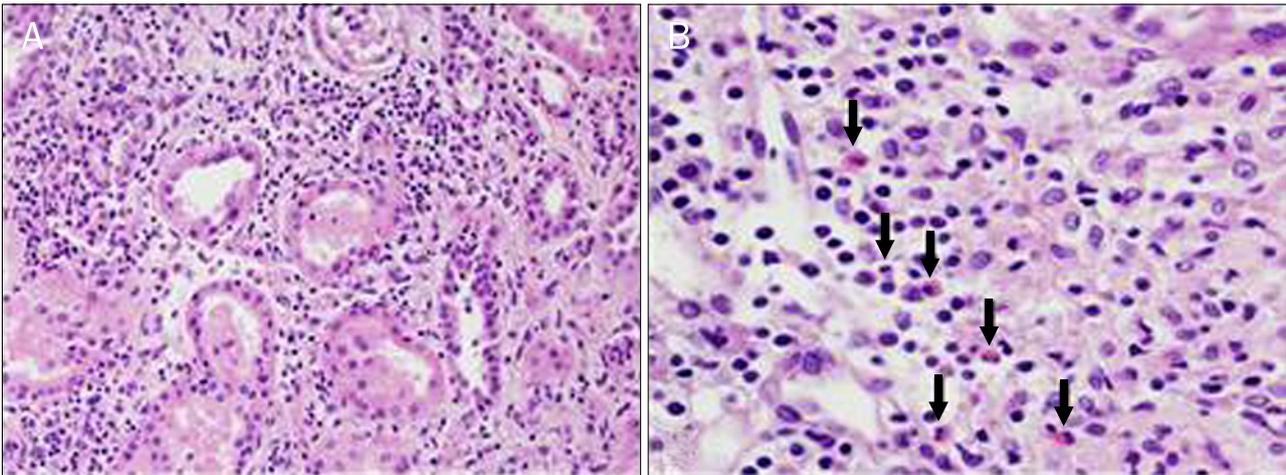


Fig. 2. Histologic examination with light microscopy of kidney. (A) There was diffuse tubular damage and infiltration of interstitial inflammation into the tubular epithelial cells (H&E, $\times 100$). (B) Inflammatory cell infiltration was superimposed on chronic tubulointerstitial nephritis, which manifested as tubular atrophy with attendant interstitial fibrosis. Infiltration of various inflammatory cells, including lymphocytes, plasma cells, eosinophils, and a few neutrophils, was observed, and a higher proportion of eosinophil infiltration (arrows) was noted (H&E, $\times 400$).

(Fig. 2).

Concomitant use of infliximab with mesalazine was supposed to induce ATIN because the patient denied taking any medications other than mesalazine and infliximab. Considering that mesalazine had been maintained for 5.6 years without complication and renal biopsy showed active inflammatory response with a significant number of eosinophils, although there was superimposed chronic interstitial nephritis, infliximab was considered to trigger ATIN in concomitant use of mesalazine. Serum creatinine had also increased according to the schedule of infliximab infusion, which was administered every two months.

Oral prednisolone was started for control of the ATIN. Because TNF- α antibody treatment should be sustained for control of Crohn's disease, adalimumab, a fully humanized TNF- α antibody, was administered subcutaneously with mesalazine instead of infliximab, possibly to minimize immunologic reaction. The serum creatinine level showed partial recovery to 1.6 mg/dL after two weeks of steroid therapy, and stabilized.

DISCUSSION

ATIN is observed in 2-3% of all renal biopsy samples; however, the number increases to 6.5-27% when the analysis is restricted to AKI patients.^{8,9} The causes of ATIN are variable. Idiopathic cases such as tubulointerstitial nephritis and uveitis syndrome and anti-tubular basement membrane disease

have been reported. Systemic diseases such as sarcoidosis, systemic lupus erythematosus, and Sjögren's syndrome are also known to be associated with ATIN. Among various underlying causes, drug-induced ATIN is the most prevalent, consisting of more than 75% cases of ATIN, followed by infection (15%).^{1,4} Theoretically, any drug is capable of triggering ATIN. Antibiotics, antiviral medications, anticonvulsants, analgesics, and anti-ulcer medications have frequently been associated with ATIN.⁴

In the current case, the patient had been treated with infliximab and mesalazine exclusively. Several cases of delayed onset of mesalazine-induced ATIN have been reported previously.^{10,11} However, the median duration of mesalazine treatment was less than two years, and chronic interstitial nephritis with interstitial fibrosis and lymphocytic infiltration was mainly manifested in patients who experienced renal dysfunction after taking mesalazine more than 1.5 years. ATIN in Crohn's disease with a prolonged period of maintenance treatment more than five years has rarely been reported.^{11,12} Given that the patient had been taking mesalazine for more than five years without any noticeable effects on renal function, the possibility of infliximab as a triggering agent for ATIN was suspected. Temporal association between aggravation of renal function and the interval of infliximab administration and the immunogenicity of infliximab, possibly due to its chimeric nature,¹³ supported our suspicion that infliximab triggered development of ATIN in the current case.

Renal complication related to infliximab has rarely been reported. In fact, infliximab has been used for therapeutic treatment of granulomatous tubulointerstitial nephritis and amyloidosis secondary to Crohn's disease. However, recent studies have reported renal involvement during anti-TNF- α treatment, including infliximab, adalimumab, and etanercept, a soluble TNF- α receptor approved for management of rheumatoid arthritis. Lupus nephritis, vasculitis, and glomerulonephritis, such as Henoch-Schönlein purpura and membranous nephropathy, have been reported after anti-TNF- α treatment.^{14,15} One case of ATIN after etanercept treatment has been reported.¹⁶ However, the case is the first report of ATIN in a patient with Crohn's disease treated with infliximab and mesalazine.

The problems of ATIN related to anti-TNF- α treatment are the difficulty of diagnosis and treatment. Low suspicion of ATIN as the cause of renal dysfunction in patients treated with anti-TNF- α treatment for Crohn's disease or rheumatoid arthritis could complicate early diagnosis. Absence of typical symptoms or signs of ATIN may also delay diagnosis. Fever, rash, and eosinophilia are classic clinical features of ATIN; however, less than 10% of patients show all three findings. Although proteinuria, hematuria, and leukocyturia may be present on urinalysis, these findings are not diagnostic for ATIN.⁴ Eosinophiluria was once thought to be a typical finding; however, its role in diagnosis of drug-induced ATIN is limited due to low sensitivity and specificity.¹⁷⁻¹⁹ Renal biopsy is essential for diagnosis of ATIN and the presence of interstitial inflammation and tubulitis are the main pathologic findings.⁴

In our case, purpuric rash, which may have been an extra-renal manifestation of ATIN during the first episode of renal dysfunction, was accompanied by arthralgia, which led us to misrecognize the condition as Henoch-Schönlein purpura. The absence of abnormal findings on urinalysis initially, and the substantially long duration of exposure to infliximab, also reduced our suspicion of ATIN, preventing early diagnosis and treatment.

The difficulty of ATIN treatment related to anti-TNF- α treatment in Crohn's disease is that there are few therapeutic options for Crohn's disease besides anti-TNF- α treatment. Early detection of causative agents and removal of the offending drug are the mainstays of therapy for drug-induced ATIN, and are crucial to avoidance of serious and progressive injury. However, anti-TNF- α antibody treatment cannot be dis-

continued even after diagnosis of ATIN possibly related to infliximab, as in our case, because it is the most powerful method for control of Crohn's disease. In the current case, anti-TNF- α antibody treatment was sustained, and steroid treatment was initiated in order to reduce the inflammation of ATIN. The use of steroids for treatment of drug-induced ATIN has remained controversial¹; however, recent studies have suggested that steroids should be started as soon as drug-induced ATIN is diagnosed in order to prevent interstitial fibrosis and to help in recovery of renal function.²⁰ It is not certain whether adalimumab, a fully humanized anti-TNF- α antibody, is the best possible choice to minimize the immunologic reaction in the kidney. The role of adalimumab as a replacement for infliximab should be examined in further studies.

ATIN could develop even after a prolonged period of maintenance treatment with infliximab and mesalazine in Crohn's disease. Early diagnosis via renal biopsy should be made promptly whenever renal dysfunction manifests in patients with Crohn's disease on anti-TNF- α antibody treatment with mesalazine.

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