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Case Report

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Etodolac induced acute interstitial nephritis and autoimmune hemolytic anemia

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Abstract
In spite of the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) such as etodolac, induction of drug-dependent antibodies that cause hemolytic anemia and acute tubulointerstitiel nephritis are rarely reported. Currently, there is no way of identifying individuals who are at risk to develop this kind of complications. In patients who present with acute immune hemolysis and acute renal failure, it is important that a careful history of medication be obtained, potential sensitizing medications be identified. In this article we describe a patient with acute autoimmune hemolytic anemia and acute renal failure related with etodolac.

Keywords: Etodolac, acute interstitial nephritis, autoimmune hemolytic anemia

Introduction

Acute interstitial nephritis (AIN) is an inflammatory parenchymal renal disease with major involvement of the tubules and interstitial regions of the kidney. It is most often caused by drug-induced (60-70%) and also caused by autoimmune or systemic disesase (systemic lupus erythematosus, Sjögren's Syndrome, sarcoidosis), malignancies and infections (Legionella, leptospirosis, streptocacal organism) [1,2]. AIN is known to have a high potential for reversibility if identified early. Pathogenesis of AIN involves cellular immunity with antibody-dependent. Meanwhile, Nonsteroidal anti-inflammatory drugs (NSAIDs) are also associated with autoimmune hemolytic anemia. It is a rare complication and its incidence remains uncertain as there are a few factors leading to misdiagnosis [3]. In this article, we report a patient with AIN and autoimmune hemolytic anemia caused by etodolac.

Case

A 34-year-old female was admitted to a government hospital with history of stomach pain, nause, mildly icterus and pinkish discoloration of urine. Four days before admission, she used etodolac for lomber pain. There was no history of autoimmune or systemic disease, or any recent pharyngeal or cuteneous infection. She was hospitalized and treated with saline because of dehidration findings. As creatinin level was increased and anuria developed during follow up, she underwent hemodialysis and referred to our center. Physical examination on the admission, revealed no pretibial edema and maculopapular rash. Respiratory and circulatory system examination were normal. She had a left jugulary temporary hemodialysis catheter. The patient's laboratory tests were as follows (**Table**): white blood cells (WBC) 8100/ml, Hgb 8g/dl, platelet 219000/ml, blood ure nitrogen(BUN) 34.1 mg/dl, creatinine 10.22mg/dl, total proteine 5.4g/dl, albumine 3g/dl, total bilirubin 0.54 mg/dl, indirect bilirubin 1mg/dl, LDH 347 U/L. She had 2.2 g/day proteinuria. Nine WBC, 5 red blood cells (RBC) per high power field was determined in urine analysis. Renal ultrasonography revealed bilateral normal sized kidneys with no evidence of renal artery stenosis or renal vein thrombosis. Schistocyte was not seen in peripheral blood smear. Antinuclear antibody, cANCA, pANCA and serologic studies for hepatitis B and C were negative. Complement 3 and 4 levels were in normal range. Direct coombs test was positive for IgG. A kidney biopsy was performed. Biopsy revealed interstitial inflammation and tubular destruction **(Figure)**. The patient was initiated intravenously metilprednisolon 500 mg for three days. Then, the patient continued oral metilprednisolone 60 mg/day. Her hemoglobin level increased and creatinine level was declined. After the second dialysis session, dialysis was stopped. On the 8th hospital day, the Direct coombs test was negative and, she was discharged with a Hb level of 10.8 g/dl and a creatinine level of 2.7 mg/dl. Metilprednisolone gradually decreased and at the 25th days of the treatment it was withdrawn and her serum creatinine level was 0.8 mg/dl.

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Table 1. Laboratory data of our patient

	At the government hospital First day	At the government hospital 2nd day	At the government hospital 7thday	1st day of our clinic	After first 500mg steroid	After second 500mg steroid	After third 500mg steroid	25th day of oral steroid
HGB (g/dl)	12.3	11.7	8.3	8	8.7	8.9	10.8	11.5
PLT (/ml)	331000	268000	203000	219000	296000	331000	518000	170000
BUN(mg/dl)	78	100	54	34.1	35	35	51	10.76
CREATININE(mg/dl)	2.06	5.84	7.66	10.22	6.89	3.99	2.72	0.78
LDH (U/L)	927	-	305	347	-	360	302	244
ALBUMIN(g/dl)	4.3			3.1	3.2	3.3	3.4	3.9
TOTAL BILIRUBIN(mg/dl)	5.54	1.24	0.45	0.54	0.33	0.25	0.33	
DIRECT BILIRUBIN(mg/dl)	0.66	0.49	0.21	0.24	0.17	0.13	0.13	

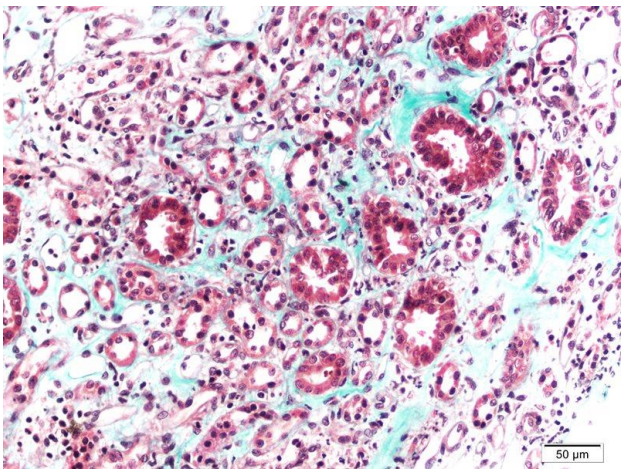

Figure 1. Disseminated active chronic inflammation at tubulointertisial space and erythrocyte cylinders in tubular lumens

Discussion

This report presents a young woman patient who developed severe, coombs-positive hemolytic anemia and AIN after taking etodolac. Drug-induced AIN occurs after one or two weeks of drug exposure. Typical presentation is sudden impairment in renal function, associated with mild proetinuria (<1 g/day) and abnormal urinalysis in a patient with flank pain, normal blood pressure and no edema. Extrarenal symptoms are low grade fever, maculopapular rash, mild arthralgia and eosinophilia. Eosinophilia helps to diagnose AIN but absence of eosinophilia does not exclude [4,5]. The main difference is that extrarenal symptoms are present in only about 10% of patients. Renal diseases caused by NSAIDs must be differentiated from other NSAID-induced nephropathy, including hemodynamically mediated acute kidney injury AKI, papillary necrosis and membranous nephropathy [6,7]. Certain diagnosis is established by renal biopsy. Pathology of AIN involves interstitial edema, interstitial inflammation, and tubulitis with a predominance of CD4+ T lymphocytes and mononuclear cells, with variable numbers of eosinophils. This is a result of a type B idiosyncratic non-immunoglobulin-E-mediated immune reaction marked by cell-mediated immune injury to the renal tubulointerstitium. The drug becomes immunogenic via various mechanisms such as haptenization, antigen mimicry, and neo-antigen formation. Renal interstitial dendritic cells, and renal tubular epithelial cells play an important role in this immunologic injury [8]. Autoimmun hemolytic anemia due to NSAIDs is usually acute and associated with renal failure. The drug may alter antigens on the red cell, resulting in the production of antibodies that cross-react with the unaltered antigen, or the drug may associate with structures on the red cell and thus be part of the antigen in a haptenic reaction. Products of the complement cascade and cytokines may also contribute to renal damage [9,10].

Avoiding from potential causative agent is essential and unless there is no improvement in renal funcitons at the end of the first week glucorticoid therapy can take place. Although the optimal dose and duration is unclear it is frequently recommended to start prednisone at a dose 1mg/kg (maximum of 40-60 mg) at least for one or two weeks, gradually decreasing the dose when serum creatinine returned tobaseline level, and to finish the treatment within two or three months. Improvement occurs in the first one or two weeks in most of the patients. In cases of more severe acute renal failure, i.v. methylprednisolone (0.5 to 1 g/day for three days) may be choosen as initial therapy .

In conclusion, all clinicians must keep in mind that NSAIDs can cause multisystemic toxicities such as hemolytic anemia and acute renal failure and there is at present no way of identifying individuals who are at risk to develop these complications [11,12].

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