Prevalence of Monoclonal Gammopathy Among Patients with Psoriatic Arthritis

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ABSTRACT. ***Objective.*** The occurrence of monoclonal gammopathy is common in chronic inflammatory disorders such as chronic infections and autoimmune disorders. There is limited information about the prevalence of monoclonal gammopathy in psoriatic arthritis (PsA). We investigated the prevalence, type, and associated features of monoclonal gammopathy in patients with PsA.

Methods. We performed a cross-sectional analysis of patients followed from 2008 to 2011 at the University of Toronto PsA clinic. The presence of monoclonal gammopathy was defined as the occurrence of a discrete band in the gammaglobulin region on at least 2 separate serum protein electrophoresis tests performed 6 months apart. Comparisons between patients with and those without monoclonal gammopathy were performed using t tests for continuous variables and chi-square tests for categorical variables.

Results. Of the 361 patients with PsA, 35 (9.7%) had evidence of monoclonal gammopathy in at least 2 separate blood tests. Seven (24%) of the 29 patients who were tested for Bence Jones protein were found to be positive. One patient was diagnosed as having multiple myeloma. Patients with monoclonal gammopathy were older ($p = 0.001$), had a longer duration of psoriasis ($p = 0.02$) and PsA ($p = 0.006$), were less likely to use disease-modifying antirheumatic drugs ($p = 0.05$), and had higher sedimentation rate ($p = 0.01$) and lower hemoglobin levels ($p = 0.02$). Patients with monoclonal gammopathy also trended toward having more active disease, with a higher active joint count ($p = 0.07$).

Conclusion. Monoclonal gammopathy occurs in patients with PsA more commonly than in the general population. Its prevalence is associated with measures of disease activity and duration. (First Release Jan 15 2012; J Rheumatol 2012;39:564–7; doi:10.3899/jrheum.111054)

Key Indexing Terms:
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Psoriasis is an immune-mediated skin disease affecting 2%–3% of the population[1]. Psoriatic arthritis (PsA) is an inflammatory arthritis that affects about one-third of people with psoriasis[2]. T cells, particularly those from the CD8+ lineage, play an important role in the pathogenesis of both diseases, while B cell hyperactivity and autoantibody production are not characteristic features of either psoriasis or PsA[3].

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder[4]. It is defined by the presence of a serum monoclonal protein, at a concentration < 3 g/dl, and bone marrow with < 10% monoclonal plasma cells, in the absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, renal insufficiency, hyperviscosity) related to the proliferative process[5]. The prevalence of MGUS among whites is estimated to be about 1.5% in those above the age of 50 years and increases to 3% by 70 years of age[6]. In a population-based study from Olmsted County, Minnesota, USA, the prevalence of MGUS was 3.2% among those who were ≥ 50 years of age. The prevalence increased to 5.3% in persons ≥ 70 years of age[7]. It can be categorized into 3 subtypes based on the type of monoclonal antibody, as follows: (1) Non-IgM MGUS (IgG, IgA, IgD MGUS) accounts for 80% of MGUS and can potentially progress to multiple myeloma (MM). Less frequently it may progress to AL amyloidosis, light-chain deposition disease, or another lymphoproliferative disorder. (2) IgM MGUS accounts for 17% of cases of MGUS. It can

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progress to Waldenstrom macroglobulinemia or rarely to IgM MM. (3) Light chain MGUS may progress through idiopathic Bence Jones proteinuria to light-chain MM, AL amyloidosis, or light-chain deposition disease.

The occurrence of monoclonal immunoglobulins is frequent in chronic inflammatory disorders such as chronic infections and autoimmune disorders[8]. There is limited information in the literature about the prevalence of MGUS in PsA. Two case reports described the development of MM in patients with PsA[9,10], and a recent case series described the occurrence of 8 cases of MGUS following treatment with anti-tumor necrosis factor-α (TNF-α) agents among patients with psoriatic disease[11]. We aimed to investigate the prevalence, type, and associated features of monoclonal gammopathy in patients with PsA.

MATERIALS AND METHODS

The study population was recruited from a cohort of patients followed prospectively from 2008 to 2011 at the University of Toronto PsA clinic. All patients fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR)[12]. Patients were evaluated according to a standard protocol every 6–12 months[2]. At each visit, symptoms, examination results (including complete musculoskeletal examination and assessment of psoriasis severity), current use of medications, and laboratory findings including biannual serum protein electrophoresis were recorded in a database. All subjects' written consent was obtained according to the Declaration of Helsinki. The study was approved by the University Health Network Ethics Board.

Monoclonal gammopathy was defined as the occurrence of a discrete band in the gammaglobulin region on at least 2 separate serum protein electrophoresis tests performed 6 months apart. In those patients, further studies were performed including serum and urine immunoelectrophoresis, immune quantitation, and Bence Jones proteins in the urine. Bone marrow aspirates and biopsies and radiographic skeletal surveys for lytic lesions were infrequently obtained. In addition, complete blood count, erythrocyte sedimentation rate (ESR), and kidney functions were assessed at each visit.

We performed a cross-sectional comparison of patients with and those without serum monoclonal globulins. Demographic, laboratory, and clinical characteristics obtained at the last clinic visit were compared between the 2 groups. Additional information included active joint count, swollen joint count, the presence of enthesitis or dactylitic digits, clinically damaged joint count, the Psoriasis Area and Severity Index score, concomitant use of disease-modifying antirheumatic drugs (DMARD), biologic medications, hemoglobin levels, rheumatoid factor, creatinine, C-reactive protein, and ESR. An actively inflamed joint was defined as one having stress pain and/or effusion. Sixty-eight joints were assessed for tenderness and 66 for swelling. A clinically damaged joint (68 assessed joints) was defined as the presence of limitation of range of movement of > 20% of the range not related to the presence of joint effusion, presence of joint deformity, subluxation, loosening, or ankylosis.

Statistical analysis. Continuous data were described as mean ± SD and categorical variables as percentages. Comparisons between patients with and those without monoclonal gammopathy were performed using t tests for continuous variables and chi-square tests for categorical variables. A stepwise logistic regression was used to identify covariates occurring more or less frequently in patients with monoclonal gammopathy compared to those without monoclonal gammopathy. The covariates that were considered statistically significant were retained in the multivariate regression if the p value from the 2-sided Wald test was < 0.05. Statistical analysis was performed using the SAS statistical software (version 9.2).

RESULTS

Of the 404 patients with PsA assessed in the PsA clinic between 2008 and 2011, 43 patients were excluded for the following reasons: 23 had polyclonal gammaglobulinemia, 2 low gammaglobulin levels, 9 had no blood test results, and 9 had only 1 test confirming monoclonal gammopathy. Of 361 patients included in the study, 35 (9.7%) had evidence of monoclonal gammopathy in at least 2 separate blood tests. Twenty-nine patients had the following monoclonal band types: 21 (72%) had IgG, 6 (20.7%) had IgM, and 2 (7.3%) had IgA. Most of the patients (23 out of 35) had very low levels of monoclonal immunoglobulins that could not be quantified. In the remaining 12 patients the median level of monoclonal immunoglobulins was 7 g/dl (range 2 to 12 g/dl). Seven (24%) of the 29 patients who were tested for Bence Jones protein were found to be positive, 4 with kappa band and 3 lambda band. Two patients had a skeletal survey, and both were negative. Of the 5 patients who had a bone marrow biopsy, one was diagnosed as having MM. Two of the 35 patients with monoclonal gammopathy died during the study period: one from MM; the other patient was diagnosed with a metastatic cancer with unknown primary and died from pneumonia.

Univariate analysis showed that patients with monoclonal gammopathy were older (p = 0.001), had a longer duration of psoriasis (p = 0.02) and PsA (p = 0.006), were less likely to use DMARD (p = 0.05), and had higher ESR levels (p = 0.01) and lower hemoglobin levels (p = 0.02). Patients with monoclonal gammopathy also showed a trend toward having more active disease, with higher active joint count (p = 0.07; Table 1). A multivariate logistic regression analysis showed that increase in age (OR 1.04, 95% CI 1.01–1.07, p = 0.01) and ESR (OR 1.02, 95% CI 1.0–1.04, p = 0.001) remained significantly associated with the presence of monoclonal gammopathy (Table 2). These results mean that for every 1-year increase in age the odds of monoclonal gammopathy increase by 4%, and for every 1-mm/h increase in ESR the odds of monoclonal gammopathy increase by 2%.

DISCUSSION

We assessed the prevalence of monoclonal gammopathy among patients with PsA and its association with clinical and laboratory factors. The prevalence of monoclonal gammopathy in our cohort was 9.7%, which is high compared to the reported prevalence in whites (1.5% to 3% depending on age)[6,7]. Monoclonal gammopathy is considered a premalignant condition that precedes the onset of MM; however, only 1 case of MM was detected in the group that had serum monoclonal antibodies. Although the prevalence of cancer was higher in the monoclonal gammaglobulin group it was not statistically significant, possibly due to the small sample size. The prevalence of lymphoid cancer, particularly T cell non-Hodgkin's lymphoma, was found to be increased in

Table 1. Comparison between psoriatic arthritis patients with and those without monoclonal gammopathy.

Characteristic	Monoclonal Gammopathy, n = 35	Controls, n = 326	p
Age, yrs (± SD)	61.3 (10.8)	53.4 (13.2)	0.001
Sex, male, n (%)	21 (60.0)	223 (61.8)	0.84
White, n (%)	29 (82.9)	313 (86.9)	0.51
Duration of psoriasis, yrs (± SD)	31.5 (16.9)	25.7 (13.8)	0.02
Duration of PsA, yrs (± SD)	22.0 (12.6)	16.4 (11.1)	0.006
Swollen joint count (± SD)	0.29 (0.71)	0.32 (0.93)	0.82
Active joint count (± SD)	6.7 (9.6)	3.4 (6.3)	0.07
Clinically damaged joint count (± SD)	16.0 (14.2)	13.1 (13.8)	0.32
Dactylitis, n (%)	3 (9.7)	17 (5.0)	0.27
Enthesitis, n (%)	3 (9.4)	43 (12.4)	0.62
DMARD use, n (%)	10 (28.6)	192 (54.2)	0.05
Biologics use, n (%)	14 (40.0)	141 (40.2)	0.98
CRP, mg/dl (± SD)	8.0 (6.3)	6.6 (7.5)	0.51
Creatinine, μmol/l (± SD)	88.1 (38.5)	79.7 (24.3)	0.22
Leukocyte level, $\times 10^9$/l (± SD)	7.0 (6.4)	7.2 (7.0)	0.72
ESR, mm/h (± SD)	21.1 (19.7)	11.7 (15.0)	0.01
Hemoglobin, g/l (± SD)	131.6 (21.0)	140.3 (15.4)	0.02
Gammaglobulin, mg/dl (± SD)	10.2 (3.2)	9.9 (5.6)	0.68
Rheumatoid factor-negative (%)	17 (94.4)	185 (96.9)	0.65
Functional comorbidity index (± SD)	1.8 (1.3)	1.4 (1.5)	0.19
Cancer ever, n (%)	7 (20)	44 (12.2)	0.19
Body mass index, kg/m^2 (± SD)	31.1 (8.9)	29.5 (6.3)	0.30

PsA: psoriatic arthritis: DMARD: disease-modifying antirheumatic drugs; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 2. The association between demographic and disease-related variables and monoclonal gammopathy compared to without monoclonal gammopathy in patients with PsA; multivariate logistic regression analysis (n = 361).

Covariate	Univariate Model OR	(95% CI)	p	Reduced Model OR	(95% CI)	p
Age, yrs	1.05	(1.02, 1.08)	0.001	1.04	(1.01, 1.07)	0.01
Duration of psoriasis, yrs	1.03	(1.00, 1.05)	0.02	—	—	—
Duration of PsA, yrs	1.04	(1.01, 1.07)	0.008	—	—	—
DMARD use, yes/no	2.11	(0.98, 4.52)	0.06	—	—	—
ESR, mm/h	1.03	(1.01, 1.04)	0.002	1.02	(1.00, 1.04)	0.001
Hemoglobin, g/l	0.97	(0.95, 0.99)	0.003	—	—	—

Definitions as in Table 1.

patients with psoriasis compared to the general population in a large population-based study[13]. While MM has not been associated with psoriasis and other autoimmune conditions, one population-based study has found an association between MM and ankylosing spondylitis, which shares similar clinical and genetic characteristics with PsA[13,14]. It has been suggested that the chronic inflammation that characterizes autoimmune conditions as well as impairment of T cell control may lead to the development of lymphoid cancers. The high prevalence of monoclonal gammopathy in our study population may reflect the presence of chronic immune dysregulation that characterizes both psoriasis and PsA. However, since MM is infrequent in patients with PsA, the identification of this abnormality does not necessarily reflect a higher risk of developing MM.

Monoclonal gammopathy was associated with measures of disease activity including longer disease duration and higher sedimentation rate. These results are in accord with similar findings by Ali, *et al*, who reported higher ESR levels in lupus patients with monoclonal gammopathy compared to patients without this abnormality[15]. However, it is unclear whether the elevated ESR levels result from the increased monoclonal antibody production or whether the increased disease activity with chronic stimulation of lymphocytes leads to clonal transformation of lymphocytes and the production of monoclonal antibodies. A recent publica-

tion by Prignano, *et al*[11] reported the development of monoclonal gammopathy among 8 out of 300 patients with psoriasis or PsA who were treated with anti-TNF-α agents. After cessation of the treatment there was a progressive decline in monoclonal gammaglobulin levels. In our study, proportions of patients treated with anti-TNF-α agents were similar among those with and those without monoclonal gammopathy; however, the cross-sectional design of the study precludes a firm conclusion about any temporal association between anti-TNF-α treatment and development of MGUS. Treatment with anti-TNF-α agents may also be a marker of more active disease that, as in our study, was associated with MGUS.

Monoclonal immunoglobulins of heterogenous type occur in patients with PsA more commonly than in the general population. However, the occurrence of MM was low. The presence of MGUS was associated with measures of disease activity and disease duration, which may reflect dysregulation of the immune system that is common to both psoriasis and PsA.

REFERENCES

1. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005;64 Suppl 2:ii18-23; discussion ii4-5.
2. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA) — An analysis of 220 patients. Q J Med 1987;62:127-41.
3. Gaspari AA. Innate and adaptive immunity and the pathophysiology of psoriasis. J Am Acad Dermatol 2006;54 Suppl 2:S67-80.
4. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: A prospective study. Blood 2009;113:5412-7.
5. Hillengass J, Moehler T, Hundemer M. Monoclonal gammopathy and smoldering multiple myeloma: Diagnosis, staging, prognosis, management. Recent Results Cancer Res 2011;183:113-31.
6. Crawford J, Eye MK, Cohen HJ. Evaluation of monoclonal gammopathies in the "well" elderly. Am J Med 1987;82:39-45.
7. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006;354:1362-9.
8. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood 2008;111:3388-94.
9. Peltonen L, Nikoskelainen E, Katka K, Tyrkko J. Monoclonal IgG immunoglobulinemia with subsequent myeloma in psoriatic arthritis. Dermatologica 1984;169:207-10.
10. Scherf I, Nahir M, Brick R, Joffe G, Tatarsky J. Monoclonal IgG immunoglobulinemia in psoriatic arthritis. Dermatologica 1980;160:348-50.
11. Prignano F, Pescitelli L, Ricceri F, Ermini A, Lotti T. Development of MGUS in psoriatic patients: A possible undiagnosed event during anti-TNF-α-treatment. J Eur Acad Dermatol Venereol 2011 Aug 11. [E-pub ahead of print]
12. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
13. Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int J Cancer 2009;125:398-405.
14. Landgren O, Linet MS, McMaster ML, Gridley G, Hemminki K, Goldin LR. Familial characteristics of autoimmune and hematologic disorders in 8,406 multiple myeloma patients: A population-based case-control study. Int J Cancer 2006;118:3095-8.
15. Ali YM, Urowitz MB, Ibanez D, Gladman DD. Monoclonal gammopathy in systemic lupus erythematosus. Lupus 2007; 16:426-9.