IgG4 and IgG-positive plasma cell infiltration and high correlation with disease activity in patients with inflammatory bowel disease undergoing colectomy

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Abstract

Background

The aims of this study were to identify the distribution and the role of IgG-positive and IgG4-positive plasma cell infiltration in colonic mucosa in patients with inflammatory bowel disease (IBD).

Methods

Patients with IBD who were free from immunosuppressive agents were consecutively enrolled from 2010 to 2014. Sections from surgical specimens were stained with monoclonal antihuman IgG4 and IgG antibody using standard immunohistochemical techniques.

Results

In total, 49 patients (30 CD and 19 UC) were included in this study. There was abundant infiltration of IgG4-positive plasma cells in 4 patients with UC (IgG4-present, 21.1%) and 6 patients with CD (IgG4-present, 20.0%). A significantly higher number of IgG-positive cells and IgG4-positive cells were found in patients with CD and UC than in control group. Higher proportions of IgG4 correlated with higher endoscopic activity scoring, higher revised Mayo score, lower haemoglobin, higher erythrocyte sedimentation rate, higher high sensitive C-reactive protein (hsCRP) and higher D-dimer in patients with UC (P < 0.05). A significant difference was identified in terms of disease activity in the IgG-present group compared with the group with the IgG-absent group (69.2% vs 16.7% P < 0.05). If the cut-off value was set at 25 cells/HPF for IgG, the sensitivity and specificity of predicting severity potential in UC was 90.0% and 55.6%, respectively. The area under the curve was 0.633 by receiver operating characteristic analysis.

Conclusions

These findings suggest that IgG4 infiltration appears to be a relevant marker of inflammatory process caused by immune dysregulation in patients with IBD.

Background

Inflammatory bowel disease (IBD) has long been considered a group of immune-mediated disorders, resulting from dysregulated T and B cell immunity (1). Histopathological findings are characterized by localization of lymphocytes and plasma cells suggesting that abnormal expression of immunoglobulin (IgG) and its subtypes occur. Immune responses producing IgG and IgG4 appear to be associated with pathogenic effects in inflammatory bowel disease. IgG4 is a subclass of immunoglobulin. Recent investigations have suggested that IgG4 is a dynamic molecule undergoing Fab arm exchange. The presence of enhanced IgG4 in the setting of chronic mucosal inflammation may represent a physiological
attempt to decrease inflammatory injury mediated by enhanced plasma cell activity prone to tissue scarring and damage (2).

It has been reported that disordered serum IgG was associated with disease outcome in patients with IBD (3). In addition, several studies reported IgG4-positive plasma cell infiltration in the colonic mucosa of patients with UC without autoimmune pancreatitis. However, the distribution of IgG4 plasma cells in colonic surgical specimens, its significance, and its relation to prognosis and therapeutic responses in patients with IBD is unclear.

The aims of this study were to identify the distribution and number of IgG and IgG4 in patients with IBD and to evaluate its association with clinical characteristics and therapeutic responses in IBD.

**Methods**

**Patients**

A total of 49 patients with inflammatory bowel disease who underwent surgery were enrolled in this study. All patients, including 30 CD and 19 UC, were definitively diagnosed by pathology after colectomy. All patients were free from steroid and immunosuppressive agents. Disease severity in patients with UC was determined clinically by the Truelove and Witts’ score and endoscopically by the Mayo endoscopic score as described (4). Disease severity in patients with CD was determined clinically by CDAI score and endoscopically by SEDES score as described. Control sections were from distant normal colon tissues from patients with colonic cancer who underwent curative surgery. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

**Immunohistochemistry staining of IgG4 and IgG**

Sections were prepared from formalin-fixed, paraffin-embedded surgical specimens. These sections were stained with routine haematoxylin and eosin. Monoclonal antihuman IgG4 and IgG antibodies (Binding Site, Birmingham, UK) were applied to these sections using standard immunohistochemical techniques. Numbers of immunohistochemically identified IgG4-positive plasma cells were counted in a minimum of 5 high-power fields (HPFs) in each specimen, and an average was obtained. Degree of IgG4-positive plasma cell infiltration was categorized into two groups: IgG4-present – ≥ average 10 IgG4-positive plasma cells/HPF; and IgG4-absent – 0 to 9 IgG4-positive plasma cells/HPF. Degree of IgG-positive plasma cell infiltration was categorized into two groups: IgG-present – ≥ average 25 IgG-positive plasma cells/HPF; and IgG-absent – 0 to 25 IgG-positive plasma cells/HPF).

**Statistical analysis**

Data were expressed as the means ± standard deviation (SD). Chi-square and non-parametric tests were used to determine the differences between groups using SPSS 11.5 software (IBM, Armonk, New York, US). For numeric variable relationship analysis, the Spearman correlation coefficient was used. \( P < 0.05 \) was considered statistically significant.
Results

Demographic and Clinical characteristics

The phenotypic characteristics of IBD patients are shown in Table 1. Among 19 patients with UC, there were 11 males and 8 females. The mean age was 46.5 ± 16.3 years. Two patients (10.5%) underwent emergency colectomy due to complications.

|                          | All IBD | CD     | UC     | Control |
|--------------------------|---------|--------|--------|---------|
| N                        | 49      | 30     | 19     | 20      |
| Age (mean ± SD) (yr)     | 41.0 ± 15.7 | 37.5 ± 14.5 | 46.5 ± 16.3 | 44.5 ± 14.2 |
| Gender (male)            | 31 (63.3) | 20 (66.7) | 11 (57.9) | 13 (65.0) |
| Smoking history          | 19 (38.8) | 13 (43.3) | 6 (31.6)  | 5 (25.0)  |
| Drinking history         | 14 (28.6) | 8 (26.7)  | 6 (31.6)  | 2 (10.0)  |
| Appendectomy             | 8 (16.3)  | 8 (26.7)  | 0        | 2 (10.0)  |

P* for comparison between CD patients and control group

P** for comparison between UC patients and control group

Among 36 patients with CD, there were 20 males and 10 females. The mean age was 37.5 ± 14.5 years. Twenty-one patients (70.0%) underwent emergency colectomy due to complications.

There were no significant differences in terms of age, gender, smoking history, drinking history or appendectomy among the CD, UC and Control groups (P > 0.05) (Table 1).

Distribution of IgG4-positive cells and IgG-positive cells in the colonic mucosa of UC patients, CD patients and control sections

Infiltration of IgG4-positive and IgG-positive plasma cells was detected in 9 patients with UC (47.4%). Abundant infiltration of IgG4-positive plasma cells with an average of 10 IgG4-positive plasma cells/HPF was detected in 4 patients with UC (IgG4-present patients, 21.1%) (Table 2, Fig. 1) The positive cells were mainly distributed in the mucosa or submucosa.
Table 2
Comparison of IgG and IgG4 between IBD and control groups

|                      | All N = 49 | CD N = 30 | UC N = 19 | P*   | Control N = 20 | P**   | P***   |
|----------------------|------------|-----------|-----------|------|----------------|-------|--------|
| Detection of IgG, n (%) | 48 (98.0)  | 29 (96.7) | 19 (100.0)| 1.000| 16 (80.0)      | 0.143 | < 0.05 |
| The average number of IgG counts, n/HPF | 55.6 ± 46.0 | 58.0 ± 51.0 | 51.8 ± 38.1 | 0.649| 4.9 ± 5.6      | < 0.001| < 0.001|
| IgG counts > 25/HPF, n (%) | 31 (63.3)  | 18 (60.0) | 13 (68.4) | 0.551| 0              | < 0.001| < 0.001|
| The average number of IgG4 counts, n/HPF | 4.5 ± 5.6  | 5.3 ± 6.9 | 3.2 ± 5.0 | 0.265| 0.2 ± 0.5      | < 0.05 | < 0.05 |
| IgG4 counts > 10/HPF, n (%) | 10 (20.4)  | 6 (20.0)  | 4 (21.1)  | 1.000| 0              | 0.345 | < 0.05 |
| IgG4/IgG, % | 9.2 ± 10.1 | 11.2 ± 9.8 | 6.0 ± 10.0 | 0.077| 7.6 ± 16.7     | < 0.05 | 0.713  |

P* for comparison between CD and UC patients

P** for comparison between CD patients and control group

P*** for comparison between UC patients and control group

Infiltration of IgG4-positive and IgG-positive plasma cells was detected in 29 patients with CD (96.7%). Abundant infiltration of IgG4-positive plasma cells with 10 IgG4-positive plasma cells/HPF was detected in 6 patients with CD (IgG4-present patients, 20.0%) (Fig. 1) The positive cells were mainly distributed in the mucosa or submucosa.

There were significant differences in terms of the average number of IgG counts, the number of IgG4 and the ratio of IgG4 to IgG between the CD and control groups (58.0 ± 51.0 vs 4.9 ± 5.6, P < 0.001; 96.7% vs 70.0%, P < 0.001; 11.2 ± 9.8 vs 7.6 ± 16.7, respectively, P = 0.033). There were significant differences in terms of the average number of IgG counts, the average number of IgG4 counts and average 10 IgG4-positive plasma cells between the UC and control groups (51.8 ± 38.1 vs 4.9 ± 5.6, P < 0.001; 3.2 ± 5.0 vs 0.2 ± 0.5, P = 0.010; 21.1% vs 0%, P=0.030; and 11.2 ± 9.8 vs 7.6 ± 16.7, respectively, P = 0.033).

There were more IgG4-positive cells in the CD group than in the UC group (96.7% vs 47.4% P < 0.001). However, there were no significant differences in terms of average 10 IgG4-positive plasma cells or the ratio of IgG4 to IgG between patients with UC and CD.

The association of IgG4 and IgG with clinical characteristics of patients with IBD
IgG4-positive plasma cell infiltration was categorized into two groups: IgG4-present – ≥ average 10 IgG4-positive plasma cells/HPF; and IgG4-absent – 0–9 IgG4-positive plasma cells.

IgG4-present and IgG4-absent patients with UC showed no significant differences in terms of age, gender, smoking history, drinking history, Montreal type (E2, E3) or disease severity according to Truelove and Witts’ score. A significant difference was identified in terms of endoscopic activity (grade 1, 2 or 3) and higher Mayo score in the group with IgG4-present patients than in the IgG4-absent group (100% vs 46.7% \( P = 0.033 \)). More severe anaemia, higher ESR level, higher hsCRP and higher D-dimer were associated with greater IgG4-positive plasma cell infiltration in colonic mucosa \( (P < 0.05) \) (Table 3). A higher ratio of IgG to IgG was also associated with higher D-dimer, ESR and hsCRP (Table 3).
|                               | All       | IgG4-absent | IgG4-present | P      |
|-------------------------------|-----------|-------------|--------------|--------|
| N = 19                        | N = 15    | N = 4       |              |        |
| Age, y                        | 46.5 ± 16.3 | 47.6 ± 17.0 | 42.3 ± 14.4  | 0.574  |
| Gender, n (%)                 | 11 (57.9)  | 8 (53.3)    | 3 (75.0)     | 0.603  |
| Smoking history               | 6 (31.6)  | 4 (26.7)    | 2 (50.0)     | 0.557  |
| Drinking history              | 6 (31.6)  | 4 (26.7)    | 2 (50.0)     | 0.557  |
| Montreal type, n (%)          |           |             |              | 0.386  |
| E1                            | 0         | 0           | 0            |        |
| E2                            | 2 (10.5)  | 1 (6.7)     | 1 (25.0)     |        |
| E3                            | 17 (89.5) | 14 (93.3)   | 3 (75.0)     |        |
| Disease severity, n (%)       |           |             |              | 0.117  |
| Moderate                      | 9 (47.4)  | 8 (53.3)    | 1 (25.0)     |        |
| Severe                        | 10 (52.6) | 7 (46.7)    | 3 (75.0)     |        |
| Laboratory data               |           |             |              |        |
| WBC, *10^9/l                  | 7.7 ± 3.6 | 7.6 ± 3.4   | 8.4 ± 4.8    | 0.706  |
| EOS, *10^9/l                  | 0.10 ± 0.11 | 0.11 ± 0.12 | 0.07 ± 0.06  | 0.426  |
| HGB, g/l                      | 105.7 ± 18.1 | 109.7 ± 15.9 | 90.5 ± 20.9  | 0.056  |
| PLT, *10^9/l                  | 292.3 ± 100.2 | 281.8 ± 103.5 | 331.5 ± 87.9 | 0.394  |
| Alb, g/l                      | 32.7 ± 5.2 | 33.7 ± 4.8  | 29.0 ± 5.5   | 0.108  |
| D-Dimer                       | 1.0 ± 1.0 | 0.5 ± 0.2   | 2.4 ± 1.1    | < 0.001|
| K, mmol/l                     | 3.9 ± 0.4 | 3.9 ± 0.5   | 3.9 ± 0.4    | 0.833  |
| ESR, mm/h                     | 30.7 ± 21.1 | 24.6 ± 15.7 | 55.3 ± 24.8  | < 0.05 |
| hsCRP, mg/l                   | 28.9 ± 31.7 | 19.5 ± 21.6 | 59.6 ± 43.0  | < 0.05 |
| IgG, mmol/l                   | 12.2 ± 4.1 | 14.7 ± 3.2  | 8.5 ± 1.2    | 0.088  |
| Endoscopic activity, n (%)    |           |             |              | < 0.05 |
| Mayo 1 or 2                   | 8 (42.1)  | 8 (53.3)    | 0            |        |
| Mayo 3                        | 11 (57.9) | 7 (46.7)    | 4 (100.0)    |        |
|                                | All      | IgG4-absent | IgG4-present | p       |
|--------------------------------|----------|-------------|--------------|---------|
| Truelove-Witts score          | 17.3 ± 4.0 | 16.4 ± 3.9  | 20.5 ± 2.6   | 0.071   |
| Revised Mayo score            | 8.2 ± 2.7  | 7.6 ± 2.7   | 10.5 ± 1.9   | < 0.05  |
| Serious complication n (%)    |          |             |              |         |
| Intestinal perforation        | 1 (5.3)   | 1 (6.7)     | 0            | 1.000   |
| Intestinal obstruction        | 2 (10.5)  | 1 (6.7)     | 1 (50.0)     | 0.386   |
| Toxic megacolon               | 1 (5.3)   | 0           | 1 (25.0)     | 0.211   |
| Gastrointestinal massive Haemorrhage | 4 (21.1) | 3 (20.0)    | 1 (25.0)     | 1.000   |
| Colectomy                     |          |             |              | 0.440   |
| Emergency colectomy, n (%)    | 2 (10.5)  | 2 (13.3)    | 0            |         |
| Selective colectomy           | 17 (89.5) | 13 (86.7)   | 4 (100.0)    |         |

IgG-present and IgG-absent patients with UC showed no significant differences with respect to age, gender, smoking history, drinking history or Montreal type (E2, E3). A significant difference was identified in terms of disease activity in the IgG-present group compared with the IgG-absent group (69.2% vs 16.7% *P* < 0.05). Higher PLT level was associated with greater IgG-positive plasma cell infiltration in colonic mucosa (*P* < 0.05) (Table 4).
## Table 4
Comparison of clinical data between IgG > 25/HPF and IgG < 25/HPF in UC

|                                | All          | IgG-absent  | IgG-present  |
|--------------------------------|--------------|-------------|-------------|
|                                | N = 19       | N = 6       | N = 13      | P           |
| Age, y                         | 46.5 ± 16.3  | 50.8 ± 15.8 | 44.5 ± 16.7 | 0.444       |
| Gender, n (%)                  | 11 (57.9)    | 4 (66.7)    | 7 (53.8)    | 0.494       |
| Smoking history                | 6 (31.6)     | 3 (50.0)    | 3 (23.1)    | 0.320       |
| Drinking history               | 6 (31.6)     | 3 (50.0)    | 3 (23.1)    | 0.320       |
| Montreal type, n (%)           |              |             |             |             |
| E1                             | 0            | 0           | 0           | 1.000       |
| E2                             | 2 (10.5)     | 0 (0.0)     | 2 (15.4)    |             |
| E3                             | 17 (89.5)    | 6 (100.0)   | 11 (84.6)   |             |
| Disease severity, n (%)        |              |             |             | < 0.05      |
| Moderate                       | 9 (47.4)     | 5 (83.3)    | 4 (30.8)    |             |
| Severe                         | 10 (52.6)    | 1 (16.7)    | 9 (69.2)    |             |
| Laboratory data                |              |             |             |             |
| WBC, *10^9/l                   | 7.7 ± 3.6    | 8.3 ± 4.4   | 7.5 ± 3.3   | 0.645       |
| EOS, *10^9/l                   | 0.10 ± 0.11  | 0.13 ± 0.12 | 0.09 ± 0.10 | 0.580       |
| HGB, g/l                       | 105.7 ± 18.1 | 111.2 ± 19.0| 103.2 ± 17.9| 0.385       |
| PLT, *10^9/l                   | 292.3 ± 100.2| 227.0 ± 82.2| 322.4 ± 95.6| < 0.05      |
| Alb, g/l                       | 32.7 ± 5.2   | 34.5 ± 5.4  | 31.9 ± 5.2  | 0.331       |
| D-Dimer                        | 1.0 ± 1.0    | 0.5 ± 0.2   | 1.2 ± 1.1   | 0.295       |
| K, mmol/l                      | 3.9 ± 0.5    | 3.9 ± 0.7   | 3.9 ± 0.4   | 0.861       |
| ESR, mm/h                      | 30.7 ± 21.1  | 30.5 ± 15.7 | 30.9 ± 24.9 | 0.974       |
| hsCRP, mg/l                    | 28.9 ± 31.7  | 24.3 ± 26.7 | 31.4 ± 35.2 | 0.673       |
| Endoscopic activity, n (%)     |              |             |             | 1.000       |
| Grade 1 or 2                   | 8 (42.1)     | 3 (50.0)    | 5 (38.2)    |             |
| Grade 3                        | 11 (57.9)    | 3 (50.0)    | 8 (61.5)    |             |
| Truelove-Witts score           | 17.3 ± 4.0   | 16.0 ± 3.4  | 17.8 ± 4.2  | 0.397       |
IgG4-present and IgG4-absent patients with CD showed no significant differences with respect to age, gender, extent of colitis, Montreal type (L1, L2, L3, L4) or disease severity. Higher hsCRP was associated with greater IgG4-absent plasma cell infiltration in colonic mucosa (12.6 ± 10.7 vs 54.3 ± 47.7, *P* < 0.05).

### ROC analysis to predict the severity of UC

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive potential of IgG and IgG4 for the diagnosis of IBD. The potential of IgG and IgG4 to predict the diagnosis of IBD was weak on analysis.

The potential for severity of UC was analysed in this study. If the cut-off value was set at 25 cells /HPF for IgG, the sensitivity and specificity for predicting severity potential in UC were 90.0% and 55.6%, respectively. The area under the curve was 0.633 by receiver operating characteristic [ROC] analysis. However, the IgG4 potentials were too weak to analyse.

### Discussion

In the present study, substantially high proportions of IgG4 and IgG were observed in patients with IBD. There was abundant infiltration of IgG4-positive plasma cells in 4 UC patients (IgG4-present, 21.1%) and 6 CD patients (IgG4-present, 20.0%). High proportions of IgG4 might be associated with higher endoscopic activity scoring, revised Mayo score, more severe anaemia, higher ESR level, higher hsCRP and higher D-dimer in the patients with UC. High proportions of IgG occurred substantially in colonic mucosa of severe UC. Higher infiltration of IgG4 was observed in CD patients with higher hsCRP.

The abnormal expression of immunoglobulin (IgG) and its subtypes in plasma cells may occur and be characterized in autoimmune diseases. It was reported that infiltration of many IgG4-positive plasma
cells was occasionally detected in the colonic mucosa of AIP patients. In addition, 5.6% of patients with AIP had accompanying IBD. Therefore, the relationship between colitis and IgG4 was highly concerned. However, Rebours (5) compared IgG4 plasma cell infiltration in the digestive tract mucosa of patients with AIP type 1 and 2, normal subjects and patients with IBD but without AIP. IgG4-positive plasma cells were not more numerous in the digestive mucosa of AIP patients than in controls, but they were more abundant in the colon of IBD patients than in AIP patients (0.2/HPF, VS. 6.6/HPF, VS. 3.8/HPF, VS. 0.3/HPF). Another study indicated the same results (6). All these suggested that the relationship of IBD and IgG4 may be independent of AIP or other autoimmune diseases. Despite these interesting reports, it remains unclear as to what role these IgG4 plasma cells play in the disease course of patients with IBD.

In our study, we found abundant infiltration of IgG4-positive plasma cells in 4 UC patients (IgG4-present, 21.1%) and 6 CD patients (IgG4-present, 20.0%). This result showed similar infiltration proportions as those of other studies. These studies reported a distribution and significance of IgG4-positive plasma cells in biopsy tissue of IBD at 24%-64%. Moreover, Virk et al. reported significantly lower numbers of IgG4-positive plasma cells in patients with lymphocytic/collagenous colitis than in patients with IBD (P = 0.0001). All these studies showed that higher IgG4-positive cells appeared in colonic tissue with IBD (7, 8).

Although there was no significant difference in terms of IgG4-abundant infiltration in the CD and UC groups (20% vs 21%) with no agreement with a few published studies, IgG4 appeared to be more associated with disease activity in patients with UC than with CD in our study. There was a significant association of high proportions of IgG4 with higher endoscopic activity scoring, higher revised Mayo scores, more severe anaemia, higher ESR levels and higher hsCRP in patients with UC, but there was only an association with lower hsCRP in patients with CD. In addition, more severe anaemia and higher D-dimer appeared in patients with UC, possibly associated with inflammatory activity. However, the real roles of IgG4 in IgG4-related disease are not clear. Few studies showed that IgG4 appeared to be associated with pathogenic effects and some suggested protective effects. Recent data on the regulation of IgG4 showed that IgG4-related disease may reflect an excessive production of anti-inflammatory cytokines such as interleukin-10, triggering an overwhelming expansion of IgG4-producing plasma cells (9). IL10 is a cytokine associated with UC pathogenesis. This may explain the results in the present study.

IgG4 and IgG were higher in colonic mucosa in severe UC patients. In the present study, the sensitivity and specificity of predicting severity potential in UC were 90.0% and 55.6%, respectively, at 25 cells/HPF for IgG.

Key limitations of this study were retrospective nature of the study design and the relatively small number of patients. In addition, IgG4-positive plasma cell infiltration should be examined before any therapy.

In conclusion, these findings suggested that IgG4 infiltration appears to be a relevant marker of the inflammatory process caused by immune dysregulation in patients with IBD. Further studies are needed to confirm the predictive value of peripheral blood and tissue IgG4 in the diagnosis, therapeutic responses and recurrence of IBD.
Abbreviations

IBD
inflammatory bowel disease.
IgG
immunoglobulin
UC
Ulcerative colitis
CD
Crohn's disease
HPFs
high-power fields

Declarations

Ethics approval and consent to participate

All aspects of this study were approved by the Peking Union Medical College Hospital & Chinese Academy Medical Science Ethics Committee (IRB number:S-K1142).

All patients participating gave written informed consent and authorization for use of data.

Consent for publication

Not applicable

Competing Interests

The authors have declared that no competing interests exist.

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Author contributions

HY: data acquisition, analysis and interpretation, drafting of the manuscript and statistical analysis;

BC, ZW, XYS, BW, MJ, HMZ, HL, JL, YL, BT: data acquisition and analysis; JMQ: study concept and design, critical revision of manuscript for important intellectual content, and study supervision.
All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures
Figure 1

Abundant infiltration of IgG4-positive plasma cells with an average of 10 IgG4-positive plasma cells/HPF was detected in 4 patients with UC (IgG4-present patients, 21.1%)