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SHORT COMMUNICATION

Symptomatic noncompressive motoromyelopathy presents as early manifestation in ankylosing spondylitis

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Abstract Ankylosing spondylitis (AS) is an autoimmune spondyloarthropathy involving principally the sacroiliac joint and axial skeleton. Spinal cord involvement is an infrequent and late complication. It mostly results from compressive myelopathy due to skeletal osteopathy and usually presents with radiculomyelopathic sensory and motor deficits. To report three patients who suffered a progressive paraparesis/tetraparesis compatible with motor myelopathy without typical skeletal symptom. Myelopathy of unknown origin was initially interpreted in these patients. Radiography did not show typical change at sacroiliac joint or vertebrate. Spinal magnetic resonance image revealed cord atrophy at cervical and thoracic segment. A positivity of B27 antigen was found afterward. Their spondyloarthropathic symptoms developed within six months later with radiographic sacroiliitis. Seropositive AS with noncompressive myelopathy was finally established. Patients showed a reverse of motor impairment when their pain was well undercontrolled. Motor myelopathy may be neglected or underestimated in AS, in especially when typical skeletal symptom is absent or minimal. It may progress surreptitiously to harm spinal function or superimpose to crippling disability in compressive spinal cord injury. Therefore, a careful evaluation and monitor of spinal cord function is important for AS patient despite spinal deformity is not observed.

Keywords Ankylosing spondylitis · Spinal cord · Myelopathy · Myelopathy with unknown origin · Motor · Noncompressive myelopathy · Autoimmune · Spondyloarthropathy · Motor neuron

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Introduction

Ankylosing spondylitis (AS), which is also known as Bechterew's or Marie-Strümpell disease, is a chronic systemic inflammatory rheumatic disorder that primarily affects the sacroiliac joints, axial skeleton, and spine [1]. Generally, it begins in joint and back stiffness, loss of motion, deformity and disability as life progresses. The prevalence is 0.1–0.2%, and man to woman ratio is 4–10:1. Over 90% of AS patients carries B27 antigen [1]. Neurological involvement is usually an infrequent and late complication [2–4], and almost results from spinal cord compression due to trauma, dislocation of vertebrates or surgical intervention [5, 6]. Noncompressive myelopathy (NCM) is barely mentioned in AS. Herein, we report three NCM patients who did not exhibit typical skeletal symptom at initial were finally confirmed the seropositive AS. This experience alerts an underestimation of AS or autoimmune disease in NCM with unknown origin and also

alarms the role of noncompressive injury of spinal cord in compressive myelopathy in AS patients.

Patients and methods

We encountered three patients to present with a progressive spastic paraparesis or tetraparesis. Survey included tests for biochemistry, urinalysis, hemorheology, Venereal Disease Research Laboratory test, antinuclear factor, anticardiolipin antibody-IgG, lupus anticoagulant, anti-beta2-glycoprotein I antibody, IgA, IgG, IgM, immunoelectrophoresis, cyanocobalamin, folate, and virology (HIV, HTLV-I, HTLV-II, *Cytomegalovirus*, *Varicellar-Zoster virus*, *Herpes Simplex Virus*); cerebrospinal fluid analysis (cytology, glucose, total proteins, albumin, albumin index, IgG, IgA, IgM, Reiber's formulation); radiograph of sacroiliac joint, and lumbar and cervical spine, nerve conduction velocity study (median, ulnar, radial, peroneal, tibial and sural nerves), F wave, H reflex, electromyogram, somatosensory evoked potential, motor evoked potential (MEP), visual evoked potential, brainstem auditory evoked potential, and spinal and brain magnetic resonance imaging (MRI). The disease activity was assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional activity by Bath Ankylosing Spondylitis Functional Index (BASFI), and diagnosis of AS by modified New York criteria. Cord atrophy was assessed by a reduction of sagittal diameter of cord [7] under MRI.

Results

These three patients were women and their age ranged from 19 to 46 years at the time of presentation. They did not experience focal reversible or irreversible neurological deficit, visual defect, intoxication, traumatic injury, skin rash, unknown fever, oral or genital ulcer, uveitis, erythrema nodosum or cutaneous lesion, effusion or ascites, valvular disease, vasculitis, skin pigmentation, ecchymosis or thrombocytopenia before. There was no contributory history in their family. Seropositive AS was finally diagnosed basing on positive HLA-B27 antigen, subsequent typical skeletal symptom, and radiographic sacroiliitis fulfilling the modified New York criteria.

Case description

Case 1

A 21-year-old lady experienced fatigue and tightness and pain over shoulder and upper proximal limb at both sides for 3 years and lumbago for half a year before presentation. Her pain was mild and tolerable, occurred spontaneously at any time, was relieved by exercise or rest, and peaked by prolonged walking, standing, or lifting. She could walk, ride motorcycle, and climb stairs properly. Neurological examination revealed mild spasticity, motor soft signs (positive Hoffmann sign, trunk-thigh sign and Hoover sign), and hyper-reflexia (knee and ankle jerk bilaterally) of both legs. Lhermitte's sign, Patrick's test, Schober's test, and straight leg rising test were absent. There was no spinal tenderness on percussion, or limitation of cervical rotation, extension or flexion. Abnormal laboratory data included erythrocyte sedimentation rate to be 30 mm, serum IgA 609 mg/dl (normal: 253.1 $\pm$ 17.3 mg/dl), IgM 265 mg/dl (normal: 151.4 $\pm$ 12.2 mg/dl), IgG-anticardiolipin antibody 18.2 GPL/ml (normal: <12 GPL/ml) and positive HLA-B27 antigen. Conventional radiography did not show structural change at cervical, thoracic or lumbosacral vertebrate. Margin erosion and subchondral sclerosis (lower part) were seen at left sacroiliac joint (SIJ) than right side (Fig. 1a). Grade 2 sacroiliitis was considered. The MEP was compatible with cord injury below cervical level. EMG revealed chronic neurogenic denervation over L5 and S1 innervated muscles. Head MRI did not disclose significant change. Spinal MRI revealed mild C7-T1 cord atrophy (Fig. 1b) [3]. Cerebrospinal fluid analysis was normal. BASDAI was 2.8 and BASFI was 2.9, respectively. She refused treatment. One year later, she returned and complained having typical morning stiffness, persistent lumbago, and limitation of lumbar motion for 6 months. Her limb tightness and shoulder joint pain also worsened. SIJ radiograph showed a mild deterioration of sclerosis (Fig. 1c). Scintillography showed strong isotope uptake at bilateral SIJ (Fig. 1d). Lumbar radiograph still did not reveal typical vertebral change. BASDAI increased to 6.5 and BASFI to 6.0, respectively. Her pain did not respond well to nonsteroidal anti-inflammatory drugs, corticosteroid and sulfasalazine, and was well mitigated by methotrexate, which also ameliorated her motor weakness and attenuated hyper-reflexic reaction. One more year ago, her sclerosis mildly progressed at both SIJ (Fig. 1e). BASDAI decreased to 2.8 and BASFI to 3.0, respectively.

Case 2

A 19-year-old lady experienced tightness over shoulder and upper proximal limb at both sides, and mild neck pain occasionally for 1 year before presentation. Her tightness and pain was mild and tolerable, occurred spontaneously at any time, was not relieved by rest or exercise, and peaked by prolonged walking, standing, or lifting. She could walk, ride bike, and climb stairs properly. Neurological examination revealed mild spasticity, motor soft signs (Wartenberg's sign, finger flexor reflex and Hoffmann sign at both

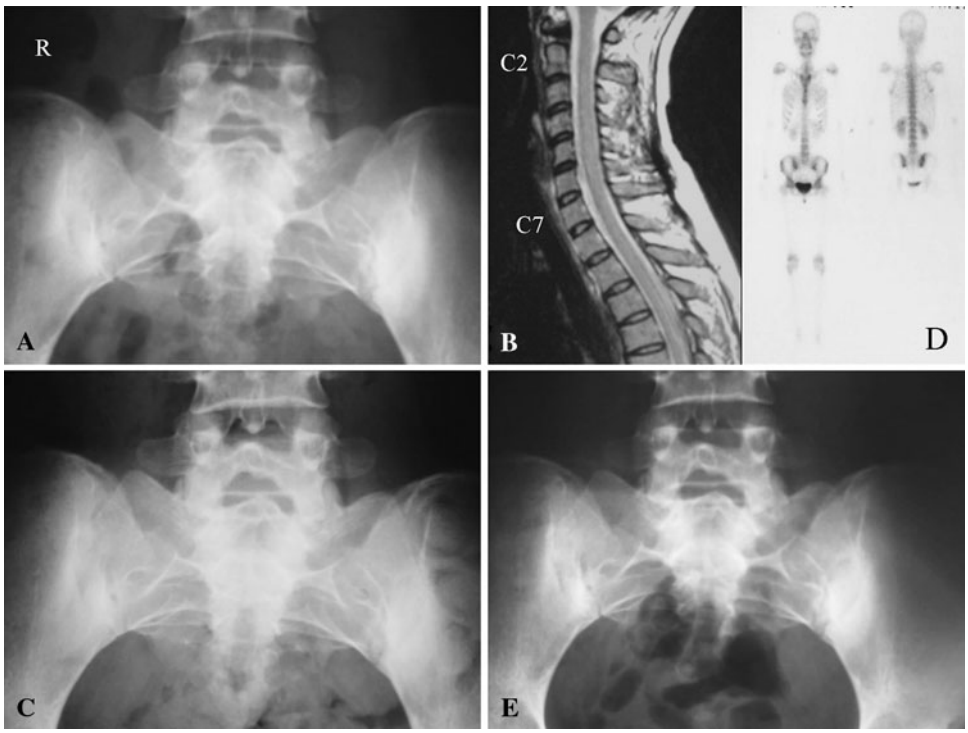

Fig. 1 Radiography showed margin erosion and subchondral sclerosis of lower part of sacroiliac joint, especially left side (**a**). Spinal magnetic resonance imaging revealed cord atrophy at C7-T1 level (**b**). One year later, mild progression of sacroiliitis joint was seen (**c**). Scintillography disclosed radioisotope uptake at bilateral sacroiliac joints (**d**). On next year, sclerosis mildly progressed at left sacroiliac joint (**e**). *R* right side

hands), and hyper-reflexia (knee and ankle jerk bilaterally) of both legs. Lhermitte's sign, Patrick's test, Schober's test, and straight leg rising test were absent. There was no spinal tenderness on percussion, or limitation of cervical rotation, extension or flexion. Abnormal laboratory data were positive HLA-B27 antigen. Conventional radiography did not show structural change at cervical, thoracic, or lumbosacral vertebrate, nor SIJ (Fig. 2a). The MEP was compatible with cord injury at cervical level. EMG revealed chronic neurogenic denervation over C6-T1 innervated muscles. Head MRI did not disclose significant change. Spinal MRI revealed mild cord atrophy at C7-T2 level (Fig. 2b). Cerebrospinal fluid analysis was normal. BASDAI was 2.7 and BASFI was 2.8, respectively. Her pain was initially controlled by nonsteroidal anti-inflammatory agents and she lost follow-up afterward. Six months later, she returned and complained having typical morning stiffness, persistent lumbago, and limitation of lumbar motion for three months. Her limb tightness joint and pain also worsened. SIJ radiograph showed mild erosion of margin at left side compatible with Grade 2 sacroiliitis. Scintillography showed strong isotope uptake at bilateral SIJ (Fig. 2c). Cervical and lumbar radiograph did not reveal typical change. BASDAI increased to 6.0 and BASFI to 5.4, respectively. Nonsteroidal anti-inflammatory drugs and corticosteroid were subsequently initiated. Finally, her pain was well mitigated by sulfasalazine, which also ameliorated her motor weakness and attenuated hyper-reflexic reaction. BASDAI decreased to 2.3 and BASFI to 2.3, respectively.

Case 3

A 46-year-old lady experienced tightness and pain over shoulder and hand at both sides, following at foot, and flank occasionally for 2 years before presentation. Her tightness and pain was mild and tolerable, occurred spontaneously at any time, was not relieved by rest or exercise, and peaked by prolonged walking, standing or lifting. Three months before presentation, her flank pain became more severe at morning or in cold. She could walk, ride motorcycle, and climb stairs, but was unable to hold chopsticks properly as in previous. Neurological examination revealed mild spasticity, motor soft signs (Wartenberg's sign, finger flexor reflex and Hoffmann sign at both hands), and hyper-reflexia (knee and ankle jerk bilaterally) of both upper and lower limbs. Lhermitte's sign, Patrick's test, Schober's test, and straight leg rising test were absent. There was no spinal tenderness on percussion, or limitation of cervical rotation, extension, or flexion. Cervical motoromyelopathy was interpreted. Abnormal laboratory data included erythrocyte sedimentation rate to be 28 mm, serum IgM 240 mg/dl (normal: 151.4 ± 12.2 mg/dl), and positive HLA-B27 antigen. Cervical and lumbosarcal radiography showed mild degenerative change. No vertebral change was seen at thoracic spine. SIJ radiography showed equivocal reactive change (Fig. 3a). The MEP was compatible with cord injury at cervical level. EMG revealed chronic neurogenic denervation over C5-T1 innervated muscles. Head MRI did not disclose significant change. Spinal MRI revealed mild

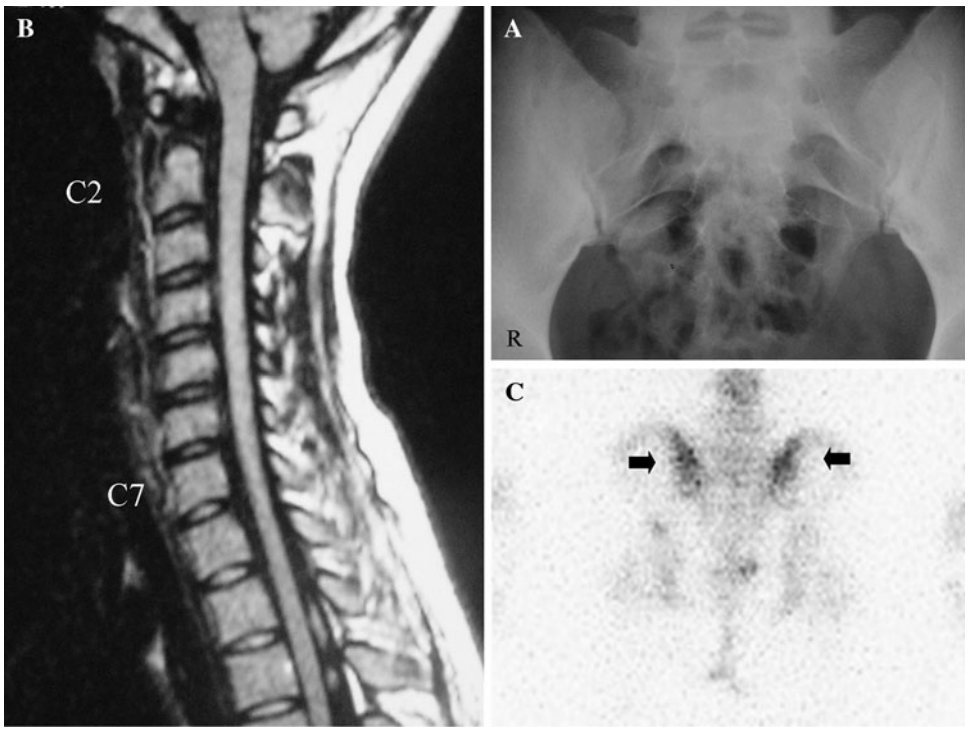

Fig. 2 No significant reactive change was seen at sacroiliac joint (**a**). Spinal magnetic resonance imaging revealed cord atrophy at C7-T2 level (**b**). Six months later, scintillography disclosed radioisotope uptake at bilateral sacroiliac joints (*arrow*) (**c**). *R* right side

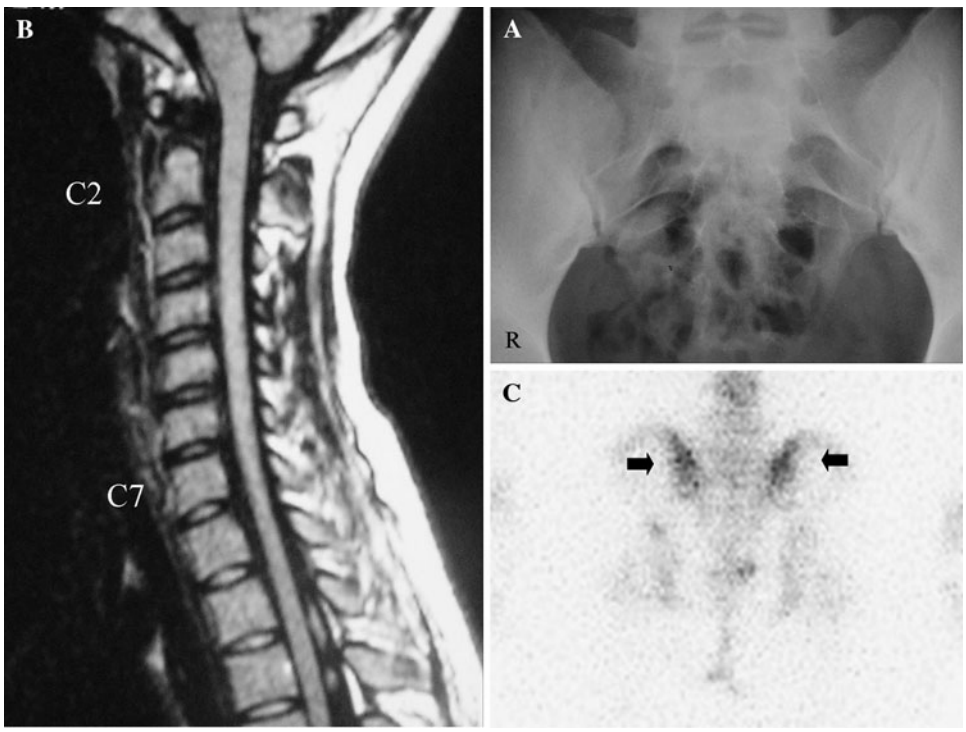

Fig. 3 Radiography showed equivocal reactive change at sacroiliac joints (**a**). Spinal magnetic resonance imaging revealed cord atrophy at C5-T1 level (**b**). One year later, scintillography disclosed radioisotope uptake at bilateral sacroiliac joints (*arrow*) (**c**). *R* right side

lower cervical cord atrophy (Fig. 3b). Cerebrospinal fluid analysis was not studied as family refused lumbar puncture. BASDAI was 2.8 and BASFI was 3.0, respectively. She preferred traditional treatment afterward. One more year later, she returned and complained having typical morning stiffness, persistent lumbago, and limitation of lumbar motion for at last 7 months. Her limb tightness joint and pain also progressively worsened. SIJ radiograph showed Grade 3 sacroiliitis. Scintillography showed strong isotope uptake at bilateral SIJ (Fig. 3c). Cervical and lumbar

radiograph did not reveal any change. BASDAI increased to 6.9 and BASFI to 6.1, respectively. Her pain was finally well mitigated by sulfasalazine, which also ameliorated her motor weakness and attenuated hyper-reflexic reaction. BASDAI decreased to 2.6 and BASFI to 2.7, respectively.

Summary of electrodiagnostic and laboratory tests

The H reflex, latency, amplitude, and conduction velocity were within reference range, whereas dispersion was found in F wave in our patients.

The cytology, biochemistry, blood–brain barrier index, and IgG-Link index in CSF were normal in our patients. Antibodies to HTLV-I and HTLV-II did not increase in blood and CSF. There was no oligoclonal band recovered in CSF. Multiple sclerosis is unlikely in them.

An increase in blood IgA level was detected in two patients. No paraproteinemia was found.

Follow-up

They were followed up 8–11 years after their initial presentation. During this period, typical sacroiliac pain refractory to rest, lumbar stiffness, and limitation of lumbar movement developed progressively within six months after initial presentation in all of them. Their limb tightness and weakness at distal hand represented by soft signs also worsened.

Uveitis occurred in Case 1 at 5 years later. Till now, they did not experience unknown urinary symptom.

Discussion

In contrast to overwhelming publications of spondylotic compressive myelopathy in AS, NCM has been reported in only ten AS patients in literature [8–17]. It doubts if the association between NCM and AS is really underestimated or an accidental finding merely. Unfortunately, cord injury is only concerned in case of spinal fracture and is barely mentioned without vertebral disorder. Nevertheless, variable magnitude of spinal blocking has already been demonstrated in 63–71% of AS patients without spinal fracture [18, 19], implicating the fact that subclinical spinal cord injury is underestimated in AS. On the other hand, AS may be overlooked in symptomatic NCM when typical skeletal symptom is absent or minimal, especially in women who tend to manifest skeletal symptoms at neck, shoulder, upper chest, or peripheral joint instead of lower spinal column [20] as our patients. Since the frequency of NCM in AS may be higher than expected in previous concept, a careful evaluation and monitor of noncompressive persecution on spinal cord may help to establish a more appropriate treatment program for AS patients with symptomatic myelopathy.

Based on the clinical course and laboratory results in previous reports, we categorize two types of NCM in AS. The first type is a concomitant intraspinal secondaries including multiple sclerosis [8–13], chronic ischemia [14], cord traction [15], irradiation [16], or demyelination [17] ranging from acute to chronic onset. The second type is acute or subacute transverse myelitis [21, 22] or arachnoiditis [22, 23] without evidence of infection or other collagen disease. In our patients, they exhibited multisegmental spinal atrophy with chronic progression different from previous cases and that adds a new manner of noncompressive damage in AS patients.

Generally, sensory impairment predominates in autoimmune-associated myelopathy [24, 25] and compressive myelopathy in AS patients [5], whereas motoropathy has only been reported in a few cases of de Gorgerot-Sjogren syndrome [26–28], rheumatoid arthritis [29, 30], or polyarthritis sporadically but not in AS yet. In our patients, electrodiagnostic study suggested a predominant involvement of motor neuron but not sensory neuron. It is expected that their spinal atrophy results from a selective involvement of spinal motoroneurons and their descending pathways rather than nonspecific damage of spinal neurons or tracts. Therefore, a different pathomechanism is supposed in this subgroup of autoimmune-associated motor myelopathy from other NCM in autoimmune diseases.

Currently, spinal motoroneuron has been found vulnerable for inflammatory molecules. Such as tumor necrosis factor alpha (TNFα), an inflammatory product of Th1 cells, is recently found to mediate neurotoxicity of spinal motoroneuron in amyotrophic lateral sclerosis [31, 32] and HTLV-I-associated myelopathy [33]. Cytokines can mediate neuronal damage through multiple pathways. In de Gorgerot-Sjogren syndrome, rheumatoid arthritis, or AS [34], an alteration of T-cell subset physiology and distribution with cytokines generation, like TNFα, has already been established. If so, generation of specific cytokines reactive to spinal motoroneuron may correspond for a predominance of motoropathy in these autoimmune diseases. A benign course of motor function in our patients from motor neuron disease or HTLV-I-associated myelopathy may reflect variation of immune status or network reaction in AS.

Spinal fracture in AS patients is three times more common than in general population. Occult fracture, vertebral instability, ligamentous hypertrophy/ossification, and soft tissue proliferation are frequently found in AS patients. They may not directly compress the cord to produce myelopathic symptom but may cause cord injury by repetitive spinal movements. Subclinical neuronal death may ensue. We cannot completely exclude this possibility

precipitating for cord injury in our patients although there is no evidence of these changes supported by their neuroimaging study.

Classical sacroiliac and lumbar pain developed within 6 months after their presentation. Although they responded favorably to treatment, spinal stiffness still progressed and gradually disturbed their daily living activity. In contrast to motor neuron disease, our patients do not have notable muscle wasting or bulbar weakness. The clinical course of motor function is also benign in them. Their muscle tightness and motor weakness became stable when their back pain was undercontrolled, supporting a possible relation between inflammation and motoropathy in them. Nevertheless, we remind two points. First, noncompressive motor myelopathy can present as early manifestation of AS and that should be differentiated in NCM in clinical practice when the underlying is unknown in 60–70% of NCM patients despite of extensive investigation. Second, autoimmune-associated myelopathy can range in a wide spectrum of neurological course and presentation.

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