The presentation of nephrotic syndrome during immunosuppressive treatment for aplastic anemia with monosomy 7 in a 16-year-old boy: a case report

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Abstract

Most cases of aplastic anemia (AA) complicated by nephrotic syndrome (NS) have been reported to be the effects of chronic graft-versus-host disease after hematopoietic stem cell transplantation (HSCT). We describe a 16-year-old boy with AA with monosomy 7 who developed NS during immunosuppressive treatment for AA alone without HSCT. Recently, there appeared a report of MIRAGE syndrome caused by gain-of-function mutation of *SAMD9* gene on chromosome 7 who developed NS. No such mutation was detected in our patient and thus the genetic factors leading to the complication of two diseases remain unknown at this time.

Introduction:

Cases of aplastic anemia (AA) and nephrotic syndrome (NS) are rare, and most of them are considered to be the effects of chronic graft-versus-host disease (GVHD) after allogenic hematopoietic stem cell transplantation (HSCT)[1)].

Herein, we report a case of idiopathic AA with monosomy 7 that developed NS during immunosuppressive treatment (IST) alone without HSCT. To the best of our knowledge, this patient is the first case of NS presenting during follow-up for AA without HSCT.

We discuss the possible contribution of monosomy 7 or the *SAMD9*and *SAMD9L* genes on chromosome 7 to the concomitant occurrence of NS in AA.

Case report:

A previously healthy 13-year-old Japanese boy was admitted to our hospital with a 1-month history of fatigue, poor complexion, and purpura. He had no history of congenital anomalies, prior association with hepatitis, radiation exposure, or ingestion of drugs that might be associated with AA. At admission to our hospital, his vital signs were normal, and there was no clinical evidence of hepatomegaly or splenomegaly. Heart sounds and lungs were normal. Laboratory data on admission were as follows: red blood cell count, 1.43×10^{12} /L; white blood cell count, 2.38×10^{9} /L with 14% neutrophils, 80% lymphocytes, 2% monocytes, 4% eosinophils and no myeloblasts; hemoglobin level, 5.1 g/dL; platelet count, 0.9×10^{9} /L; and reticulocyte count, 25.7×10^{9} /L. A bone marrow biopsy showed markedly hypocellular bone marrow without apparent dysplasia or blasts, the karyotype was 46,XY [20], and 1.0% of marrow cells had monosomy 7 as determined by 7q31 interphase fluorescence *in situ*hybridization (FISH) analysis. We diagnosed idiopathic AA after excluding congenital AA based on a normal chromosomal breakage test and no shortening of the telomere length. IST was started with rabbit anti-thymocyte globulin (2.5 mg/kg, 110 mg/day, days 1 to 5), cyclosporine (CsA; 5 mg/kg, 220

mg/day), methylprednisolone (2 mg/kg, 88 mg/day, days 1 to 7), and prednisolone (45 mg/day, days 8 to 14; 30 mg/day, days 15 to 19; 20 mg/day, days 20 to 24; and 10 mg/day, days 25 to 29). Transfusions were given as needed for anemia and thrombocytopenia during IST. Recovery of hematopoiesis was gradually observed, and transfusions became unnecessary from 54 days after IST. A bone marrow biopsy at 4 months after the start of IST showed normocellular bone marrow without apparent dysplasia or blasts, but 14.0% of the marrow cells had monosomy 7 as determined by FISH analysis. The proportion of cells with monosomy 7 fluctuated over the course of regular bone marrow biopsies, but the dosage of CsA was gradually decreased without any additional treatment, because no dysplasia and blasts were seen. However, about 3 years after the diagnosis of AA, the patient was readmitted to our hospital due to a sudden weight gain of 10 kg and anasarca.

At the time of NS onset at readmission, a physical examination showed the following: body height, 169 cm; body weight, 65.9 kg; body temperature 36.4°C; respiratory rate, 12 breaths/min; blood pressure, 115/61 mmHg; and anasarca edema, including on the eyelids, face, and pretibial regions. A blood test at the same time showed the following: total protein, 4.2 g/dL; albumin, 2.1 g/dL; lactate dehydrogenase, 237 U/L; and total cholesterol, 361 mg/dL. Urinary examinations showed the following: urinary protein, 4+; occult blood in urine, 3+; urine density, 1.015; and urinary protein, 8.32g/day, and urinary protein-to-creatinine ratio, 7.09 g/g creatinine, by 24-h urine collection. Pathological examination of a renal biopsy sample revealed minor glomerular abnormalities (WHO 1995) without mesangial cell proliferation, segmental glomerulosclerosis, or crescentic formation. Based on the above results, we diagnosed minimal change NS (Figure 1).

The patient was started on corticosteroid therapy with 60 mg/day of prednisolone in addition to the previously administered CsA. At 17 days after the start of treatment, he achieved a complete response with a urinary protein level of 0.11g/day and urinary protein-to-creatinine ratio of 0.1 g/g creatinine by 24-h urine collection, and a serum albumin level of 2.5 mg/dL. He was tapered off prednisolone 1 week later, and was discharged 21 days after the start of treatment. The proportion of bone marrow cells with monosomy 7 by FISH analysis was the highest at 81% after the onset of NS. Figure 2 shows the course of the case from the onset of AA, including the proportions of cells with monosomy 7. We performed genetic testing, because the combination of both diseases is rare but this case did not have any mutations in germline *SAMD9/9L* mutation ($SAMD9/9L^{mut}$) or somatic *GATA2* mutation ($GATA2^{mut}$). At this time, the genetic factors that lead to the development of both diseases remain unknown.

Discussion:

In this report, we described a case of NS that developed during follow-up for AA with monosomy 7 without HSCT. We performed a literature review of cases with both diseases, and analyzed genetic factors that may predispose to their onset.

Previous studies have reported that clonal evolution is a major complication for AA treated with IST[2), 3)]. Patel et al. reported that in a large cohort of 666 adult subjects with severe AA treated with IST, monosomy 7 appeared in 38 subjects, and 33 of the 38 subjects developed it within 5 years of starting IST[4)].

NS has been described as a clinical form of chronic GVHD, but only a limited number of cases have been reported[1)]. Kim et al. reported that a 13-year-old Asian boy developed NS 22 months after allogeneic HSCT for severe AA possibly due to the effects of chronic GVHD[5)]. Our case developed NS during IST alone without HSCT for AA, and to the best of our knowledge, there has been only one report of a case with a similar course in the past. Abrams et al. reported a case of 9-year-old boy who presented NS that was pathologically diagnosed as minimal change NS, and that gradually progressed to concurrent idiopathic AA[6)]. Prior to the diagnosis of AA, he had frequent relapses of NS. However, after the start of IST for AA, the NS remained in remission. Unfortunately, no information about monosomy 7 was presented in this report.

Recently, several groups have reported germline $SAMD9/9L^{mut}$ in addition to somatic $GATA2^{mut}$ as a predisposing factor for cytopenia, bone marrow failure, and myelodysplastic syndrome with non-random monosomy 7 or deletion of 7q[7)]. Sahoo et al. reported that almost half of the myelodysplastic syndrome patients with monosomy 7 or del(7q) carried mutations in either $SAMD9/9L^{mut}$ (21%) or $GATA2^{mut}$ mutations (30%)[8)].

They reported that the prevalence of $GATA2^{mut}$increased with age, whereas $SAMD9/9L^{mut}$ were found at similar frequencies across all age groups. Recently, there was a case report of a girl with myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome caused by a gain-of-function mutation in the*SAMD9* gene on chromosome 7 who developed steroid-resistant NS[9)].

Based on this background, we examined the case for such genetic abnormalities, but there were no somatic/germline gene mutations in$SAMD9/9L^{mut}$ or$GATA2^{mut}$ in our case. The genetic factors associated with hematopoietic failure and NS are currently unknown, but it is possible that some common genetic factors exist, because the patient developed NS when the proportion of cells with monosomy 7 was increased. The prognosis of the patient appears favorable at this point, but it will be necessary to carefully monitor the rate of IST tapering, in the future, including consideration of hematopoiesis and the proportion of cells with monosomy7.

In conclusion, this is the first detailed report of NS associated with AA that was treated without HSCT. Some common immunological and genetic factors might be involved in the development of both AA and NS. Identification of these factors is expected in the future with the accumulation of data from more cases of AA and NS.

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Figure legend:

Figure 1 . Renal biopsy specimens:

(a) Elastica-Masson trichrome staining showing no typical interstitial fibrosis, inflammatory fibrosis, tubular atrophy, or segmental sclerosis.

(b) Periodic acid-methenamine silver and hematoxylin-eosin staining showing no proliferation of mesangial cells, crescentic glomerulonephritis, or endocapillary hypercellularity.

Figure 2 . The course of the disease.