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Commentary

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Drug Induced Tubulo-interstitial Nephritis, New Insight for Diagnosis

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INTRODUCTION

In recent years there has been a greater focus on drug-induced tubulointerstitial nephritis. The problem with this disease is that the real situation has not been well understood in spite of an unmistakable increase in incidence in recent years. Its diagnosis is difficult because there are not many symptoms, and many cases are probably being missed. The present situation is that chronic kidney disease (CKD) is induced by continued use of drugs that can cause the condition, and this in turn increases the number of patients who require dialysis. Polypharmacy (the prescription of concurrent use of multiple medications) in an aging society is viewed as a problem to be addressed from the perspective of both the healthcare economy and the adverse reactions. One polypharmacy-related problem that should not be overlooked is drug-induced tubulointerstitial nephritis. Here I shall explain this disease, mainly its background and countermeasures. I shall then give some suggestions about how medical professionals should deal with this disease.

DISEASE NAMES AND DEFINITIONS

Drug-induced tubulointerstitial renal disorder (or nephritis) is a pathological condition where inflammatory cells infiltrate into the interstitium, which occupies most of the kidney volume, and into renal tubules, lowering renal function. Renal tubular cells, interstitial cells and vascular endothelial cells are the cells that constitute the interstitium. These cells perform reabsorption and secretion, which are the major functions of the kidneys. The interstitial cells are also known to be producers of erythropoietin.[1)] Capillaries of the kidneys consist of glomerular capillaries and peritubular capillaries (PTC) downstream of them. The interstitium has an abundance of PTC and inflammation is induced when white blood cells leak out of the PTC into the interstitium. Inflammation is not confined to the interstitium. It affects the renal tubules also. Although the formal name of this condition is tubulointerstitial nephritis, it is generally shortened as "interstitial nephritis".

Interstitial nephritis is classified into acute interstitial nephritis (AIN) and chronic interstitial nephritis (CIN). Except for drugs specific to CIN such as cyclosporine, Chinese herb (aristolochic acid) and cadmium, other drugs having a similar effect can in the long term make AIN progress to CIN with accompanying changes in the pathological tissues. In AIN, the patients show various symptoms of acute kidney injury (AKI) in a short time after start of the drug administration, but the renal function can be restored with proper treatment. With CIN, the time of disease onset is not clear, or it develops by progression from AIN. Clinically, it presents the pathological condition of CKD. Histologically, it shows fibrosis of interstitial tissue and sclerosis of glomeruli, and the renal function fails to recover. In either case, as the lesions can be seen in the interstitium and/or the renal tubules, in English it is sometimes called acute tubulointerstitial nephritis (ATIN) or chronic tubulointerstitial nephritis (CTIN). In Japan, however, the commonly used abbreviations are AIN and CIN.

CASE PRESENTATION

In our hospital we are also coming across increasing numbers of interstitial nephritis cases. During the four years 2016–2019, there were 29 cases diagnosed through biopsy, which

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is twice as many as we had during the four years before that. However, AIN cases that present all the typical clinical symptoms are rather rare. They usually have very few subjective or objective symptoms, and most are cases where biopsy was conducted because of some anomalies detected in other tests or cases clinically diagnosed as AIN/CIN without biopsy.

Therefore, we will present here a typical drug-induced interstitial nephritis case encountered in our hospital, along with tissue findings from the kidney biopsy.

The patient was a 54-year-old woman who was hospitalized with the chief complaint of a 39°C fever for a week. The physician she had consulted earlier had prescribed the antipyretic analgesic acetaminophen (Caronal) and the antimicrobial clarithromycin (Claris). Blood tests had revealed an elevated inflammatory reaction for which she was given the antimicrobial drug garenoxacin (Geninax). However, the fever persisted, and she had a lack of appetite, because of which she was referred to our hospital for detailed examination and treatment. On day 3 of hospitalization some erythematous patches appeared on her trunk. Tests showed proteinuria (+) and occult blood (–). The results of urine sediment analysis were white blood cells 10–19/HPF, bacteria (–), hyaline cast (+), white blood cells 14,500/μL (eosinophil was 0 % at hospitalization and reached a maximum of 8 % during hospital stay), Cr (Creatinine) 0.99 mg/dL, CRP (C-reactive protein) 26.4 mg/dL, Ccr (Creatinine clearance) 26.5 mL/min, NAG (N-acetyl-ß-D-glucosaminidase)15 IU/L and ß2MG (ß2 -microglobulin) 12,100 μg/L. Urine cytology tests revealed no increase in eosinophils on the day of hospitalization but an increase to 14 % on day 2 of hospitalization. Abdominal ultrasonography and CT revealed bilateral enlargement of both kidneys and gallium scintigraphy showed accumulation in both the kidneys. Kidney biopsy revealed the main lesions in renal tubules and the interstitium (***Fig. 1***) which led to the diagnosis of drug-induced interstitial nephritis. During hospitalization, Cr increased to 2.44 mg/dL, but it returned to normal levels after 2 months as a result of stopping the aforementioned drugs, and treatment with 30 mg prednisolone. The suspect drugs, Caronal, Claris and Geninax, all turned out to be negative in the lymphocyte stimulation test (LST).

EPIDEMIOLOGY
(PARTICULARLY ABOUT PROTON PUMP INHIBITOR-INDUCED INTERSTITIAL NEPHRITIS)

According to the Japan Renal Biopsy Registry, 26,535 cases were registered during 2007–2015. Of these, 328 (1.24 %) were clinicopathologically diagnosed to have drug-induced kidney injury and only 159 (0.60 %) of them were diagnosed to have acute or chronic interstitial nephritis.[2)] This is the statistical data of only cases that had been biopsied. I suspect that there may have been many other cases diagnosed clinically as "suspected cases" without doing biopsy or missed altogether. Typical of such cases are those with interstitial nephritis induced by proton pump inhibitors (PPI), which has begun to draw attention in recent years.

PPI became commercially available around 1990. Unlike the H_2 receptor antagonists conventionally used at that time, PPI showed no adverse effects like hematopoietic disorders because of which they were considered as safe drugs that could be used without dose adjustment even on patients with renal disorders. Because of this, the drug was easily prescribed on a global scale for long-term use for gastroduodenal ulcers and reflux esophagitis, and as a prophylactic against gastric ulcer in patients under treatment with steroids, aspirin, or non-steroidal anti-inflammatory analgesic drugs (NSAIDs). However, recently, especially after 2010s, adverse reactions have been reported in various fields of medicine, drug-

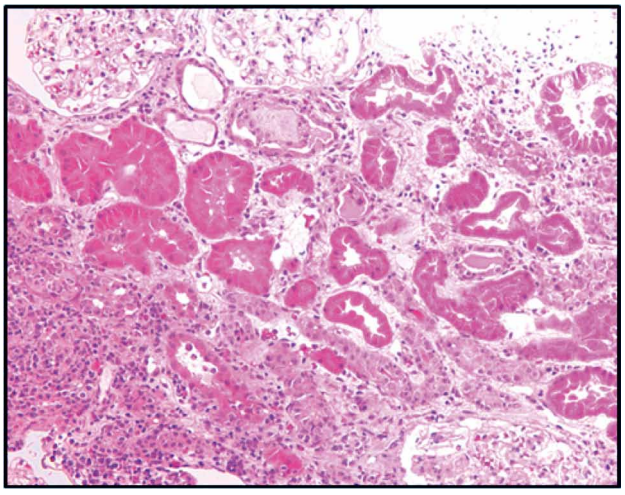

Fig. 1 *Kidney biopsy findings of the case presented (PAS stained)*
There was no abnormality of glomerular bodies. A high degree of cell infiltration, mainly by plasma cells and small round cells, can be seen all over the interstitium, as also some scattered eosinophils. There are signs of swelling and degeneration of renal tubules, and necrotic signs of basement membrane collapse.

induced interstitial nephritis being the most frequently reported. Since 1992, when a patient under PPI treatment was first diagnosed through kidney biopsy to have interstitial nephritis,[3] it was still not considered to be much of a problem for quite some time. After entering the 21st century, reports that claimed high frequency of CKD among patients administered PPI have appeared one after another as a result of studies carried out with large-scale databases of Oceania and North America. In addition to these, several reports on complications such as pneumonia, bone fractures, intestinal infections, dementia, etc. have also appeared one after another around the same time. Thus, it has now become widely known that PPI are not safe for the patients. In the latest meta-analysis conducted in 2018, the administration of PPI was shown to be significantly more associated with onset of AKI and CKD than in the group that was not given PPI or the group that was administered a histamine H_2 receptor antagonist.[4] Although there is no large statistical survey data in Japan, large numbers of cases have been reported and the Japanese Society of Nephrology has issued cautions and recommendations.[5]

Some noteworthy statistical data that suggests an increasing trend in the incidence of drug-induced interstitial nephritis in Japan is available.[6] According to the country-wide survey of chronic dialysis cases conducted by the Japanese Society for Dialysis Therapy, there were 120 cases of interstitial nephritis in Japan in 2018 (0.3 % of the 38,147 new dialysis patients with renal failure), which is not very high. Interstitial nephritis was added as a category of primary diseases only in 2017. In the statistical data compiled before that, it was apparently missed or reported under "others" because there were only a few such cases. Besides this, there has been no increase in the number of patients with systemic diseases that can cause non-drug induced interstitial nephritis. Therefore, the recent increase in interstitial nephritis in the statistical data mentioned above can be attributed to increase of drug-induced interstitial nephritis, and apparently some patients with AIN progress to the chronic state of CIN, which further advances to end-stage renal failure. The aforementioned statistical survey has 5,136 (13.5 %) cases classified under "cause unknown". It is assumed that even among such cases there must be cases that should otherwise have been diagnosed as interstitial nephritis. Thus, there is greater caution and interest among specialists about interstitial nephritis because of the increased PPI-associated development of AIN/CIN cases. As a result, this disease is now recognized as one that is brought about by an independent cause. Although not shown in the above statistics, CKD caused mainly by glomerular nephritis, diabetic nephropathy, or a nephrosclerosis shows rapid aggravation by drugs. There is therefore no doubt that interstitial nephritis has a non-negligible impact on the increase of dialysis patients who now exceed 340,000 in Japan, although this is not shown in the table of statistical data.

CAUSES, PATHOPHYSIOLOGY, AND PATHOLOGICAL FINDINGS

Histopathologically, the same findings as interstitial nephritis are seen in systemic autoimmune diseases such as sarcoidosis and Sjogren's syndrome, infections such as that caused by cytomegalovirus, and nephritis caused by urinary tract infections. However, the drug-induced interstitial nephritis and autoimmune diseases are grouped together under the same action mechanism because interstitial cells are damaged due to activation of immunocompetent cells. As many as 70–85 % of interstitial nephritis cases are drug-induced. Any drug can theoretically be a cause, but currently three are major suspects. These are the conventional two suspects (NSAIDs and antimicrobial agents) and PPI. Presently kidney injury caused by anticancer agents, especially immune checkpoint inhibitors like nivolumab, is drawing attention. Some reports claim that the incidence of interstitial nephritis is particularly high among those taking PPI.[7] This seems to suggest that drug-induced AIN develops and gets aggravated more easily by a combination of drugs rather than a single drug. ***Table 1*** shows the drugs that cause relatively high incidence of interstitial nephritis.

Various mechanisms lead to drug-induced kidney injury. Even if we look at the injury caused to renal tubules only, heavy metals like mercury, lithium, aminoglycoside antibiotics, and anti-cancer agents like cisplatin, all directly damage cells of the renal tubules. NSAIDs inhibit the prostaglandin pathway which in turn causes reduced renal

Table 1 *Drugs that can cause interstitial nephritis*

Type	Drug
Antimicrobials	β-lactam drugs (Penicillin, Cephalosporin), Quinolone, Ethambutol, Isoniazid, Macrolide, Rifampicin, Sulfonamide, Tetracycline, Vancomycin
NSAIDs	Almost all the drugs
Gastrointestinal drugs	PPI, H_2 Receptor Antagonists, Mesalazine
Diuretics	Furosemide, Thiazide, Triamterene
Antineoplastic agents	Ifosfamide, Tyrosine Kinase Inhibitors, Pemetrexed, Immune Checkpoint Inhibitors
Others	Alloprinol, Amlodipine, Diltiazem, Captopril, Carbamazepine, Azathioprine, Clofibrate, Phenytoin, Propylthiouracil, Synthetic Narcotics, Antiviral drugs (Acyclovir, etc.)

blood flow and acute tubular necrosis (ATN), and thus have direct toxicity. Quite a few NSAIDs cause both ATN and AIN type of injury. If it is direct toxicity, the decline in renal function occurs relatively rapidly, and it is easier to clinically diagnose the condition from the time interval between start of drug administration and disease onset. On the other hand, with ß lactam antibiotics and PPI, which show only AIN type injury, although the condition is acute, the earliest onset may occur only 4–5 days from the start of the drug administration, or even a few months later in some cases. This makes it difficult to specify the time of disease onset. The reasons for this are that the onset mechanism of AIN, unlike the direct toxicity model of ATN, involves a delayed hypersensitivity reaction that falls under the Type IV allergic reactions as per Gell and Coombs classification. In other words, the drug does not directly damage the cells of the renal tubules but causes kidney injury over time in a dose-independent manner through immune cells. It has been observed in some patients that the first drug administration may not cause any problems, but a second administration causes AIN.

The endogenous interstitial nephritis arising from autoimmune diseases and exogenous drug-induced interstitial nephritis have the same onset mechanism, although the causes are different. In autoimmune diseases, renal tubular cells which are part of the normal tissue are targeted. In drug-induced nephritis, however, the drug itself is not an antigen. The causal drug is a small molecule and therefore is not an antigen by itself, but when it becomes an antigen (haptination) by combining with other substances, the mechanism of the antigen becoming a target for attack by activated immunocompetent cells kicks in, leading to destruction of the tubular cells. Thus, the same histopathological signs will be seen whether it is autoimmune disease-associated or drug-induced interstitial nephritis.

The characteristic signs of AIN are infiltration of inflammatory cells mainly comprising lymphocytes, mononuclear cells and plasma cells, mostly in the interstitium and edema of the interstitium. Sloughing and necrosis of renal tubular cells, and destruction and blockage of the lumen structure occur when the injury reaches the renal tubules. Apart from the mononuclear cells, polymorphonuclear leukocytes and eosinophils also infiltrate, and some cases have granulomas created by aggregation of macrophages. In CIN, the characteristic features of interstitial fibrosis involving collagen fibrils and atrophy of renal tubules. The glomeruli also get sclerosed as a secondary development. There are many cases where the tissue presents both AIN and CIN characteristics.

DIAGNOSIS

(ESPECIALLY ABOUT ABNORMAL FINDINGS IN URINE SEDIMENT ANALYSIS)

Fever, rashes and increase in eosinophils are the three classic clinical symptoms used to diagnose drug-induced AIN. However, these are the findings seen in AIN caused by ß-lactam antibiotics such as penicillin and cephalosporin and they are not seen in all types of drug-induced AIN. Not many patients with PPI-induced AIN, which has been identified as a problem in recent years, develop these symptoms. Because of this, this unexpected side effect was recognized only nearly 20 years after the drug became commercially available, with increase in CKD cases. The incidence of these symptoms are reported to be mild fever in 35–70 % cases, rashes in 25–40 %, and increased eosinophils in 25–40 %, and not more than 10 % of the cases have all the three symptoms. Apart from these, back pain and lower back strain arising from acute enlargement of the kidneys are the first symptoms in about 30 % of the patients. Gross hematuria is seen in 5–15 % of the patients and joint pain in more than 25 %. Close attention is required as some patients present with symptoms like nausea, vomiting, diarrhea, etc. which cannot be distinguished from symptoms of common cold or gastroenteritis. After having such symptoms, the patients show progressive decrease in kidney function and increase in Cr level, and signs characteristic of CKD such as decreased urine volume, edema and increased blood pressure become apparent. A common abnormal finding in urine test is mild proteinuria of not more than 2 g/day. 70–80 % of the patients show microscopic hematuria, but red blood cell casts are rarely seen. The urine sediment analysis is negative for bacteria in a high proportion, 75–85 %, of the patients but they have white blood cell-positive sterile pyuria.

Initially, eosinophils in urine were drawing attention as a characteristic sign of AIN and it was considered a highly sensitive test parameter for AIN caused by a small group of specific drugs.[8] However, a large-scale examination that covered patients confirmed through kidney biopsy to have AIN revealed that urine eosinophils did not have very high diagnostic value, as shown by the sensitivity of 60 % and specificity of 85 %.[9] Currently it is considered only as some additional supporting evidence. The reasons for the low sensitivity and specificity are that urine eosinophils are seen in other infections and kidney diseases like connective tissue disease, and also the fact that the urine test results may be normal at the early stage of the disease. Moreover, the detection of urine eosinophils is not suitable as a screening test because special staining of urine sediments is required. On the other hand, various biomarkers have been studied in the fields of blood and urine biochemistry but no biomarker specific to AIN could be identified so far. In diagnostic imaging, kidney enlargement can be seen by abdominal ultrasonography and CT scans and gallium scintigraphy gives positive results in the acute phase. But neither of these is specific to AIN. Therefore, I decided to revisit the quantitative tests for urine eosinophils and white blood cells which were once considered to have not much diagnostic value.

In a retrospective clinical study conducted recently at our hospital, the diagnostic value of quantification of urine eosinophils was examined with cases where the quantification was done strictly through direct observation by medical technologists, from among cases that were clinically diagnosed as AIN during the previous 10 years.[10] The diagnostic performance was the highest when the urine eosinophil fraction threshold was set at 5 %. But it was still not suitable as a screening test because the sensitivity was 48.5 %, specificity 83.7 %, and area under ROC 0.65. Nevertheless, in an analysis limited to pyuria cases, a threshold set at 6 % showed the highest diagnostic performance with sensitivity 80.0 %, specificity 80.9 %, and area under ROC 0.83. Therefore, the quantification of

eosinophils in urine seems to be a beneficial test if we limit the cases to those suspected of having AIN. The aforementioned study that gave a negative result about the usefulness of the urine eosinophil count, the eosinophils were counted visually by medical technologists and reported in semi-quantitative terms such as "1 % or more" or "5 % or more", without strictly setting the abnormal range for the eosinophil counts. I then paid attention to the quantification of sterile pyuria, and assumed that a simple and accurate screening for AIN would be possible if the abnormal range is set after accurate quantification of white blood cells and bacteria in the urine using automated particle analyzers which are being rapidly inducted in Japanese medical institutions. Here, in ***Fig. 2***, I have suggested the flow chart algorithm for this procedure.

Let me now explain the flowchart. With patients under long-term treatment with a suspect drug such as a PPI, the urine test is to be done regularly. Qualitative urine tests check for the presence of white blood cells and bacteria but, if possible, set the threshold value for positivity for an automated urine particle analyzer. In an examination conducted at our hospital using one such analyzer, we defined pyuria as a white blood cell count of 28 or more per μL (corresponds to 5 white blood cells per HPF) and for bacteria 100 or more per μL as positive. In the next step of the flowchart, bacteriuria positive cases are excluded as abnormal test result cases arising from urinary tract infection and only bacteria negative and white blood cell positive sterile pyuria cases are selected. Furthermore, cases with connective tissue disease, etc. are excluded after clinical diagnosis. The remaining cases are considered to be suspected cases of AIN or CIN. Where possible, treatment with the suspect drug is halted to see if this improves on urine test results. The diagnostic probability for AIN would improve further if the eosinophil count in the urine sediment of the suspected cases is also measured after special staining of the sediment. However, we cannot rule out AIN even if the person is negative for urine eosinophils. Kidney biopsy must also be considered for such difficult-to-diagnose cases and those with severely lowered kidney function.

As of now, we have to rely on kidney biopsy for definitive diagnosis of AIN. But biopsy is a test accompanied by certain risks and it is difficult to use in all suspected AIN cases. In reality, therefore, with patients suspected of having drug-induced interstitial nephritis, stopping the suspect drug and observing whether there is reduction in kidney injury and

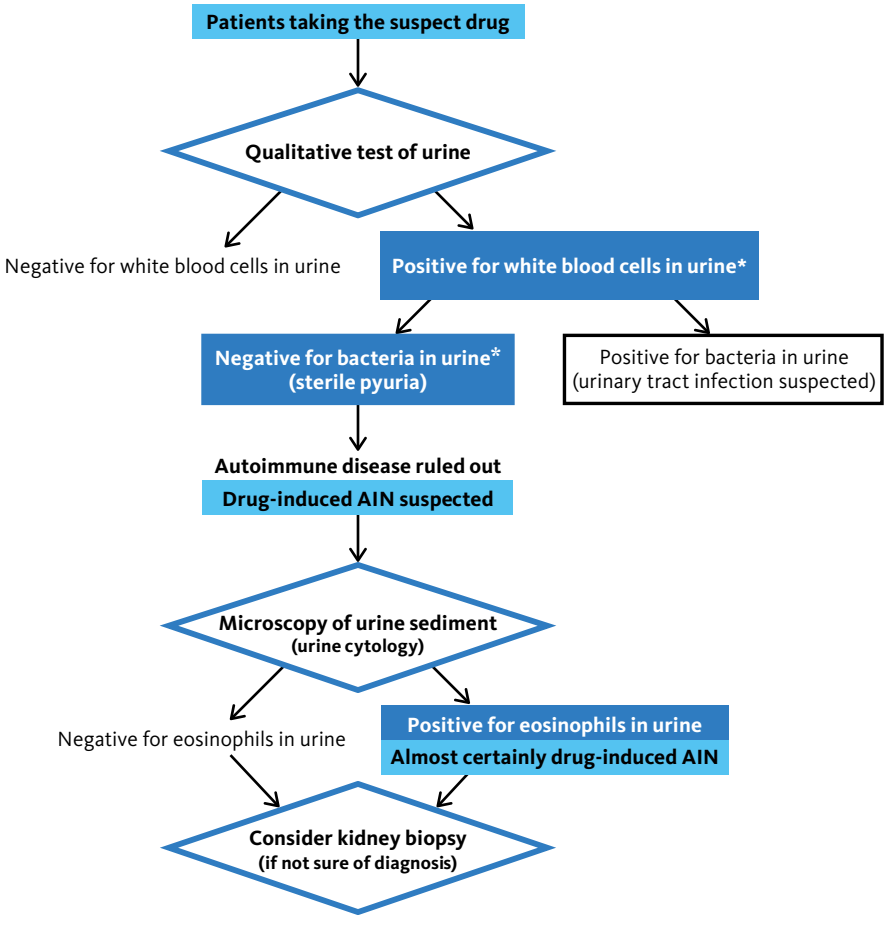

Fig. 2 *Diagnostic flowchart for drug-induced AIN*
**If possible, set the threshold using an automated urine particle analyzer.*

improvement in urine test findings would be the most useful and handy method of diagnosis. Kidney biopsy is currently done only for cases where the condition is difficult to differentiate from other types of kidney injury or to decide whether the use of steroidal drugs, discussed later, is appropriate.

TREATMENT AND PROGNOSIS

AIN/CIN is difficult to diagnose compared to glomerular diseases, but the treatment is easier. Interstitial nephritis is far easier to treat than diabetic nephropathy which progresses rapidly, or nephrosclerosis for which there is no standard therapy yet. It is possible to recover completely from AIN. Original kidney function is recovered in about 65 % of the cases after the diagnosis, and it is said that only 12.5 % of the cases advance to end-stage renal failure. Even if it progresses to CIN, the rate of progression to renal failure is slow. Prognosis of CKD is graded two-dimensionally using the glomerular filtration rate (GFR) and the severity of proteinuria. Even if two patients have the same GFR, the one with higher urinary protein excretion will have poorer prognosis. With interstitial nephritis, even if it is CIN, urinary protein excretion is less compared to CKD arising from glomerular disease. Therefore, progression to renal failure is slow and the prognosis is relatively good. This statement can be made from the cell characteristics also. Renal tubular cells are easily regenerated compared to the constituent cells of glomerular bodies, and the original kidney function can be restored once the cause is removed and inflammation ends.

As with autoimmune diseases, steroids are effective for treating drug-induced interstitial nephritis. However, many cases recover by just halting the causal drug alone. There has been no randomized comparative study on the effectiveness of steroids in the treatment of AIN. Only retrospective studies have been undertaken. AIN caused by sarcoidosis or an autoimmune disease is an absolute indication for the use of steroids, but drug-induced AIN is only a relative indication, and steroids can be used only under the following 3 scenarios: (1) Kidney function does not recover even after stopping the suspect drug, (2) There is a rapid decline in kidney function, (3) Tissue findings in kidney biopsy show diffuse infiltration by cells but only a small area is affected by fibrosis.

CONCLUSION

The concept of CKD has been proposed after we entered the new millennium, and various measures are being adopted all over the world for early detection and early intervention. In spite of this, the number of new dialysis patients has been increasing year after year, and the situation is currently not fully controlled. CKD advances quietly and one of the reasons why it is often missed is that it has very few subjective symptoms until the patient reaches the stage of end-stage renal failure. Early detection of glomerular nephritis and diabetic kidney disease is possible through urine tests and blood tests. But with interstitial nephritis, the urine test reveals no abnormality in the early stage, which makes it difficult to detect the disease. Prevention of lifestyle diseases like diabetes and hypertension is the starting point of control measures against CKD and currently efforts are being made from the public health perspective as well. On the other hand, no wide-spread effort is being made to reduce the quantum of prescription of suspect drugs like PPI which can cause drug-induced interstitial nephritis.

The average age of new dialysis patients is increasing every year. Form this also it is feared that drug-induced interstitial nephritis is wide-spread in a latent form among elderly patients who are prescribed multiple drugs. For early detection of this scary disease, which is increasing the number of dialysis patients in an invisible way, it is crucial to go back to the basics of testing for kidney disease. In other words, if we pay attention to the counts of white blood cells and bacteria in urine sediment analysis or detect increase in the Cr level at an early stage, diagnosis would be possible without biopsy. It is hoped that not only medical technologists, pharmacists and physicians, but all medical professionals would deepen their understanding of this disease and make efforts to improve their diagnostic capabilities.

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