Occurrence of gout in rheumatoid arthritis: it does happen! A population-based study

Aim: It has been a popular belief that gout does not typically occur in patients with rheumatoid arthritis (RA). Our aim was to assess the occurrence, prevalence, clinical presentation and possible risk factors for gout in patients with RA. **Patients & methods:** We retrospectively reviewed a population-based incidence cohort of patients who fulfilled 1987 ACR criteria for RA between 1980 and 2007. The cumulative prevalence of gout in RA adjusted for the competing risk of death was estimated. **Results:** Among the 813 patients with RA, six were diagnosed with gout prior to RA incidence and 22 patients developed gout during a total of 9771 person-years of follow-up. Nine out of 22 patients had crystal-proven gout. The 25-year cumulative prevalence of gout diagnosed by clinical criteria in patients with RA was 5.3%. **Conclusion:** Gout does occur in patients with rheumatoid arthritis, however, at a lower rate than in the general population.

KEYWORDS: epidemiology gout occurrence prevalence rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory condition primarily involving the joints [1]. Gout is an arthropathy characterized by monosodium urate crystal deposition that occurs in association with hyperuricemia [2]. The coexistence of gout and RA is rarely reported. Only 33 cases with coexisting RA and gout have been reported in the English literature to date. It is a popular belief that RA and gout do not, or rarely, coexist with each other. Our aim was to assess the occurrence, prevalence, clinical presentation and risk factors for gout in RA in a populationbased cohort. We also compared the occurrence of gout in RA between 1980 and 1994 versus 1995 and 2007.

Patients & methods

Incident RA cases between 1 January 1980 and 31 December 2007 among residents of Olmsted County (MN, USA) were previously identified using the Rochester Epidemiology Project, which virtually links all medical records of Olmsted County residents [3]. RA was defined according to the 1987 ACR criteria as previously described [4,5]. All medical records of patients with RA were retrospectively reviewed and longitudinally followed until death, migration or April 2012. Patients with coexisting gout and RA were identified. Gout was defined using the physician diagnosis along with typical monosodium urate crystal positivity in synovial fluid or the 1977 American Rheumatism Association clinical criteria for gout. We excluded calcium

pyrophosphate-associated arthritis, hyperuricemia without gout, septic arthritis and traumatic arthritis. We also excluded RA patients who were misdiagnosed with gout initially. Descriptive statistics (e.g., means, percentages and so on) were used to summarize characteristics of the RA patients and the subset of patients with RA and gout. The cumulative prevalence and incidence of gout in RA were estimated using product-limit life table methods adjusted for the competing risk of death [6]. Cox models were used to assess risk factors for gout in RA. Patients with prevalent gout at the time of RA incidence were excluded from the analysis of risk factors, since they were not at risk of developing gout during follow-up.

The observed prevalence of gout in patients with RA on 1 January 2008 was calculated. This was compared with the expected prevalence rate obtained using data obtained from the National Health and Nutrition Examination Survey (NHANES) 2007–2008 [7]. A standardized prevalence ratio, which is the ratio of observed to expected prevalent cases, was calculated. In total, 95% CIs for the standardized prevalence ratio were calculated, assuming the expected rates are fixed and the observed events follow a Poisson distribution.

Results

The cohort included 813 patients with incident RA between 1 January 1980 and 31 December 2007. The characteristics of the 813 patients



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Table 1. Characteristics of 813 patients with rheumatoid arthritis included in the study.

Characteristics at rheumatoid arthritis incidence	Value
Age (years), mean (±SD)	55.9 (±15.7)
Female, n (%)	556 (68)
Length of follow-up (total person-years: 9771; years), mean (±SD)	12.0 (±7.2)
ESR at index (mm/h), mean (±SD)	24.8 (±20.5)
Highest ESR in first year (mm/h), mean (±SD)	32.7 (±25.7)
Rheumatoid factor positive, n (%)	537 (66)
Severe extra-articular features (anytime) [†] , n (%)	90 (11)
Current smoker, n (%)	178 (22)
Former smoker, n (%)	271 (33)
Medication use anytime during follow-up	
Corticosteroid use, n (%)	627 (77)
NSAID use, n (%)	737 (91)
Daily low-dose aspirin use, n (%)	349 (43)
[†] Defined according to Malmö criteria [15]. ESR: Erythrocyte sedimentation rate (Westergen); SD: Standard deviation.	

are listed in TABLE 1. All patients were 18 years or older; there were 556 women (68%) and 257 men (32%). The mean age at diagnosis of RA was 55.9 years. The average length of follow-up was 9.6 years with 9771 total person-years. Rheumatoid factor was positive in 537 (66%) patients. A total of 627 (77%) patients had received corticosteroids, 737 (91%) had taken an NSAID for the treatment of RA sometime during their disease course and 349 (43%) used low-dose aspirin daily.

Out of the 813 patients with RA, 22 patients had coexisting gout and RA. The characteristics of these 22 patients are listed in TABLE 2. Mean age at the time of gout diagnosis was 69.6 years. Mean BMI of these patients was 33.4 kg/m². Rheumatoid factor and/or anticitrullinated protein was present in 14 out of 22 patients (64%). The mean uric acid level at the onset of gout was 8.2 mg/dl (normal reference ranges: male 4.3-8.0; female 2.7-6.1 mg/dl; information available for 17 out of 22 patients). The mean creatinine level at the onset of gout was 1.4 mg/dl (normal reference ranges: male 0.8-1.3; female 0.8-1.1 mg/dl; information available for 18 out of 22 patients). Diuretic use at onset of gout included nine (41%) out of 22 patients on thiazides and seven (32%) patients on furosemide. Recurrent attacks of gout was present in nine (41%) out of 22 patients and one (4%) out of 22 patients had a documented clinical history of tophi. The metatarsal phalangeal joint was involved in 12 (55%) cases, and urate crystals were identified in synovial fluid in nine (41%) patients.

Out of the 22 patients with coexistent gout and RA, six had gout prior to RA incidence date. Including these six with prevalent gout, the 25-year cumulative prevalence of gout diagnosed by clinical criteria in this cohort of patients with RA was 5.3% (95% CI: 2.0–8.6%) (FIGURE 1). Excluding the six with prevalent gout, the 25-year cumulative incidence of gout was 2.4% (95% CI: 1.1–3.6%). Including only the nine patients with crystal-proven gout attacks following RA incidence, the minimum 25-year cumulative incidence of gout diagnosed by clinical criteria was 1.3% (95% CI: 0.3–2.3%).

On 1 January 2008, the prevalence of gout in RA patients in Olmsted County was 1.9% (11 out of 582 patients). This is compared with the expected prevalence rate of 5.2% or 30 patients based on data from NHANES for the general population [7]. The standardized prevalence ratio of observed to expected number of cases of gout (based on age- and sex-specific prevalence rates from NHANES) in RA was 0.36 (95% CI: 0.18–0.65), indicating gout in patients with RA was significantly less common compared with the general population.

Risk factor analyses were limited as the analysis could only be based on the 16 patients with RA who developed gout after the RA incidence. The risk factors for gout in RA were found to be older age (hazard ratio [HR]: 1.5 per 10-year increase; 95% CI: 1.03-2.18), male sex (HR: 3.18; 95% CI 1.12-8.99) and obesity (HR: 3.5; 95% CI: 1.12-10.91). The presence of erosions and/or destructive changes on radiographs was associated with a fourfold lower likelihood of developing gout (HR: 0.24; 95% CI: 0.07-0.88). Gout was more common among patients diagnosed with RA in recent years (1995-2007) than those diagnosed in earlier years (1980-1994; HR: 5.6; 95% CI: 1.60-19.57). Rheumatoid factor positivity (HR: 1.36; 95% CI: 0.49-3.78) and alcoholism (HR: 3.20; 95% CI: 0.86-11.91) were not significantly associated with the development of gout in RA in this cohort.

Discussion

The co-occurrence of gout and RA is rarely reported. In addition to the widespread belief that gout and RA do not, or rarely, coexist in the same patient, it can be difficult to clinically differentiate RA from polyarticular tophaceous gout especially when gout involves the hands. Only 33 cases with coexisting RA and gout have been reported in the English literature prior to this study. These include a report of eight cases of coexisting RA and gout between 1994 and 2005 at Chang Gung Memorial Hospital (Taiwan); this report also included the features of 24 previously reported similar cases in the English literature [8]. A further case with coexisting chronic gout and RA was reported in 2007 [9]. Of these 33 previously reported cases, 23 had gout preceding the diagnosis of RA, whereas in our study, only six out of 22 patients had a diagnosis of gout prior to incidence of RA [8,9]. All the previously reported cases of coexisting gout and RA had microscopic evidence of monosodium urate crystals in the synovial fluid or tophus. Rheumatoid factor was present in 24 out of the 33 previously reported cases compared with 14 out of 22 cases in our study. There was predominance of males, with 23 out of the 33 previously reported cases affecting men similar to our findings [8,9].

The prevalence of gout in patients with RA was significantly lower than the expected ageand sex-specific prevalence rate from the general population [7]. There are a number of reasons for this, including the possibility that estrogens and progesterone cause better renal clearance of uric acid in women with RA, decreasing the risk of gout in these patients [10]. Glucocorticoids and NSAIDs used in RA can also potentially mask the clinical manifestations of gout. Urate crystals can block activation of T and B cells, and they also have antioxidant and antiphagocytic properties, which may contribute to lower incidence of coexistent RA and gout [11]. In addition, IL-6 in RA may reduce the likelihood of overt gout owing to its uricosuric properties [12]. We also consider that potential cases of gout never clinically developed, as 77% of patients with RA were on glucocorticoid therapy and 91% on NSAIDs at some point during their follow-up. Several RA patients did not have polarized microscopy performed on the synovial fluid. For these reasons it is possible that some of the patients with RA who developed gout may have been missed in our study.

The development of gout occurred more frequently in patients with RA diagnosed in recent years (1995–2007) than among patients with RA diagnosed in earlier years (1980–1994). The reasons for the increased incidence in patients diagnosed with RA in the recent years is unclear; however, this may be owing to an increase in the incidence of risk factors for gout, such as obesity, hypertension and chronic kidney disease, and increased use of IL-6 inhibitor in the recent years. The use of high doses of aspirin that have uricosuric properties in patients with RA in the earlier Table 2. Characteristics of 22 patients with coexisting gout and rheumatoid arthritis.

Characteristics at gout diagnosis	Value
Age (years), mean (±SD)	69.6 (±10.4)
Female sex, n (%)	12 (54)
BMI (kg/m²), mean (±SD)	33.4 (±9.1)
Rheumatoid factor and/or ACPA positivity, n (%)	14 (64)
Uric acid (n = 17; mg/dl), mean (\pm SD)	8.2 (±2.3)
Creatinine (n = 18; mg/dl), mean (\pm SD)	1.4 (±0.5)
History of thiazide use, n (%)	9 (41)
History of furosemide use, n (%)	7 (32)
History of recurrent attacks of gout, n (%)	9 (41)
Involvement of metatarsal phalangeal joint, n (%)	12 (54)
Tophi, n (%)	1 (4)
Identification of urate crystals, n (%)	9 (41)
ACPA: Anticitrullinated protein antibody; SD: Standard deviation.	

decades may also explain the lower occurrence of gout in RA in 1980–1994 versus 1995–2007. In our study, age, male sex and obesity were identified as risk factors for gout in patients with RA, which are risk factors for gout identified in the general population [13]. Erosions and destructive changes in RA were associated with lower incidence of gout in RA in our study. The reasons for this are speculative; a possibility may be related to increased use of glucocorticoids and/or NSAIDs in these patients.

Limitations of this study include the retrospective nature, nonavailability of anticitrullinated protein testing in some patients and absence of microscopic analysis of synovial fluid in some



Figure 1. Cumulative prevalence of gout among 813 patients with rheumatoid arthritis. RA: Rheumatoid arthritis. patients in the study. A formal analysis of incidence rate and prevalence of gout in patients with RA compared with a control group of patients without RA was not carried out.

Conclusion

Contrary to popular belief, gout does occur in patients with RA although at a lower rate. This finding stresses the importance of synovial fluid analysis for crystals in suspicious cases of coexistent RA and gout. Dual-energy computed tomography is a newer modality that may help in making the diagnosis of gout when synovial fluid is not available for crystal analysis [14]. The risk factors for gout in RA generally mirror those in the general population.

Future perspective

If the risk factors for gout, such as obesity, hypertension and chronic kidney disease, continue to increase in incidence, the incidence of gout in RA may also increase in the future. With increased usage of ultrasound-guidance for small joint aspirations and advanced imaging techniques, such as dual-energy computed tomography, gout may be detected more often in patients with RA in future. As IL-6 may reduce the likelihood of overt gout, increased usage of anti-IL-6 agents in RA may also unveil gout, which may be clinically suppressed in these patients.

Disclaimer

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- The coexistence of gout and rheumatoid arthritis (RA) is only rarely reported.
- Our aim was to assess the occurrence, prevalence and risk factors for gout in RA in a population-based cohort.

Patients & methods

- We retrospectively reviewed a population-based incidence cohort of patients who fulfilled 1987 ACR criteria for RA between 1980 and 2007.
- Gout was defined using the physician diagnosis along with typical monosodium urate crystal positivity in synovial fluid or the 1977 American Rheumatism Association clinical criteria for gout.
- Cumulative prevalence of gout in RA adjusted for the competing risk of death was estimated. Cox models were used to assess risk factors for gout in RA.

Results

- The 25-year cumulative incidence of gout in RA was 2.4%.
- On 1 January 2008, the prevalence of gout in this population-based cohort of patients with RA was 1.9%.
- The risk factors for gout in RA were found to be older age, male sex and obesity.

Discussion

- The prevalence of gout in patients with RA was significantly lower than the expected age- and sex-specific prevalence rate from the general population.
- The development of gout occurred more frequently in patients with RA diagnosed in recent years (1995–2007) than among patients with RA diagnosed in earlier years (1980–1994).
- The reasons for the increased incidence in patients diagnosed with RA in recent years may be owing to an increase in the incidence of risk factors for gout, such as obesity, hypertension and chronic kidney disease, in recent decades.
- In our study, age, male sex and obesity were identified as risk factors for gout in patients with RA, which are risk factors for gout identified in the general population.
- Contrary to popular belief, gout does occur in patients with RA, although at a lower rate. This finding stresses the importance of synovial fluid analysis for crystals or dual-energy computed tomography imaging in suspicious cases of coexistent RA and gout.

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