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Case Report

IgA Vasculitis following COVID-19 Vaccination

Naoya Nishimura[a], Yasuko Shiomichi[b] , Satoshi Takeuchi[b], Shun Akamine[c], Reiko Yoneda[c], Seiji Yoshizawa[a]

[a]Department of Rheumatology, [b]Dermatology, and [c]Pathology, Hamanomachi Hospital, Fukuoka, Japan

Corresponding Author: Naoya Nishimura,

Department of Rheumatology, Hamanomachi Hospital,

3-3-1 Nagahama, Fukuoka 810-8539, Fukuoka, Japan

Tel: 092-721-0831, Email: nishimura-n@hamanomachi.jp

Abstract

IgA vasculitis is generally triggered by infectious causes, but it has also been reported after immunization with various vaccines. Herein, we report two cases of IgA vasculitis after receiving the first or second dose of the Pfizer-BioNTech BNT16B2b2 mRNA vaccine. Two men, aged 22 and 30 years, developed palpable purpura on the extremities and arthritis. One patient also complained of fever and gastrointestinal symptoms. Laboratory findings revealed mild leukocytosis and slightly elevated C-reactive protein level, although platelet count and coagulation profile were within normal levels in both cases. Proteinuria and microhematuria were seen in one patient. Skin biopsies were performed in both patients and revealed leukocytoclastic vasculitis. The deposit of IgA and C3 was shown on immunofluorescence studies in one patient. Both patients were diagnosed with IgA vasculitis and treated with prednisolone, and their symptoms resolved within 1 week after initiation of treatment. The COVID-19 mRNA vaccine could trigger IgA vasculitis; however, a coincidence cannot be ruled out.

Key Words

IgA vasculitis, Henoch-Schönlein purpura, mRNA vaccine, COVID-19, autoimmune/inflammatory syndrome induced by adjuvants

Introduction

IgA vasculitis, previously also known as Henoch-Schönlein purpura, is an immune-mediated systemic small-vessel vasculitis characterized as cutaneous palpable purpura, arthritis, abdominal pain, and renal disease. It occurs primarily in childhood and in most cases is self-limited. Although adult cases of IgA vasculitis are less common, adults have significantly worse renal outcomes than children do. The exact etiology of IgA vasculitis is still unknown but seems to be related to genetic, environmental, and infectious causes. One-half of IgA vasculitis cases are preceded by upper respiratory tract infection, which possibly explains the association between IgA vasculitis and infection. In addition, cases of IgA vasculitis have been reported to be presented following immunization with various vaccines, suggesting that vaccines also could trigger IgA vasculitis. Herein, we report two cases of IgA vasculitis following the COVID-19 mRNA vaccination.

Case presentation

Case 1

A 30-year-old Japanese man was admitted to our hospital with a rash on the extremities, fever, abdominal pain, and arthralgia. Five days before admission, he received a second dose of the Pfizer-BioNTech BNT16B2b2 mRNA vaccine. He complained of mild fatigue and myalgia after the first and second vaccination doses, but these symptoms were resolved within a few days. The patient was not taking any new medications and showed no signs of infection, including COVID-19, before admission. Physical examination revealed palpable purpura on the extremities and trunk (Figure 1), fever, abdominal pain, and swelling of the left knee. Laboratory findings indicated a white blood cell (WBC) count of 11,200/μL (normal, <8,600/μL), with neutrophils accounting for 90%, and C-reactive protein (CRP) of 1.18 mg/dL (normal, <0.15 mg/dL), IgA of 307 mg/dL (normal, 93–393 mg/dL). Microhematuria of 30–49/HPF and mild proteinuria of 0.20 g/g of creatinine was also observed. Hemoglobin, platelet count, liver enzymes, renal function, and coagulation tests were within normal limits. Antinuclear antibody was positive with a low titer, and myeloperoxidase antineutrophil cytoplasmic antibody (ANCA) and proteinase-3 ANCA were negative. Skin biopsy of the lesion on the left forearm revealed erosion in the epidermis with neutrophilic infiltration, extravasation of red blood cells (RBCs), nuclear debris in the perivascular area, and fibrin deposit, all of which were consistent with leukocytoclastic vasculitis (Figure 2). No definite deposit of IgA and only slight deposits of C3 of the vessel walls were evident on immunofluorescence studies of the second skin site (Figure 3). His clinical presentation was consistent with the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology

European Society classification criteria (1,2), and the diagnosis of IgA vasculitis was made. He was treated with intravenous prednisolone (PSL) 60 mg daily for 3 days, followed by oral PSL 40 mg daily. His symptoms were improved within 1 week after treatment began, except for hematuria and proteinuria. Although abnormalities in urinalysis persisted, they improved after 1 month. PSL was gradually tapered, as there was no exacerbation of IgA vasculitis.

Case 2

A 22-year-old Japanese man was admitted to our hospital with a rash on the lower limbs and arthralgia. He had a history of recurring tonsillitis. He received the first dose of the Phizer-BioNTech BNT16B2b2 vaccine 6 days before onset without any symptoms after the vaccination. He was not taking any new medications but complained of discomfort in the throat before onset. Although he visited a dermatologist for a skin rash on the lower limbs and was prescribed medication, the rash was spread and the pain of the left knee also appeared, then he was consulted to our hospital. Physical examination revealed palpable purpura on the lower limbs (Figure 4), swelling of the left knee, and only mild swelling of the tonsils. He did not complain of fever or gastrointestinal symptoms. Laboratory findings indicated a WBC count of 10,000/μL (normal, <8,600/μL), with neutrophils accounting for 81%, and CRP of 0.27 mg/dL (normal, <0.15 mg/dL). IgA was not measured. Hemoglobin, platelet count, liver enzymes, renal function, urinalysis, and coagulation tests were within normal limits. Anti-streptolysin O antibody (ASO) was 72 IU/mL (normal, <239 IU/mL) and anti-streptokinase antibody (ASK) was x320 (normal, <x2560). Skin biopsy of the lesion on the right lower leg revealed neutrophilic infiltration, extravasation of RBCs, nuclear debris in the perivascular area, and fibrin deposit, all of which were consistent with leukocytoclastic vasculitis (Figure 5). Moreover, immunofluorescence studies of the second skin site revealed the deposits of C3 and the slight deposits of IgA of the vessel walls (Figure 6). He was diagnosed with IgA vasculitis and treated with oral PSL 30 mg daily. His symptoms were improved within 1 week after treatment. PSL was gradually tapered, as there was no exacerbation of IgA vasculitis.

Discussion

Vaccines and autoimmune responses are closely related. The vaccine aims to induce a host immune response to antigens and to elicit a memory T-cell response over time. However, vaccines are also able to elicit immune responses toward the autoimmune reaction. Adjuvants are often administered with vaccines to enhance their immunogenicity by triggering innate and adaptive immune responses. However, the adjuvants also can

induce different conditions: the so-called autoimmune/inflammatory syndrome induced by adjuvants (3). The mRNA vaccines such as Pfizer-BioNTech BNT16B2b2 or Moderna mRNA-1273 have been first approved against COVID-19. The mechanism of the mRNA vaccine is that mRNA is used as a template in dendritic cells to produce proteins, and some of the produced proteins are presented to lymphocytes to trigger the immune response. Although the mRNA vaccines do not require an adjuvant, mRNA itself also can stimulate the innate immune response and promote immune induction via pattern-recognition receptors such as Toll-like receptor (TLR) 3, TLR7, or retinoid-inducible gene I (4).

Although the exact etiology of IgA vasculitis remains unclear, infectious, genetic, and environmental causes have been suggested. As for the infectious causes, one-half of IgA vasculitis cases are preceded by upper respiratory tract infection, suggesting a correlation between respiratory pathogens and IgA vasculitis (5). An abnormal inflammatory process derived from immune reactions to various antigens is thought to contribute to the pathogenesis of IgA vasculitis. Interactions between leukocytes and vascular endothelial cells induce the development of IgA vasculitis. Endothelial cell damage, perivascular leukocyte infiltrates, cytokines, and chemokines are the important factors of this process (6,7). In addition, the vascular deposition of the IgA1-containing immune complex plays a pathogenic role (8). Complement activation, cellular damage, and IgA deposition suggest that IgA vasculitis is an IgA-mediated dysregulation of the immune responses to the antigen. The binding and activation of complement cause IgA to cross-react with endothelial cells and damage the cells. In IgA vasculitis, the dysregulated immune responses induced by these processes result in inflammation. Various inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-6, and IL-8 are involved. In addition, various TLRs, including TLR3 and TLR7, were found to be upregulated in IgA vasculitis (9,10). These receptors are mainly expressed on immune cells, including dendritic cells and macrophages, which suggest the involvement of innate immune responses. Inflammation triggered by the adjuvant has similarities with the inflammation caused by infection, which could trigger IgA vasculitis.

Moreover, other possible mechanisms are also suggested. The first is molecular mimicry between self-peptides and viral spike protein. mRNA encoding the spike protein of SARS-CoV-2 is encapsulated in lipid nanoparticles in the COVID-19 mRNA vaccine. The anti-spike protein IgA antibody was significantly increased after Moderna mRNA-1273 vaccination (11). This report suggests the interaction between SARS-CoV-2 spike protein and pre-existing autoreactive IgA antibodies. The second is delayed-type hypersensitivity reaction. The cases of IgA nephropathy flare following both COVID19 mRNA vaccination have been described (12–15). These patients did not be exposed to SARS-CoV-2 priory, suggesting the involvement of cell-mediated immune

responses.

Although previous studies found no causal association between vaccination and subsequent development of IgA vasculitis (16), some cases of IgA vasculitis following the immunization with the various vaccines have been reported (17–19). No cases of IgA vasculitis were reported in Phizer-BioNTech BNT16B2b2 (20) or Moderna mRNA-1273 (21) vaccine trials, there have been reports of cases presented (22) or relapsed (11) following the COVID-19 mRNA vaccine. Taken together, these reports suggest that the COVID-19 mRNA vaccine has the potential to induce IgA vasculitis, although it is a rare adverse event.

Although IgA deposition in the epidermis is observed in the majority of cases of IgA vasculitis, there were no deposits of IgA and only slight deposits of C3 in immunofluorescence studies in Case 1. It has been reported that a subset of IgA vasculitis cases exists in which vascular IgA deposits in the epidermis appear to be negative. The deposition of IgA in the skin site was shown in 80% of cases and C3 was in only 20% of cases in adult IgA vasculitis (23). Furthermore, another study showed that the direct immunofluorescence positivity drops to around 15% if the biopsy is performed more than 7 days after onset (24). In our case, the skin biopsy was performed after PSL began, so we cannot deny the possibility of a false negative. Moreover, another possible hypothesis is also suggested. As we mentioned above, the vascular deposition of the IgA1-containing immune complex plays a pathogenic role in IgA vasculitis. Increased IgA production by the mucosal immune system in response to pathogenic antigens such as bacteria or viruses has been suggested as the mechanism for the development of IgA vasculitis. On the other hand, a possible mechanism suspected in the triggering of COVID-19 mRNA vaccine-induced IgA vasculitis is the activation of the innate immune system as we mentioned above. Indeed, the serum IgA level was not elevated in our case, suggesting that the direct innate immune cell activation also could contribute to the development of vasculitis. This could explain the difference between common IgA vasculitis and COVID-19 mRNA vaccine-induced IgA vasculitis. Renal biopsy was not performed in Case 1 because the patient did not complicate by acute kidney injury. Because a previous study showed granular global mesangial deposits of IgA in the case of COVID-19 mRNA vaccine-induced IgA nephropathy (25), such changes could have been seen in our case if the renal biopsy had been performed. If the patient showed acute kidney injury, we should perform the renal biopsy to differentiate between rapidly progressive glomerulonephritis and other conditions. In Case 2, tonsillitis seems to trigger IgA vasculitis, but we cannot deny the possibility that the tonsillitis was also induced by COVID-19 mRNA vaccination. Laboratory findings showed that CRP was only slightly elevated and ASO and ASK were within normal limits, which were often elevated in bacterial tonsillitis. Moreover, tonsil organoids induced adaptive immune responses upon

adenovirus vector-based COVID-19 vaccine *ex vivo* (26). This report suggests that the spike protein induced by the COVID-19 vaccine could stimulate tonsils.

With the COVID-19 pandemic spreading worldwide, vaccination campaigns are proceeding rapidly. Physicians should be aware of this complication while continuing to encourage vaccination.

Patient Consent

The patients in this case report provided written informed consent for its publication.

Conflict of interest

None

Ethical Approval

Not applicable

References

1. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69:798–806.
2. Hočevar A, Rotar Z, Jurčić V, Pižem J, Čučnik S, Vizjak A, et al. IgA vasculitis in adults: The performance of the EULAR/PRINTO/PRES classification criteria in adults. Arthritis Res Ther. 2016;18:16–20.
3. Guimarães LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacol Res. 2015;100:190–209.
4. Kormann MSD, Hasenpusch G, Aneja MK, Nica G, Flemmer AW, Herber-Jonat S, et al. Expression of therapeutic proteins after delivery of chemically modified mRNA in mice. Nat Biotechnol. 2011;29:154–9.
5. Rigante D, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch-Schönlein purpura? Autoimmun Rev. 2013;12:1016–21.
6. Dursun I, Düsünsel R, Poyrazoglu HM, Gunduz Z, Patıroglu T, Ülger H, et al. Circulating endothelial microparticles in children with Henoch-Schönlein purpura; Preliminary results. Rheumatol Int. 2011;31:1595–600.

7. Chen T, Guo ZP, Li MM, Li JY, Jiao XY, Zhang YH, et al. Tumour necrosis factor-like weak inducer of apoptosis (TWEAK), an important mediator of endothelial inflammation, is associated with the pathogenesis of Henoch-Schonlein purpura. Clin Exp Immunol. 2011;166:64–71.
8. Inoue CN, Matsutani S, Ishidoya M, Homma R, Chiba Y, Nagasaka T. Periodontal and ENT therapy in the treatment of pediatric henoch-schönlein purpura and IgA nephropathy. Adv Otorhinolaryngol. 2011;72:53–6.
9. Saito A, Komatsuda A, Kaga H, Sato R, Togashi M, Okuyama S, et al. Different Expression Patterns of Toll-Like Receptor mRNAs in Blood Mononuclear Cells of IgA Nephropathy and IgA Vasculitis with Nephritis. Tohoku J Exp Med. 2016;240:199–208.
10. Chang H, Zhang QY, Lin Y, Cheng N, Zhang SQ. Correlation of TLR2 and TLR4 expressions in peripheral blood mononuclear cells to Th1- and Th2-type immune responses in children with henoch-schönlein purpura. Int J Clin Exp Med. 2015;8:13532–9.
11. Obeid M, Fenwick C, Pantaleo G. Reactivation of IgA vasculitis after COVID-19 vaccination. Lancet Rheumatol. 2021;3:e617.
12. 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.
13. 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.
14. Plasse R, Nee R, Gao S, Olson S. Acute kidney injury with gross hematuria and IgA nephropathy after COVID-19 vaccination. Kidney Int. 2021;100:944–5.
15. Perrin P, Bassand X, Benotmane I, Bouvier N. Gross hematuria following SARS-CoV-2 vaccination in patients with IgA nephropathy. Kidney Int. 2021;100:466–8.
16. Bonetto C, Trotta F, Felicetti P, Alarcón GS, Santuccio C, Bachtiar NS, et al. Vasculitis as an adverse event following immunization – Systematic literature review. Vaccine. 2016;34:6641–51.
17. Malek A, Gomez-Villegas SI, de la Hoz A, Nowbakht C, Arias CA. A 19-year old man with IgA vasculitis after vaccination. Brazilian J Infect Dis. 2018;22:442–4.
18. Watanabe T. Henoch-Schönlein purpura following influenza vaccinations during the pandemic of influenza A (H1N1). Pediatr Nephrol. 2011;26:795–8.
19. Sexton K, McNicholas A, Galloway Y, Radke S, Kieft C, Stehr-Green P, et al. Henoch-Schönlein purpura and meningococcal B vaccination. Arch Dis Child. 2009;94:224–6.

20. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383:2603–15.
21. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403–16.
22. Hines AM, Murphy N, Mullin C, Barillas J, Barrientos JC. Henoch-Schönlein purpura presenting post COVID-19 vaccination. Vaccine. 2021;39:4571–2.
23. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev. 2015;14:579–85.
24. Minz RW, Chhabra S, Singh S, Radotra B, Kumar B. Direct immunofluorescence of skin biopsy: Perspective of an immunopathologist. Indian J Dermatol Venereol Leprol. 2010;76:150–8.
25. Kudose S, Friedmann P, Albajrami O, D'Agati VD. Histologic correlates of gross hematuria following Moderna COVID-19 vaccine in patients with IgA nephropathy. Kidney Int. 2021;100:468–9.
26. Wagar LE, Salahudeen A, Constantz CM, Wendel BS, Lyons MM, Mallajosyula V, et al. Modeling human adaptive immune responses with tonsil organoids. Nat Med. 2021;27:125–35.

Figure Legends

Figure 1

Palpable purpura on the lower limbs (A) and right hand (B) (Case 1).

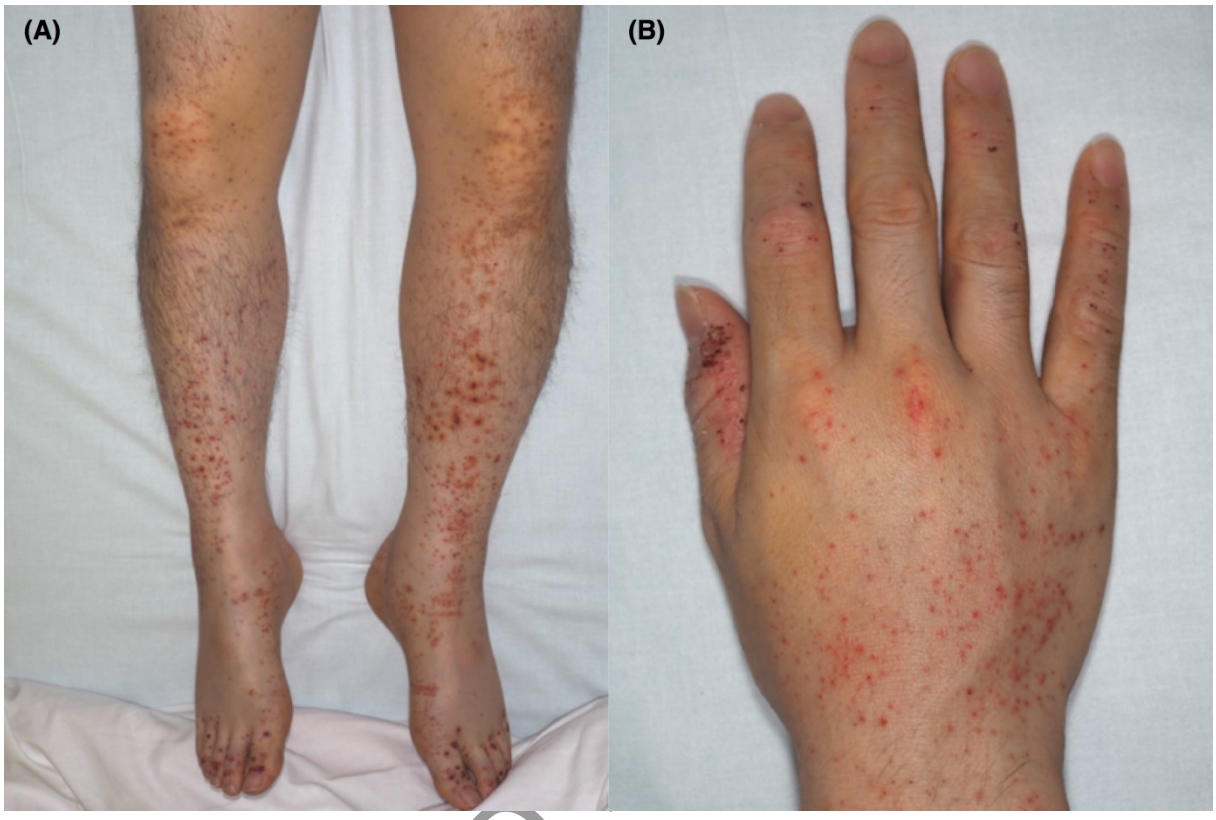

Figure 2

Histopathologic study of the patient's right forearm (Case 1). Erosions are seen on some parts of the epidermis (A). Inflammatory infiltration of neutrophils and lymphocytes, extravasation of red blood cells, nuclear debris (B), and inflammatory infiltrate with eosinophils (C) in the perivascular area. Fibrinoid necrosis is also noted (D). (A) Hematoxylin and eosin staining x40. (B–D) Hematoxylin and eosin staining x400.

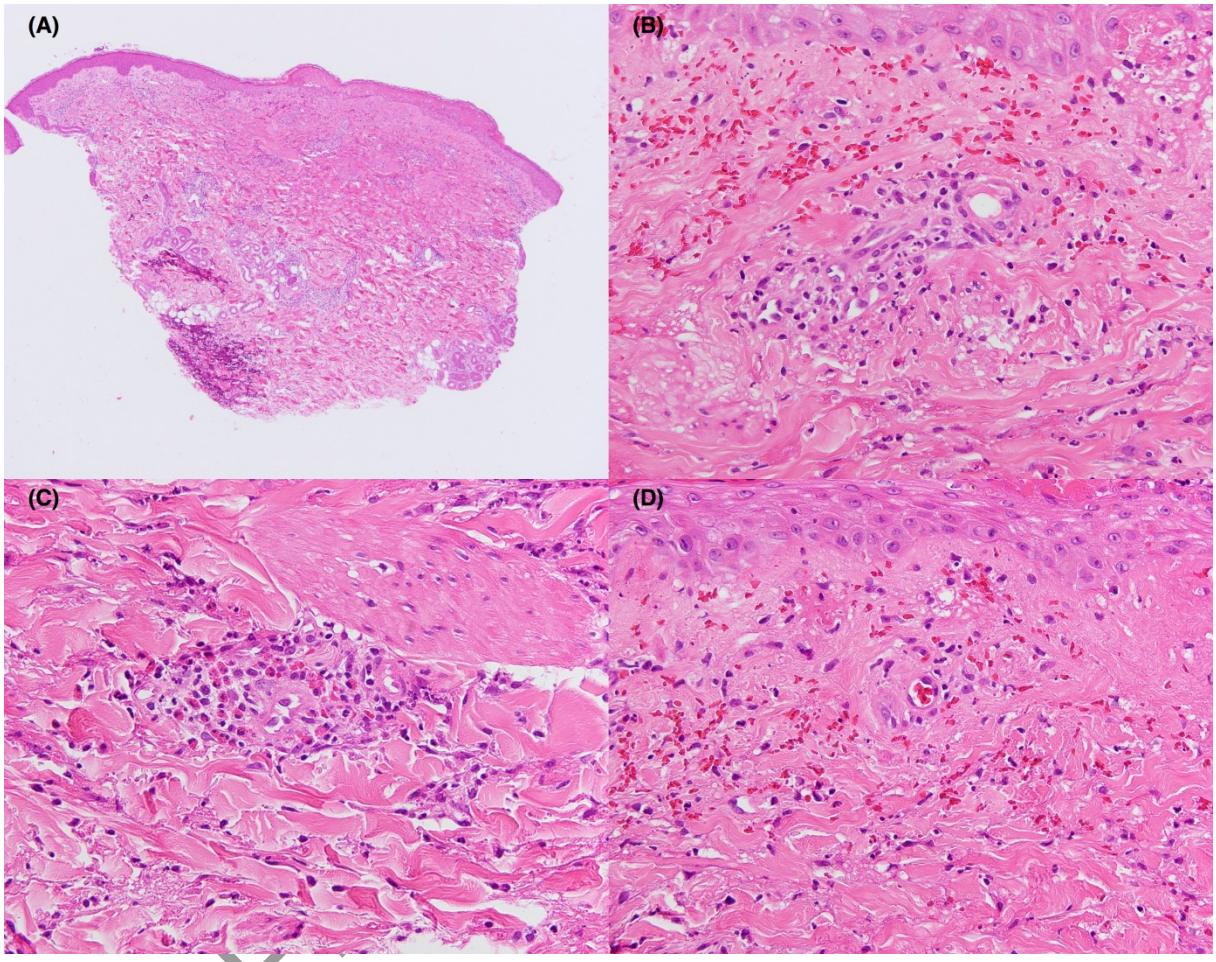

Figure 3

Immunofluorescence studies of the patient's right forearm (Case 1). No definite deposit of IgA (A) and only slight deposits of C3 (B) of the vessel walls were observed.

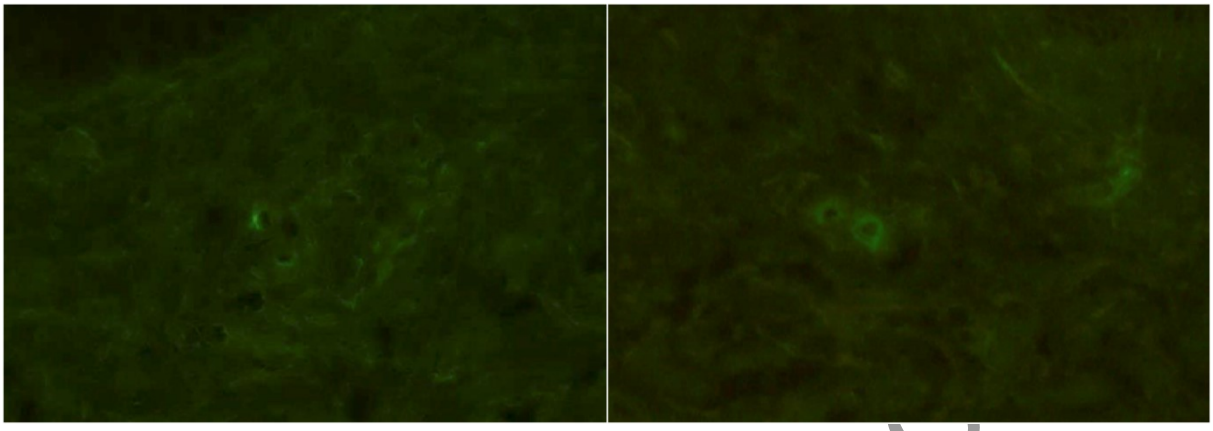

Figure 4

Palpable purpura on the lower limbs (A–B) (Case 2). The skin biopsy was taken from the purpura of the right lower leg (B).

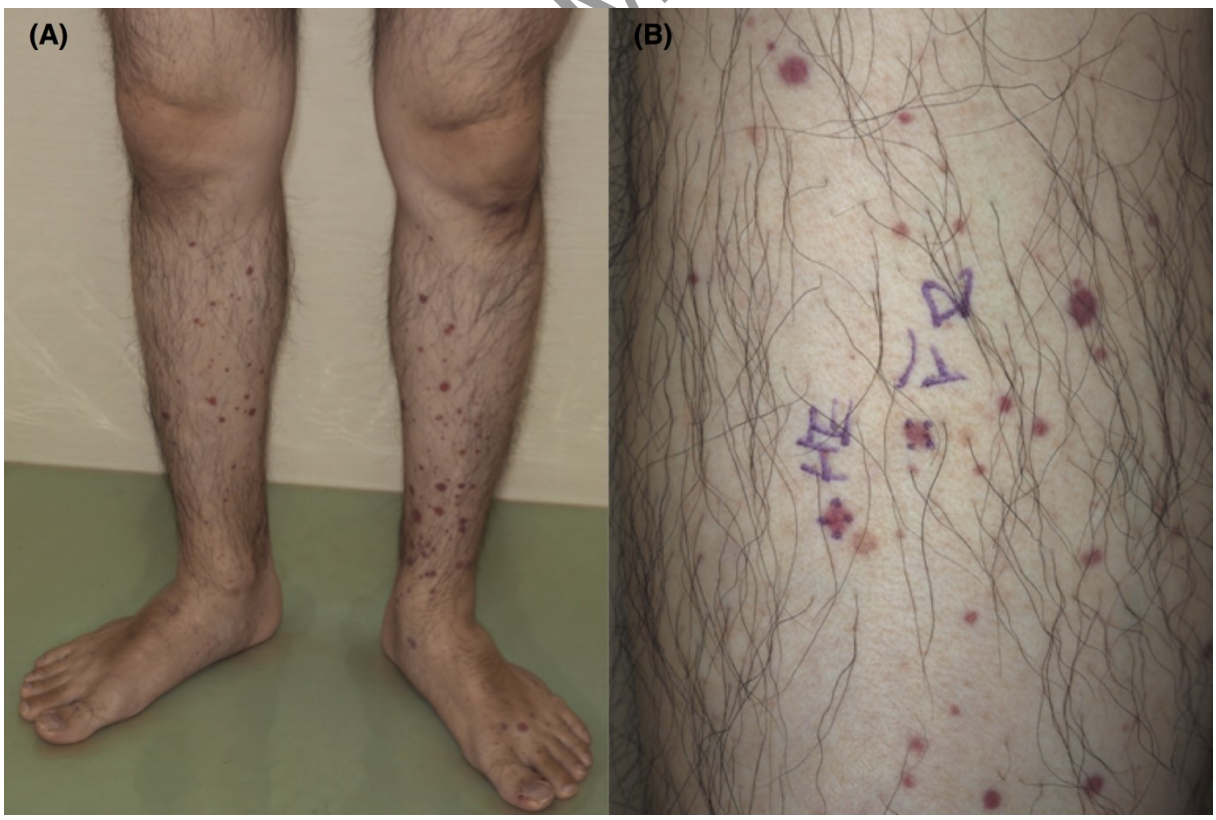

Figure 5

Histopathologic study of the patient's right lower leg (Case 2). Inflammatory infiltration of neutrophils, extravasation of red blood cells, nuclear debris, and fibrinoid necrosis are seen in the perivascular area (A–B). (A) Hematoxylin and eosin staining x40. (B) Hematoxylin and eosin staining x400.

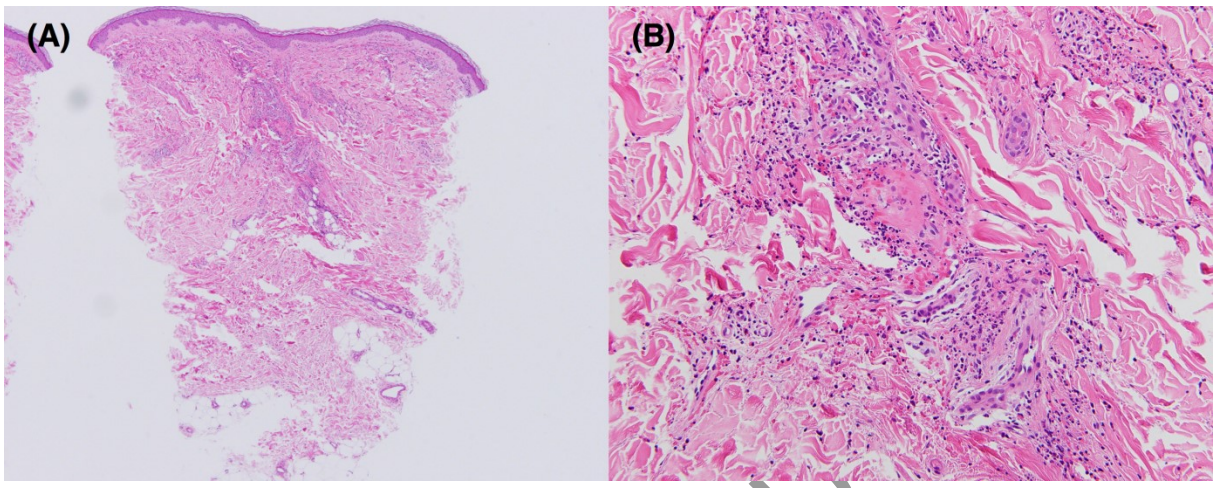

Figure 6

Immunofluorescence studies of the patient's right lower leg (Case 2). The slight deposits of IgA (A) and the deposit of C3 (B) of the vessel walls were observed.