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ORIGINAL ARTICLE

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A study of ten Japanese patients with seronegative spondylarthropathy: a tentative proposal

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Abstract We reviewed ten patients with seronegative spondylarthropathy (SNSA), who all fulfilled the European Spondylarthropathy Study Group criteria for spondylarthropathy (SpA); seven patients also met the Amor criteria for SpA. Seronegative spondylarthropathy was not a uniform syndrome but rather a wide spectrum of complex disease with characteristics of sacroiliitis and enthesopathy. The most frequent symptom at diagnosis of SNSA was inflammatory low back pain, followed by asymmetric oligoarthralgia and Achilles tendonitis and/or plantar fasciitis. Systemic complications were revealed as eye and skin involvement. Imaging methods including pelvic radiography, scintigraphy, and computed tomography scanning were useful in detecting spondylarthropathic changes, which were characteristic of SNSA. Human leukocyte antigen (HLA) typing showed various patterns among patients, in which HLA-B27 was positive in three patients with ankylosing spondylitis. HLA-B51, which is a well-known genetic factor associated with Behçet's disease (BD), was positive in two patients who were apparently distinct from BD. Two patients with palmoplantar pustulosis showed symptoms and signs characteristic of SNSA. Although we have few SNSA patients in the present study, we would like to propose that HLA-B51 positive SpA would be considered as a subset of SNSA, and that pustulotic SpA also would be classified as a member of SNSA. This led us to suggest the possibility to change the concept of SNSA proposed by Moll et al. The optimal treatment remains to be defined, but sulfasalazine was effectively used with almost all patients in combination with nonsteroidal anti-inflammatory drugs.

Key words Behçet's disease · Human leukocyte antigen (HLA)-B27 · Human leukocyte antigen (HLA)-B51 · Palmoplantar pustulosis · Seronegative spondylarthropathy (SNSA)

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Introduction

The concept of a closely interlinked group of seronegative spondylarthropathy (SNSA) consisting of ankylosing spondylitis (AS), psoriatic arthritis (PsA), Reiter's syndrome, Behçet's disease (BD), ulcerative colitis, Crohn's disease, and Whipple's disease was originally developed by Moll et al.[1] Since SNSA constitutes a heterogeneous group of disorders with common genetic and clinical characteristics, they formulated the clinical, serological, radiological, and genetic features common to this group of patients. Therefore, SNSA is not a uniform syndrome but rather a wide spectrum of disease manifestations, with highly variable expression and disease course, often requiring a provisional diagnosis.[2] The classification criteria for SNSA proposed in recent years claimed to encompass the definite diseases (AS, PsA, Reiter's syndrome, and arthritis associated with inflammatory bowel disease) as well as the undifferentiated syndromes in the group.[3,4] The strength of disease association with the HLA-B27 antigen varies markedly among the various SNSP forms as well as among different ethnic populations.[5] It was reported that in a study on 119 patients with HLA-B27-positive oligoarthritis during a follow-up period of 2–6 years, 25% progressed to a definite SNSA, 26% had recurrent oligoarthritis, and 34% became asymptomatic.[6] The combination of spondylitis, sacroiliitis, enthesopathy, arthritis of the extremities, and negative rheumatoid factor (RF) is common in the disease states of SNSA. However, licensed information is available about SNSA in the Japanese population, in which HLA-B27 is less common than in Caucasians.

Although we reviewed only 10 patients with SNSA and discussed clinical features with special reference to both HLA-B27 and -B51 antigens and HLA-B51 is a well-known genetic factor for BD, we would like to propose dogmatically a HLA-B51-positive SNSA which is strictly different from BD. Further, we suggest reform of the criteria for SNSA to include spondylarthropathy (SpA) associated with pustulosis within SNSA, not withstanding the absence of the familial aggregation.

Patients and methods

This is a retrospective study reviewing clinical aspects of 10 patients with a diagnosis of SNSA registered with our rheumatology clinic between January 2001 and December 2004. The following baseline information was obtained on each patient from case records: signs and symptoms at the first visit, family history of SNSA, and presence or absence of sacroiliitis and enthesopathy at the time of initial presentation. Re-evaluation consisted of detailed history regarding various symptoms such as joint pain, heel pain, or pain at the insertion of Achilles tendon, uveitis, skin lesions, recurrent diarrhea or urethritis, development of similar symptoms in any other family member, and a detailed treatment history. Investigations included laboratory data (complete blood cell count, erythrocyte sedimentation rate, C-reactive protein), and radiographs of pelvis and lumbosacral spine. All patients fulfilled the European Spondylarthropathy Study Group (ESSG) criteria for SpA.[4] The Amor criteria for SpA[3] were also applied.

Clinical evaluation included a search for initial symptoms and the presence of axial involvement, peripheral involvement, and heel enthesopathy during the study. Initial symptoms included inflammatory low back pain (ILBP) without radiographic sacroiliitis, asymmetric oligoarthritis (predominantly affecting large joints in the lower limbs), and heel enthesopathy (Achilles tendonitis and/or plantar fasciitis). Inflammatory low back pain was considered according to established criteria.[7]

Pelvic radiographs were obtained from all patients after informed consent. These X-ray films were read in a random manner by the grading system of sacroiliitis according to the New York criteria.[8] Imaging methods performed during the study included pelvic and calcaneal radiography, computed tomography (CT) scanning, and scintigraphy. Patients were diagnosed with AS when they fulfilled the modified New York criteria, and as psoriatic arthritis and arthritis associated with palmoplantar pustulosis if they presented with characteristic psoriatic or palmoplantar pustulotic skin lesions.

Enthesopathy was documented as past or present pain or tenderness on examination of the insertion of the Achilles tendon, plantar fascia or other joints, present pain and tenderness at the iliac crest, greater trochanters, ischial tuberosities, and/or tibial tuberosities. It was found typically as enthesopathy of SpA occurring in association with an oligoarthritis involving the large joints of the lower limbs.

HLA-A and -B antigen typing was performed by the method of polymerase chain reaction-reverse sequence-specific oligonucleotide (PCR-rSSO) in all patients. The presence of HLA-B27, the B7 cross-reactive group (CREG) antigens, and other antigens were ascertained.[9]

Disease improvement was defined as complete remission of clinical symptoms for a period of at least 6 months without symptomatic medication, associated with normal pelvic radiography. Medications, which included sulphasalazine (SASP), nonsteroidal anti-inflammatory drugs (NSAIDs), and prednisolone (PSL), were administered to all patients. Skin biopsy at the site of calf purpura was performed in case 5 to obtain a histological diagnosis during an active disease process.

Results

Four men and six women were reviewed (Table 1). The mean age was 36.5 years old (range 21–59) and the symptom duration before diagnosis of SNSA was 17.4 months (range 4–32). Although all patients in the study fulfilled the ESSG criteria for SpA, when we applied the Amor criteria for SpA, three patients (cases 3, 7, and 10) with a 5-point score in the Amor criteria were included into the study. It is necessary for SNSA to fulfill at least six points by the Amor criteria. SNSA consisted of three cases of AS, four undifferentiated spondylarthropathy (uSpA), one PsA, and two reactive (pustulotic) arthritis. The first manifestations were ILBP with four radiographic sacroiliitis (5 cases), asymmetric oligoarthritis predominantly affecting large joints in the lower limbs (3 cases), and two heel enthesopathies (1 case with Achilles tendonitis and 1 case with plantar fasciitis).

Imaging methods performed included pelvic and calcaneal radiography. Seventy percent of the patients showed sarcoiliitis radiographically. Figure 1A illustrates sacroiliitis in case 5. A computed tomography scan also showed irregular changes of bilateral sacroiliac joints and bone erosions (Fig. 1B,C). Scintigraphy using either radioactive technetium (^{99m}Tc) or gallium (^{67}Ga) was useful to detect joint lesions and inflammatory articular changes. In case 8, ^{99m}Tc-scintigraphy revealed increased uptake in the sternoclavicular joint, sternal angle area, sternocostal joint, costochondral junction, axial skelton, and sacroiliac joint (Fig. 2A,B). In case 4, ^{67}Ga-scintigraphy also revealed an abnormal increased uptake in the bilateral sacroiliac joints and axial joints (Fig. 2C), identical to distribution of radiographical changes.

Not only subjective but also objective enthesopathies were documented in 70% of the patients, including Achilles tendonitis, plantar fasciitis, knee, wrist, and/or elbow tendonitis. Complications recognized during the study were four cases of eye inflammation (uveitis or keratoconjuctivitis); plantar pustulotic lesions in case 2 (Fig. 3A); sternoclavicular joint swelling and pain in case 8 (Fig. 3B); psoriasis in cases 3 and 7; recurrent enteritis, diarrhea, and

Table 1. Patients' characteristics of SNSA

Case/ Age/Sex	Complaining duration (months)	Disease	Points of Amor criteria	At diagnosis of SNSA			Complications	HLA typing	Medication			Outcome
				Clinical symptom	Sacroiliitis	Enthesopathy			SASP (mg/day)	NSAID (mg/day)	PSL (mg/day)	
1/21/F	8	uSpA	5	Achilles pain	(−)	(+)	Uveitis	A24, A31, A54, B60	None	Loxoprofen 120	None	Favorable
2/51/F	6	PPP	6	ILBP	(−)	(−)	Pustulotic skin	A2, A24, B7, B54	750	Diclofenac 50	None	Favorable
3/25/M	21	AS	8	ILBP	(+)	(−)	Psoriasis	A2, A99, B27, B54	500	Sulindac 200	None	Relatively good
4/23/M	32	AS	9	ILBP	(+)	(−)	Uveitis	A2, A24, B27, B54	1000	Etodolac 200	None	Favorable
5/25/M	12	AS	12	ILBP	(+)	(+)	Sternoclavicular pain, abdominal pain, anaphylactoid purpura	A2, B27, B54	1000 +MTX	Lornoxicam 10	3.5	Relatively good
6/41/M	15	uSpA	5	Asymmetric oligoarthralgia	(+)	(+)	Diarrhea	A24, B31, B35 B39, B52	1000	Sulindac 200	None	Favorable
7/59/F	4	PsA	6	ILBP	(+)	(+)	Keratoconjuncti-vitis, psoriasis	A11, A26, B39 B51	1000	Sulindac 200	2	Favorable
8/58/F	28	PPP	6	Asymmetric oligoarthralgia	(−)	(+)	Pustulotic skin, sternoclavicular pain, abdominal pain	A11, A24, B54, B60	1000	None	5	Favorable
9/31/F	21	uSpA	7	Plantar pain	(+)	(+)	Abdominal pain, genital ulcer, diarrhea	A24, A26, B52, B61	100 +MTX	Loxoprofen 120	10	Relatively poor
10/28/F	27	uSpA	5	Asymmetric oligoarthralgia	(+)	(+)	Uveitis	A24, A26, B51, B61	2000 +MTX, CyA	None	15	Relatively poor

SNSA, seronegative spondylarthropathy; HLA, human leukocyte antigen; SASP, sulfphasalazine; NSAID, nonsteroidal anti-inflammotory drug; PSL, prednisolone; uSpA, undifferentiated spondy-larthropathy; PPP, palmoplantar pustulosis; ILBP, inflammatory low back pain; AS, ankylosing spondylitis; MTX, methotrexate; PsA, psoriatic arthritis; CyA, cyclosporin A

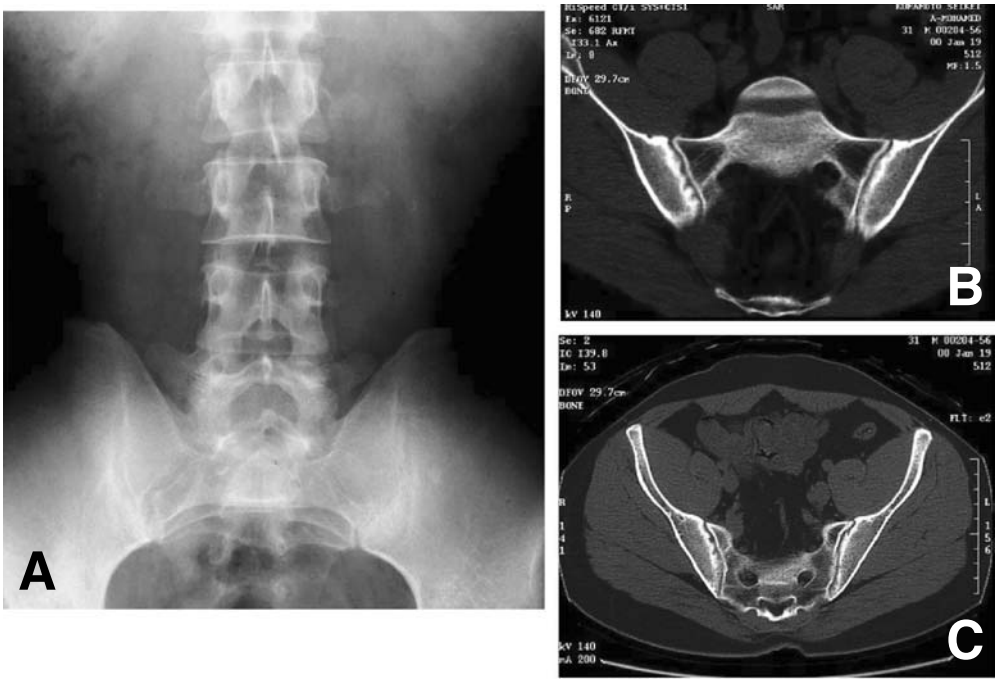

Fig. 1. **A** Pelvic radiograph in case 5. Bilateral sacroiliitis was illustrated. **B,C** In the same patient, computed tomography scan showed irregular changes of bilateral sacroiliac joints and bone erosions

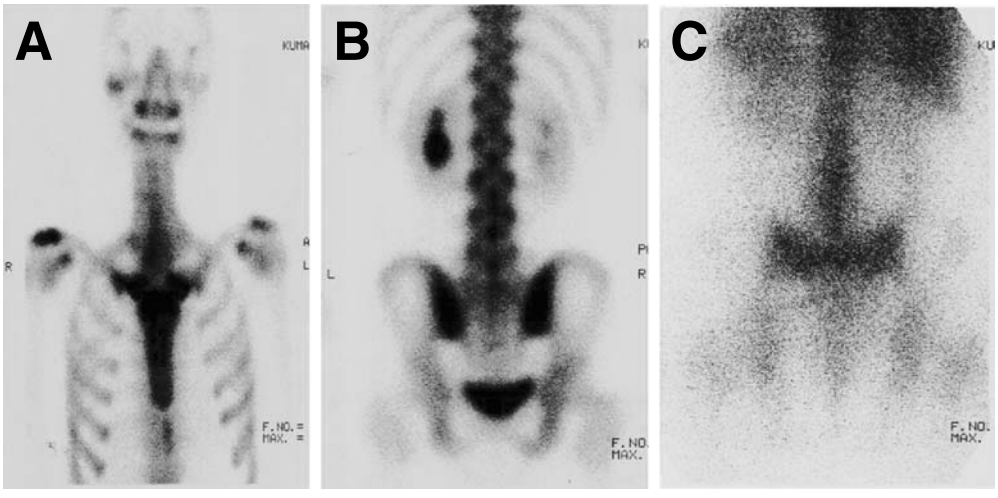

Fig. 2. **A,B** In case 8, ^{99m}Tc-scintigraphy revealed increased uptake in the sternoclavicular joint, sternal angle area, sternocostal joint, costochondral junction, axial skelton, and sacroiliac joint. **C** In case 4, ^{67}Ga-scintigraphy also revealed an abnormal increased uptake in the bilateral sacroiliac joints and axial joints

abdominal pain in case 6; in particular, transient genital ulcer in case 9. We have confirmed that clinical evaluations in cases 7 and 10 did not meet the criteria for BD.[10] These two patients have not yet fulfilled the criteria for BD upon follow-up. In case 5, anaphylactoid purpura was recognized in his calfs, revealing leukocytoclastic vasculitis by biopsy (Fig. 3C,D).

Human leukocyte antigen typing showed a variety of alleles among the patients (Table 1). Three were HLA-B27-positive. HLA-B27 can also be associated with HLA-B7 CREG antigens (B7, B22, B42, B60), and these alleles were observed in some patients. It is noteworthy to indicate that two patients (cases 7 and 10) had HLA-B51, which is strongly associated with BD, although they showed no clinical characteristics of BD as mentioned above. Case 7 reported a family history of psoriasis and manifested the HLA-B39 antigen which is associated with psoriatic arthritis.[11] HLA-B52, which was recognized in cases 6 and 9, is well known to be strongly associated with ulcerative colitis in Japanese patients.[12]

All patients were treated with SASP, NSAIDs, and PSL during the course of their illness. Nine patients were medicated with SASP, either alone or in combination with methotrexate (MTX) or cyclosporine (CyA). These therapies enabled eight patients to be active in daily life and to achieve a satisfactory outcome.

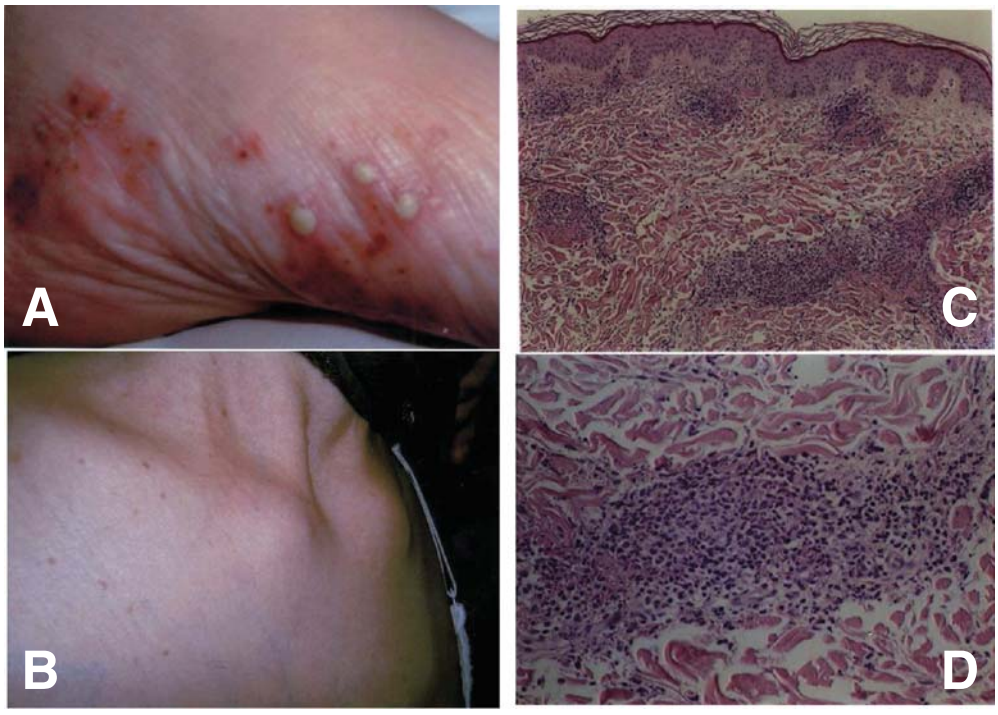

Fig. 3. **A** Plantar pustulotic lesions in case 2. The patient also had similar lesions in her palmar regions. **B** Anterior chest wall symptoms in case 8. Swelling at the bilateral costoclavicular and the manubriosternal regions are visible. **C** Leukocyte infiltration into the dermis and perivascular lesion (H&E stain, ×100) in case 5. **D** Leukocytoclastic vasculitis was revealed in the same lesion (H&E stain, ×400)

Discussion

Some of the diseases considered seronegative "variants of classical rheumatoid arthritis (RA)" are inter related to such an extent that they may be included in a single group: SNSA.[13] Ankylosing spondylitis, a prototype of SNSA, is a chronic systemic inflammatory disorder of the axial skeleton, mainly affecting the sarcoiliac joint and spine. The inclusion criteria include a negative test for RF, absence of subcutaneous rheumatoid nodules, inflammatory peripheral arthritis (often asymmetric), radiological sacroiliitis with or without AS, evidence of overlap between members of the group, and a tendency to familial aggregation.[1] In these patients systemic complications may develop in addition to joint involvement.

The ESSG criteria can be particularly useful in studies of SpA in countries where HLA-B27 is not so frequent as it is in Europe, as the criteria can encompass both HLA-B27-positive and -negative SpA patients. The Amor point-scale set of 12 criteria also has a good sensitivity and specificity.[3] Although three HLA-B27-negative SpA patients in the present study scored 5 points (6 points would be necessary) in the Amor set criteria, we included them as undifferentiated SpA (uSpA) in the study because they fulfilled the ESSG criteria. Inflammatory low back pain was the most frequent initial manifestation at the diagnosis of SNSA. HLA-B27 was positive in three patients (Table 1). It was reported that HLA-B27, enthesopathy, and asymmetric oligoarthritis were likely to be associated with the Amor criteria ≥6, whereas ILBP tended to be linked to the Amor criteria < 6.[2] It was interesting that the first clinical symptom observed in patients with 5 points of the Amor criteria in the present study was other than ILBP. They were all diagnosed as uSpA. Although the Amor criteria are excellent for classification of SNSA, we should be careful to differentiate diseases not only by the Amor criteria but also by several criteria to optimize diagnosis. For example, fibromyalgia syndrome, which is a condition that manifests as chronic pain with tender points throughout the musculoskelton, can be misdiagnosed as SNSA when the Amor criteria are simply applied.[14] To detect active sacroiliitis, bone scintigraphy and CT scanning were useful tools in cases 4 and 5 (Fig. 1B,C). Comparative studies showed that magnetic resonance imaging (MRI) can be more accurate than conventional radiography,[15–18] and would be preferable for diagnosis of sacroiliitis in SNSA.

HLA-B27 has been recognized as a representative of a spectrum of diseases, ranging from the majority of HLA-B27-positive individuals who have no disease at all, through those with isolated eye or skin involvement, to those with critical eye, heart, and peripheral joint compromise of typical AS, and especially in SNSA. As currently defined, reactive arthritis is restricted to the conditions frequently associated with HLA-B27 and does not include rheumatic fever, Lyme arthritis, arthritis associated with ulcerative colitis, or regional enteritis and postviral arthritides.[19] Reactive arthritis is induced by two important factors. One is the well-known arthritis-causing microorganisms which are *Shigella*, *Salmonella*, and *Chlamydia trachomatis*. Another host factor is HLA-B27. These are historically and statistically well-defined factors in this disease. However, some exceptions have been reported; infection with *Vibrio parahaemolyticus* or *Chlamydia pneumoniae* also induce reactive arthritis.[20] Moreover, from 20% to 30% of patients with reactive arthritis do not have HLA-B27, therefore, B27 is not included in the diagnostic criteria for reactive arthri-

tis. It is important to study HLA typing in Japanese patients with SNSA since the incidence of B27 is less than 1% in Japan.[21] A positive family history of a definite SpA, predominantly AS, was mentioned in 9% of the patients, similar to that observed in AS or Reiter's syndrome.[22] The presence of uSpA in SNSA is common in the families of patients with AS, predominantly those who are HLA-B27-positive patients,[23] and can also be associated with HLA-B7 CREG antigens.[24] In addition to B27, the antigens that cross-react with B27 antigens are encoded by some alleles that have also been linked to AS and Reiter's syndrome.[21] It was reported that the amino acid sequence of the B pocket in B27 was homologous to that of B39.[25,26] From these reports and our results (Table 1), it is suggested that various HLA alleles beyond B27 may also play roles in the pathogenesis of SNSA. Since HLA-B52 was reported as a susceptibility gene strongly related to Japanese inflammatory bowel diseases,[12] it was of interest that HLA-B52 was positive in case 9, who manifested gastrointestinal symptoms in her clinical course. This suggests that genetic factors cross-react between SNSA and inflammatory bowel diseases in the development of disease. We need to elucidate the importance of HLA in establishing the different patterns of SNSA.

Behçet's disease is known as a systemic disorder with mucocutaneous, ophthalmologic, neurological, cardiovascular, pulmonary, gastrointestinal, urogenital, and musculoskeletal involvement. The underlying pathological process is a chronically relapsing vasculitis affecting vessels of any size and any organ.[27] The etiology of BD remains unknown, even though viral infection and/or autoimmune disease have been frequently discussed. In addition to mucocutaneous manifestations in BD, arthritis in BD has been reported to have clinical features similar to those in SNSA, such as peripheral oligoarthritis, sacroiliitis, or enthesopathies.[28,29] As mentioned above, the diseases in SNSA share several common features, of which one of the most salient is the association with the HLA-B27 antigen. So far, there have been conflicting results for the prevalence of HLA-B27 in patients with BD.[30] It was reported that the overall frequency of HLA-B27 in BD patients was significantly increased, and that the level was similar to that found in psoriasis,[31] with an increased incidence of HLA-B27 in BD patients with arthritis.[32] On the other hand, others reported no association with HLA-B27 with BD.[33] The prevalence of HLA-B27 in the general population has shown a considerable geographic variation, and that in healthy Japanese in one study was 0.4%.[34] In the present study we found two patients (cases 7 and 10) with HLA-B51-positive and HLA-B27-negative SNSA who concurrently could not fulfill the criteria for BD. As the HLA-B51 antigen has been the well-known genetic factor associated with BD, the presence of HLA-B51 lends support to BD. The prevalence of HLA-B51 in BD appears to be higher in countries adjacent to the ancient Silk Road, including Japan.[35] We have been following the clinical course of cases 7 and 10 for 8.4 years and 6.7 years, respectively. Although they did not present clinical characteristics of BD at all and have never met the criteria for BD so far, they were HLA-B51 positive (Table 1). The hypothesis that BD could be a part of SNSA seems to be unlikely. One possibility of the more likely explanation may be coexistence of BD and SNSA. Therefore, HLA-B51-related SpA is proposed and HLA-B51 might be implicated in the pathogenesis of reactive arthritis.[20] These cases would support a hypothesis that patients with HLA-B51-related SpA might have a variant form of SNSA. It has been reported that among all genes, DR4 contributes around 30% in the pathogenesis of RA and B27 contributes from 16% to 50% in AS.[35] Probably, at a much lower percentage, HLA-B51 can contribute to reactive arthritis. The issue about HLA-B51-related SpA or HLA-B27-negative SNSA should be elucidated, especially in Japan.

SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome increasingly seems to be a member of an intriguing spectrum of relatively uncommon and presumably autoimmune disorders only somewhat related to PsA.[36] One key feature that suggests the presence of SAPHO syndrome is prominent anterior chest wall symptoms (Fig. 3B), e.g., asymmetric and nonerosive swelling and/or pain of the sternoclavicular joint, sternal angle area, sternocostal joint, and costochondral junction. ^{99m}Tc-scintigraphy reveals increased uptake in the affected areas (Fig. 2A,B) in all cases, despite normal conventional chest radiographs. A correlation of SAPHO syndrome with HLA-B27 has not been clearly established.[37,38] SAPHO syndrome and SNSA have several features in common, i.e., the occurrence of sacroiliitis,[39] association with psoriasis,[40] and coincidence with chronic inflammatory bowel disease.[41] Although pustulotic SpA is apparently distinct from RA, it is very close to AS or PsA. Because spondylitis and sacroiliitis seen in the SNSA group are similar and almost indistinguishable from each other, according to the first concept of SNSA by Moll et al.,[1] diseases belonging to SNSA share many properties. It is clear that pustulotic SpA has all these features except perhaps familial aggregation and inter-relationship. We have no data to support the possibility that pustulotic SpA shows familial aggregation and inter-relationship, although some reports suggested this.[42] However, further clinical and epidemiological investigations are necessary to clarify this point and while we surely recognize that there were few patients to be dogmatic about in the present study, we would like to venture to propose a concept to classify pustulotic SpA as one member of SNSA, as shown in cases 2 and 8 in Table 1. To understand pustulotic SpA as a member of SNSA is important, not only from the academic but also the practical point of view. Long-term studies evaluating the outcome or prognosis of SNSA and case-control studies whose sampling and measuring bias are reduced as much as possible in different countries are necessary to establish whether each disease, including SNSA, represents a distinct pattern.

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