Gross hematuria after SARS-CoV-2 vaccination: questionnaire survey in Japan

Keiichi Matsuzaki1,2 · Ryousuke Aoki1,3 · Yoshihito Nihei1,3 · Hitoshi Suzuki1,3 · Masao Kihara1,3 · Takashi Yokoo1,4 · Naoki Kashihara1,5 · Ichie Narita1,6 · Yusuke Suzuki1,3,7

Received: 29 September 2021 / Accepted: 4 November 2021 / Published online: 13 November 2021 © The Author(s) 2021

Abstract

Background Recent clinical reports indicate a correlation between gross hematuria after the coronavirus 2019 (COVID-19) vaccination in patients with glomerulonephritis, especially immunoglobulin A nephropathy (IgAN). Furthermore, healthcare workers in Japan were initially vaccinated with an mRNA vaccine from February 17, 2021, and some of them experienced gross hematuria after receiving the vaccination.

Methods We conducted a web-based survey of the councilor members of the Japanese Society of Nephrology (581 members, 382 facilities) to elucidate the relationship between gross hematuria and COVID-19 vaccination.

Results In the first survey, 27 cases (female: 22, 81.5%) of gross hematuria were reported after receiving a COVID-19 vaccination. Of them, 19 (70.4%) patients were already diagnosed with IgAN at the occurrence of gross hematuria. Proteinuria appeared in eight of the 14 (57.1%) cases with no proteinuria before vaccination and hematuria in five of the seven (71.4%) cases with no hematuria before vaccination. The second survey revealed that a renal biopsy was performed after vaccination in four cases, all of whom were diagnosed with IgAN. Only one case showed a slightly increased serum creatinine level, and no patients progressed to severe renal dysfunction.

Conclusion This study clarified the clinical features of gross hematuria after a COVID-19 vaccination. Because there was no obvious progression to severe renal dysfunction, safety of the COVID-19 vaccination is warranted at least in the protocol of inoculation twice.

Keywords SARS-CoV-2 vaccination · Coronavirus 2019 · Gross hematuria · IgA nephropathy · mRNA vaccination

Introduction

The effective control of coronavirus disease 2019 (COVID-19) can only be achieved by implementing a global vaccination strategy. Recently, several types of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed, mainly in Western countries, and vaccination rollout has commenced [1–6]. From February 17, 2021, healthcare workers in Japan were initially vaccinated with an mRNA vaccine (BNT162b2 [COMIRNATY], Pfizer-BioNTech; Pfizer, New York, NY, and BioNTech, Mainz, Germany).
show the details of urinary abnormalities after receiving the COVID-19 vaccination. Proteinuria appeared in eight of the 14 (57.1%) cases with no proteinuria before vaccination. Hematuria appeared in five of the seven (71.4%) cases with no hematuria before vaccination. All the four patients who received tonsillectomy did not show the worsening proteinuria and hematuria.

In the secondary survey, information on 25 of the 27 cases was returned (response rate: 92.6%). Increased levels of urinary protein were noted in two cases (7.4%). Regarding hematuria, 23 cases (85.2%) improved as well as before vaccination. A renal biopsy was performed after vaccination in four cases, all of which were diagnosed as IgAN. Notably, only one case showed a slight increase in the level of serum creatinine, and no patients progressed to severe renal dysfunction.

**Discussion**

We investigated the clinical characteristics of gross hematuria after COVID-19 vaccination in Japan. Although cases of gross hematuria after the COVID-19 vaccination were observed, only one case showed increased levels of serum creatinine. To the best of our knowledge, this is the first case series of gross hematuria after receiving the COVID-19 vaccination.

Our survey showed that gross hematuria after receiving the COVID-19 vaccination was skewed toward females, comprising 81.4% of cases. The amount of female healthcare workers (medical doctors, public health nurses, midwives, registered nurses, and licensed practical nurses) in Japan is four times that of male healthcare workers, suggesting that such gender bias might partly reflect the female-dominant occurrence of gross hematuria. Another reason is difference in immune responses between males and females. It is widely accepted that both innate and adaptive immune responses differ between males and females and likely contribute to differences between the sexes in response to vaccines [15, 16]. Therefore, the occurrence of gross hematuria may be biased toward females.

There are several reports of gross hematuria after receiving the COVID-19 vaccination [9–13]. To date, vaccinations based on several mechanisms that trigger an immune response have been administered; however, gross hematuria was only reported after receiving an mRNA vaccination. The BNT162b2 (Pfizer-BioNTech) and the Moderna mRNA-1273 (Cambridge, MA) vaccines use a nucleoside-modified, purified mRNA lipid nanoparticle-encapsulated platform. This novel RNA platform induces stronger antigen-specific cluster of differentiation (CD)4+ and CD8+ T cell responses in experimental animals [17]. Because the CD4+ and CD8+ T cells activated by vaccination produce

Several studies have reported the appearance of gross hematuria after COVID-19 vaccination in patients with glomerulonephritis, especially those with immunoglobulin A nephropathy (IgAN) [9–13]. A recent systematic review reported a higher prevalence of patients with IgAN in Asian than in Caucasian populations [14]. Thus, investigation of the frequency and clinical features of gross hematuria after receiving the COVID-19 vaccination in Japan and Asia is vital for the clinical management of IgAN under the current pandemic situation. To this end, the joint research team from the Japanese Society of Nephrology and the Progressive Renal Diseases Research, Research on intractable disease, from the Ministry of Health, Labour and Welfare of Japan conducted a clinical survey of gross hematuria associated with COVID-19 vaccination using a web-based questionnaire.

**Methods**

The first survey comprised a web-based questionnaire that was emailed to councilor members of the Japanese Society of Nephrology (581 members in 382 facilities) between June 2 and June 20, 2021. The questionnaire asked about cases of gross hematuria that were observed after receiving the COVID-19 vaccination and their outcomes (Table 1). Then, between June 9 and June 19, 2021, a second survey was emailed to the members who reported cases of gross hematuria. The second survey asked about the incidence of elevated serum creatinine levels, the status of proteinuria and hematuria, and pathological diagnosis (if a renal biopsy was performed).

**Results**

Figure 1 shows the outline of this study. In the first survey, 72 members (response rate: 18.8% of facilities) reported 27 cases of gross hematuria after receiving the COVID-19 vaccination. The baseline characteristics of the patients with gross hematuria are presented in Table 2. Most of the patients were aged 20–29 years (40.7%), and those aged 20–39 years accounted for 66.7% of the study cohort. Female patients comprised 81.5% of cases. Furthermore, 88.9% of cases occurred after vaccination with BNT162b2 (Pfizer-BioNTech). Of the 19 cases (70.4%) already diagnosed as IgAN, eight cases (29.6%) did not undergo renal biopsy for diagnosis. Figure 2 shows the length of time between COVID-19 vaccination and the appearance of gross hematuria, with 23 cases (85.2%) occurring within 3 days after the vaccination. Figure 3 shows the duration of the gross hematuria, with 18 cases (66.7%) disappeared gross hematuria until 3 days after its appearance. Tables 3 and 4 show the details of urinary abnormalities after receiving the COVID-19 vaccination. Proteinuria appeared in eight of the 14 (57.1%) cases with no proteinuria before vaccination. Hematuria appeared in five of the seven (71.4%) cases with no hematuria before vaccination. All the four patients who received tonsillectomy did not show the worsening proteinuria and hematuria.
Table 1  Contents of questionnaire in first survey

| Question number | Questions                                                                 | Response                                                                 |
|-----------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Q1-1            | How old is this patient?                                                  | 1. ≤ 19<br>2. 20–29<br>3. 30–39<br>4. 40–49<br>5. 50–59<br>6. 60–69<br>7. ≥ 70 |
| Q1-2            | What is the patient's gender?                                             | 1. Male<br>2. Female                                                    |
| Q1-3            | Has this patient undergone a renal biopsy? If yes, what was their diagnosis? | 1. Diagnosed with IgA nephropathy<br>2. Did not perform a renal biopsy |
| Q1-4            | Check all the following treatments used in this case                      | 1. Tonsillectomy<br>2. Steroid pulse therapy<br>3. Oral corticosteroid<br>4. RAS-I<br>5. Antiplatelet drugs<br>6. Others |
| Q2-1            | What type of vaccine was used in this patient?                            | 1. COMIRNATY Intramuscular Injection (Pfizer-BioNTech)<br>2. COVID-19 Vaccine Moderna Intramuscular Injection (Moderna/Takeda)<br>3. VAXZEVRIA Intramuscular Injection (AstraZeneca)<br>4. Others |
| Q2-2            | After what vaccination did you point out the gross hematuria?             | 1. After first dose vaccination<br>2. After second dose vaccination<br>3. Both first dose and second dose vaccination<br>4. Others |
| Q2-3            | How many days after vaccination did the gross hematuria appear?           | 1. ≤ 1 day<br>2. 2–3 days<br>3. 4–7 days (almost 1 week)<br>4. 8–14 days (almost 2 weeks)<br>5. 15–28 days (almost 3–4 weeks)<br>6. Others |
| Q2-4            | How long did the gross hematuria continue?                                | 1. ≤ 1 day<br>2. 2–3 days<br>3. 4–7 days (almost 1 week)<br>4. Over 8 days<br>5. Others |
| Q2-5            | Did an adverse reaction to the vaccination occur in the patient with the gross hematuria? | 1. Did not experience an adverse reaction<br>2. Unknown<br>3. Fever (≥ 37.5 °C)<br>4. Headache<br>5. General fatigue<br>6. Chills<br>7. Muscle pain<br>8. Joint pain<br>9. Others |
| Q3-1            | Did this patient have proteinuria prior to the vaccination?              | 1. Yes<br>2. No                                                        |
several proinflammatory cytokines, including interferon-γ and tumor necrosis factor-α, we wondered whether these vaccines could activate or exacerbate immune-mediated glomerular disease [9] or induce de novo glomerulonephritis, particularly IgAN. In this study, three cases were newly diagnosed as IgAN by a kidney biopsy that was taken because of the appearance of gross hematuria after receiving a COVID-19 vaccination. This suggests that such immune activation may be largely related to the mechanism of onset of glomerular nephritis.

Another point of interest is the association between IgAN pathogenesis and Toll-like receptors (TLRs), which are a family of innate immune receptors whose activation is crucial to induct the innate and adaptive immune responses [18]. Increased amounts of aberrantly glycosylated IgA have been thought to the first hit in pathogenesis of IgAN [19]. We previously demonstrated the association with TLR9, which recognizes single-stranded DNA containing unmethylated CpG motifs, and the synthesis of these IgA [20, 21]. On the other hand, Zheng et al. recently showed that TLR7, which recognizes endogenous or exogenous single-stranded RNAs [22], is also involved in the production of aberrantly glycosylated IgA1 [20], indicating that there might be some link between TLR signaling and the pathogenesis of IgAN. Thus, it is possible that mRNA vaccination affects the production of aberrant glycosylated IgA via TLR signaling.

Our study had several limitations. First, there was a possibility of selection bias, because the response rate was only 18.8% from 382 facilities. Furthermore, because councilor members tended to be affiliated with the large hospitals, our results did not include patients who were followed-up in small clinics. Second, because the questionnaire was a once-off survey, the clinical course of these cases could differ depending on the timing of the response. Therefore, we plan to conduct a prospective cohort study in the future that will overcome these limitations. Third, the study population was mainly healthcare workers. Generally, healthcare workers have easy access to a hospital. This may have resulted in a high rate of diagnosis of IgAN.

In conclusion, this small survey clarified the clinical features of gross hematuria after the COVID-19 vaccination in Japan. Although the nephrologists should, therefore, carefully and periodically follow-up on the urinary findings, the safety of the COVID-19 vaccination is warranted at least in the protocol of inoculation twice because these cases showed no obvious progression to severe renal dysfunction. Further
studies are necessary to investigate the underlying mechanism of gross hematuria following COVID-19 vaccination.

**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1007/s10157-021-02157-x](https://doi.org/10.1007/s10157-021-02157-x).

**Acknowledgements** We gratefully acknowledge the councilor members of the Japanese Society of Nephrology who responded to our questionnaire. We thank the IgA nephropathy Working Group who belong to Intractable Renal Diseases Research, Research on rare and intractable diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan.

**Author contributions** K.M and Y.S had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: K.M, Y.S. Acquisition, analysis, or interpretation of data: K.M, R.A, H.S, M.K, Y.S. Drafting of the manuscript: K.M. Critical revision of the manuscript for important intellectual content: Y.N, T.Y, N.K, I.N, Y.S. Statistical analysis: K.M, R.A. Obtained funding: I.N, Y.S. Administrative, technical, or material support: K.M, N.K, I.N, Y.S. Supervision: T.Y, N.K, I.N, Y.S.

**Funding** This study was supported in part by a Grant-in-Aid for Intractable Renal Diseases Research, Research on rare and intractable diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan.

---

**Table 2** Baseline characteristics of the 27 cases with the appearance of gross hematuria after receiving a COVID-19 vaccination

| Characteristic                                      | Cases (n = 27) |
|----------------------------------------------------|----------------|
| Age                                                |                |
| 20–29                                              | 11             |
| 30–39                                              | 7              |
| 40–49                                              | 5              |
| 50–59                                              | 1              |
| 60–69                                              | 1              |
| ≥ 70                                               | 2              |
| Sex                                                |                |
| Male                                               | 5              |
| Female                                             | 22             |
| Treatments (multiple answers allowed)               |                |
| Tonsillectomy                                      | 4              |
| Steroid pulse therapy                              | 3              |
| Oral corticosteroid                                | 3              |
| RAS-I                                              | 4              |
| Antiplatelet drugs                                 | 2              |
| Others                                             | 1              |
| Never                                              | 5              |
| Did not answer                                     | 11             |
| Type of the vaccine                                |                |
| COMIRNATY Intramuscular Injection (Pfizer-BioNTech) | 24             |
| COVID-19 Vaccine Moderna Intramuscular Injection (Moderna/Takeda) | 2 |
| Unknown                                            | 1              |
| Vaccination dose                                   |                |
| First dose                                         | 8              |
| Second dose                                        | 17             |
| Both first and second doses                        | 2              |
| Adverse reactions (multiple answers allowed)       |                |
| Fever (≥ 37.5°C)                                   | 17             |
| Fatigue                                            | 9              |
| Headache                                           | 4              |
| Chills                                             | 1              |
| Muscle pain                                        | 1              |
| Pain at the application site                       | 1              |
| Back pain                                          | 1              |
| None                                               | 3              |
| Unknown                                            | 5              |

*COVID-19* coronavirus disease 2019; *RAS-I* renin–angiotensin system inhibitor
**Fig. 2** Length of time between COVID-19 vaccination and the appearance of gross hematuria

- ≤1 day: 10 patients (37.0%)
- 2—3 days: 13 patients (48.1%)
- 4—7 days: 3 patients (11.1%)
- 8—14 days: 1 patient (3.7%)
- ≥15 days: 3 patients (11.1%)

**Fig. 3** Duration of gross hematuria after receiving the COVID-19 vaccination

- ≤1 day: 9 patients (33.3%)
- 2—3 days: 9 patients (33.3%)
- 4—7 days: 4 patients (14.8%)
- Over 8 days: 3 patients (11.1%)
- Unknown/continued: 2 patients (7.4%)

**Table 3** Details of proteinuria after receiving a COVID-19 vaccination

| Details of proteinuria | All cases (n = 27) | Cases diagnosed IgA nephropathy (n = 19) | Cases without diagnose (n = 8) |
|------------------------|--------------------|----------------------------------------|-------------------------------|
| Cases with proteinuria before the vaccination |                     |                                        |                               |
| Exacerbated proteinuria | 4                  | 3                                      | 1                             |
| Did not exacerbated proteinuria | 8                  | 6                                      | 2                             |
| Unknown | 1                  | 1                                      | 0                             |
| Cases with no proteinuria before the vaccination |                     |                                        |                               |
| Appearance of proteinuria | 8                  | 5                                      | 3                             |
| No proteinuria | 5                  | 4                                      | 1                             |
| Unknown | 1                  | 0                                      | 1                             |
Table 4 Details of hematuria after receiving a COVID-19 vaccination

| Details of hematuria | All cases (n = 27) | Cases diagnosed IgA nephropathy (n = 19) | Cases without diagnose (n = 8) |
|---------------------|-------------------|------------------------------------------|-----------------------------|
| Cases with hematuria before the vaccination |                   |                                          |                             |
| Exacerbated hematuria | 9                 | 5                                        | 4                           |
| Did not exacerbate hematuria | 7                 | 6                                        | 1                           |
| Unknown               | 4                 | 3                                        | 1                           |
| Cases with no hematuria before the vaccination |                   |                                          |                             |
| Appearance of hematuria | 5                 | 3                                        | 0                           |
| No hematuria          | 2                 | 2                                        | 2                           |

References

1. Anderson EJ, Roupheal NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383:2427–38.

2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15.

3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111.

4. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384:2187–201.

5. Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021;326:35–45.

6. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5 vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020;396:479–88.

7. Official Website of the Prime Minister of Japan and His cabinet, “Vaccinating order”. 2021. https://japan.kantei.go.jp/ongoingtopics/pdf/202105_vaccinating_order.pdf. Accessed 30 September 2021.

8. Official Website of the Prime Minister of Japan and His cabinet, “Total number of vaccine doses administered to date”. 2021. https://japan.kantei.go.jp/ongoingtopics/vaccine.html. Accessed 30 Sep 2021.

9. Negrea L, Rovin BH. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. Kidney Int. 2021;99:1487.

10. Rahim SEG, Lin JT, Wang JC. A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination. Kidney Int. 2021;100:238.

11. Tan HZ, Tan KY, Choo JCJ, et al. Is COVID-19 vaccination unmasking glomerulonephritis? Kidney Int. 2021;100:469–71.

12. Perrin P, Bassand X, Benotmane I, et al. Gross hematuria following SARS-CoV-2 vaccination in patients with IgA nephropathy. Kidney Int. 2021;100:466–8.

13. Hanna C, Herrera Hernandez LP, Bu L, et al. IgA nephropathy presenting as macroscopic hematuria in 2 pediatric patients after receiving the Pfizer COVID-19 vaccine. Kidney Int. 2021;100:705–6.

14. Schena FP, Nistor I. Epidemiology of IgA nephropathy: a global perspective. Semin Nephrol. 2018;38:435–42.

15. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38.

16. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 2015;109:9–15.

17. Pardi N, Hogan MJ, Naradikian MS, et al. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. J Exp Med. 2018;215:1571–88.

18. Lind NA, Rael VE, Pestal K, et al. Regulation of the nucleic acid-sensing Toll-like receptors. Nat Rev Immunol. 2021. https://doi.org/10.1038/s41577-021-00577-0.

19. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22:1795–803.

20. Suzuki H, Suzuki Y, Narita I, et al. Toll-like receptor 9 affects severity of IgA nephropathy. J Am Soc Nephrol. 2008;19:2384–95.

21. Makita Y, Suzuki H, Kano T, et al. TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6-mediated pathways in IgA nephropathy. Kidney Int. 2020;97:340–9.

22. Zheng N, Xie K, Ye H, et al. TLR7 in B cells promotes renal inflammation and Gd-IgA1 synthesis in IgA nephropathy. JCI Insight. 2020;5: e136965.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.