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Post-streptococcal acute glomerulonephritis can be a risk factor for accelerating kidney dysfunction in Alport syndrome - A case experience -

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ABSTRACT

Alport syndrome (AS) is a progressive kidney disease. Male cases with X-linked AS (XLAS) are reported to develop end-stage kidney disease (ESKD) at the age of around 20 to 30 years. One risk factor for developing ESKD at a young age is a genotype of having truncating variants in the *COL4A5* gene. However, to date, other such factors have remained unclear. Here, we describe a 15-year-old Japanese boy with XLAS who had a missense variant in the *COL4A5* gene. He presented with gross hematuria, severe proteinuria, oliguria, systemic edema, body weight gain, and hypertension after pharyngitis. Blood examination showed kidney dysfunction, hypocomplementemia, and elevated antistreptolysin-O level. We diagnosed him with poststreptococcal acute glomerulonephritis (PSAGN) and he was stopped treatment by lisinopril, and received supportive treatment. However, he showed an unusual clinical course for PSAGN and consequently developed ESKD 15 months after the onset of PSAGN without recovery from the kidney dysfunction. This case showed that the onset of PSAGN can be a risk factor for AS patients to develop ESKD at a young age.

Keywords: COL4A5, AGN, PSAGN, risk factor

INTRODUCTION

Alport syndrome (AS) is a progressive kidney disease and male cases with X-linked AS (XLAS) progress to end-stage kidney disease (ESKD) in their 20 to 30s [1].

Although there is no radical therapy for this condition and it is difficult to stop its progression, the pre-ESKD period can be prolonged by using angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers [2, 3]. One risk factor for developing ESKD at a young age is a genotype of having truncating variants in the *COL4A5* gene [4-6]. However, to date, other such factors have remained unclear.

Some reports show that having modifier gene variants contribute to the early development of ESKD [7, 8]. The influence of other environmental or acquired factors including infection, obesity, or the co-occurrence of other nephritis is unknown. Here, we report a case with XLAS, in which ESKD developed at the age of 17 after the co-occurrence of poststreptococcal acute glomerulonephritis (PSAGN). The clinical course clearly showed the contribution of PSAGN to accelerating the development of kidney dysfunction in this case.

CASE DESCRIPTION

A 15-year-old boy with XLAS presented at the emergency room (ER) after sudden gross hematuria. He had already been genetically diagnosed with XLAS for having c.3491G>A (p.Gly1164Asp). Only a part of his clinical and genetic information is presented in the supplementary file of our previous report [9]. His mother and grandmother also suffered from XLAS and had the same variants (Figure 1). He had pharyngitis without fever 2 weeks ahead of this episode. At the presentation in the ER, he had general malaise and showed remarkable systemic edema. His body weight was

58.1 kg, which had increased by 6 kg since the onset of this condition. His blood pressure was 134/79 mmHg despite oral intake of lisinopril against Alport syndrome (AS) since the age of 3 years old. Upon laboratory examination, the most significant finding was elevated serum creatinine of 7.12 mg/dl (eGFR 11.8 mL/min/1.73 m²) at presentation. It had been 1.36 mg/dl (eGFR 49.6 mL/min/1.73 m²) just before the development of this condition. His serum protein level was 5.4 g/dl and albumin was 2.9 g/dl. He had no obvious pleural effusion or ascites on X-ray or ultrasonography. On urinalysis, he showed heavy proteinuria, with a protein/creatinine ratio of 2.4 g/gCr and gross hematuria. Kidney ultrasound showed high echogenicity without structural abnormalities or nephrolithiasis. A significant decrease of serum C3 (16 mg/dL) was evident and antistreptolysin-O (845 IU/mL) and antistreptokinase (20,480) levels were increased. Anti-nuclear antibodies, and hepatitis B and C serologies were negative. Thus, the patient was diagnosed with PSAGN. Renal biopsy was not performed. After stopping lisinopril, treatment with a low-salt diet, water restriction, and furosemide administration was started. Soon after starting this treatment, the patient's systemic edema and hypertension gradually improved. The serum C3 level recovered to the normal range. However, the serum creatinine level decreased to 2.68 mg/dl (eGFR 26.6 mL/min/1.73 m²) at its lowest and then started to gradually elevate, while severe proteinuria persisted. At 15 months from the onset of PSAGN, he progressed to ESKD and started hemodialysis (Figure 2).

DISCUSSION

AS is a progressive, inherited kidney disease characterized by sensorineural hearing loss and ocular abnormalities [10, 1]. There are three inheritance modes in AS:

X-linked, autosomal recessive (ARAS), and autosomal dominant (ADAS). XLAS is caused by pathogenic variants in *COL4A5*, which encodes type IV collagen $\alpha 5$ chain. Male XLAS cases develop ESKD around a median age of 20–30 years old, while female XLAS cases develop ESKD around a median age of 60–70 years old [1]. The diagnosis of this disease is achieved based on either genetic or pathological findings; however, recently it has tended to be identified by gene tests.

In male XLAS cases, it is clear that this disease shows a strong genotype–phenotype correlation. In cases with truncating variants in *COL4A5*, ESKD develops more than 10 years earlier than in cases with non-truncating variants [4-6]. In addition to this, digenic variants with other COL4A genes or modifier genes may also lead to more severe phenotypes [7, 8]. Other environmental or acquired risk factors for the development of ESKD at a younger age have remained unclear.

PSAGN is a form of nephritis developing after Group A streptococcus infection. It is thought to be a glomerular immune complex disease leading to complement activation, which in turn leads to acute kidney injury. A typical case of PSAGN has a good prognosis with the normalization of creatinine within a month.

It is natural for some AS patients to have streptococcus infection and some of them may develop PSAGN. However, there have been no reports including case reports describing the onset of PSAGN in AS patients. Therefore, this is the first report of such a case. The clinical course of our case is very suggestive. The pathogenic mechanism behind PSAGN remains unknown, despite it being a common kidney disease. However, type IV collagen abnormalities may not be directly related to the mechanisms of onset of PSAGN, but could have accelerated the progression of ESKD in this case. After PSAGN, the complement level completely normalized, but eGFR

did not recover to the previous level and, 15 months after the onset of PSAGN, at the age of 17, the patient developed ESKD.

Talking about the co-occurrence of PSAGN and chronic kidney diseases (CKD), there are only a couple of case reports or series showing PSAGN and IgA nephropathy (IgAN) in adults [11-14] and a child [15] or PSAGN and Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) [16-19]. Although all cases with IgAN showed benign clinical course and kidney function recovered to the normal range, most of the CAKUT cases showed unfavorable clinical courses. Some of them showed very similar clinical courses to our case in which PSAGN accelerated the development of ESKD [17-19]. In some cases, severe proteinuria remained after the recovery of PSAGN [16, 19]. It means PSAGN does not always accelerate kidney dysfunction in all cases with CKD but in some cases with severe kidney diseases like CAKUT and in those cases, PSAGN can be a risk of severe course. We also think PSAGN does not always change the course for all AS patients. Our case already had stage II CKD at the onset of PSAGN. Therefore, we should care about the onset of PSAGN for cases with advanced CKD.

We did not conduct a pathological evaluation for this case after the onset of PSAGN.

Although there is no evidence-based treatment for PSAGN, there are some case reports showing the efficacy of steroid therapy for PSAGN [20, 21]. So, we carefully considered the indication of kidney biopsy for this case. However, as we showed in the figure, the eGFR was below 30ml/min/1.73m² after the onset of PSAGN. So, we judged that harm may outweigh benefits by conducting kidney biopsy in this case.

From our case, we learned that secondary factors can change the clinical course to more severe in AS. Especially, PSAGN can be the factor of accelerating the deterioration of

kidney function like our case. From this point, prevention of development of PSAGN at the onset of streptococcus infection should be considered. Although a recent systematic review failed to show the efficacy of antibiotics effect for the prevention of PSAGN because of the lack of evidence[22], it is still recommended in high-burden countries to use antibiotics to prevent the onset[23]. We have to consider antibiotic therapy for cases with chronic kidney diseases and suspected or diagnoses with group A Streptococcus infections to prevent the development of post-streptococcal glomerulonephritis.

This case was taking an ACE inhibitor until the diagnosis of PSAGN. It should be noted that renin-angiotensin axis inhibitors (RA inhibitors) cause or exacerbate acute kidney injury (AKI) especially in cases with dehydration or sepsis[24]. After the initiation of RA inhibitors for patients with chronic kidney disease, a reduction in GFR is frequently observed which is caused by relaxation of the efferent arteriole. This reduction is usually rapidly recovered after the withdrawal of these drugs. Also, the AKI related to these drugs in the hypovolemic state is always reversible[24]. However, our case had a more serious event of PSAGN and although it was stopped immediately after the diagnosis of PSAGN, we cannot omit the possibility of lisinopril contributed to the poor prognosis in this case.

To the best of our knowledge, this is the first report describing a case of PSAGN in Alport syndrome. Since gross hematuria may commonly occur in AS patients during upper respiratory tract infection, we have to take PSAGN into consideration and watch the clinical course carefully.

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Compliance with ethical standards

Conflict of interest:

This study was supported by Grants-in-Aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (subject ID: 16K19642 to Tomohiko Yamamura and 17H04189 to Kazumoto Iijima, and 19K08726 to Kandai Nozu) and by the Japan Agency for Medical Research and Development (AMED) (Grant Number JP19ek0109231h0003 to Kazumoto Iijima and Kandai Nozu).

Kandai Nozu and Kazumoto Iijima have filed a patent application on the development of antisense nucleotides for exon skipping therapy in Alport syndrome.

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Kandai Nozu has received consulting fees from Kyowa Kirin Co., Ltd.; and lecture fees from Kyowa Kirin Co., Ltd., Novartis Pharmaceuticals Corporation, and Chugai Pharmaceutical Co., Ltd.

Human and animal rights:

This article does not describe any studies with human participants or animals performed by any of the authors.

Informed consent:

No information identifying the individual patient is published, and personal information is protected. The patient, his parents and his grandmother provided informed consent for the publication of this case report.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (IRB approval number 301) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Figure legends

Figure 1 Chromatograms of the Sanger sequencing results in this family

The patient had a hemizygous variant of c.3419G>A (p.Gly1164Asp) in exon 39 of *COL4A5*. His mother and his grandmother also had the same variant in a heterozygous state.

Figure 2 Clinical course of this case

Kidney function decreased immediately after the onset of PSAGN and did not fully recover after the episode. The patient developed end-stage kidney disease 15 months after the onset of PSAGN.

eGFR: estimated glomerular filtration rate

P/C: urine protein creatinine ratio

PSAGN: poststreptococcal acute glomerulonephritis

ESKD: end-stage kidney disease

Figure 1

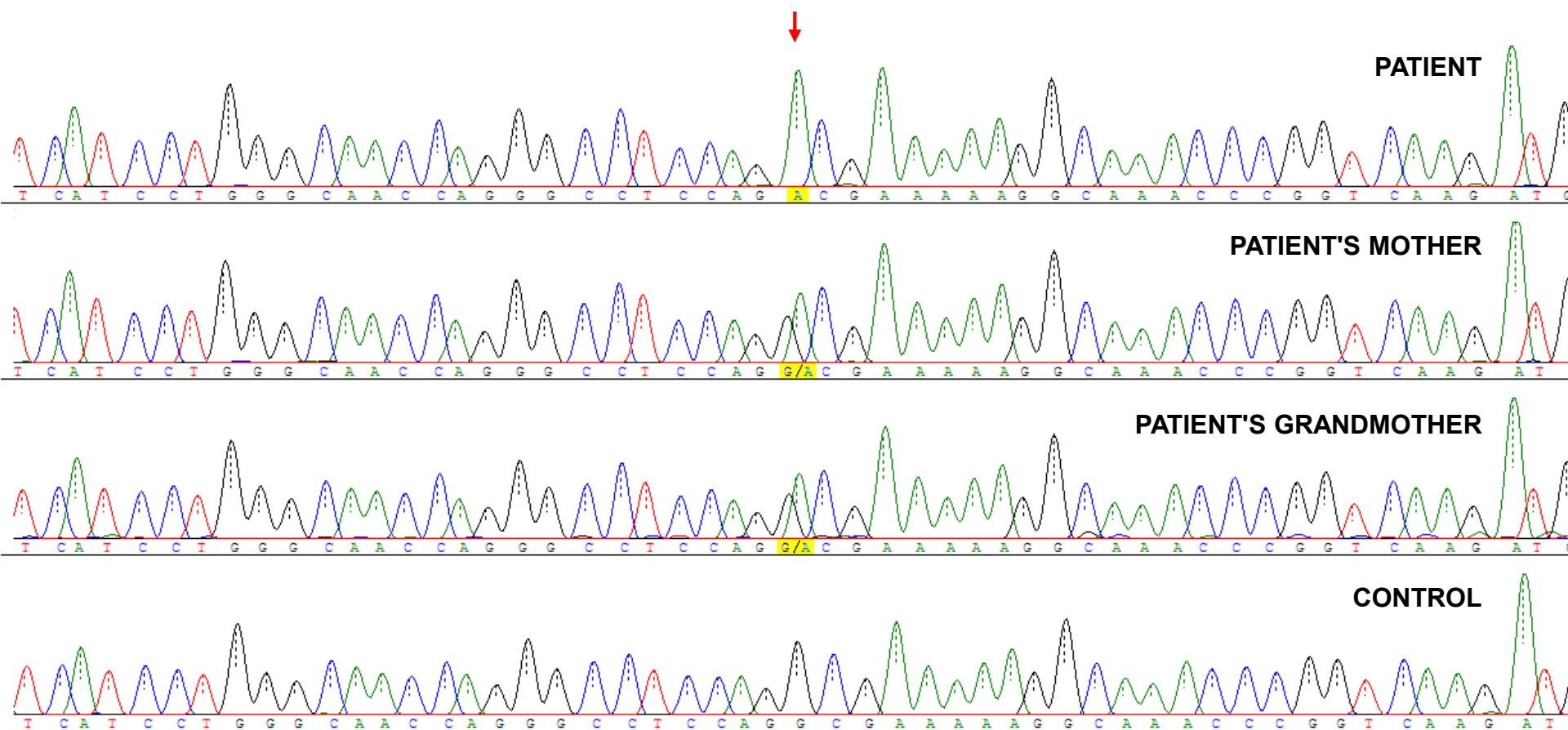


Figure 2

