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Even mild hemolysis in paroxysmal nocturnal hemoglobinuria could severely compromise the quality of life due to long-term sustained intolerant fatigue

Kazuya Sakai*

Department of Hematology, Nara City Hospital, 50-1 Higashikidera-Cho 1 Chome, Nara city, Nara 630-8305, Japan

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ABSTRACT

Fatigue is one of the most common symptoms associated with paroxysmal nocturnal hemoglobinuria (PNH), a rare acquired disorder of hematopoietic stem cells. While it directly impairs lifestyle leading to poor quality of life (QOL), it is not well recognized that fatigue could not depend on the disease activity or percentage of glycosylphosphatidylinositol-deficient granulocyte. We describe the case of a 78-year-old woman, with mild hemolysis and a 20-year history of severe sustained fatigue, whose QOL drastically improved with eculizumab followed by ravulizumab. We also used the novel aplastic anemia and PNH specific QOL tool to evaluate multiple statuses of the patient.

1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disorder of hematopoietic stem cells, characterized by hemolytic anemia, bone marrow failure, and thrombosis. [1] A multinational phase III study reported that eculizumab, C5 monoclonal antibody therapy, effectively prevents complement attacks in patients with PNH who suffer from severe hemolytic attacks [2]. As a result, both the levels of complement-induced hemolysis and quality of life (QOL) in patients with high disease activity have improved dramatically. [3] While fatigue is one of the most common symptoms associated with PNH and directly impairs lifestyle leading to a poor QOL[3], it is not well recognized in previous studies that the fatigue could not depend on the disease activity (lactic acid dehydrogenase (LDH) over or under 1.5 x upper limit of normal) or percentage of glycosylphosphatidylinositol (GPI) -deficient granulocyte. [4,5] Eculizumab is expensive and must be used indefinitely to maintain a sustained effect. Hence, it is not prescribed in cases of severe fatigue with only a mild LDH elevation or anemia; instead these patients undergo ongoing follow-up examinations. Here, we present a case of an elderly patient with mild hemolysis, suffering from severe sustained fatigue for more than 20 years, who was successfully treated with eculizumab. This report suggests that withholding C5 monoclonal antibody treatment for those with mild hemolytic episodes monitored in a watch-and-wait approach is not always the best option considering the possible QOL impairment.

2. Case report

A 78-year-old woman with no remarkable medical history had suffered from gradually progressive fatigue from around 50 years of age. Although, her occupation involved sedentary desk work, sustained fatigue restricted her other daily activities including the chores at home and climbing stairs. During work-related social functions, the extent of physical lassitude required laying down to rest. At the age of 62, an annual medical checkup revealed mild anemia and she was subsequently diagnosed with mild aplastic anemia (AA) based on the histopathological findings of a bone marrow specimen. Regular red blood cell (RBC) transfusions and immune-suppressive agents were deemed as not required, and she instead underwent ongoing follow-up examinations without treatment. Nine years later, flow cytometry revealed a CD55 and CD59 defect in 34% of her RBCs and 62% of her granulocytes. Hence, a diagnosis of AA-PNH was established, instead of AA. However, her hemolytic presentation did not reach the moderate severity (hemoglobin (Hb) <10 g/dL and LDH $>$ 4–5 $\times$ the upper limit of normal) according to past Japanese PNH reference guide in 2014. Eculizumab therapy was relatively suitable for patients with moderate hemolysis. In the next year, an apparent hemolytic attack associated with dark urine and dizziness occurred following a viral infection; at this time she had a decreased hemoglobin (7.7 g/dL) and elevated LDH

* Kazuya Sakai, MD, PhD. Department of Hematology, Nara City Hospital, 50-1 Higashikidera-Cho 1 Chome, Nara city, Nara 630-8305, Japan; TEL.: +81-742-24-1251; E-mail: ks13122@naramed-u.ac.jp

E-mail address: ks13122@naramed-u.ac.jp.

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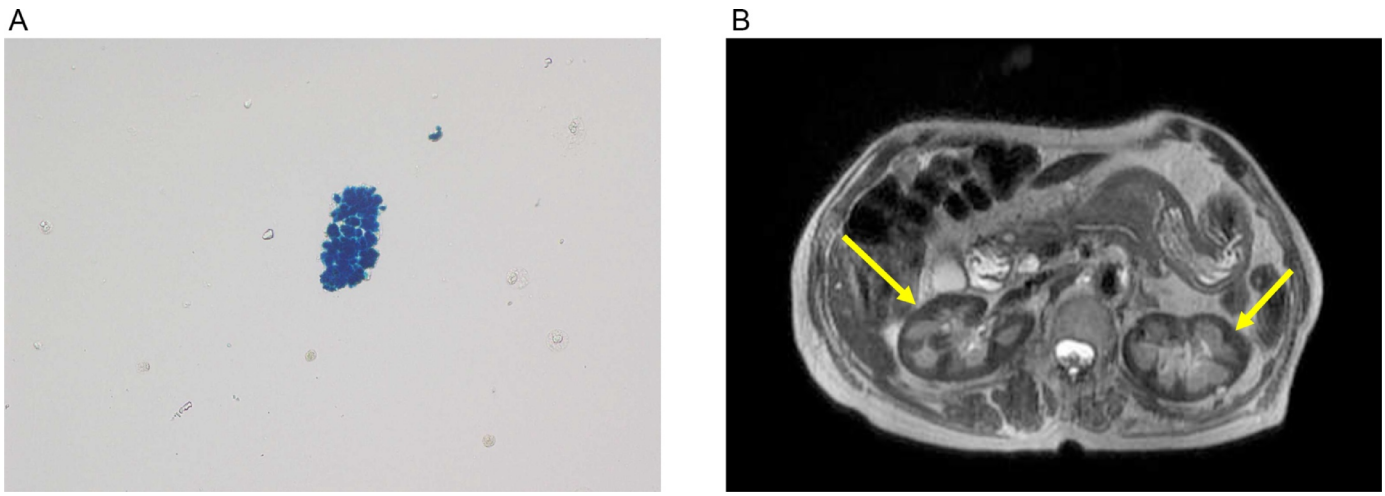

Fig.. 1.. Chronic renal impairment due to sustained hemolysis.
(A) Hemosiderin detected in the patient's urine with Berlin blue stain. (B) T2-weighted magnetic resonance imaging revealing hypo intensity, indicating hemosiderin deposits bilaterally in both renal cortices (shown by yellow arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(935 IU/L) levels (**Supplemental Table 1**). Once she received two bags of packed RBCs, her hemoglobin level elevated to 10 g/dL, and all her symptoms except sustained fatigue were resolved.

She was then referred to our hospital at the age of 76 only for mild anemia and hemolysis (Hb: approximately 10 g/dL, LDH: 500–600 IU/L), although she had sustained fatigue that resulted in difficulty in walking without a stick. Subsequently, we screened her for PNH-associated complications with flow cytometry, bone marrow biopsy, and CT scanning, as well as routine blood and urine testing. Urinalysis repeatedly showed mild occult blood due to hemosiderinuria (**Figure 1**, Table 1), and T2-weighted magnetic resonance imaging identified a hypointensity indicating hemosiderin deposits bilaterally in both renal cortices (**Fig. 1B**). The percentage of CD55 and CD59 defected RBCs was 32.2% in flow cytometry, suggesting that the PNH clone size had not changed over six years, and the clone type was type III. Unfortunately, that of CD55 and CD59 defected granulocytes was not available. A diagnosis of bone marrow failure with PNH was not established because the bone marrow histology indicated normoblastic growth with RBC linage proliferation (M/E ratio: 1.1), and no significant myelodysplasia or fibrosis was observed. Organ damage associated with chronic kidney disease was confirmed based on screening findings of sustained hemolysis and hemosiderin deposits in the kidneys.

A thorough medical interrogation revealed sustained intolerable fatigue that restricted routine activities. Based on her symptoms, including renal damage, mild to moderate anemia, and severe physical lassitude, we considered that eculizumab therapy would be required and started after vaccination against meningococcus. Subsequently, her LDH level was reduced to a normal range, and her fatigue dramatically improved without any adverse events from the eculizumab therapy (**Supplemental Table 1**). She was able to play outside with her grandchildren and participate in gardening. However, the short intervals between eculizumab therapy were troublesome because she lived alone and had to travel a long distance to reach the hospital. When she was 78 years old, the long-acting agent, ravulizumab, was approved in Japan. This drug subsequently replaced the eculizumab therapy, and continued successful improvements in fatigue resolution and lifestyle were observed. As ravulizumab is administered once in two months, her burden associated with frequent hospital visits is reduced. The hemosiderin deposits in both renal cortices were still detected in the following MRI performed 12 months later.

3. Discussion

PNH is a rare hematological disorder characterized by complement-mediated hemolysis, bone marrow failure, and thrombosis. Severe and sustained hemolysis is associated with a variety of symptoms, including difficulty swallowing, pulmonary hypertension, shortness of breath, abdominal pain, dark urine, and fatigue. As a result, patients with PNH often suffer from an impaired health-related QOL [6]. Since the degree of hemolysis is strongly related to the disease severity and GPI-deficiency clone size [5], a physician can easily decide if an anti-human C5 monoclonal antibody should be used in patients showing severe hemolysis and/or progressive anemia. Two anti-human C5 monoclonal antibody therapies, eculizumab, and ravulizumab were approved for PNH in 2010 and 2019, respectively. The efficacy of ravulizumab was similar to that of eculizumab in two recent studies [7]. However, both drugs were excluded for PNH coverage in those with mild hemolysis under the National Health Insurance policy due to their high cost. It should be noted that the positive rate of fatigue does not correlate to disease activity (LDH over or under 1.5 x upper limit of normal) and the percentage of GPI-deficient granulocyte. Although our patient did not develop severe hemolysis and did not depend on blood transfusions, unbearable and sustained fatigue deteriorated both her physical and mental statuses for more than two decades. Following the identification of chronic kidney disease and associated organ damage resulting from sustained hemolysis during additional screening for complications of PNH, eculizumab and ravulizumab administration were found to be applicable under insurance regulations.

Fatigue is a nonspecific symptom of PNH and often occurs in patients with infection, malignancies, taking certain drugs, and orthopedic injuries. Thus, physicians must identify whether symptoms of fatigue are due to PNH. Fatigue directly affects QOL, but the commonly utilized QOL scoring system, the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [8] or the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire [9], are intended for patients with malignancies and is not appropriate for PNH patients. In our case, we successfully used the novel AA/PNH specific QOL tool (QLQ-AA/PNH), which was reported as effective in a phase III study [10]. QLQ-AA/PNH consists of 54 items regarding both physical disability and mental status. **Table 1** shows the results of QLQ-AA/PNH evaluation before and after the eculizumab treatment. To date, the scoring algorithm of this instrument is not available until phase IV is completed. Before the commencement of eculizumab treatment, the patient suffered from

Table 1.
Improvement of QOL score in QLQ-AA/PNH.

Question	1:Not al all, 2: A little, 3: Quit a bit, 4: Very much	Before eculizumab treatment	After eculizumab treatment
During 2 weeks			
1	Were you tired?	4	1
2	Did you need to rest?	4	1
3	Were you exhausted for several days after exertion?	3	1
4	Did you have difficulties getting out of bed in the morning?	4	1
5	Did your body feel heavy?	3	1
6	Did it bother you that you had to pay attention to small symptoms, in case they could indicate something serious?	4	1
7	Were you short of breath?	4	1
8	Have you experienced problems with an increased tendency to bleed?	1	1
9	Have you been more susceptible to infection/s?	1	1
10	Have you experienced problems with swelling or inflammation in your mouth?	3	1
11	Have you suffered from sleep disturbance?	3	2
12	Have you felt impaired by pain in your daily life?	3	1
13	Have you had difficulties standing for a longer period of time?	4	2
14	Did you find it difficult to take a long stroll/walk?	4	2
15	Have you had difficulties climbing stairs?	4	2
16	Were you limited at work or during any other daily activity?	4	1
17	Have you had problems managing your household tasks?	4	1
18	Was it a burden to you that you had to ration your energy?	3	1
19	Have you lacked the strength for your private life and hobbies?	2	1
20	Was your normal rhythm of life disturbed?	4	2
21	Have you been unable to get up the energy to do anything, or have you felt sluggish?	1	1
22	Was it a burden to you to have to abstain from sports?	3	2
23	Did it bother you not being able to make plans ahead of the time?	3	1
24	Did it bother you not being able to be spontaneous?	3	2
25	Did it bother you that you had to be cautious?	2	2
26	Did you always have to take care not to catch any infections?	3	3
27	Have you had difficulties concentrating?	3	2
28	Did you feel irritable?	3	1
29	Has everything revolved around your illness?	3	1
30	Did it bother you to constantly be confronted with your illness?	3	1
31	Did you have the feeling you were missing out on life?	3	1
32	Did it burden you to be labelled "sick“?	1	1
33	Have you felt burdened by thoughts about an uncertain future?	3	2
34	Have you suffered, because your environment has been burdened by your illness?	3	1
35	Has it frustrated you that you have had to justify yourself as to why, for example, you were unable to do something?	2	1
36	Have you feared a deterioration in your blood results?	4	2
37	Have you felt burdened by your blood results?	4	1
38	Have you been afraid that treatments might fail?	3	1
39	Have you been concerned that there would be no more viable treatment for you?	2	1
40	Have you been afraid of relapse or deterioration?	3	1
41	Have visible signs of your illness (e.g. paleness, bruises, dark urine, yellow skin color) constantly reminded you of your illness?	4	1
42	Did you feel vulnerable?	3	1
43	Have you felt at the mercy of your illness?	4	1
44	Have you worried a lot?	3	1
45	Have you felt depressed?	1	1
46	Did you feel less attractive because of your illness?	1	1
47	Have you had less interest in sexuality?	1	1
48	Could you enjoy sexuality less?	1	1
49	Did you feel comfortable in your own body?	1	1
50	Have you been able to achieve what you wanted to?	1	1
51	Were you proud of what you achieved despite the illness?	3	2
52	Did you feel supported by friends and family?	2	1
During 6 months			
53	Were you able to go on vacation the way that you wanted to?	2	1
54	Did you miss interaction with other patients?	1	1

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both severe physical restrictions and marked anxiety, and was unsatisfied with her lifestyle. Surprisingly, the administration of eculizumab improved her questionnaire score, and she reported a dramatic lifestyle improvement. Our case demonstrates that QLQ-AA/PNH may be useful for objective evaluation of eculizumab and ravulizumab efficacy, in addition to the assessment of QOL in those with fatigue.

In the literature, few reports describe the improvement of hemosiderin deposits in renal cortices after eculizumab treatment in detail. Some case reports showed that it took one to three years to clear hemosiderin deposits in MRI images after anti-C5 blocking therapy [11–13]. Based on our case and these case reports, we speculate the amount of hemosiderin deposits would be quite different among patients with PNH and need more than one year to improve. A large-scale cohort study is required to reveal how hemosiderin deposits affect renal function and would be removed after the C5 blockage.

In conclusion, this case report demonstrates that severe physical lassitude can occur in patients with PNH without severe hemolysis and that the administration of anti-human C5 monoclonal antibodies is warranted in such cases, with the potential to improve QOL. Furthermore, AA/PNH (QLQ-AA/PNH) effectively evaluated multiple

statuses of the patient, including physical, psychological, and social issues.

Author contribution

KS treated the patient, collected data, and wrote the paper.

Declaration of Competing Interest

The author has no conflicts of interest concerning this case report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2020.100224.

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