



## A case report on the cytokine signature profile of immunoglobulin G<sub>4</sub>-related disease

J Dällenbach, L Moi, G Humair, I Letovanec, M Perreau, S Cherix, D Comte & J Vaucher

To cite this article: J Dällenbach, L Moi, G Humair, I Letovanec, M Perreau, S Cherix, D Comte & J Vaucher (2020) A case report on the cytokine signature profile of immunoglobulin G<sub>4</sub>-related disease, *Scandinavian Journal of Rheumatology*, 49:4, 332-333, DOI: 10.1080/03009742.2020.1711964

To link to this article: <https://doi.org/10.1080/03009742.2020.1711964>



Published online: 17 Apr 2020.



Submit your article to this journal [↗](#)



Article views: 83



View related articles [↗](#)



View Crossmark data [↗](#)

## LETTER

## A case report on the cytokine signature profile of immunoglobulin G<sub>4</sub>-related disease

J Dällenbach<sup>1</sup>, L Moi<sup>2</sup>, G Humair<sup>1</sup>, I Letovanec<sup>3</sup>, M Perreau<sup>2,4</sup>, S Cherix<sup>5</sup>, D Comte<sup>2,4\*</sup>, J Vaucher<sup>1,4\*</sup>

<sup>1</sup>Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

<sup>2</sup>Service of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland

<sup>3</sup>Service of Pathology, Lausanne University Hospital, Lausanne, Switzerland

<sup>4</sup>Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

<sup>5</sup>Department of Orthopaedics and Traumatology, Lausanne University Hospital, Lausanne, Switzerland

Our patient was a 52-year-old woman admitted for investigations of a left lumbosacral paravertebral mass and high-grade fever of unknown origin. Baseline blood tests showed a slightly elevated neutrophilia (12 070 cells/ $\mu$ L). C-reactive protein was elevated at 355 mg/L (reference < 10 mg/L) and erythrocyte sedimentation rate was > 110 mm/h (reference < 20 mm/h). Computed tomography and magnetic resonance imaging of the lumbar vertebral column showed a mass effect of 8 × 3.5 × 4.5 cm on the left paravertebral musculature at the level of L5–S1. [<sup>18</sup>F]Fluorodeoxyglucose (FDG) positron emission tomography revealed intense FDG uptake by the left paravertebral mass. Tissue biopsy of the mass revealed a dense lymphoplasmacytic infiltration with storiform fibrosis and obliterative phlebitis, compatible with a diagnosis of immunoglobulin G<sub>4</sub> (IgG<sub>4</sub>)-related disease. Further analyses showed an elevated serum IgG<sub>4</sub> level (1.720 g/L; reference range 0.011–1.04 g/L). Analysis of the B-lymphocytes subpopulation showed an increased number of circulating plasma cells (6255 cells/mL; reference range 1–653 cells/mL) with 5.9% plasmablasts, of which 0.3% (18 cells/mL) were IgG<sub>4</sub>-plasmablasts. A diagnosis of IgG<sub>4</sub>-related disease was made. The patient received a 3 day course of intravenous glucocorticoids, followed by oral prednisone. Symptoms and systemic inflammation subsided within a week. Rituximab was then added as a glucocorticoid-sparing agent.

This research has been performed in accordance with the Declaration of Helsinki, and written, signed informed consent has been obtained from the patient.

The pathogenesis of IgG<sub>4</sub>-related disease is poorly understood. The disease can affect virtually any organ through a chronic fibroinflammatory process (1). Currently, evidence points towards a complex interplay between T cells and innate immune cells with the participation of activated B cells. Knowing that IgG<sub>4</sub> antibodies have anti-inflammatory properties, the presence of IgG<sub>4</sub>-secreting plasmablasts may represent a response to inflammatory stimuli (1). These processes are controlled by the

production of a large range of proinflammatory and anti-inflammatory cytokines (1). We thus aimed to determine the cytokine profile of a patient with IgG<sub>4</sub>-related disease. Cytokines were measured based on Luminex xMAP® Technology using a sandwich enzyme-linked immunoassay approach (ProcartaPlex™; Thermo Fisher, Switzerland), before and 24 h after administration of intravenous glucocorticoids. The cytokine profile of the patient was compared to those of 44 controls free from inflammation and obtained using the same approach. The selection of presented cytokines was restricted to those higher than 2 standard deviations from the controls.

Elevated cytokines were implicated in different functional pathways linked, among others, to T-cell polarization and innate immune system activation (Figure 1). Levels of

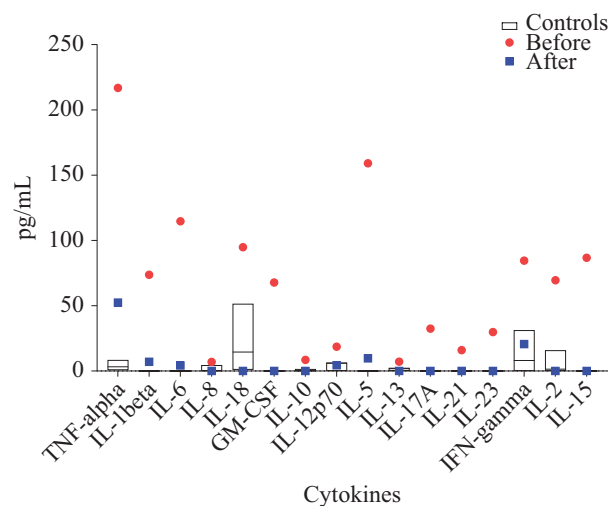


Figure 1. Cytokine elevation in immunoglobulin G<sub>4</sub>-related disease and controls. Cytokines were measured based on Luminex xMAP Technology before (circles) and 24 h after administration of intravenous glucocorticoids (squares). The cytokine profile of the patient was compared to those of 44 controls (boxes with central bars indicating the median). TNF, tumour necrosis factor; IL, interleukin; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon.

inflammatory cytokine, comprising tumour necrosis factor- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-8, IL-18, and granulocyte-macrophage colony-stimulating factor, were relatively high, which was consistent with the high degree of inflammation. Among these, IL-6 is an upstream inflammatory cytokine that has a central role in inflammatory response propagation, and functionally promotes B-cell differentiation to mature plasma cells. Inflammatory cytokines, including IL-6 upregulation in the adventitia, have been shown to contribute to the pathogenesis of aortic aneurysms in IgG<sub>4</sub>-related disease (2).

There was also a significant elevation of interleukin IL-5 and, to a lesser extent, IL-13, both produced by T-helper type 2 (Th2) cells. This is consistent with previous findings showing that affected tissues are predominantly infiltrated by Th2 cells in IgG<sub>4</sub>-related disease (1, 3). In addition, IL-5 and IL-13 play a role in IgG<sub>4</sub>-related disease through activation of IgE production and eosinophilic infiltration (4). IL-13 also induces fibrosis, another hallmark of IgG<sub>4</sub>-related disease. Other profibrotic cytokines, such as IL-1 $\beta$  and interferon- $\gamma$ , were elevated in this case (5).

In association with IL-10, which was also elevated here, Th2 cytokines support IgG<sub>4</sub> production by plasmablasts and plasma cells (6). In vitro, IL-13, IL-10, and IL-21 have also been shown to influence IgG<sub>4</sub> production (6).

This case illustrates that a wide range of functional pathways are implicated in IgG<sub>4</sub>-related disease pathophysiology. The number of elevated cytokines, and consequently inflammatory responses, appears to be larger than in other inflammatory diseases, such as systemic lupus erythematosus (7, 8). In the onset of complex multisystem autoimmune disorders, cytokine multiplex analysis may thus represent a useful test to characterize the immune pathways involved in the pathogenesis of the disease. Further studies are needed to examine its potential implication as a diagnostic tool and as a predictor of the response to specific treatments, such as IL-6 blockade or even Th2 cytokine blockade (anti-IL-5 or anti-IL-4/IL-13 receptor monoclonal antibodies).

We postulate here that the cytokine signature profile is a key element in understanding the underlying IgG<sub>4</sub>-antibody biology, explaining the particular dynamics of IgG<sub>4</sub>-antibodies leading to a fibroinflammatory response and, finally, predicting the potential effects of different kinds of treatment.

#### Disclosure statement

No potential conflict of interest was reported by the authors.

#### References

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG<sub>4</sub>-related disease. *Lancet* 2015;385:1460–71.
2. Kasashima S, Kawashima A, Kasashima F, Endo M, Matsumoto Y, Kawakami K. Inflammatory features, including symptoms, increased serum interleukin-6, and C-reactive protein, in IgG<sub>4</sub>-related vascular diseases. *Heart Vessels* 2018;33:1471–81.
3. Yoshikawa T, Watanabe T, Minaga K, Kamata K, Kudo M. Cytokines produced by innate immune cells in IgG<sub>4</sub>-related disease. *Mod Rheumatol* 2018;18:1–18.
4. Miyabe K, Zen Y, Cornell LD, Rajagopalan G, Chowdhary VR, Roberts LR, et al. Gastrointestinal and extra-intestinal manifestations of IgG<sub>4</sub>-related disease. *Gastroenterology* 2018;155:990–1003.
5. Masunaga A, Ishibashi F, Koh E, Oide T, Sekine Y, Hiroshima K. Possible relationship between fibrosis of IgG<sub>4</sub>-related thymitis and the profibrotic cytokines, transforming growth factor beta 1, interleukin 1 beta and interferon gamma: a case report. *Diagn Pathol* 2018;13:6.
6. Lighaam LC, Rispens T. The immunobiology of immunoglobulin G<sub>4</sub>. *Semin Liver Dis* 2016;36:200–15.
7. Guimarães PM, Scavuzzi BM, Stadtlober NP, Franchi Santos LFDR, Lozovoy MAB, Iriyoda TMV, et al. Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: cytokine profiles. *Immunol Cell Biol* 2017;95:824–31.
8. Koenig KF, Groeschl I, Pesickova SS, Tesar V, Eisenberger U, Trendelenburg M. Serum cytokine profile in patients with active lupus nephritis. *Cytokine* 2012;60:4101–16.

\*These authors share senior authorship

Jérôme Dällenbach, Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV), 46, Rue du Bugnon, 1011 Lausanne, Switzerland.

E-mail: [jerome.dallenbach@chuv.ch](mailto:jerome.dallenbach@chuv.ch)

Accepted 2 January 2020