Acta Derm Venereol 2014; 94: 327–328

SHORT COMMUNICATION

Immunoglobulin G4-related Disease Associated with Cutaneous Vasculitis

Tamihiro Kawakami[1], Nao Yamaguchi[1], Yoshinao Soma[1], Ken Yokoyama[2], Sayuri Shirai[2] and Kenjiro Kimura[2]
Departments of [1]Dermatology, and [2]Internal Medicine, Division of Nephrology and Hypertension, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan. E-mail: tami@marianna-u.ac.jp
Accepted Jun 3, 2013; Epub ahead of print Oct 3, 2013

Immunoglobulin G (IgG) is composed of 4 Ig isotypes. A new entity called IgG4-related disease has recently been established (1). This disorder is characterised by an elevated serum level of IgG4 and an infiltration of $IgG4^+$ plasma cells, as well as lymphocyte infiltration of various organs. IgG4 is the only subclass of human IgG that is unable to activate complement by the classical pathway. In the present report, we examine two patients with IgG4-related disease associated with cutaneous vasculitis.

CASE REPORTS

Case 1. A 57-year-old man presented with swelling of cervical, axillary, subclavian, and inguinal lymph nodes that developed over the past year. During this period, the patient often felt tired, had a decreased appetite, and developed arthralgia. He also found palpable purpura patches and confluent purpuric lesions on his lower legs (Fig. 1A). Laboratory findings showed an increased total serum protein 10.7 g/dl (normal range 6.7–8.3 g/dl), decreased serum albumin 2.4 g/dl (4.0–5.1 g/dl), and hypergammaglobulinaemia 5.31 g/dl (0.74–1.66 g/dl). Serum levels of IgG were abnormally high 5,556 mg/dl (870–1,700 mg/dl) and the subclass IgG4 accounted for more than 1,500 mg/dl (4.8–105 mg/dl). Serum C3 and C4 titres were low at 39 mg/dl (65–135 mg/dl) and 3 mg/dl (13–35 mg/dl), respectively. He had normal range of serum eosinophil count, creatinine, and blood urea nitrogen. Serologic specimens tested negative for antineutrophil-cytoplasmic antibody, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus.

Skin biopsy specimens obtained from the purpura of the left lower extremity demonstrated leukocytoclastic vasculitis in the dermis with infiltration of inflammatory cells mainly composed of neutrophils around the vessels (Fig. 1B). Direct immunofluorescence (DIF) microscopy revealed apparent positive staining with complement 3 (C3) deposition in the affected vessels. DIF was negative for IgG in the vessel walls. We used immunostaining for anti-human monoclonal IgG antibody (Histofine, Nichirei Biosciences Inc., Tokyo, Japan) and anti-human monoclonal IgG4 antibody (Histofine, Nichirei Biosciences Inc., Tokyo, Japan) to detect IgG^+ and $IgG4^+$ cells, respectively. Neither anti-human IgG nor IgG4 antibody staining revealed any inflammatory cells in the cutaneous vasculitis using the histochemical method. In contrast, tissue biopsies of the lymphadenopathy obtained from the right retroauricular nodes revealed infiltration of IgG positive lymphocytes and plasma cells (Fig. 1C). Immunostaining also detected numerous aggregates of $IgG4^+$ lymphocytes and plasma cells in the same sample of the lymphadenopathy. The ratio of $IgG4^+$ cells to IgG^+ cells was > 50%.

The patient was diagnosed with IgG4-related disease associated with cutaneous vasculitis. Treatment with prednisolone (30 mg/day) was effective for the cutaneous lesions and lymph-

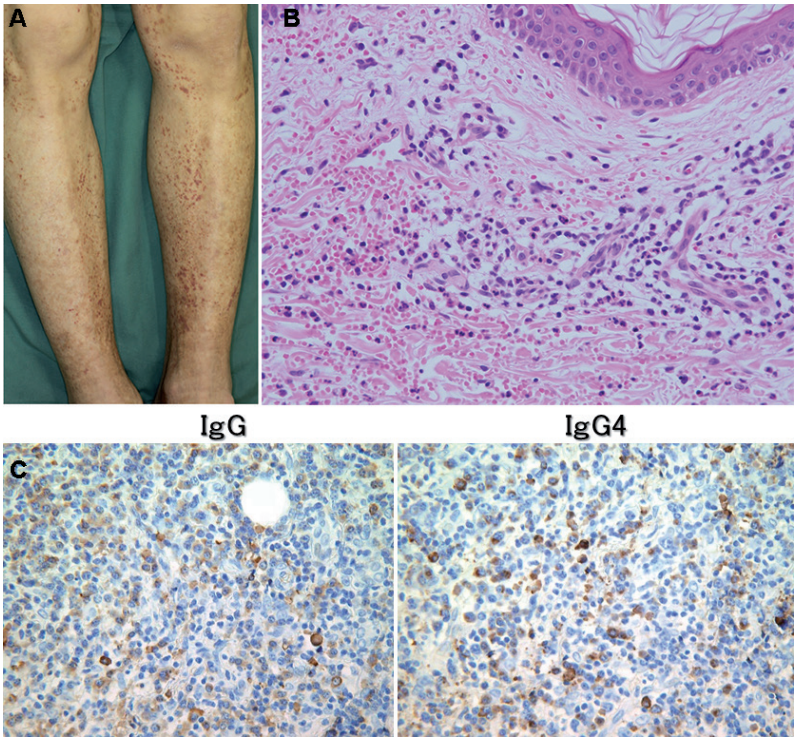

Fig. 1. Palpable purpura present on both lower extremities (Case 1) (A). Skin biopsy specimen of purpura demonstrates leukocytoclastic vasculitis in the dermis (Haematoxylin-eosin, original magnification ×400) (B). Tissue biopsies of the lymphadenopathy obtained from right retroauricular nodes reveal infiltration of IgG positive lymphocytes and plasma cells using histochemical staining (Immunoperoxidase, original magnification ×400). The ratio of IgG4-positive plasma cells to IgG-positive plasma cells was more than 50% (C).

adenopathy. Serum IgG and IgG4 levels decreased to within the normal range following treatment.

Case 2. A 73-year-old woman presented with bilateral parotid and submandibular gland swelling, palpable purpura on her legs, a recurrent sensation of sand or gravel in the eyes, and a daily feeling of dry mouth for several months. She had previously undergone surgery to evacuate superior swollen eyelids 4 years earlier. Palpable and haemorrhagic purpuric eruptions present on both lower extremities (Fig. S1A[1]). Laboratory findings showed an increased total serum protein 9.5 g/dl, decrease serum albumin 2.5 g/dl, and hypergammaglobulinaemia 5.34 g/dl. Serum levels of IgG were abnormally high at 5,307 mg/dl and the subclass IgG4 accounted for more than 1,500 mg/dl. Serum C3 and C4 titres were low at 41 mg/dl and 1 mg/dl, respectively. She had normal range of serum eosinophil count, creatinine, and blood urea nitrogen. Serologic specimens tested negative for cytomegalovirus, herpes simplex virus, and Epstein-Barr virus except slightly elevated antineutrophil-cytoplasmic antibody.

Skin biopsy specimens obtained from the purpura of the right lower extremity demonstrated leukocytoclastic vasculitis with a predominance of neutrophil infiltration in the upper dermis. DIF findings of the skin biopsy revealed C3 deposition in the affected vessels (Fig. S1B[1]). DIF was negative for IgG in the vessel walls. Anti-human IgG and IgG4 antibody staining did not reveal any positive cells in the cutaneous vasculitis. In contrast, histopathological findings from the superior eyelid swelling revealed infiltration of IgG positive lymphocytes and plasma cells by the histochemistry method. We detected numerous aggregates of IgG4-positive lymphocytes and plasma cells in the same sample of the superior eyelid swelling. The ratio of IgG4-positive cells to IgG-positive cells was more than 50%. Her renal biopsy revealed a mass-forming dense inflammatory cell infiltrate in the cortex and medulla, with tubulointerstitial fibrosis. The infiltrate was mainly composed of IgG4-positive plasma cells.

The patient was diagnosed with IgG4-related disease including dacryoadenitis and tubulointerstitial nephritis associated with cutaneous vasculitis. As a result of treatment with 30 mg/day prednisolone, the swelling in the parotid and submandibular glands improved and the sicca complexes of the eye and mouth ameliorated. This treatment regimen also led to an improvement in the serum IgG and IgG4 levels.

DISCUSSION

The classification criteria for placement in the IgG4-related group includes having both an elevated serum level of IgG4 of ≥135 mg/dl and an IgG4:IgG ratio of infiltrating plasma cells of ≥40%. The present cases fulfilled both these criteria and were subsequently diagnosed as IgG4-related disease. These 2 patients represent a rare case of IgG4-related disease associated with cutaneous vasculitis. Sato et al. (2) reported that skin infiltratation was rich in plasma cells with IgG4 positive in patients with IgG4-related skin disease. Histopathological examination in our patients revealed leukocytoclastic vasculitis in the cutaneous lesions. Cell infiltrations in the cutaneous lesions did not overexpress IgG4 on the vasculitis in the skin biopsies, although serum IgG4 levels were elevated. Hussain et al. (3) suggested that IgG4 could stimulate neutrophils via Fc receptors and may play a role in the pathogenesis of small vessel vasculitis. The increase in serum IgG4 might trigger neutrophils in the cutaneous vessels and lead to leukocytoclastic vasculitis. We propose that the cutaneous vasculitis seen in our patients could be somehow indirectly related to IgG4-related disease.

The pathogenic mechanisms of IgG4-related disease are not completely understood, although they are probably autoimmune. In the present patients, DIF studies showed deposits of C3 within the affected vessels of cutaneous vasculitis. Compared with the other IgG subclasses, IgG4 has a negligible ability to activate the classic complement pathway (1, 4). However, it has been shown in mice that non-complement-activating subclasses of antibodies may synergise with other IgG subclasses to activate complement through the lectin pathway (5). Moreover, IgG4 has the tendency to interact with other immunoglobulins, such as rheumatoid factor, and reveals an intrinsic affinity for IgG when coated to a solid phase (6, 7). These findings suggest that, if IgG4 is not just a bystander in the immune process within the cutaneous vasculitis, it might use non-classical pathways for complement activation. Further studies are needed to elucidate the mechanisms underlying such immune response of IgG4 in cutaneous vasculitis.

ACKNOWLEDGEMENTS

This work was supported by grants from the Scientific Research Fund of the Ministry of Education, Science, Sports and Culture, Japan (Grant-in-Aid for Scientific Research, No 20591356 and 23591658).

The authors declare no conflict of interest.

REFERENCES

1. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 2011; 23: 57–66.
2. Sato Y, Takeuchi M, Takata K, Ohno K, Iwaki N, Orita Y, et al. Clinicopathologic analysis of IgG4-related skin disease. Modern Pathology 2013; 26: 523–532.
3. Hussain A, Pankhurst T, Goodall M, Colman R, Jefferis R, Savage CO, et al. Chimeric IgG4 PR3-ANCA induces selective inflammatory responses from neutrophils through engagement of Fcγ receptors. Immunology 2009; 128: 236–244.
4. Ito T, Kitahara K, Umemura T, Ota M, Shimozuru Y, Kawa S, et al. A novel heterophilic antibody interaction involves IgG4. Scand J Immunol 2010; 71: 109–114.
5. Murata K, Fox-Talbot K, Qian Z, Takahashi K, Stahl GL, Baldwin WM 3rd, et al. Synergistic deposition of C4d by complement-activating and non-activating antibodies in cardiac transplants. Am J Transplant 2007; 7: 2605–2614.
6. Zack DJ, Stempniak M, Wong AL, Weisbart RH. Localization of an Fc-binding reactivity to the constant region of human IgG4. Implications for the pathogenesis of rheumatoid arthritis. J Immunol 1995; 155: 5057–5063.
7. Rispens T, Ooievaar-De HP, Vermeulen E, Schuurman J, van der Neut KM, Aalberse RC. Human IgG4 binds to IgG4 and conformationally altered IgG1 via Fc-Fc interactions. J Immunol 2009; 182: 4275–4281.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1707