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Increased circulating Th22 cells in patients with acute gouty arthritis

A CONSORT-compliant article

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Abstract

Background: T-helper 22 (Th22) cells are involved in host immunity against pathogen invasion and have been implicated in the pathogenesis of inflammatory diseases. However, the roles of Th22 cells in acute gouty arthritis remain unclear.

Methods: A case–control study was employed to illustrate the clinical significance of Th22 cells in acute gouty arthritis. In this study, 27 patients with acute gouty arthritis, 22 patients with intercritical gout (IG), and 20 healthy controls were recruited, and peripheral blood cells and plasma were collected for the detection of Th22, Th17, and Th1 cells, and plasma interleukin (IL)-22.

Results: The relative and absolute numbers of Th22 and Th17 cells were significantly higher in patients with acute gouty arthritis than in patients with IG and healthy controls. Plasma IL-22 levels were consistently higher in patients with acute gouty arthritis than in patients with IG and healthy controls ($P < .05$). Th22 cell numbers were positively correlated with Th1 ($r = 0.648$, $P < .05$) and Th17 ($r = 0.379$, $P < .05$) cell numbers in patients with gout. Moreover, Th22 cell numbers and plasma IL-22 levels were positively correlated with C-reactive protein levels (Th22: $r = 0.444$, $P < .05$; IL-22: $r = 0.282$, $P < .05$).

Conclusion: Our results indicate that peripheral blood levels of Th22 cells increase during acute gouty arthritis suggesting a role for these cells in the pathophysiology of the disease.

Abbreviations: AG = acute gout, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IFN= interferon, IG = intercritical gout, IL = interleukin, Th = T-helper.

Keywords: arthritis, gout, interleukin-22, Th22 cell

1. Introduction

Acute gout (AG) is a form of acute sterile inflammation caused by the inflammatory reaction of joint tissue to monosodium urate crystals within the joint. T cell subsets and cytokines play important roles in the pathogenesis of acute gouty arthritis, with proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) contributing to inflammation.[1] Acute gouty arthritis is a self-limited disease that can be spontaneously alleviated by transforming growth factor-β (TGF-β).[2] Although various studies have described the presence of local inflammatory mediators in the synovial fluid during gout attacks,[3] to our knowledge, few studies have focused on systemic inflammatory markers in acute gouty arthritis.

Recently, a new phenotype of T helper (Th) cells, Th22, has been described.[4] Th22 cells secrete the signature cytokine IL-22, which is produced mainly by Th22, Th1, and Th17 cells,[5] but do not secrete IL-17 or interferon (IFN)-γ. Th22 differentiation is induced in the presence of IL-6 and TNF-α. Th17 cells, which characteristically secrete IL-17, have been implicated in inflammation mediated by many inflammatory diseases, including multiple sclerosis, psoriasis, and inflammatory arthritis. Th17 differentiation is induced in the presence of IL-1β, IL-6, and TGF-β.[6]

The cytokines IL-1β, IL-6, TNF-α, and TGF-β, which induce differentiation of Th17 and Th22 cells from $CD4^+$ naïve T cells, are significantly upregulated in AG, suggesting that Th17 and Th22 cells may be involved in gouty inflammation. However, the roles of these T cell subsets in gouty inflammation remain to be clarified. In this study, the percentage and absolute number of Th22, Th17, and Th1 cells, and the level of plasma IL-22 were analyzed in patients with gout.

2. Materials and methods

2.1. Ethics statement

Enrollment took place between May 2014 and April 2015 at the Affiliated Hospital of North Sichuan Medical College, China. The study was approved by the Medical Ethical Committee of the Affiliated Hospital of North Sichuan Medical College. Written informed consent was obtained from each participant.

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2.2. Recruitment of patients

A total of 49 male patients with gout, according to the 2011 recommendations for the diagnosis and management of gout and hyperuricemia,[7] and 20 age-matched healthy male individuals (healthy controls, HCs) were recruited for this study. Exclusion criteria were: failure to consent to the study; suffering from another clinical condition that causes hyperuricemia or cytokine production, such as hemolytic anemia, myeloproliferative disorders, psoriasis, sarcoidosis, acute or chronic renal failure, alcohol intoxication, diabetic ketoacidosis, lactic acidosis, glycogen storage disease type I, hypo- or hyperparathyroidism, or concurrent infections. The healthy controls were selected randomly and had no clinical history of gout, arthritis, or rheumatic disease. The 49 gouty patients consisted of 27 patients with acute gouty arthritis (AG), which was characterized by the presence of arthritis, and 22 patients with intercritical gout (IG), which was characterized by a confirmed history of gout, but a current absence of symptoms. The patients with AG were enrolled in the study within 1 day of injury onset. To explore the relationship between T cell dynamics and clinical outcomes from acute gouty arthritis, 11 AG patients were followed up for 4 weeks. Samples were collected at week 0 (baseline), week 2, and week 4 for Th22, Th17, and Th1 detection.

2.3. Flow cytometric analysis

Intracellular cytokines were detected by flow cytometry to indicate the different T cell subsets. Briefly, heparinized peripheral whole blood (400 μL) was mixed with an equal volume of RPMI 1640 medium and incubated for 4 hours at 37° C at 5% CO_2 in the presence of Cell Stimulation Cocktail (eBioscience, San Diego, CA), which is a mixture of phorbol 12-myristate 13-acetate (PMA), ionomycin, brefeldin A, and monensin. PMA and ionomycin are pharmacological T-cell-activating agents that mimic the signal generated by the T-cell receptor complex. Monensin is used to block intracellular transport mechanisms, leading to an accumulation of cytokines in the cells. After incubation, the cells were stained with antihuman CD4-FITC (clone OKT4, eBioscience) at room temperature for 20 minutes. The cells were then fixed, permeabilized, and stained with phycoerythrin-conjugated antihuman IL-22 (clone 22URTI, eBioscience), antihuman IL-17A conjugated with PerCP-Cyanine5.5 (clone eBio64DEC17, eBioscience), and allophycocyanin-conjugated antihuman IFN-γ (clone 4S.B3, eBioscience). Stained cells were analyzed by flow cytometric analysis using a BD FACSCalibur cytometer together with CellQuest software (BD Bioscience, Franklin Lakes, NJ). Th22, Th17, and Th1 cells were defined as $CD4^+IFN\text{-}\gamma^-IL\text{-}17^-IL\text{-}22^+$, $CD4^+IL\text{-}17^+IFN\text{-}\gamma^-IL\text{-}22^-$, and $CD4^+IFN\text{-}\gamma^+IL\text{-}17^-IL\text{-}22^-$ T cells, respectively.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Peripheral blood was collected in heparin anticoagulant tubes. Plasma was obtained by centrifugation and stored at −20 °C prior to examination. Plasma IL-22 levels were detected using a quantitative sandwich enzyme immunoassay technique, for which ELISA kits (eBioscience) were used in accordance with the manufacturer's recommendations.

2.5. Clinical assessment

For clinical assessment of the severity of systemic inflammation in gout patients, the levels of plasma C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were measured in all participants.

2.6. Statistical analysis

Results were expressed as mean ± SD or median (range). The statistical significance of differences in T cell subpopulations and plasma cytokines among AG patients, IG patients, and HCs was determined using one way analysis of variance followed by post hoc least significant difference tests. The data, which were not normally distributed, were analyzed by the Kruskal–Wallis test (H test) and the Nemenyi test. The Pearson or Spearman correlation test was used for correlation analysis depending on the data distribution. All data were analyzed using SPSS 17.0 software. P values less than .05 were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the gout patients

The study recruited 27 AG patients, 22 IG patients, and 20 healthy controls, all of whom were age- and sex-matched. The ESR and plasma CRP levels in AG patients were significantly higher than those in IG patients and HCs ($P < .05$). The IG patients had longer disease duration than the AG patients ($P < .05$). The BMI and the rates of hypertension and diabetes in AG and IG patients were significantly higher than those in HCs ($P < .05$). These data are summarized in Table 1.

3.2. Elevated Th22 cells and IL-22 in acute gouty arthritis

We analyzed the proportion of Th22 cells based on cytokine patterns after in vitro activation by PMA/ionomycin in short-term cultures. Typical dot plots of T cell subsets from a

Table 1

Clinical and laboratory data of each group.

Variable	AG patients N = 27	IG patients N = 22	HC N = 20
Age, y	47.5 ± 6.7	46.4 ± 7.2	45.4 ± 7.9
BMI, kg/m^2 *,†	24.7 ± 2.8	23.9 ± 3.1	22.6 ± 2.3
Disease duration, y‡	1.86 ± 1.07	3.67 ± 2.56	Not available
Tophi (n)	6 (22.2%)	7 (31.8%)	Not available
Deformity (n)	2 (7.4%)	3 (13.6%)	Not available
CRP, mg/L*,‡	33.6 ± 31.5	9.4 ± 6.3	5.7 ± 2.2
ESR, mm/h*,‡	20.1 ± 16.3	9.6 ± 7.5	9.1 ± 5.8
Urate, μmol/L*,‡	502 ± 124	387 ± 130	366 ± 85
Medication			
NSAIDs (n)	11 (40.7%)	4 (18.2%)	Not available
Colchicine (n)	14 (51.9%)	7 (31.8%)	Not available
Prednisone (n)	1 (3.7%)	1 (4.5%)	Not available
Allopurinol (n)	5 (18.5%)	11 (50.0%)	Not available
Benzbromarone (n)	4 (14.8%)	6 (27.3%)	Not available
Comorbidities			
Hypertension (n)*,†	7 (25.9%)	6 (27.3%)	1 (5.0%)
Diabetes (n)*,†	8 (29.6%)	6 (22.7%)	2 (10.0%)

AG = acute gouty, BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IG = intercritical gout, HC = healthy controls, NSAIDs = nonsteroidal anti-inflammatory drugs.

* $P < .05$, between AG patients and HC.

† $P < .05$, between IG patients and HC.

‡ $P < .05$, between AG and IG patients.

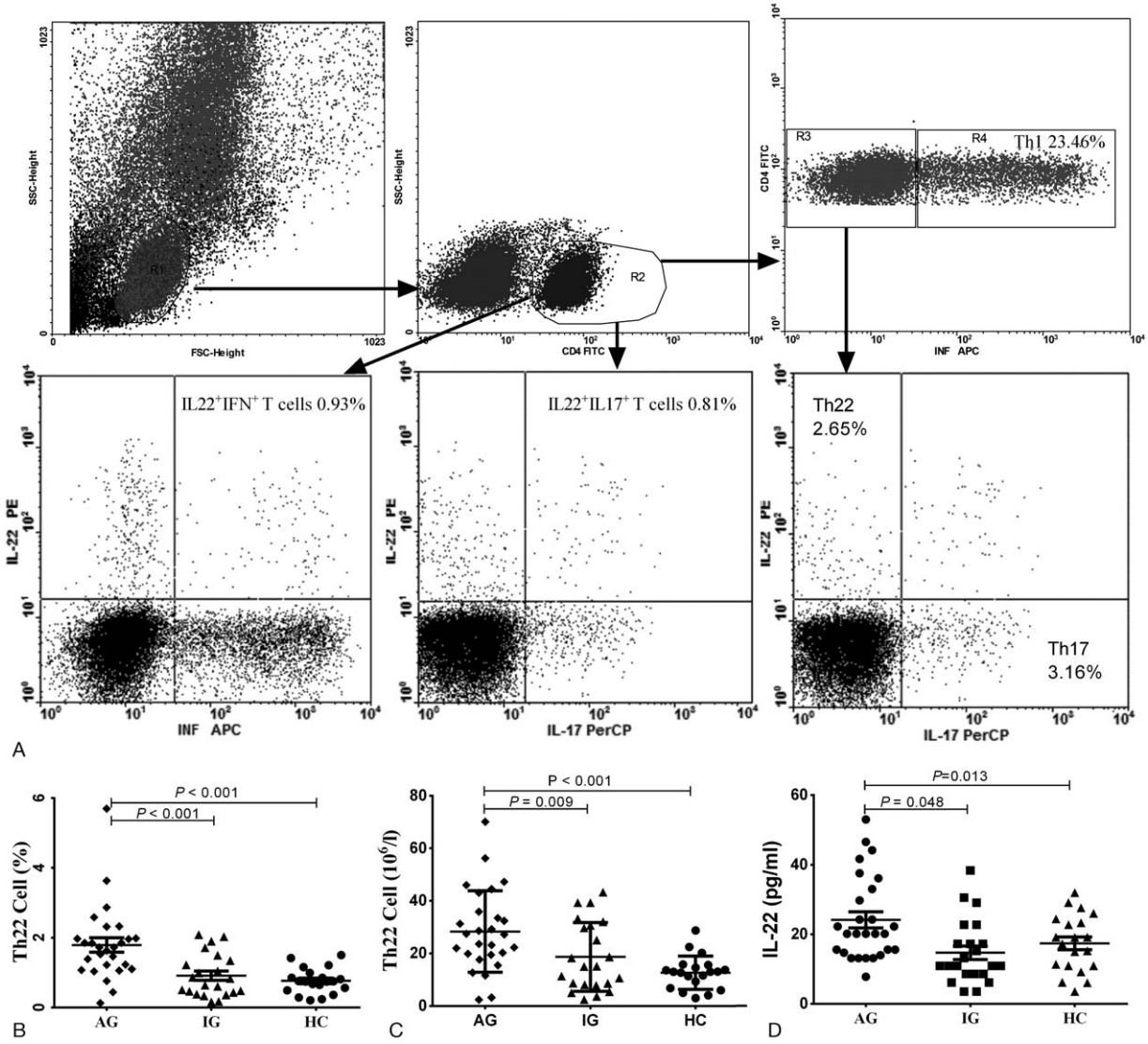

Figure 1. Th22 cells and IL-22 in AG patients, IG patients, and HCs. (A) Representative dot plots showing T cell populations in an AG patient. The Th22 cells were measured after stimulation with cell stimulation cocktail for 4 hours. The percentages of cells expressing only IL-17, IL-22, or IFN-γ were used to indicate Th17, Th22, or Th1 cell numbers. (B) The proportion of Th22 in AG, IG, and HCs. (C) Absolute number of Th22 in AG, IG, and HCs. (D) Plasma IL-22 levels in AG, IG, and HCs. AG = acute gout, IFN = interferon, IG = intercritical gout, IL = interleukin, HC = healthy controls, Th = T-helper.

representative AG patient are shown in Fig. 1A as well as the analytical strategy for flow cytometry data of each of our patients. For this study, Th22 cells are defined as those cells that only express IL-22 and do not also express IL-17 or IFN-γ. Cells that are double positive for these cytokines were quantitated separately. The percentage of Th22 cells in the T cell population was significantly higher in AG patients (1.79% ± 1.07%) than in IG patients (0.91% ± 0.61%, $P < .05$) and HCs (0.76% ± 0.39%, $P < .05$) (Fig. 1B). The absolute number of Th22 cells, which was calculated based on the total number of peripheral blood lymphocytes, was also significantly higher in AG patients (28.4 ± 5.5 × 10^6/L) than in IG patients (18.2 ± 13.3 × 10^6/L, $P < .05$) and HCs (12.2 ± 6.9 × 10^6/L, $P < .05$) (Fig. 1C). Plasma IL-22 levels were examined by ELISA and were consistently determined to be significantly higher in AG patients (26.69 ± 23.70 pg/mL) than in IG patients (14.73 ± 9.11 pg/mL, $P < .05$) and HCs (16.93 ± 7.99 pg/mL, $P < .05$) (Fig. 1D).

3.3. Elevated Th17 cells in acute gouty arthritis

The number of Th17 cells as a percentage of T cells was significantly higher in AG patients (1.81% ± 0.65%) than in IG patients (1.0% ± 0.54%, $P < .05$) and HCs (1.16% ± 0.71%, $P < .05$) (Fig. 2A). Likewise, the absolute number of Th17 cells was significantly higher in AG patients (29.5 ± 13.7 × 10^6/L) compared with IG patients (22.2 ± 12.6 × 10^6/L, $P < .05$) and HCs (17.4 ± 8.3 × 10^6/L, $P < .05$) (Fig. 2C). There was no significant difference in Th1 cells among the 3 groups (Fig. 2B and D).

3.4. Increased IL-17/IL-22 and IL-22/IFN-γ double-positive CD4 T cells in acute gouty arthritis

The percentage of $CD4^+$ $IL\text{-}17^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^-$ cells (0.78% ± 0.49%) in the T cell population was significantly higher in AG patients than in IG patients (0.30% ± 0.23%, $P < .05$) and HCs

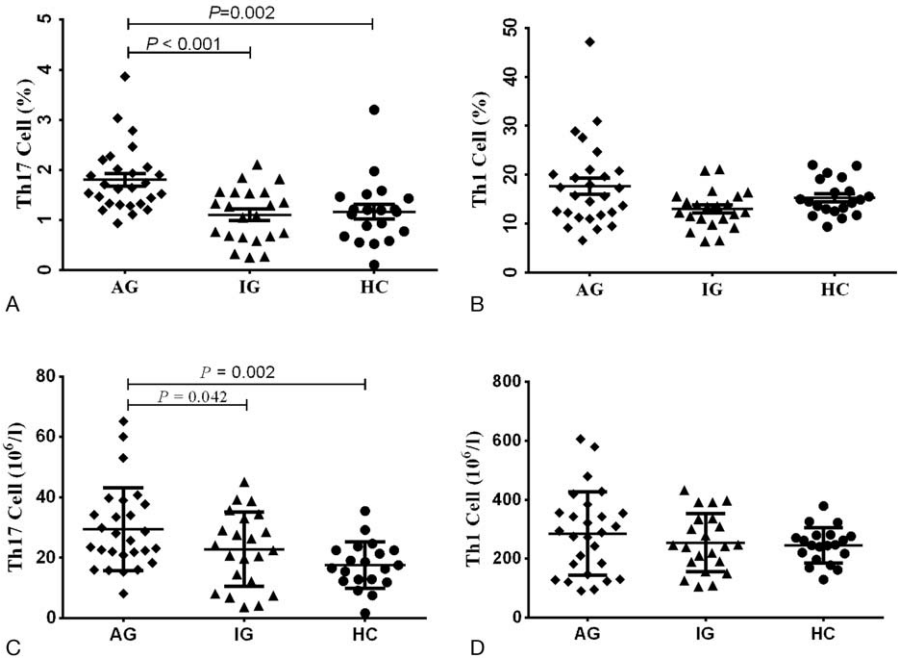

Figure 2. Th17 and Th1 cells in AG patients, IG patients, and HCs. (A) Percentage of Th17 cells. (B) Percentage of Th1 cells. (C) Absolute number of Th17 cells. (D) Absolute number of Th1 cells. The percentage of Th17 cells was significantly elevated in AG patients compared with IG patients and HCs ($P < .05$). AG = acute gout, IG = intercritical gout, HC = healthy controls, Th = T-helper.

(0.29% ± 0.21%, $P < .05$) (Fig. 3A). In addition, the proportion of $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ cells (0.75% ± 0.62%) was significantly higher in AG patients than in IG patients (0.43% ± 0.37%, $P < .05$) and HCs (0.41% ± 0.30%, $P < .05$) (Fig. 3B). The absolute numbers of double-positive CD4 T cells showed the same trends (Fig. 3C and D).

3.5. Correlations among T cell subsets in patients with gout

In patients with gout, the percentage of Th22 cells were significantly positively correlated with Th1 cells ($r = 0.684$, $P < .05$, Fig. 4A) and $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ T cells ($r = 0.713$, $P < .05$, Fig. 4B). In addition, the percentage of Th22 cells were significantly positively correlated with Th17 cells ($r = 0.397$, $P < .05$, Fig. 4C) and $CD4^+$ $IL\text{-}22^+$ $IL\text{-}17^+$ $IFN\text{-}\gamma^-$ T cells ($r = 0.681$, $P < .05$, Fig. 4D).

3.6. Correlations between Th22 cells, IL-22, and CRP

Patients with gout exhibited a significant positive correlation between the percentage of Th22 cells and plasma CRP levels ($r = 0.444$, $P = .002$) (Fig. 5A), however, not all patients showed an increase in plasma CRP. The percentages of other T cell subsets were not correlated with plasma CRP levels ($P > .05$). A weak positive correlation was also found between plasma IL-22 and CRP levels ($r = 0.282$, $P = .05$) (Fig. 5B). Furthermore, no correlation was found between T cell subsets and ESR.

3.7. Temporal changes in Th22, Th17, and Th1 cells during acute gout attacks

Patients (n = 11) were followed for 4 weeks after antiinflammatory therapy, during progression from AG to IG; samples were collected at week 0 (baseline), week 2, and week 4. The percentage of Th22 and Th17 cells decreased gradually during progression from AG to IG. The baseline percentages of Th22 and Th17 were significantly higher than the percentages of these cells at week 4 (Fig. 6, 1.45% ± 0.43% vs 0.88% ± 0.53%, 1.73% ± 0.32% vs 0.98% ± 0.49%, respectively; all $P < .01$).

4. Discussion

We report, for the first time, that peripheral Th22 cells and plasma IL-22 are significantly upregulated in patients with acute gouty arthritis. The percentage of Th22 cells were positively correlated with Th1 cells, Th17 cells, and plasma CRP in patients with gout. The percentage of Th22 cells decreased gradually during progression from AG to IG. These findings suggest that Th22 cells are aberrantly produced in the peripheral blood of patients with AG, and closely associated with acute gouty arthritis.

Th22 cells, which constitute a recently defined lineage of T cells distinct from Th1, Th2, and Th17 cells, are believed to play a complex and important role in inflammatory and autoimmune diseases.[8] The function of Th22 cells is mediated by IL-22, which protects against tissue damage by enhancing regeneration,[5] but has also been implicated in inflammatory and autoimmune diseases.[9] Th17 and Th1 cells are also considered to be important drivers of autoimmune disease and involved in the pathogenesis of arthritis.[10–12] However, the roles of Th22, Th17, and Th1 cells in acute sterile arthritis, including gout, are far from clear. Therefore, Th22, Th1, and Th17 cells, as well as double-positive ($IL\text{-}22^+$ $IL\text{-}17^+$ and $IL\text{-}22^+$ $IFN\text{-}\gamma^+$) CD4 T cells were examined in the current study.

Our results demonstrate that the percentage and absolute number of peripheral Th22 cells are significantly elevated in the peripheral blood of AG patients, compared with IG patients and

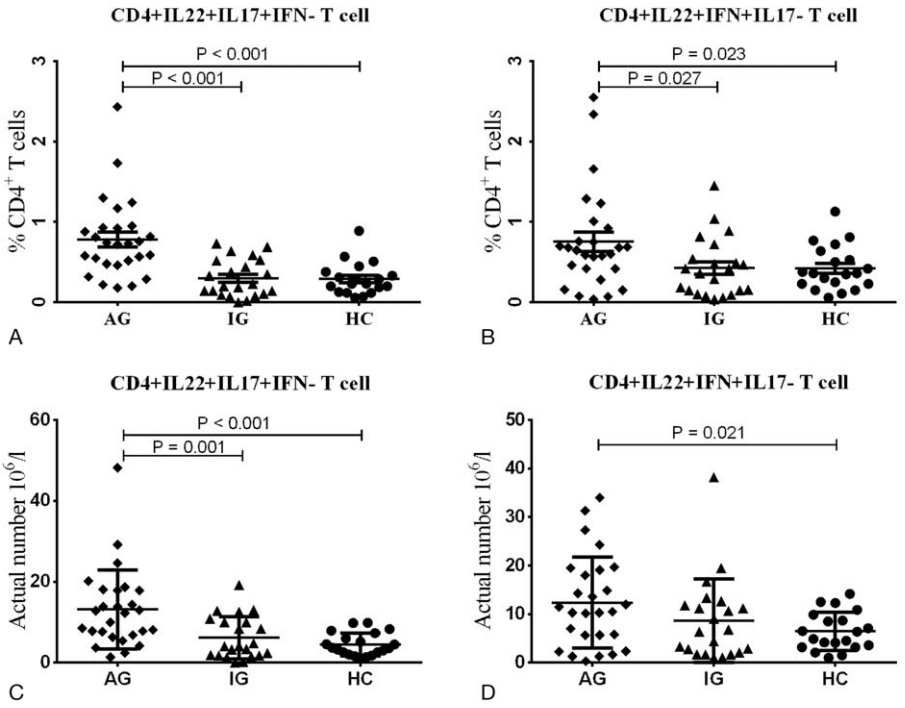

Figure 3. Double-positive CD4 T cells in AG patients, IG patients, and HCs. (A) Percentage of $CD4^+$ $IL\text{-}22^+$ $IL\text{-}17^+$ $IFN\text{-}\gamma^-$ T cells. (B) Percentage of $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ T cells. (C) Absolute number of $CD4^+$ $IL\text{-}22^+$ $IL\text{-}17^+$ $IFN\text{-}\gamma^-$ T cells. (D) Absolute number of $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ T cells. The percentages of both double-positive T cell phenotypes were significantly elevated in AG patients compared with IG patients and HCs ($P < .05$). AG = acute gout, IFN = interferon, IG = intercritical gout, IL = interleukin, HC = healthy controls.

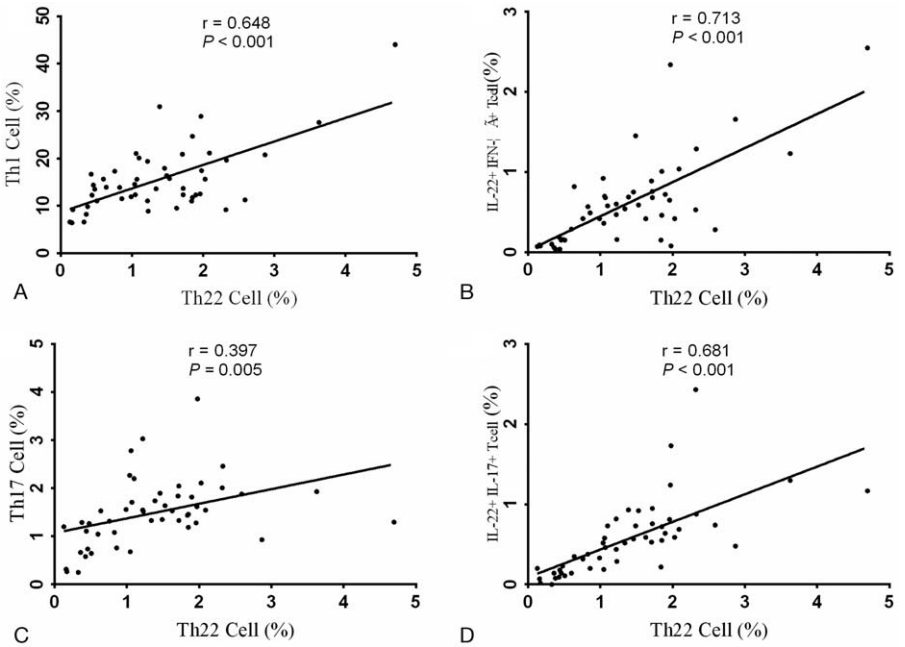

Figure 4. Correlations among T cell subsets in patients with gout. Significant positive correlations were observed between (A) Th22 and Th1 cell numbers, (B) Th22 and $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ cell numbers, (C) Th22 and Th17 cell numbers, and (D) Th22 and $CD4^+$ $IL\text{-}22^+$ $IFN\text{-}\gamma^+$ $IL\text{-}17^-$ cell numbers. IFN = interferon, IL = interleukin, Th = T-helper.

healthy controls. Consistent with the results for Th22 cells, the populations of Th17 and double-positive ($IL\text{-}22^+$ $IL\text{-}17^+$ and $IL\text{-}22^+$ $IFN\text{-}\gamma^+$) CD4 T cells were significantly higher in AG patients than in IG patients and HCs. Additionally, positive correlations between Th22 and Th17 cells, and between Th22 and double-positive T cells, were observed in patients with gout. These findings suggest that a variety of T cell subsets are aberrantly produced in patients with acute gouty arthritis. Th17 cells, which act as proinflammatory mediators, are involved in the pathogenesis of inflammation.[13,14] Th22 cells share a developmental

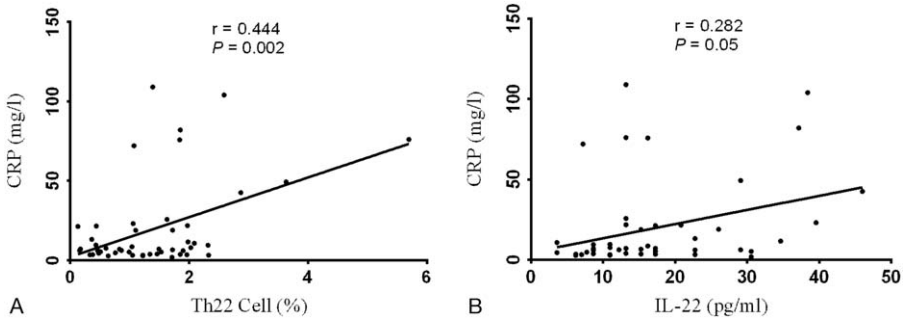

Figure 5. Correlations between Th22 cells, IL-22, and CRP in patients with gout. (A) The percentage of Th22 cells and plasma CRP levels were significantly positively correlated. (B) Plasma IL-22 and CRP levels were significantly positively correlated. CRP = C-reactive protein, IL = interleukin, Th = T-helper.

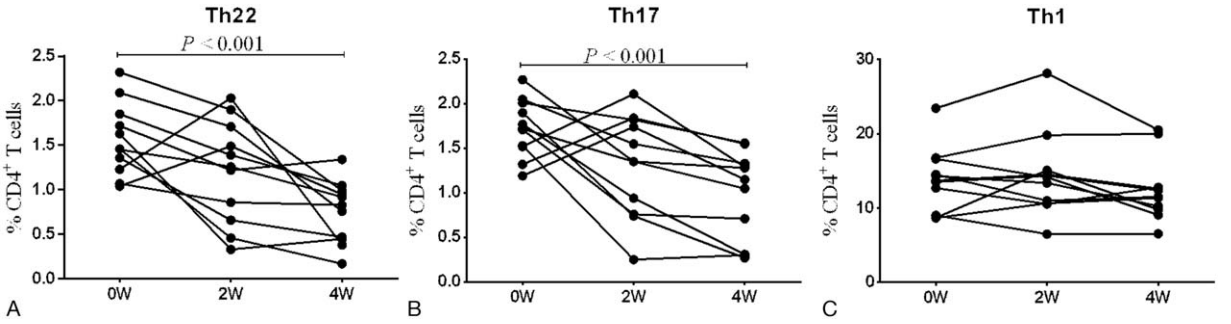

Figure 6. Temporal changes in T cells in patients with gout. (A) T-helper (Th)22 cells, (B) Th17 cells, and (C) Th1 cells.

pathway with Th17cells due to their common developmental requirement for IL-6.[15] So, the increase in peripheral Th22 cells in parallel with Th17 cells during a gout attack reflects their common induction conditions and developmental background.

Our follow-up study showed that Th22 and Th17 cells, which were maintained at higher numbers in patients with AG, decreased almost to the control level, corresponding to patients with IG, over the follow-up period (four weeks after onset), which may have been due to resolution of acute gouty inflammation. Furthermore, our data showed that if plasma CRP in an acute gouty patient is elevated then it is likely that the numbers of Th22 cells are also elevated. Statistical correlations of CRP with Th22 and IL-22 were found in this study, although the correlations are very weak and not reinforced by the ESR. These data provide further evidence that there is a closely association between the Th22 cells and acute gouty inflammation. However, the precise underlying mechanism and pathophysiologic function for the upregulation of Th22 cells in AG remains to be explored.

IL-22 is the most important functional cytokine of Th22 cells and is involved in the pathogenesis of many inflammatory diseases.[8] However, the pathophysiologic function of IL-22 is variable in different diseases.[16–19] In the present study, plasma IL-22 levels were elevated in acute gouty patients and were positively correlated with CRP levels, suggesting that IL-22 may be involved in acute gouty arthritis. IL-22 exerts its biological effects by binding to IL-22R1 and IL-10R2.[20] It has already been demonstrated that IL-22R1 mRNA is expressed in human synovial tissue in rheumatoid arthritis.[18] Marijnissen et al reported that IL-22 and IL-22R levels were elevated in inflamed synovial tissue in a mouse model of arthritis.[21] Thus, we speculate that Th22 cells and IL-22 may be overexpressed in synovial fluid and tissue in patients suffering from gout, and the upregulation of peripheral Th22 cells and IL-22 could be a spillover from local sites of inflammation. However, this needs to be confirmed by further studies.

In conclusion, our study shows that peripheral Th22 and Th17 cells are overexpressed in patients with acute gouty arthritis. The percentage of Th22 and Th17 cells decreased gradually during progression from AG to IG. These data suggest that T cell subsets are aberrantly produced in patients with acute gouty arthritis. However, this study has some limitations, for example, a cross-sectional design was used, the mechanisms and functions underlying the observed changes in Th22 cells were not investigated, and Th22 cells in synovial fluid and tophi were not studied. Further studies are therefore required to clarify the roles of Th22 cells and IL-22 in gout.

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