Mod Rheumatol (2001) 11:230–233

ORIGINAL ARTICLE

Ryuji Nagamine · Takeshi Maeda · Toshihide Shuto
Yasuharu Nakashima · Go Hirata · Yukihide Iwamoto

Menopausal syndrome in female patients with rheumatoid arthritis

Received: November 2, 2000 / Accepted: February 14, 2001

Abstract This study was performed to assess the relationship between joint symptoms in rheumatoid arthritis (RA) and symptoms in menopausal syndrome. Detailed analyses of the clinical course, laboratory data, joint symptoms, and symptoms of menopausal syndrome were performed for five patients with stage I and monocyclic-type RA. The age when joint symptoms first appeared coincided with the age of menopause in all patients, and the mean age was 51.0 years. The mean period from menopause to this study was 5.4 years. All patients showed more than six menopausal syndrome symptoms. Two patients were confirmed gynecologically to have definite menopausal syndrome, and accordingly hormone replacement therapy (HRT) was given. In one patient, the polyarthralgia disappeared after she received HRT. All the American College of Rheumatology (ACR) criteria, with the exception of subcutaneous nodules, can be explained as symptoms related to estrogen deficiency in menopausal syndrome because estrogen regulates the production of inflammatory cytokines such as IL-1, IL-6, and TNFα, and these cytokines are produced in greater abundance in conditions of estrogen deficiency. Estrogen deficiency at the menopause influences joint symptoms and inflammatory parameters in rheumatoid arthritis. Estrogen deficiency in menopausal syndrome may induce joint symptoms resembling RA.

Key words Diagnostic criteria · Estrogen · Interleukin · Menopausal syndrome · Rheumatoid arthritis

R. Nagamine (✉)
Department of Orthopaedic Surgery, Kyushu Rosai Hospital, 1-3-1 Kuzuharatakamatsu, Kokuraminami-ku, Kitakyushu 800-0296, Japan
Tel. +81-93-471-1121; Fax +81-93-473-0627

T. Maeda · T. Shuto · Y. Nakashima · G. Hirata · Y. Iwamoto
Department of Orthopaedic Surgery, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

Introduction

In some patients who had been diagnosed as suffering from rheumatoid arthritis (RA), no destructive changes had appeared in any of their joints, and no active arthritis could be identified in any joints several years after the diagnosis. These patients in stage I by the classification of Steinbrocker et al.,[1] are also classified as having monocyclic-type RA.[2] In these patients, either the RA is inactive, or there is a possibility that they did not have RA. In some of these patients, the symptoms of RA had occurred during the menopause, and their symptoms were found to resemble menopausal symptoms. Gynecologically, polyarthralgia is well known as one of the symptoms of the menopausal syndrome.[3,4] Nobunaga[5] has recently proposed a new concept for menopausal rheumatism which accepts RA-like symptoms as part of the menopausal syndrome. We hypothesized that either the menopause influences these joint symptoms, or it induces joint symptoms which are similar to those of RA. This study was performed to assess the relationship between joint symptoms and menopausal syndrome in patients with stage I and monocyclic-type RA.

Materials and methods

We reviewed the cases of 156 female patients who had been diagnosed as having RA, based on the 1987 revised American College of Rheumatology (ACR) criteria, more than 2 years before this study started.[6] The age at diagnosis of RA ranged from 40 years to 60 years. The mean age at the time of this study was 59.0 years, and the mean age at RA onset was 49.7 years. The mean period from RA onset to this study was 8.9 years. The RA stage, as defined by Steinbrocker et al.,[1] was I in 11 patients, II in 17 patients, III in 53 patients, and IV in 75 patients. In 6 out of 11 patients with stage I, joint symptoms had first appeared during the menopause. One patient had collagen disease, and this case

was excluded from the study. Therefore, five patients were finally assessed in this study. Detailed analyses of the clinical course, laboratory data, joint symptoms, and symptoms of menopausal syndrome were performed for each patient.

In order to assess the symptoms of menopausal syndrome, the Kupperman index was utilized.[3] This index considers 11 factors (vasomotor complaints such as hot flashes, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, myalgia/arthralgia, headache, palpitations, and formication). These factors are related to estrogen deficiency. Arthralgia is one factor in menopausal syndrome. For each factor, the severity was classified as none, slight, moderate, or marked. All five patients were asked to recall whether they had suffered from these symptoms at the time when their joint symptoms had first appeared, and they were also asked to record the severity of each index. The beginning of the menopause was defined as the time when menses became irregular, while the end of the menopause was defined as 1 year after the final menses.

Results

Detailed data of the patients are given in Table 1. Some of the data for case 5 were not available because the patient first came to our hospital 3 years after the joint symptoms had appeared. The age when joint symptoms first appeared coincided with the age of menopause in all patients, and the mean age was 51.0 years (SD 2.1 years; range 48–54 years). The mean period from menopause to this study was 5.4 years (SD 3.0 years; range 3–10 years). At the time of diagnosis of RA, all patients had joint symptoms and morning stiffness. Rheumatoid factor was positive in all patients. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated in all patients. However, at the time of this study, these patients could no longer be diagnosed as having RA based on the 1987 ACR criteria because they did not have enough joint symptoms. CRP was in the normal range in four patients, and ESR was in the normal range in three patients. At the time of this study, no erosive change was identified in any joints on radiographs. Periarticular bone atrophy was observed on radiographs of the hands in all five patients (Fig. 1).

All patients demonstrated more than six factors of the menopausal syndrome (Table 2). Two patients (cases 2 and 4) were determined gynecologically to have definite menopausal syndrome, and accordingly hormone replacement therapy (HRT) was given. In case 2, the values of estrogen and follicle-stimulating hormone (FSH) during the menopause were 18.6 pg/ml (normal range >20 pg/ml) and 65.7 mIU/ml (normal range <35 mIU/ml), respectively. In case 4, the values of estrogen and FSH at the time of this study were 12.0 pg/ml and 167.7 mIU/ml, respectively. These data verified a deficiency of estrogen. Figures 2 and 3 show the clinical course of case 2. In our hospital, 0.625 mg/day conjugated estrogen and 2.5 mg/day medroxyprogesterone acetate are administrated orally for HRT. Although ESR and CRP were dramatically decreased after the administration of 2.5 mg/day prednisolone and nonsteroidal anti-inflammatory drugs, the patient continued to complain of polyarthralgia after 10 months of Auranofin administration. However, the polyarthralgia disappeared after she received HRT. Grip strength was also improved after she received HRT.

Discussion

All the ACR criteria, with the exception of subcutaneous nodules, can be explained as symptoms related to estrogen deficiency in menopausal syndrome. Estrogen regulates the production of inflammatory cytokines such as IL-1, IL-6, and TNFα, and it has been proved that these inflammatory cytokines are produced in greater abundance in conditions of estrogen deficiency.[7] Horai et al.[8] reported chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin-1 receptor antagonist (IL-1ra)-deficient mice. Estrogen deficiency may induce some degree of arthritis. Estrogen deficiency also induces postmenopausal osteoporosis because IL-1 and TNFα are among the most

Table 1. The results of each case

	Age	CRP	ESR	RAHA	Swollen joint	Tender joint	Morning stiffness (m)
At menopause							
Case 1	51	1.0	27	40	8	1	300
Case 2	48	0.5	30	2560	3	4	300
Case 3	54	1.5	9	40	3	4	10
Case 4	51	4.3	79	320	6	4	60
Case 5	51	–	88	–	–	–	10
In the study							
Case 1	58	0.2	28	<40	0	1	0
Case 2	51	0.2	16	640	0	0	0
Case 3	58	0.1	6	<40	0	0	0
Case 4	54	0.9	12	40	0	0	0
Case 5	61	0.0	42	<40	0	0	0

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RAHA, rheumatoid arthritis hemagglutimation

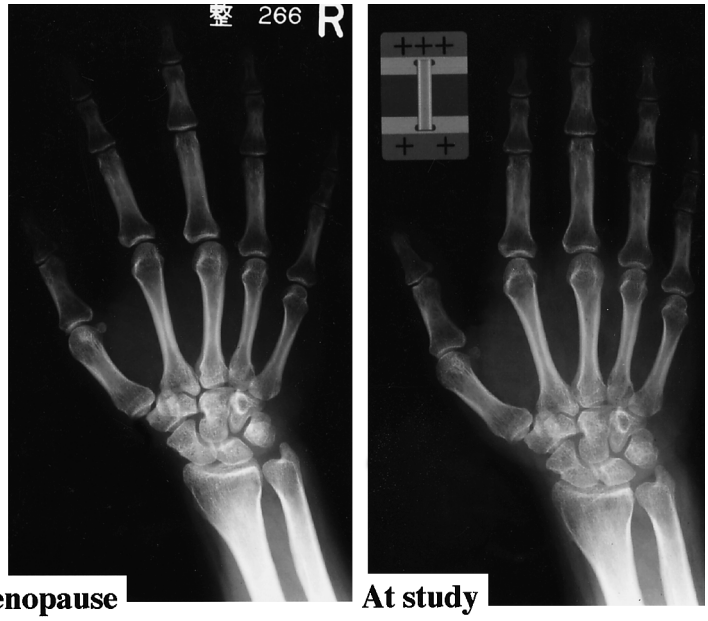

Fig. 1. Anteroposterior radiograph of the right hand in case 2. Only periarticular osteoporotic change was recognized on the radiograph of the hand (*left*) at the time of diagnosis of RA. No destructive change was identified on the radiograph of the hand (*right*) 3 years after that diagnosis

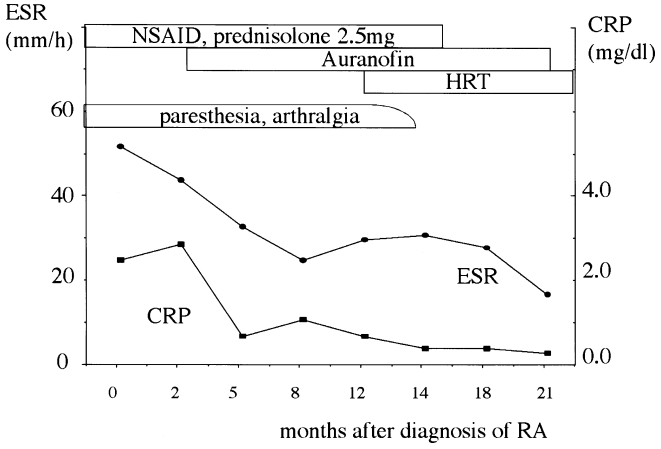

Fig. 2. Clinical course of case 2. Erythrocyte sedimentation rate (*ESR*) and C-reactive protein (*CRP*) were dramatically decreased after administration of 2.5 mg/day prednisolone and nonsteroidal anti-inflammatory drugs. However, the patient continued to complain of polyarthralgia after 10 months administration of Auranofin. Paresthesia and polyarthralgia disappeared after receiving HRT

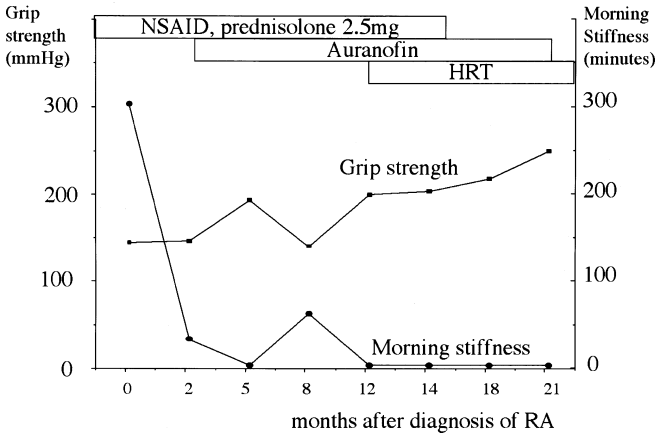

Fig. 3. Clinical course of case 2. The patient did not complain of morning stiffness after administration of prednisolone and nonsteroidal anti-inflammatory drugs (*NSAID*). Grip strength was gradually improved after receiving HRT

Table 2. Factors in menopausal syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5
Vasomotor	3	0	1	3	1
Paresthesia	2	2	1	1	0
Insomnia	3	2	0	1	0
Nervousness	3	1	2	1	2
Melancholia	3	1	2	1	0
Vertigo	1	0	2	0	1
Fatigue	2	2	2	2	1
Myalgia/ arthralgia	3	2	2	2	2
Headache	2	1	2	1	1
Palpitations	1	1	0	1	0
Formication	2	0	1	0	0

0, none; 1, slight; 2, moderate; 3, marked

powerful stimulants of bone resorption.[7,9–12] This mechanism of postmenopausal osteoporosis is the same as the periarticular bone atrophy that is seen in the early stage of RA. Inflammatory cytokines such as IL-6 also elevate CRP.[13] Since estrogen regulates the metabolism of water, and since estrogen receptors also exist in skin and connective tissue, estrogen deficiency can induce exsiccation of organs, which could lead to stiffness of joints.[4] Furthermore, IL-6 induces the differentiation of B cells and production of antibody such as rheumatoid factor.[13] Rheumatoid factor has been reported to be detected in IL-1ra-deficient mice.[8] Therefore, elevated IL-1 and IL-6 can produce rheumatoid factor. Furthermore, nervousness, melancholia, and fatigue in menopausal syndrome are also observed in patients with chronic inflammatory diseases such as RA. Based on these findings, it appears that estrogen deficiency can influence

the joint symptoms in female patients with RA. While estrogen deficiency may induce joint symptoms similar to RA in female patients with menopausal syndrome. A connection between the onset of RA and the menopause has been reported.[14,15] To our knowledge, however, there are few studies that focus on RA-like symptoms in menopausal women.

One sign, which was recognized in all five cases in this study, was joint swelling without recognizable synovitis. Although synovitis and pannus were microscopically proved in joints in IL-1ra knockout mice, no massive synovitis was reported.[8] Synovitis has not been reported in the symptoms of the patients with menopausal syndrome.[3,4] On the other hand, synovitis is the most characteristic phenomenon in early RA.[16,17] Massive synovitis may be used to differentiate RA from joint symptoms in menopausal syndrome. We asked cases 2 and 4 to allow MRI of their hands. In case 2, MRI could not be used owing to a clip in her brain. In case 4, no synovitis was detected on MRI.

In this study, five out of 156 RA patients (3.2%) were considered to have menopausal syndrome which had influenced or induced joint symptoms. Therefore, such patients are not very rare. To date, the menopause has not been taken into account when RA activity was being assessed. In fact, we do not consider the menopause when we made a diagnosis of RA. Nowadays, early diagnosis and early treatment of RA are recommended.[18,19] Although we do not disagree with the criteria for early RA, it is important to note whether there is a connection between the time of onset of RA and the menopause. Menopausal syndrome should be included as one of the differential diagnoses of early RA. Further investigations are necessary in order to assess the detailed relationship between RA and menopausal syndrome.

Abrahamsen et al.[9] reported that a lower compensatory increase in IL-1ra mRNA was demonstrated in women with rapid bone loss after the menopause. Lower monocyte IL-1ra secretion may contribute to the degree of arthritis in menopausal women.

References

1. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
2. Nakata S. History, epidemiology and prognosis of rheumatoid arthritis (in Japanese). In: Yamamoto S editor. Management of rheumatoid arthritis. Medical Review; 1997. p. 14–6.
3. Kupperman HS, Blatt MHG, Wiesbader H, Filler W. Comparative clinical evaluation of estrogenic preparation by the menopausal and amenorrheal indices. Endocrinology 1953;13:688–703.
4. Nozaki M. Hormone replacement therapy for menopausal women (in Japanese). Fukuoka Igaku Zasshi 2000;91:74–9.
5. Nagamine R, Maeda T, Shuto T, Nakashima Y, Hirata G, Iwamoto Y. Concept of menopausal rheumatism and its clinical relevance (in Japanese). Kyushu J Rheumatol 2001; in press.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
7. Pacifici R. Estrogen, cytokines, and pathogenesis of postmenopausal osteoporosis. J Bone Miner Res 1996;11:1043–51.
8. Horai R, Saijo S, Tanioka H, Nakae S, Sudo K, Okahara A, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin-1 receptor antagonist-deficient mice. J Exp Med 2000;191:313–20.
9. Abrahamsen B, Shalhoub V, Larson EK, Eriksen EF, Beck-Nielsen H, Marks SC Jr. Cytokine RNA levels in transiliac bone biopsies from healthy early postmenopausal women. Bone 2000;26:137–45.
10. Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumor necrosis factor. Nature 1986;319:516–8.
11. Rozen N, Ish-shalom S, Rachniel A, Stein H, Lewinson D. Interleukin-6 modulates trabecular and endochondral bone turnover in the nude mouse by stimulating osteoclast differentiation. Bone 2000;26:469–74.
12. Nishibe A, Morimoto S, Hirota K, Yasuda O, Ikegami H, Yamamoto T, et al. Effect of estriol and bone mineral density of lumbar vertebrae in elderly and postmenopausal women (in Japanese). Jpn J Geriatr 1996;33:353–9.
13. Ogata A, Nishimoto N, Yashizaki K. Advances in interleukin-6 therapy (in Japanese). Rinsho Byori 1999;47:321–6.
14. Lahita RG. Sex steroids and the rheumatic diseases. Arthritis Rheum 1985;28:121–6.
15. Goemaere S, Ackerman C, Goethals K, De Keyser F, Van der Straeten C, Verbruggen G, et al. Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition. J Rheumatol 1990;17:1620–2.
16. Sugimoto H, Takeda A, Hyodoh K. Early-stage rheumatoid arthritis: prospective study of the effectiveness of MR imaging for diagnosis. Radiology 2000;216:569–75.
17. Ostergaard M, Stoltenberg M, Gideon P, Sorensen K, Henriksen O, Lorenzen IB. Changes in synovial membrane and joint effusion volumes after intraarticular methylprednisolone. Quantitative assessment of inflammatory and destructive changes in arthritis by MRI. J Rheumatol 1996;23:1151–61.
18. Yamamoto S, Kashiwazaki S, Nobunaga M. Study on Japan Rheumatism Association diagnostic criteria for early rheumatoid arthritis. 2. Application of the American Rheumatism Association diagnostic criteria to Japanese patients with early rheumatoid arthritis (in Japanese). Ryumachi 1994;34:1013–8.
19. Yamamoto N, Hagino H, Teshima R. Study on sensitivity and specificity of diagnostic criteria for early rheumatoid arthritis. Mod Rheumatol 2000;10:137–40.