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Two Case Reports of Abrupt Cessation of Hormone Replacement Therapy associated with onset of Autoimmune Rheumatic Disease

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ABSTRACT

Systemic rheumatic autoimmune disease occurs predominantly in middle-aged women. Hormone replacement therapy (HRT) is used to treat menopausal symptoms worldwide. Abrupt cessation of HRT can induce recurrence of postmenopausal symptoms. In this report, two female patients developed Sjogren's syndrome and rheumatoid arthritis, respectively, following cessation of HRT. Estrogen fluctuation or deficiency is critical for inducing overt rheumatoid arthritis or systemic autoimmune rheumatic disease. However more research is needed.

Keywords: Sjogren's syndrome, Estrogen deficiency, Hormone replacement therapy (HRT), Anti-cyclic citrullinated peptide (CCP), Anti-SS-A

INTRODUCTION

Acute cessation of hormone replacement therapy (HRT) exacerbates menopausal symptoms, including palpitations, anxiety, insomnia, depression, and joint pain. The Women's Health Initiative 2002 report lists adverse effects of HRT, such as increased risk of breast cancer, uterine corpus carcinoma, and atherosclerotic disease [1]. Consequently, many women have ceased HRT or tapered the dose [2,3]. Acute termination of HRT increases the risk of developing overt rheumatoid arthritis (RA) [4] or autoimmune rheumatic diseases in those with positive rheumatoid factor (RF) antibodies, anti-cyclic citrullinated peptide (CCP) antibodies, or antinuclear antibodies (ANA). In this study, we report a case of Sjogren's syndrome (SS) and a case of RA onset following cessation of HRT for 1-3 months. We hypothesize that both conditions may be triggered by estrogen deficiency [5].

In both cases described below, HRT was prescribed for menopause or transition to menopause. HRT consisted of a 2-day 17β-estradiol (E2) patch (0.72 mg) for 26 days with dydrogesterone (10 mg) orally for 10 days, followed by 4-5 days off. This cycle repeated every 30-31 days. As five or more days off resulted in recurrence of menopausal symptoms in the second case, the drug holiday was omitted.

CASE REPORT 1: ID H15882, 1970

A 42-year-old female first noticed Raynaud's phenomenon, followed by irregular menstruation in the subsequent year **(Figure 1)**. In June 2013, she presented complaining of hot flashes, palpitations, shortness of breath, and impaired cognition. Her simplified menopausal index [6] was 60/100, and her estradiol (E2) and follicle-stimulating hormone (FSH) levels were 15.5 pg/ml and 80.2 mIU/ml,

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respectively. Her symptoms and test results were compatible with menopausal status [7], and she was placed on cyclic HRT at age 43. By September 2013, most of her menopausal symptoms had subsided (simplified menopausal index of 20 with E2 and progesterone levels of 143.2 pg/ml and 5.0 mIU/ml, respectively). In January 2014, at age 44, her E2 levels increased. HRT was terminated in December 2014. She had a low white blood cell count (3000/µl), positive ANA at a 1:640 dilution with speckled pattern, and positive anti-SS-A at a 1:16 dilution determined by micro-Ouchterlony. Three months later in March 2015, she visited the clinic with complaints of recurring severe sweating, palpitations, and insomnia, along with newly noticed dry mouth and dry eye symptoms. Human leukocyte antigen (HLA)-DRB1*04:05 and *15:02 alleles were determined the dry eye and mouth symptoms prompted assessment for Sjogren's syndrome. All tests, including a sialography grade 2 (Rubin & Holt; **Figure 2a**), minor salivary biopsy grade 3 **(Figure 2b)**, and indocyanine green-fluorescent test were positive. After three months of cyclic HRT, all menopausal symptoms ceased except the dry eyes and mouth. In 2018, erythema marginatum appeared on her palms but resolved spontaneously **(Figure 3)**.

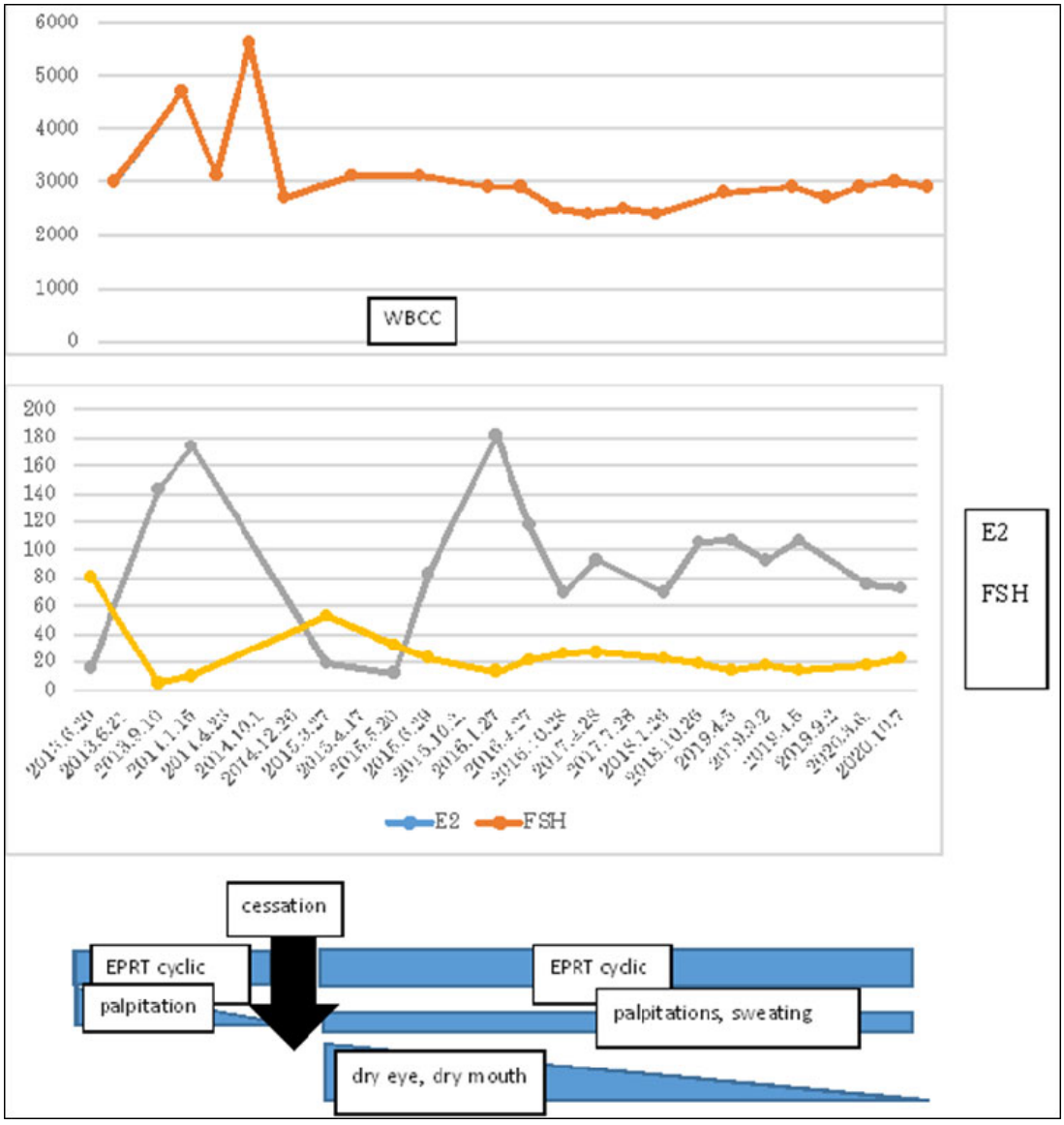

Figure 1. Case 1 clinical and laboratory course. White blood cell count remained consistently low after first visit in June 2013. Cyclic estrogen progesterone replacement therapy (EPRT) was terminated in December 2014 due to disappearance of menopausal symptoms. In March 2015, patient developed severe dry mouth and eyes in addition to palpitations. She recovered after administering HRT (E2, 11.8 pg/ml) and was weaned off medication on the last day.

RF<15 U/ml is normal; anti-CCP Ab < 4.5 U/ml is normal. E2 < 20 pg/ml and FSH >40 mIU/ml indicate menopause.

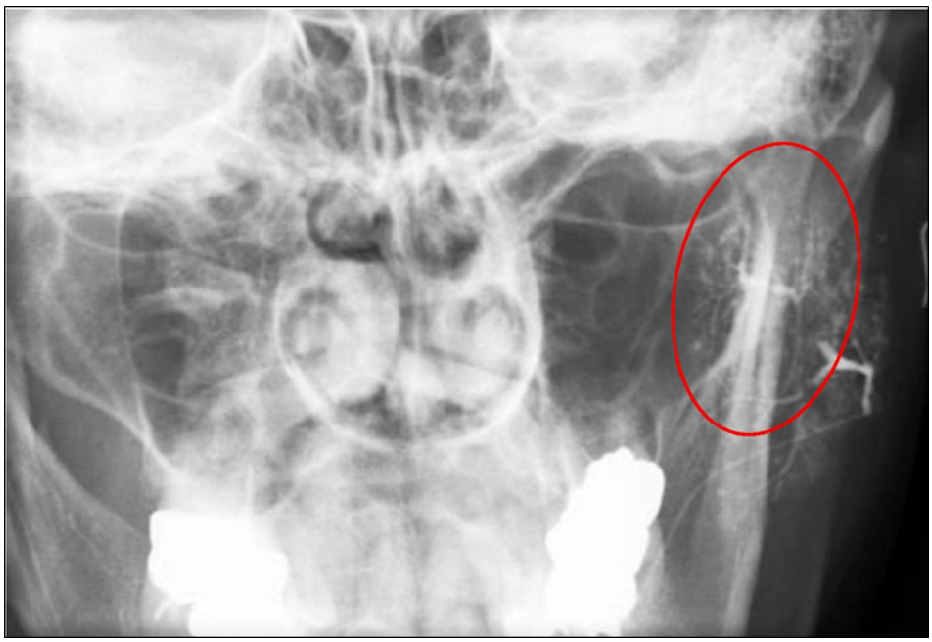

Figure 2a

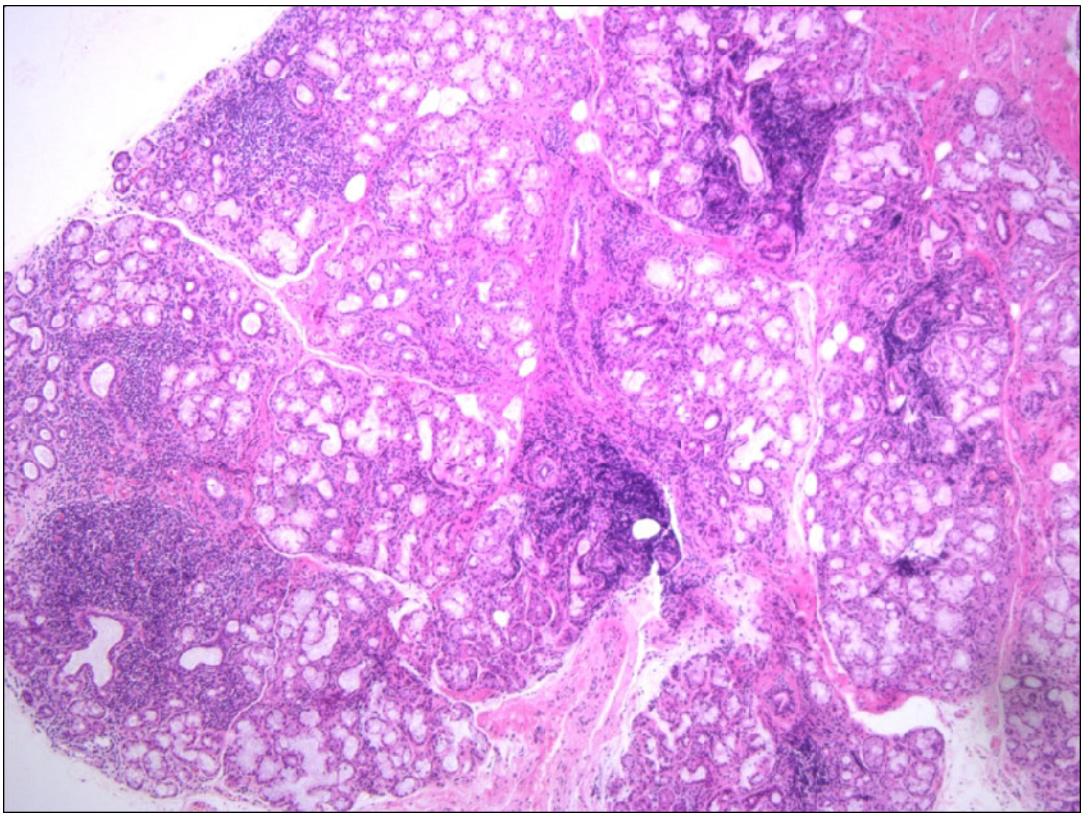

Figure 2b

Figure 2. (a) Sialogram showing dot staining compatible with stage 2 Rubin and Holt classification (2015.2). (b) Minor salivary gland specimen showing massive lymphocyte infiltration (2015.2).

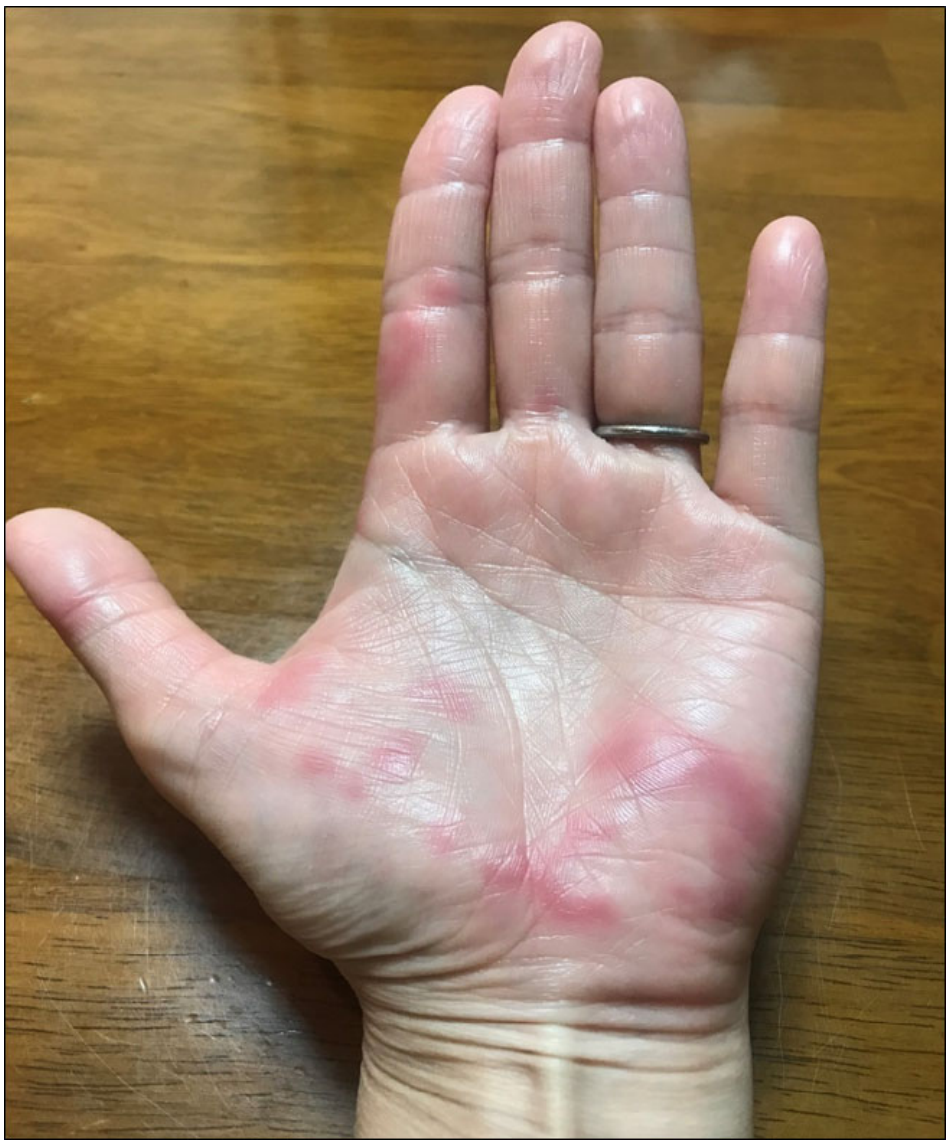

Figure 3. Hand XP showing annular erythema (2019/1/5). Patient noticed the same erythema intermittently.

CASE REPORT 2: ID H10441, 1965

In March 2016, a female patient visited the clinic complaining of palpitations, fatigue, and amenorrhea. Low-dose conjugated equine estrogen-medroxyprogesterone acetate was prescribed **(Figure 4)**. In December 2016 and December 2017, she experienced colicky right upper abdominal pain. An abdominal ultrasound showed cholelithiasis, so she stopped receiving HRT to undergo a cholecystectomy. At the end of December 2017, she complained of abrupt severe joint pain in the knees and wrists and difficulty performing activities of daily living. She had not undergone the cholecystectomy. In January 2018, the patient resumed HRT. Her joint pains gradually decreased and her quality of life improved. She visited the orthopedic clinic for further evaluation of her joint pain. The patient was prescribed methotrexate for RA based on a high titer of anti-CCP Ab (128.4/mL), but she did not take the medication. In April 2018, she presented to our clinic. Neither joint swelling nor C-reactive protein elevation were present, so cyclic HRT (E2 patch and dydrogesterone) was recommenced to prevent RA. Her joint pain disappeared completely. In April 2019, a slight elevation of C-reactive protein and multiple small gallstones were observed **(Figure 5)**. The patient underwent cholecystectomy and did not receive HRT for two weeks. In May 2019, she experienced peripheral joint pain and swelling, and a joint ultrasound showed a power Doppler signal of grade 2 **(Figures 6a & 6b)**. Methotrexate (8 mg/week) was added to her HRT regime. She has remained well.

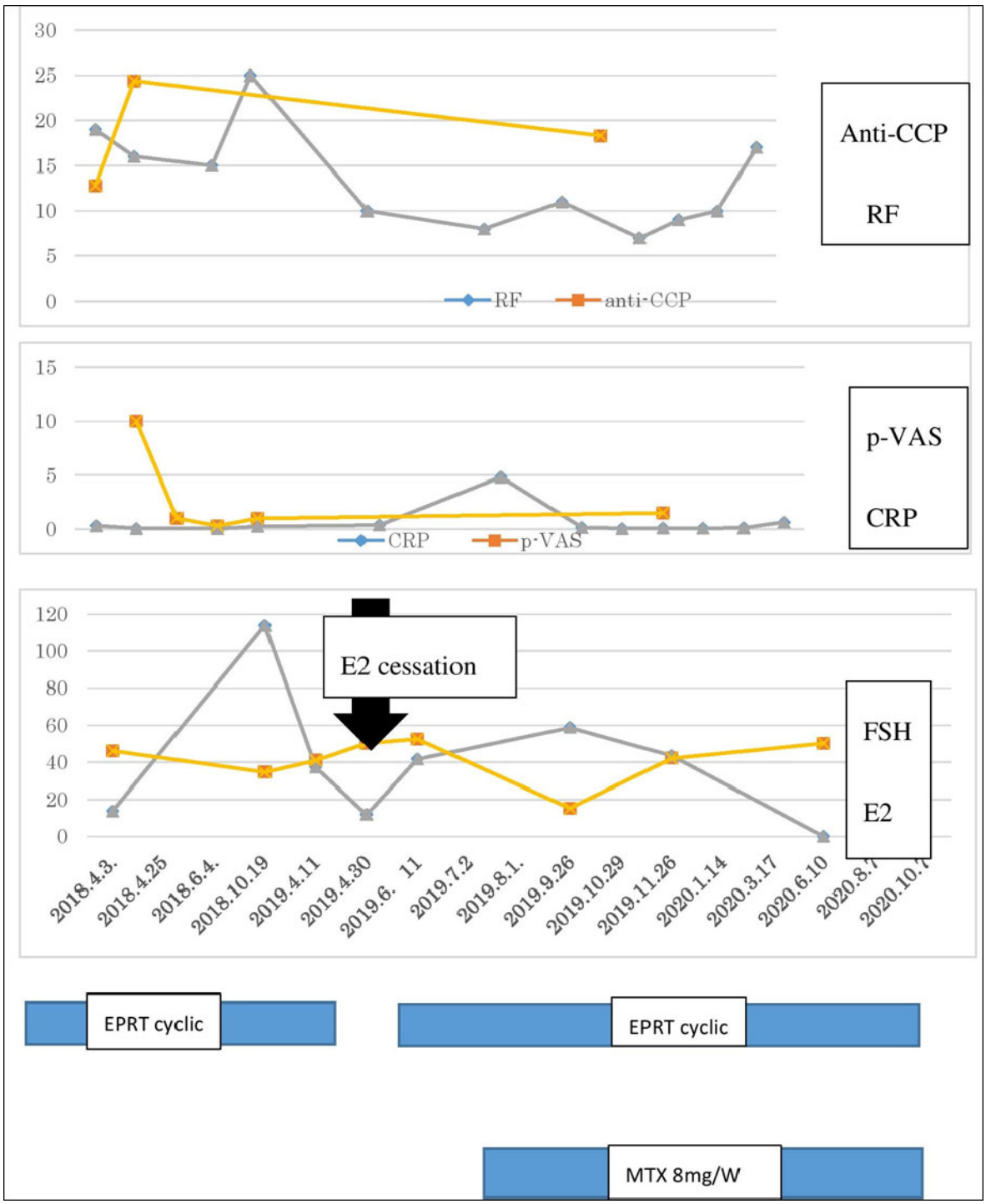

Figure 4. Case 2 clinical and laboratory course. In April 2019, HRT was terminated for two weeks for gallstone operation. Three months later, pain in multiple joints appeared. Rheumatoid arthritis was suspected due to C-reactive protein elevation and joint echogram showing Doppler signals at wrist and metacarpophalangeal joints. Patient received methotrexate (8 mg/w) and maintains good health.

RF < 15 U/ml is normal; anti-CCP Ab < 4.5 U/ml is normal. E2 < 20 pg/ml and FSH > 40 mIU/ml indicate menopause. EPRT = estrogen progesterone replacement therapy; FSH = follicle-stimulating hormone; MTX = methotrexate.

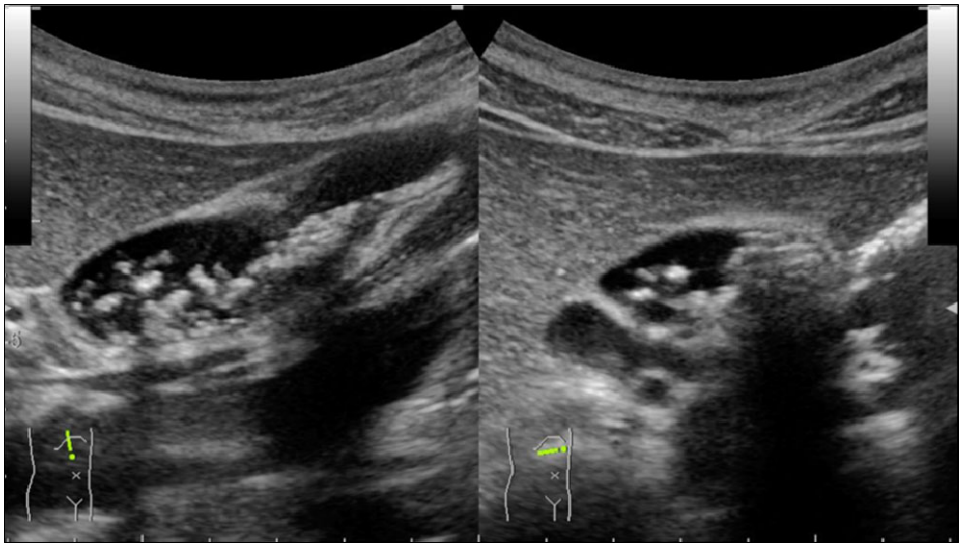

Figure 5. Echogram of gallbladder showing multiple cholelithiasis.

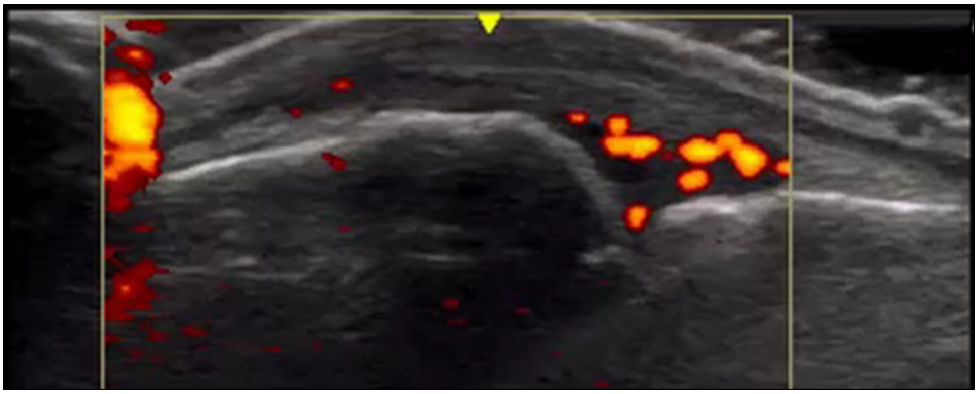

Figure 6a

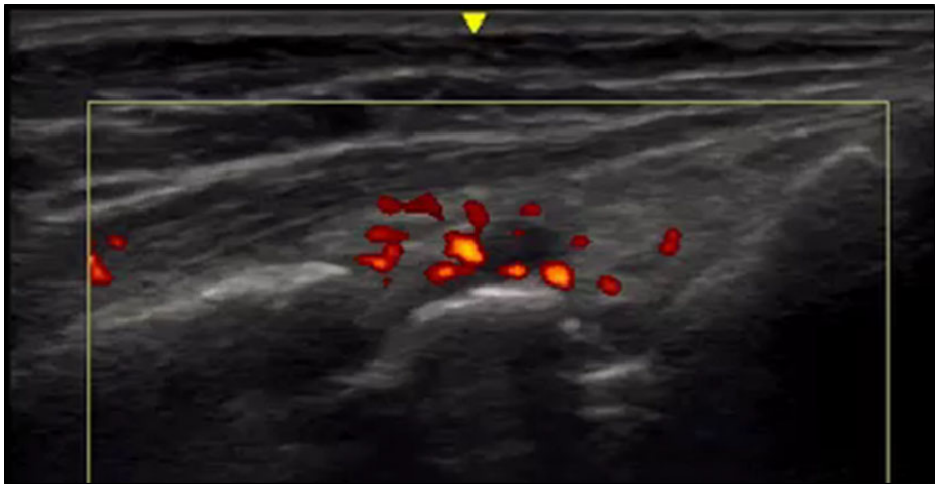

Figure 6b

Figure 6. (a) Echogram of right second metacarpophalangeal joint. Moderate synovial thickness and power Doppler signals (grade 2) were observed. (b) Echogram of radiocarpal joint. Moderate thickness of synovial membrane around radiocarpal joint and Power Doppler Signals (grade 2) were observed.

DISCUSSION

HRT use is not common in Japan, in part due to the 2002 Women's Health Initiative report highlighting its adverse effects. In general, HRT is recommended in younger, healthy women for no longer than 5 years [8]. If the benefits of HRT outweigh its risks, HRT can continue for more than 5 years in women younger than 60 years. The duration and termination of HRT depends on the patients' overall health and individual factors [9].

Over the last 20 years, menopausal women with morning stiffness, arthralgia, or positive ANA have used HRT for relief of joint pain and to prevent RA or other autoimmune rheumatic diseases [10,11]. SS demonstrates a female preponderance (male: female ratio 1:14-1:17), similar to primary biliary cirrhosis [12]. Like RA, SS onset frequently occurs between the ages of 40 to 60, when estrogen levels decrease. Childbirth appears to be a protective factor, with parous women age <45 demonstrating overall lower RA risk. The greatest risk reduction was observed in the first 5 years postpartum, with risk reduction progressively lessening over time [13]. SS and primary biliary cirrhosis both occur in middle age and may share a genetic component, HLA DR 08 [14] and 15 [15]. Interestingly, the pathological manifestations in both diseases occur as destruction of the small secretory and bile duct cells via autoreactive lymphocytes.

The cause of SS is not clearly understood. Genetic background likely plays a role, but in one study of identical twins, the odds of developing SS in both were only 15% [16]. Other causes could be environmental, particularly infection [17], or individual-level factors. In case 1, after termination of HRT, ANA was positive at a 1:1280 dilution and anti-SS-A was positive at a 1:64 dilution according to micro-Ouchterlony, suggesting escalation of autoantibody production due to estrogen deficiency [18]. Although sialography and minor salivary biopsy were not tested prior to symptom development, it is possible that cessation of HRT induced clinical SS directly.

Recently, the reverse specific sequence oligopeptide [19] method has identified HLADRB1 *04:05 and *15:02. The significance of HLADRB1 15 [20] and HLADRB1 *15:02 in SS remains unknown, however. Further research is needed to determine the role, if any, of HLADRBI 15. In case 1, HRT was a viable treatment option for preventing RA because of HLADRB1*04:05 positivity.

Estrogen deficiency or depletion is linked with peri-and post-menopausal symptoms, as well as autoimmune disease and osteoporosis [21] Pacifici R et al recently reported alteration of gut microbe induce osteoporosis [22]. Walitt et al. reported that HRT was not useful for preventing RA; however, the results may have been affected by high BMIs, smoking status, and age (average 63.5 years old) of participants at commencement of HRT [23]. In 1947, the average age of menopause onset in Japan was 50 years. As people live longer, the risk of autoimmune diseases will likely increase more for women than for men. Estrogen deficiency or depleted activation of NFkB via inhibition of kB-Ras2 is regulated via miR-125b and let-7a, which produce TNF [5] and activate Th 17 cells, [24] which can lead to the development of RA.

Our reports here are limited to two cases with symptomatic SS or RA. Further studies are needed to assess E2 and FSH fluctuation before and after onset of these conditions. In conclusion, abrupt cessation of HRT for 1 to 3 months led to onset of SS and RA in two cases, respectively. It is possible that HRT may prevent progression to RA and SS from undifferentiated arthralgia.

FUNDING

None

CONFLICT OF INTEREST

None

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