Indemonstrable Axial Spondyloarthritis: Does It Exist?

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The new entity of non-radiographic axial spondyloarthritis and classification criteria for axial spondyloarthritis were recently born as a result of growing dissonance between the perceived need for an earlier diagnosis of patients with ankylosing spondylitis and lack of accepted tools to make this diagnosis in the early stages of this disease [1]. The presence of characteristic changes on magnetic resonance imaging of sacroiliac joints or positive test for human leukocyte antigen-B27 in patients with high or even moderate clinical suspicion for spondyloarthritis now enables classification of these patients as having AxSpA in the absence of radiographic sacroiliitis on X-ray films. The sensitivity of these new criteria, based on the analysis of data of 649 patients, was established as 82.9%, still leaving approximately one of every six patients with AxSpA out of the disease frame. Thus, blind adherence to these classification criteria for diagnostic purposes may lead to under-diagnosis of a significant proportion of these patients and delay appropriate treatment. We suggest that, in the absence of validated diagnostic criteria, clinical diagnosis should still be made and appropriate treatment administered in patients with a high clinical suspicion for nrAxSpA, even if they do not satisfy current classification criteria.

AxSpA = axial spondyloarthritis
nrAxSpA = non-radiographic axial spondyloarthritis

PATIENT DESCRIPTION

A 25 year old woman with previously diagnosed fibromyalgia treated with amytriptilin at a dose of 35 mg/day was referred to a rheumatologist for further treatment. She complained of constant widespread pain and fatigue, which reportedly limited her ability to participate in most social activities. Her maximal pain was located over the lumbar spine, pelvis and neck. It was triggered by rest, worsened at night, and was accompanied by prolonged morning stiffness. Her family history was relevant for a brother with AS. Her physical examination was significant for a tendency to kyphotic posture, which she mentioned was most prominent in the early and mid-morning hours. While all points classically related to fibromyalgia were tender on pressure, the patient also had diminished Schober test of 13 cm (normal 14.5), increased finger-to-floor distance of 34 cm (normal < 5), reduced chest expansion of 2.5 cm (normal 4.5) and occiput-to-wall distance of 3 cm (normal 0). AxSpA was suspected, based on the family history of AS, persistent inflammatory-type back pain, and pronounced limitation of spinal mobility.

Extended-release etodolac at a dose of 600 mg daily was added to amitryptilin, and relevant blood tests and imaging studies were ordered. At follow-up, the patient reported good but short-term (6–8 hours) pain relief with etodolac. Her erythrocyte sedimentation rate was 90 mm/hour, serum level of C-reactive protein was three times the upper limit of normal, HLA-B27 antigen was negative, and X-ray films of the spine and sacroiliac joint were normal. MRI of the SIJ, performed later, was also considered normal. Etoricoxib and lornoxicam were not more effective than etodolac. It was therefore decided to start treatment with a biologic agent. While infliximab significantly improved her ESR and CRP levels, it was only partially effective in ameliorating the clinical symptoms, and she still had to use etodolac or etorixocib almost every morning. Golimumab, on the other hand, led to the complete disappearance of both back pain and morning stiffness but was eventually stopped because of adverse effects. The temporary cessation of anti-tumor necrosis factor treatment, which followed, resulted in significant increase in pain intensity, elevation of ESR/CRP levels and a decrease in her functional capacity.

Currently, the patient is under treatment with adalimumab, etodolac and amytriptilin and has returned to full social and physical activity. X-ray films of the SIJ and spine, obtained after 5 years of follow-up, are still normal.

AS = ankylosing spondylitis
SIJ = sacroiliac joint

COMMENT

The combination of a strong family background of AS, inflammatory back pain, characteristically decreased spinal mobility, elevated levels of laboratory parameters of inflammation, and good (even if only short-term) response to non-steroidal anti-inflammatory drugs, as observed in the patient described here, raised suspicion for the presence of AxSpA. The finding of obvious sacroiliitis and/or HLA-B27, as required by the classification criteria, would make the diagnosis straightforward. The absence of HLA-B27 antigen, however, and negative sacroiliitis imaging including MRI, complicated the

ESR = erythrocyte sedimentation rate
CRP = C-reactive protein

case. The lack of evidence for another disorder to explain the spectrum of the above features was an important factor in the decision making. Fibromyalgia, which does not induce ESR/CRP elevation, does not decrease objective spinal mobility, and is not typically dramatically improved by anti-inflammatory treatment, could only be regarded as a contributory or secondary phenomenon in this patient [2].

MRI of the SIJ, showing typical bone marrow edema subjacent to the joints, is considered the modern imaging hallmark of AxSpA and is accepted by many as necessary for the diagnosis of nrAxSpA in practice. Indeed, able to detect inflammatory changes in both soft tissues and bone, MRI allows visualization of sacroiliitis in patients in whom conventional radiography does not show any changes and provides objective evidence of disease activity. The sensitivity of MRI of the SIJ for the diagnosis of AxSpA has been calculated as only 66%, according to accepted classification criteria. However, more recently reported data suggest that the ability of MRI to reveal existing sacroiliitis may be even lower than previously thought. In one study, for example, MRI of SIJ was read as positive in only 40% of cases with histologically proven inflammation [3]. In addition, the MRI features of sacroiliitis can be volatile, turning from positive to negative and vice versa, as shown by de Hooge et al. [4] in 9% of patients with nrAxSpA when repeated after 3 months.

HLA-B27 is a major histocompatibility class I gene, tightly related to AS and present in about 90% of American AS patients of Caucasian descent. The contribution of HLA-B27 to the genetic susceptibility to AS stands, however, at only 25–40%, which suggests that other genes play a role in disease susceptibility. Of significance, the prevalence of HLA-B27 in cohorts of patients diagnosed with nrAxSpA may be significantly lower, as compared to AS patients [5]. In addition, the real prevalence of HLA-B27 in the Israeli population with its complex ethnic background, and in Israeli patients with AS or nrAxSpA, has not been fully and systematically studied, further complicating the interpretation of HLA-B27 testing in Israelis.

Thus, confirmation of the diagnosis in a patient with high suspicion for nrAxSpA may be difficult and unrewarding even after a long period of follow-up, considering that the natural history of nrAxSpA is also not known; i.e., it may not inevitably evolve into fully fledged advanced AS.

In summary, reaching a diagnosis in the absence of validated diagnostic criteria is frequently difficult and requires an individual, thoroughly weighted, approach to each patient. It may be particularly complicated if the entity is not yet well understood, as in the case of nrAxSpA.

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References

1. Slobodin G, Rosner I, Rimar D, et al. Ankylosing spondylitis: field in progress. *IMAJ* 2012; 14: 763-7.
2. Slobodin G, Reyhan I, Avshovich N, et al. Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. *Clin Rheumatol* 2011; 30 (8): 1075-80.
3. Maksymowych W. Challenges in imaging – clinical correlations. Materials of 8th International Congress on Spondyloarthritis. *Clin Exp Rheumatol* 2012; 30: 600.
4. De Hooge M, van den Berg R, Reijnierse M, et al. Localization of bone marrow edema in sacroiliac joints in spondyloarthritis patients: does the site of lesions change over a 3-month period. Materials of 8th International Congress on Spondyloarthritis. *Clin Exp Rheumatol* 2012; 30: 627.
5. Rudwaleit M. Early cohorts in spondyloarthritis. Materials of 8th International Congress on Spondyloarthritis. *Clin Exp Rheumatol* 2012; 30: 601-2.

Capsule

Activated ClpP kills persisters and eradicates a chronic biofilm infection

Chronic infections are difficult to treat with antibiotics but are caused primarily by drug-sensitive pathogens. Dormant persister cells that are tolerant to killing by antibiotics are responsible for this apparent paradox. Persisters are phenotypic variants of normal cells and pathways leading to dormancy are redundant, making it challenging to develop anti-persister compounds. Biofilms shield persisters from the immune system, suggesting that an antibiotic for treating a chronic infection should be able to eradicate the infection on its own. A compound capable of corrupting a target in dormant cells will probably kill persisters. The acyldepsipeptide antibiotic (ADEP4) has been shown to activate the ClpP protease, resulting in death of growing cells. Conlon et al. show that ADEP4-activated ClpP becomes a fairly non-specific protease and kills persisters by degrading over 400 proteins, forcing cells to self-digest. Null mutants of *clpP* arise with high probability, but combining ADEP4 with rifampicin produced complete eradication of *Staphylococcus aureus* biofilms in vitro and in a mouse model of a chronic infection. These findings indicate a general principle for killing dormant cells – activation and corruption of a target, rather than conventional inhibition. Eradication of a biofilm in an animal model by activating a protease suggests a realistic path towards developing therapies to treat chronic infections.

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Eitan Israeli

"You can out-distance that which is running after you, but not what is running inside you"

Rwandan proverb