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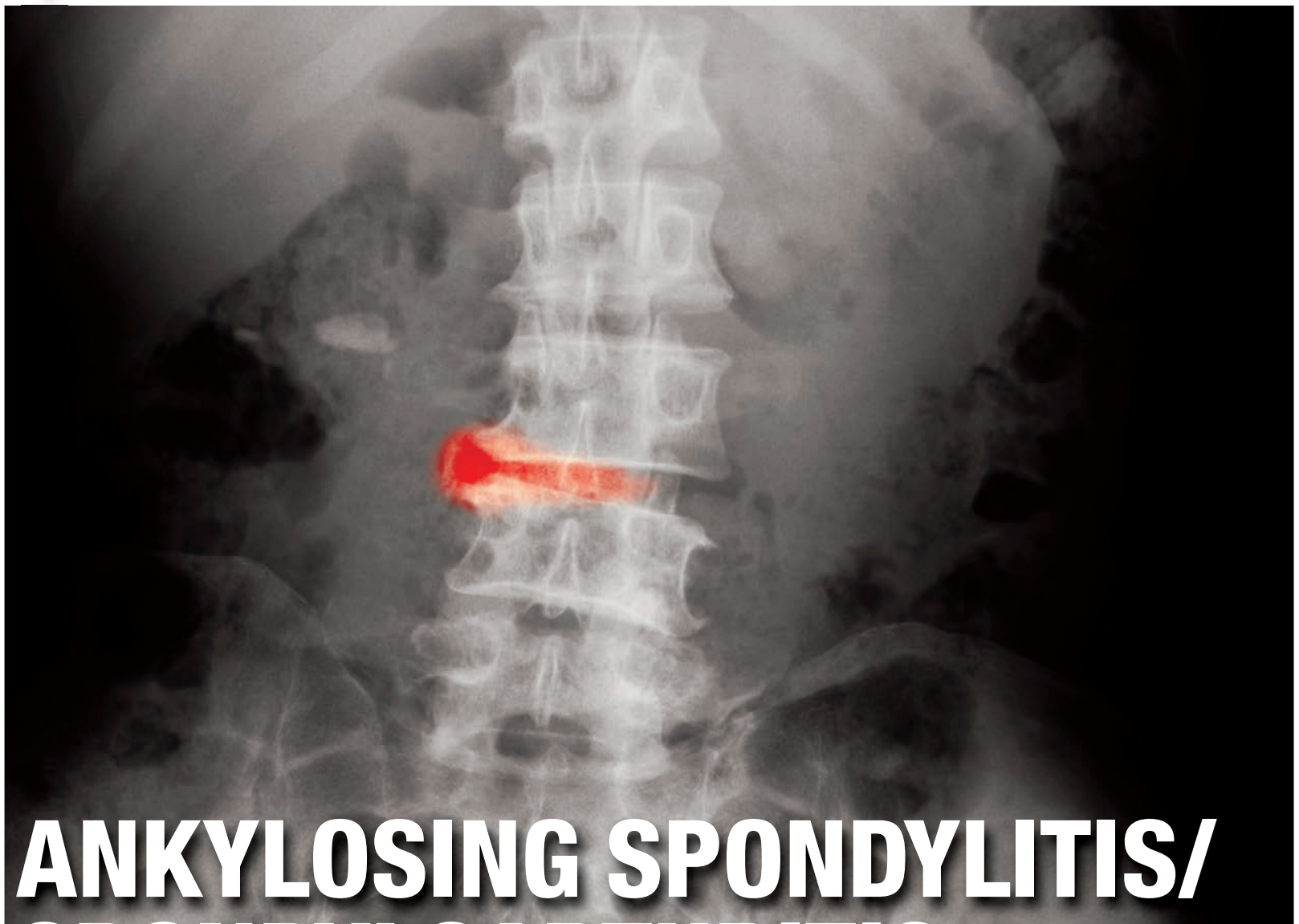


ANKYLOSING SPONDYLITIS/ SPONDYLOARTHRITIS

INSIDE

THE AUTHOR

ASSOCIATE PROFESSOR PAUL BIRD
Rheumatologist, conjoint associate professor at the University of NSW, Sydney, NSW.

Background

THE term 'spondyloarthritis' encompasses a group of related conditions with common clinical features and an increased frequency of *HLA-B27*. The shared clinical features include axial skeleton involvement (sacroiliac joints and spine), peripheral joint involvement that is commonly asymmetrical, oligoarticular, large joint, as well as enthesitis, tenosynovitis and extra-articular features, including uveitis.

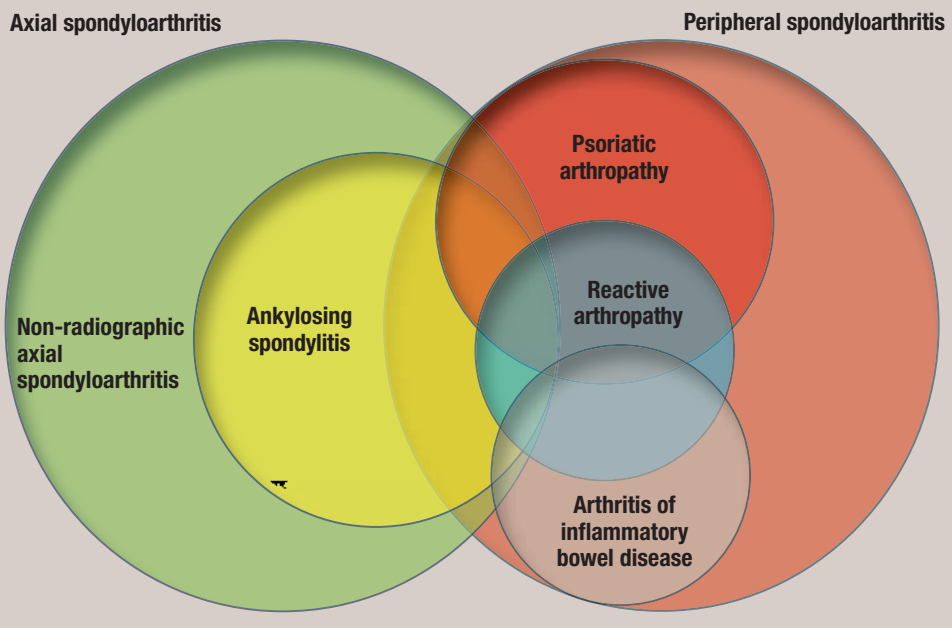
Etymologically, the term spondyloarthritis is an amalgamation of spondylo and peripheral arthritis (joint inflammation) to signify the association of peripheral and axial involvement in these conditions.

The group includes ankylosing spondylitis, psoriatic arthropathy, reactive arthropathy, spondyloarthritis associated with inflammatory bowel disease, undifferentiated spondyloarthritis and non-radiographic spondyloarthropathy.[1]

The term ankylosing spondylitis is derived from the Greek words *ankylosis* (bent or crooked) and *spondylos* (vertebra). This disease appears in specimens from antiquity emphasising its ancient origins.

In the past 10 years, new treatment for ankylosing spondylitis has dramatically altered the outcome for this group of patients. Early diagnosis is important to reduce the immense symptomatic burden and loss of function during the productive years of these patients' lives.

Figure 1. Spectrum of spondyloarthritis.



Classification of spondyloarthritis

The term spondyloarthritis includes a spectrum of disorders with similar features and an increased frequency of *HLA-B27* (see figure 1). Axial involvement leads to inflammatory lower back pain with marked morning spinal stiffness and worsening of symptoms with inactivity. Common clinical features in peripheral joints include large joint involvement, oligarthritis and monoarthritis, tenosynovitis manifesting as dactylitis, and enthesitis. Extra-articular features associated with this group of disorders include uveitis and, rarely, aortic regurgitation and upper lobe pulmonary fibrosis.

Some diseases within this group exhibit predominantly axial skeleton involvement with peripheral arthritis (chiefly large joint) occurring in a proportion of sufferers. This group is termed the axial spondyloarthropathy group and includes ankylosing spondylitis.

Ankylosing spondylitis is the best example of this end of the spectrum – primarily axial involvement with peripheral arthritis occurring in the hips and shoulders.

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The peripheral spondyloarthropathritis group of conditions within the spectrum exhibit primarily peripheral joint symptoms with axial involvement seen less frequently.

Psoriatic arthritis, reactive arthritis, and IBD associated spondyloarthropathy commonly manifest with predominantly peripheral symptoms with axial symptoms less frequent.

Undifferentiated spondyloarthropathy is a term applied to subjects who have some features of spondyloarthropathy but do not meet diagnostic criteria for ankylosing spondylitis, psoriatic arthropathy, or reactive arthropathy spondyloarthritis associated with inflammatory bowel disease.

These patients may remain undifferentiated or may differentiate over time to fit more clearly into one of the other categories.

Non-radiographic spondyloarthropathy is a relatively recent term. This group of patients have features consistent with axial spondyloarthropathy with primarily axial involvement. The defining feature of this group is that X-ray changes of sacroiliitis are absent, but the patient may have characteristic clinical features of spondyloarthropathy or MRI features consistent with sacroiliitis or spinal inflammatory disease. The natural history of this group is uncertain.

Whether patients with this condition progress to ankylosing spondylitis, spontaneously resolve or experience remission of symptoms with therapy remains unknown. It is a group that is being closely examined in clinical trials, particularly to determine whether treatment is effective.

Natural history in the axial spondyloarthritis group

There is considerable ongoing debate as to the natural history of conditions encompassed within the axial spondyloarthropathy group. While traditional ankylosing spondylitis patients generally have severe progressive disease, there is uncertainty regarding the progression of patients with milder forms of the disease, and patients with non-radiographic forms.

The natural history pathways of patients with axial spondyloarthropathy is summarised in figure 2.

New criteria to assist in diagnosis: the ASAS criteria

Prior to 2000, treatment options were limited, and the need for early diagnosis to facilitate treatment was less critical. The emergence of effective therapy in the form of anti-TNF agents and interleukin inhibitors, coupled with strong evidence that early therapy leads to marked clinical improvement, means that it is essential that efforts are made to identify these patients early.

The Assessment of Spondyloarthritis International Society (ASAS) criteria were developed in recognition of the difficulty in identifying these patients. The criteria recognise the emerging use of MRI in diagnosis and attempt to include other common features such as enthesitis in the diagnostic method.

The sensitivity of the criteria is 83% with specificity 84%. Of course, no set of criteria are perfect and the ASAS criteria continues to undergo modification as our understanding of these disorders progresses.

The criteria exist to assist rheumatologists in identifying patients with spondyloarthropathy and thereby identifying those patients who would benefit from treatment.

Criteria to assist GPs, based upon the ASAS criteria, are outlined in figure 3.

This How to Treat will focus primarily on ankylosing spondylitis as the prototypic disease within the axial spondyloarthropathy group. Recommendations regarding early diagnosis of inflammatory back pain later in this article relate to all forms of axial spondyloarthropathy.

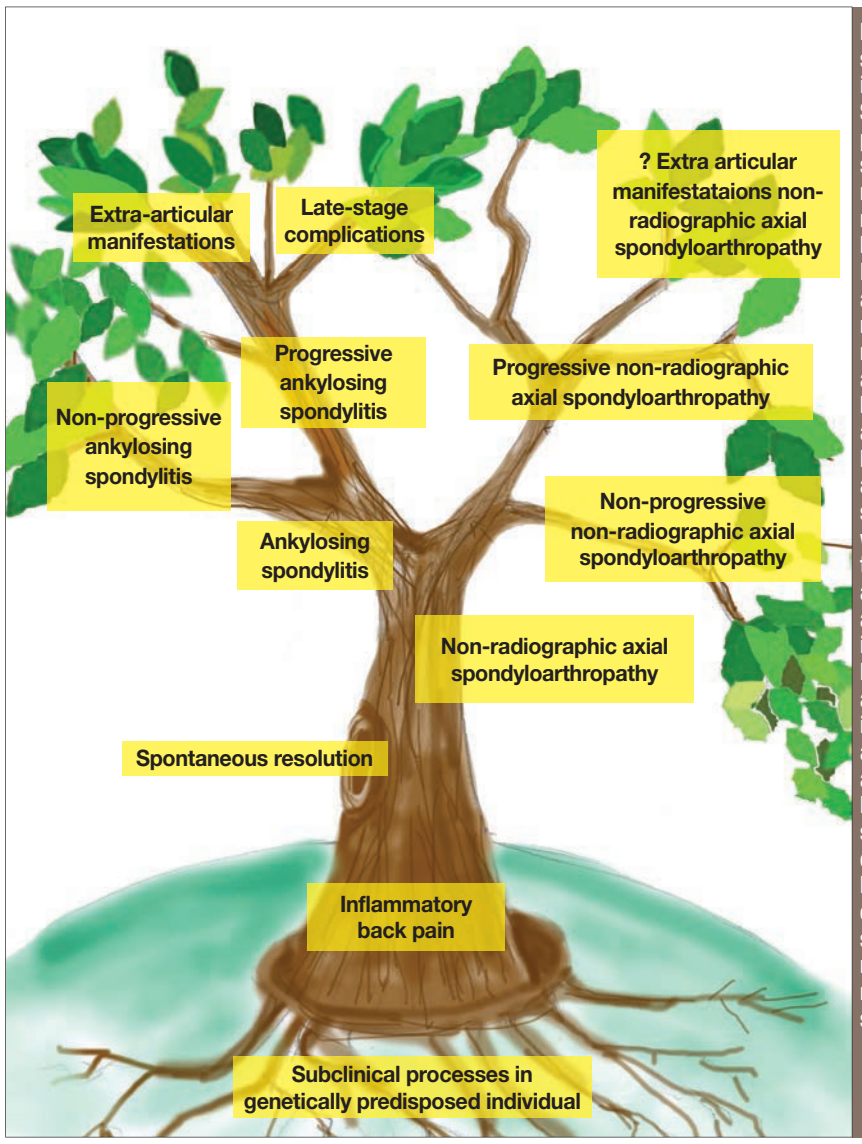

Figure 2. The roots of axial spondyloarthropathy lie in genetic inheritance. Some may be genetically predisposed to develop axial spondyloarthropathy. but never develop any clinical manifestations or may have subclinical disease. Inflammatory back pain occurs and the following pathways may result: either spontaneous resolution or non-radiographic axial spondyloarthropathy branching to progressive and non progressive forms. Progressive forms may develop ankylosis and radiographic sacroiliitis, but it is unknown whether these patients develop true ankylosing spondylitis or are a different phenotype (and are therefore separate branches in this representation.) It is not known whether the extra-articular features are the same in progressive non-radiographic axial spondyloarthropathy and ankylosing spondylitis. Most patients with ankylosing spondylitis have a progressive course, with some developing long-term complications with extra-articular features. A smaller number may have a relatively benign course with non-progressive ankylosing spondylitis.

Figure 3. ASAS criteria for the diagnosis of axial spondyloarthropathy (in patients with back pain ≥three months and age at onset < 45 years).

Sacroiliitis on Imaging* plus ≥ 1 spondyloarthritis feature**

OR

HLA-B27 plus ≥ 2 spondyloarthritis features**

***Sacroiliitis on imaging: Active/acute inflammation on MRI highly suggestive of sacroiliitis associated with spondyloarthritis OR Definite radiographic sacroiliitis according to modified New York criteria**

****Spondyloarthritis features: Inflammatory back pain, Arthritis, Enthesitis (heel), Uveitis, Dactylitis, Psoriasis, Crohn's disease/ulcerative colitis, Good response to NSAIDs, Positive family history for spondyloarthritis, HLA-B27, Elevated CRP**

ASAS criteria for the diagnosis of peripheral spondyloarthropathy

Arthritis or enthesitis or dactylitis

Plus ≥ 1 of: Psoriasis, Inflammatory bowel disease, Preceding infection, HLA-B27, Uveitis, Sacroiliitis on imaging (x-ray or MRI)

OR

Plus ≥ 2 of the remaining: Arthritis, Enthesitis, Dactylitis, Inflammatory back pain in the past, Family history for spondyloarthritis

Based on Rudwaleit M, et al. The development of assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Annals of the Rheumatic Diseases* 2009; 68:777-83; and Rudwaleit M, et al. The assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Annals of the Rheumatic Diseases* 2011; 70:25-31.

Epidemiology

THE prevalence of ankylosing spondylitis in patients of European descent is approximately 0.5-1%, with the condition occurring at similar rates in Asian populations.[2] It is rare in African populations and in Indigenous Australians. Males are more affected than females (3:1) with the typical age of onset in the late teens and early 20s. Diagnosis is often delayed because of the fluctuating nature of symptoms. The average delay from onset of symptoms to diagnosis is 8-11 years.

Aetiology and pathogenesis

ANKYLOSING spondylitis occurs with higher frequency within families. The cause remains unknown; however, it is widely recognised that *HLA-B27* is the major gene associated with the condition. *HLA-B27* occurs in 90% of patients with ankylosing spondylitis and may have a direct etipathogenetic role via interleukin 23 (IL-23) signalling. The exact triggers in individuals remain undetermined, but putative mechanisms include alterations in the gut microbiome and mechanical entheseal stress. Environmental factors associated with greater severity of disease are cigarette smoking, lower socioeconomic status and educational level.

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Pathophysiology

THE enthesis is the region at the junction between tendon and bone. This has been suggested as the key target in spondyloarthritis. The area contains a unique type of T-cell, which, when activated by Il-23, can produce the characteristic changes seen in ankylosing spondylitis.

Enthesitis occurs in the axial skeleton (spondylitis and sacroiliitis) and surrounding peripheral joints (enthesitis and tendonitis). The proposed sequence of events is enthesitis and osteitis with ossification occurring as part of the unbridled pathogenic process. Ultimately, if the process is not arrested by effective treatment, ossification of entheseal attachments and ultimately, ankyloses, will occur (see figure 4).

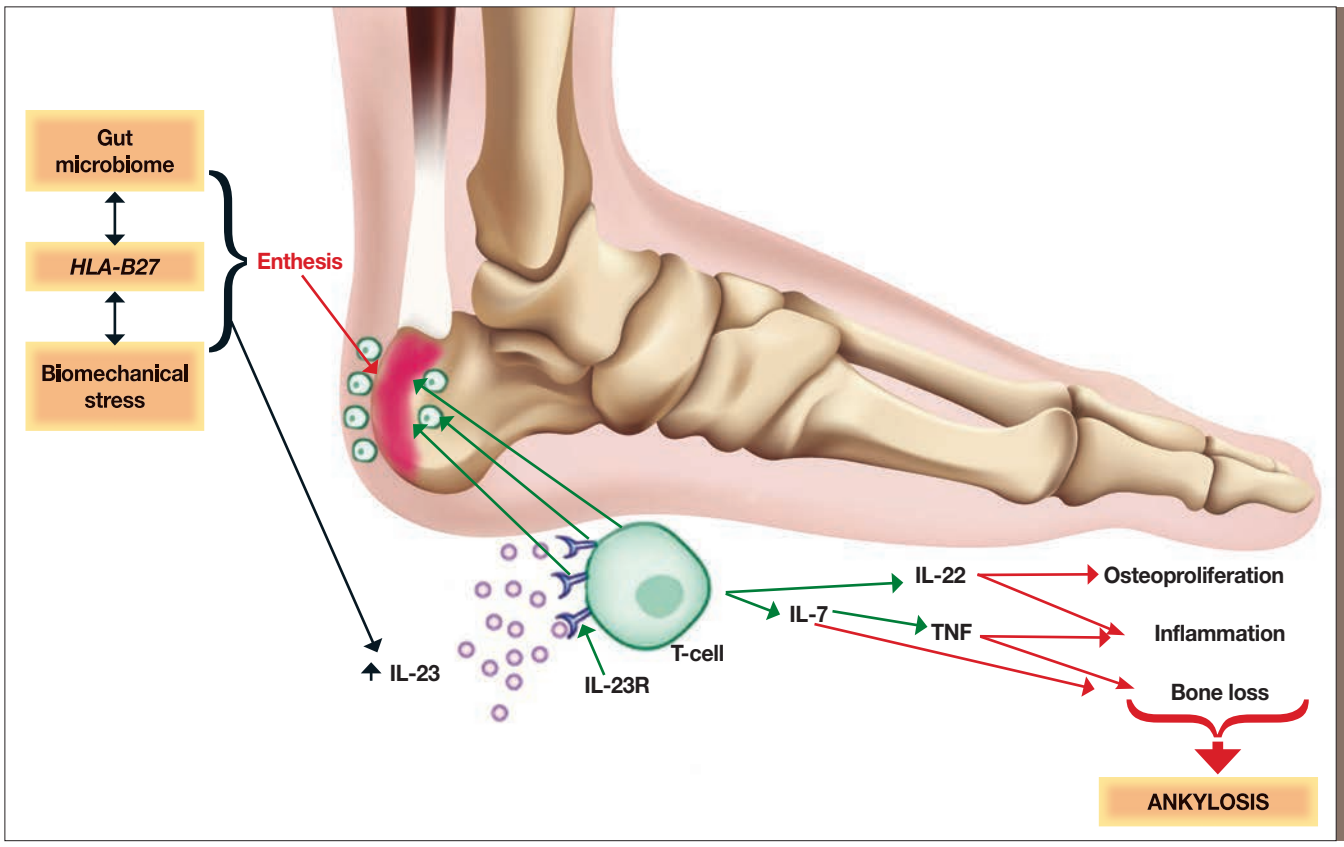

Figure 4. IL-23 and entheseal T-cells in the pathogenesis of spondyloarthritis.

Clinical features

CONSIDER ankylosing spondylitis in any patient who presents with chronic back pain (longer than three months), with symptoms starting before the age of 45. Chronicity is relevant because acute back pain is so common in primary care.

The features of back pain that signal an inflammatory cause are age at onset less than 40-45, insidious onset, pain at night (with improvement on getting up), improvement with exercise and no improvement with rest (see figure 2).

It is important to differentiate inflammatory from mechanical back pain, as outlined in figure 5. Please see the full resource online for further details.

Extra-articular features

Extra-articular features are increasingly rare with modern treatment, with the exception of uveitis, recurrent in a small proportion of patients. The most commonly reported features are anterior uveitis (30-40%), aortic regurgitation because of aortic valve root dilatation, upper lobe pulmonary fibrosis, IgA nephropathy and amyloidosis.

Anterior uveitis (predominantly unilateral) usually becomes less frequent with TNF inhibition. Notably, among the TNF inhibitors, infliximab (Remicade) and adalimumab (Humira) appear to provide the best likelihood of reducing the frequency of episodes of uveitis in patients with ankylosing spondylitis.

Other features that should increase suspicion of ankylosing spondylitis include

- Family history
- Other features of spondyloarthritis (episodes of iritis, recurrent Achilles tendonitis, dactylitis)
- Co-existent psoriasis or IBD (ankylosing spondylitis is accompanied by psoriasis or IBD in around 10% of cases)
- Dramatic response to NSAIDs

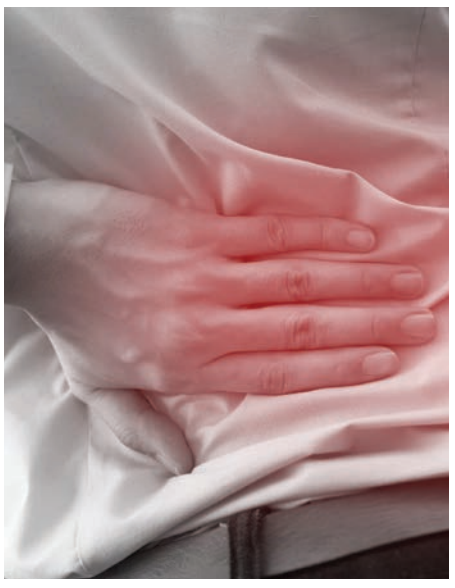

Figure 5. Differentiating inflammatory and mechanical back pain.

Diagnosis/investigations

Genetic testing

HLA-B27 still has a role in assessment of patients with suspected ankylosing spondylitis. More than 90% of patients are *HLA-B27* positive compared with 8% of the general population.

It is well recognised that *HLA-B27* forms part of the diagnostic process and is not a diagnostic test that can stand alone. However, the presence of *HLA-B27* raises the likelihood of ankylosing spondylitis in a patient with a compelling history.

Imaging

Plain radiographs

Plain radiographs of the pelvis (sacroiliac joints) are useful in patients with suspected ankylosing spondylitis; however, it is very important that the limitations of plain films are appreciated. Radiographic changes can take years to develop, with some estimates indicating that radiographic sacroiliitis may not be evident for up to 8-10 years after symptoms have developed.

It must also be recognised that

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Assessment

Having made the decision to pursue a diagnosis of AS in a patient, diagnosis will involve a combination of genetic testing, ESR and CRP, radiographs, MRI and referral to a rheumatologist. Clinical tests of spinal function such as Schober's test (to measure a patient's ability to flex the lower back) have low sensitivity and are not an adequate replacement for diagnostic imaging.

Table 1. Investigations

Investigation	Rationale
HLA-B27	Assists in establishing diagnosis, increases likelihood.
Plain AP pelvis radiograph	Helpful if positive. A negative radiograph does not rule out the diagnosis.
MRI SI joints T1 and T2	Sensitive in detecting osteitis (T2) and erosions, sclerosis (T1).
MRI lumbar spine	Rule out alternative diagnoses.
ESR, CRP	Establish baseline disease activity, predicts severe disease.

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plain radiograph sacroiliac joint changes can be subtle and underreported if the reporting radiologist is not familiar with the grading system used for documenting sacroiliac joint changes. The important point overall is that a negative radiograph does not rule out the diagnosis.

For diagnostic purposes, a plain AP pelvic X-ray is optimal. There is no benefit in obtaining radiographs of the rest of the spine unless an alternative diagnosis is being excluded or assessment of damage in long-term ankylosing spondylitis is being assessed.

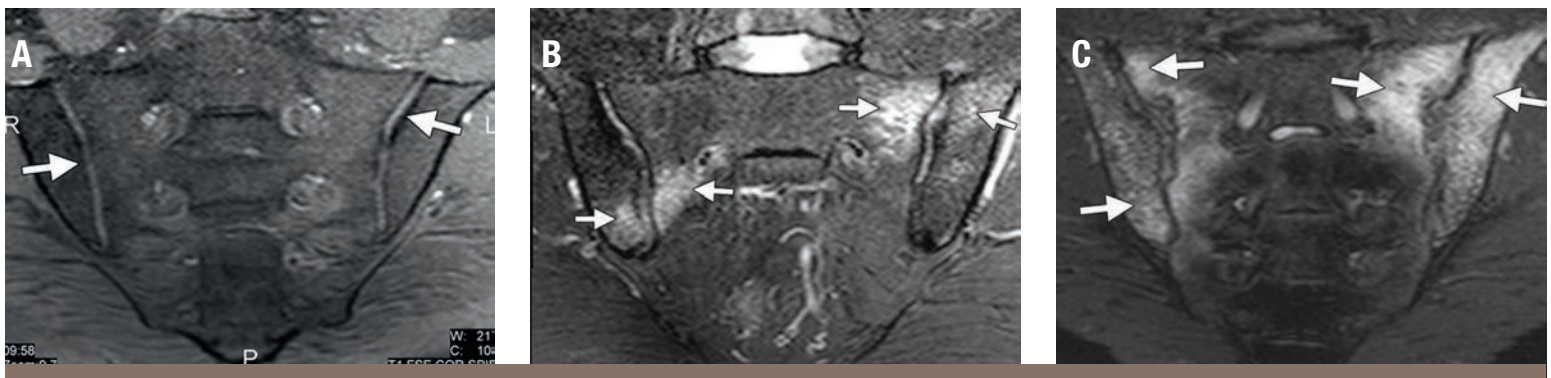

Figure 6. Sacroiliac joint abnormalities in ankylosing spondylitis. A. Normal sacroiliac joint. B. Coronal oblique fat-supressed T2-weighted images of the sacroiliac joint in a 32-year-old man with ankylosing spondylitis shows bilateral periarticular bone marrow oedema (arrows). C. Bone marrow oedema and synovitis in a 32-year-old man with ankylosing spondylitis. Coronal oblique fat-suppressed T2-weighted MR image show bilateral hyperintense sacral and iliac areas consistent synovitis.

Source: Navallas M, et al. Sacroiliitis associated with axial spondyloarthropathy: New concepts and latest trends. *Radiographics* 2013; 33:933-56.

MRI

Increased access to MRI has transformed the early diagnosis of ankylosing spondylitis. MRI can assess active inflammation of the sacroiliac joints and spine.

The most important lesion in the sacroiliac joints is osteitis (formerly bone marrow oedema), a lesion best appreciated on T2 weighted images using a fat suppressions sequence (usually short TI inversion recovery).

Ligament and tendon attachment sites are frequently involved and can be identified on the T2 weight sequence. Synovitis within the sacroiliac joint is visible on post-gadolinium T1 weight images, but is not essential for diagnosis and gadolinium is not required routinely.

Sclerosis, erosions and fat metaplasia are chronic lesions best appreciated on T1-weighted images. These lesions represent damage (erosions), and chronicity (sclerosis and fat metaplasia) (see figure 6).

Spinal MRI is less sensitive than sacroiliac MRI imaging. The predominant abnormalities are corner lesions (hyperintense on T2 weighted imaging) corresponding to the Romanus lesions identified on radiographs in long-term disease. Spondylodiscitis lesions (hyperintense on T2 imaging) correspond to radiographic Anderson lesions in chronic disease.

For practical purposes, MRI imaging should include sacroiliac joints utilising T1 and T2 weighted imaging. Gadolinium is not required for routine sacroiliac joint imaging.

The lumbar spine is included to rule out other possible entities that could mimic sacroiliac pathology. Imaging of the thoracic and cervical region is undertaken if there are specific symptoms in these regions, but not as a routine.

CT and nuclear medicine

Both CT and nuclear scintigraphy have a very limited role in the diagnosis of ankylosing spondylitis and axial spondyloarthropathy. The sensitivity and specificity of both techniques is inferior to MRI. Both CT and bone scan may be useful when other causes of back pain are suspected.

Assessing disease activity

Measurement of ESR and CRP is useful in assessing disease activity and forms part of the baseline assessment once the diagnosis of AS has been established. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (see figure 8) is a tool used by rheumatologists to assist in assessing clinical activity and forms part of the application for access to TNF inhibitors.

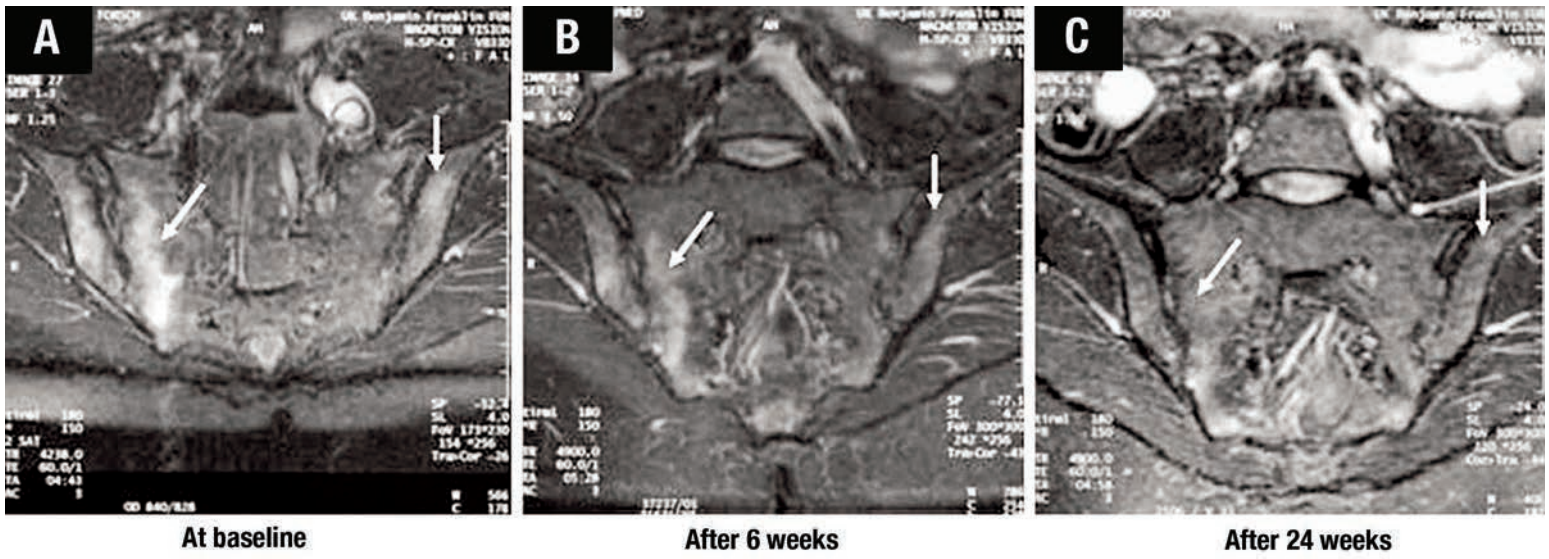

Figure 7: Sacroiliitis MRI response to anti-TNF therapy.
Source: Rudwaleit M, et al. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with Etanercept. *Annals of the Rheumatic Diseases* 2005; 64:1305-10. Reproduced with permission.

Figure 8. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Please place a mark on each line below to indicate your answer to each question relating to **the past week**

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?

   NONE _____ VERY SEVERE

2. How would you describe the overall level of AS **neck, back or hip pain** you have had?

   NONE _____ VERY SEVERE

3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?

   NONE _____ VERY SEVERE

4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?

   NONE _____ VERY SEVERE

5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**

   NONE _____ VERY SEVERE

6. How long does your morning stiffness last from the time you wake up?

   _____

   0 hrs ½ 1 1½ 2 or more hours

How to score a BASDAI

The BASDAI consists of a one to 10 scale (one being no problem and 10 being the worst problem) relating to the five major symptoms of ankylosing spondylitis. These individual scores for questions one to five are added, then divided by five. A score of four or greater suggests disease control is not optimal, and these patients may require a change in medication.

Management

Education and exercise

PATIENT education and support are vital in the management of ankylosing spondylitis. Having a diagnosis is an important first step for patients, providing them with an explanation for symptoms that may have been present for many years. Education should include an explanation of the importance of exercise and activity in maintaining spinal mobility.

NSAIDs

NSAIDs are first-line therapy for symptomatic patients with ankylosing spondylitis, but it must be emphasised that NSAIDs act to relieve symptoms. While there is evidence that NSAIDs may reduce osteo-proliferation, the use of long-term NSAIDs must be individualised. If diagnosed early, a large proportion of patients who commence specific TNF inhibition for ankylosing spondylitis will not require additional analgesia. The role of long-term NSAIDs in this group, other than for symptom relief, are questionable.

Conventional synthetic DMARDS

Methotrexate and salazopyrin have no role in the management of axial symptoms. Both agents may be useful in patients with resistant peripheral arthritis.

Table 2. TNF inhibitors used as treatment for ankylosing spondylitis

Chemical name	Etanercept	Adalimumab	Golimumab	Infliximab	Certrolizumab
Trade name	Enbrel	Humira	Simponi	Remicade	Cimzia
Mode	SC	SC	SC	IV	SC
Dose and frequency	50mg weekly	40mg every two weeks	50mg every four weeks	5mg/kg every eight weeks	40mg every four weeks

Tumour necrosis factor inhibitors

The introduction of TNF inhibition has transformed the natural history of ankylosing spondylitis. Non-response to TNF inhibitors in these patients is unusual. A large proportion have a dramatic response, with reduction and resolution of spinal symptoms, reduction in fatigue, control of peripheral arthritis, reduction in analgesia requirements, and decline in the occurrence of extra-articular manifestations.

The response to TNF inhibition is generally enduring, with more than 75% of patients maintaining therapy beyond five years.

Treatment is long term — generally attempts to withdraw medication result in disease flare for the majority of patients with AS.

There are currently five anti-TNF therapies licensed for use in Australia for the treatment of AS: etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), infliximab (Remicade) and certolizumba (Cimzia).

Each agent targets the same molecule (tumour necrosis factor), but each has subtle differences in structure that translates to differences in dose frequency, mode of administration, half-life, and effect on extra-articular features. The mode of administration of each agent is summarised in table 2.

Adverse effects associated with TNF inhibitors are uncommon, but well documented. It must be emphasised that the benefits to patients who respond to treatment are immense and the risks of therapy must be put into this context.

The most common adverse effects are injection site reaction (SC agents), which manifests as an erythematous area at the site of injection. The area is generally pruritic, raised and warm, and may persist for 48-72 hours. The reaction can be managed with conventional antihistamines and topical corticosteroids. Most local reactions will subside with ongoing therapy. However, if reactions remain troublesome, a switch to an alternate anti-TNF is recommended.

Community acquired infections do not occur with increased frequency in patients treated with anti-TNF agents, but if infections occur, usual treatment is reasonable.

Often patients will not develop the usual early signals of infection (for example, dysuria and fever with UTI), but will complain of lassitude or non-specific symptoms. If bacterial infections occur, it is reasonable to cease the anti-TNF agent until the patient has recovered and consider a more prolonged course of antibiotics if recovery is slow.

All patients are screened prior to administration for TB (QuantiFERON-TB GOLD or Mantoux, chest X-ray), hepatitis B and C, and HIV. The risk of reactivation of TB in particular is a concern in patients with previous exposure and latent disease. If latent disease is diagnosed, patients are treated with isoniazid before beginning anti-TNF therapy.

Drug-induced lupus and demyelination are now rare complications of TNF inhibitors. A lupus reaction to TNF inhibitors usually presents in a patient who has been stable for some time, but develops increasing fatigue, joint pain, low-grade fever and occasionally a skin rash or pruritus. Demyelination most commonly manifests as optic neuritis and is a very rare complication.

Assessment and monitoring

The objective of treatment is to achieve a state of minimal or no axial and peripheral joint symptoms, stable measures of spinal mobility, and optimal functional status. The rheumatologist usually assesses patients at six-monthly intervals when treatment has been stable and the patient deemed in remission.

Special cases/the future

Non-radiographic spondyloarthropathy

NEW classifications are altering the way that we approach patients with axial symptoms. Patients with axial symptoms without X-ray abnormalities are now sub-classified "non-radiographic", based upon the absence of radiographic sacroiliitis as defined by the modified New York (mNY) criteria. These criteria reflect the understanding that many patients will have MRI changes of sacroiliitis but will not have X-ray abnormalities.

The non-radiographic axial spondyloarthropathy group have similar clinical features, but the natural history of the group and its response to treatment appear to be different for the ankylosing spondylitis group. There appears to be a more equal gender ratio in this group, and the age of onset is similar to ankylosing spondylitis.

The natural history of this illness is uncertain. Whether this group progresses to ankylosing spondylitis, develops the same frequency of peripheral disease, or extra-articular features, remains unclear. Ongoing clinical trials are attempting to assess whether this group responds to TNF inhibition.

Duration of treatment

For patients with traditional ankylosing spondylitis (radiographic changes advanced, ESR and CRP high at diagnosis), it is generally recognised that treatment is long term. Attempts to withdraw treatment generally lead to disease flare.

For other groups, the duration of treatment is less clear. These include patients with milder disease, non-progressing forms, and patients with non-radiographic axial spondyloarthropathy. Ongoing studies will assist in determining the optimal duration of treatment in these groups.

Figure 9. ASAS-endorsed recommendations for early referral of patients suspected for having axial spondyloarthritis by primary care physicians or non-rheumatologists

Patients with chronic back pain (duration ≥3 months) with back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present:

- Inflammatory back pain*
- *HLA-B27* positivity
- Sacroiliitis on imaging, if available (on X-rays or MRI)†
- Peripheral manifestations (in particular arthritis, enthesitis and/or dactylitis)‡
- Extra-articular manifestation (psoriasis, inflammatory bowel disease and/or uveitis)‡
- Positive family history for spondyloarthritis‡
- Good response to non-steroidal anti-inflammatory drugs‡
- Elevated acute phase reactants§

*Any set of criteria, preferably ASAS definition of inflammatory back pain: at least four out of five parameters present: (1) age at onset ≤40 years; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; and (5) pain at night (with improvement upon getting up).

†Only if imaging available, not recommended as a routine screening parameter.

‡According to the definition applied in the classification criteria for axial spondyloarthritis:
Arthritis: past or present active synovitis diagnosed by a physician.
Enthesitis (heel): past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus.
Dactylitis: past or present dactylitis, diagnosed by a physician.
Extra-articular manifestation: past or present psoriasis, inflammatory bowel disease and/or uveitis anterior, confirmed by a physician.
Good response to NSAIDs: 24–48 h after a full dose of a NSAID the back pain is not present any more or is much better.
Family history of SpA: presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces and nephews) relatives of any of the following: (1) ankylosing spondylitis; (2) psoriasis; (3) acute uveitis; (4) reactive arthritis; and (5) inflammatory bowel disease.

§C-reactive protein serum concentration or erythrocyte sedimentation rate above upper normal limit after exclusion of other causes for elevation.

Criteria for referral

The ASAS endorsed recommendation for early referral of patients suspected of having axial spondyloarthritis by primary care physicians are included in figure 9. The most important factor is identifying the patient with inflammatory lower back pain.

Case studies

Case study one

STEPHEN was 18 when his back pain became severe and constant. He was sitting his year 12 examinations, and remembered he was constantly exhausted because of lack of sleep. He was plagued by pain at night, generally waking at 2-3 am and getting up to walk around to relieve the stiffness in his lower back. When he woke in the morning he found it hard to get out of bed because of the pain.

He was prescribed NSAIDs with relief initially, but he soon found that nothing helped his symptoms. After completing his HSC, his symptoms worsened. He was unable to continue his part-time job, found it difficult to study and withdrew from his friends. He stopped exercising and playing sport, and postponed his enrolment to university, fearing that he would not be able to complete his studies.

He had developed significant depression requiring psychological intervention and treatment with SSRIs. Despite these measures, his depression remained overwhelming.

He had similar symptoms when he was 15. He had seen his GP, and blood tests and X-rays had been performed. The X-ray had shown a possible pars interarticularis defect, but this was not conclusive. An MRI of the lumbar spine had been normal. He spent a lot of time in physiotherapy, and his symptoms had waxed and waned; but he found if he exercised regularly, that he could manage.

The symptoms seemed to be improving by the time he turned 16, and given the all-clear, he had returned to sport. He reported that during this time his pain never really completely disappeared, but with intermittent NSAIDs, physiotherapy support and regular massage, he was able to put his symptoms in the background and figured that he would just have to live with some back pain.

Increasing pain, despite multiple courses of NSAIDs, led to a further visit to his GP. The GP recognised the pain was severe and that the presentation was unusual for a simple mechanical problem. Stephen was referred to a rheumatologist for assessment.

At rheumatology review, it was noted that he had no significant family history, no history of psoriasis, no gastrointestinal symptoms or urinary symptoms. He had been troubled by recurrent bilateral Achilles tendonitis for two years, episodes treated by self-referral to a physiotherapist. Range of motion of the lumbar spine was severely restricted.

Genetic testing confirmed *HLA-B27* positive, ESR was 38, CRP 55. MRI of the lumbar spine and sacroiliac joints revealed normal lumbar spine with marked osteitis of sacroiliac joints bilaterally, as well as small erosions. Plain X-ray of the pelvis demonstrated grade 2 changes of sacroiliitis bilaterally.

Stephen was commenced on a TNF inhibitor. Within three months, his back pain and stiffness had resolved completely. The Achilles tendonitis ceased to be an ongoing issue. He began to sleep well at night and his fatigue resolved. Within four months of starting therapy, he ceased all NSAIDs and required no analgesia. He returned to sport, resumed a part-time job and within 12 months of diagnosis, he was able to begin his university studies. With the pain resolved, his depression became manageable without medication.

Nine years later, Stephen attends

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the rheumatology practice every six months for assessment. He continues to remain well, has no adverse effects from therapy and has an ongoing excellent response.

Important points:
Inflammatory lower back pain can be insidious in onset. The important factors in this patient are the prolonged history, and the symptoms strongly suggestive of inflammatory pain. The investigations provide excellent supportive evidence of ankylosing spondylitis.

Case study two

Rebecca reported lower back pain and fatigue as her primary symptoms. At 28, she had put most of the year-long fatigue down to a busy work and social schedule. She had iron studies and thyroid studies performed, and when no obvious cause was found, she decided she would just have to get on with it and stop complaining, or modify her lifestyle.

It had not occurred to her that her back pain could be related. She had experienced lower back pain ever since she had taken a long ride in a bus while backpacking in South-East Asia in her late teens. It was a long

trip and the road was very rough. She felt stiff and sore after she got off the bus. The pain was severe for 48 hours, but gradually resolved over two weeks, and Rebecca related all of her back pain since then to that bus ride.

Generally the episodes occurred randomly with no clear precipitant. Each episode would last up to two months, during which she would take up to six over-the-counter ibuprofen per day to control her pain. She had two sets of lumbar spine radiographs over the years. These had been normal and she had learned to manage her episodes of pain as they occurred, seeking physiotherapy assistance if the pain was severe.

Further questioning revealed a family history of psoriatic arthritis. Her father had been affected and required treatment with methotrexate. She had no psoriasis on history or examination, but abdominal symptoms had been problematic over a number of years.

She described lower abdominal cramping and frequency of bowel motions that usually accompanied her episodes of lower back pain. She had put this down to the anti-inflammatories that she had been taking and did not mention it to her GP. There had been no episodes of dactylitis or recurrent tendonitis. There were no urinary symptoms.

In the past six months, her episodes of back pain had become constant. Rebecca described severe morning stiffness and felt too exhausted to exercise. Her sleep pattern was poor, constantly interrupted by pain. The abdominal symptoms had become more intrusive. The previous plain radiographs were reviewed and there was no abnormality in the lumbar spine.

During initial investigations, she was referred to a gastroenterologist for investigation of the abdominal symptoms. An endoscopy and colonoscopy with terminal ileal biopsy was normal.

Further investigations excluded an infective cause for the abdominal symptoms and urine examination was normal. *HLA-B27* was not detected, ESR 25, CRP 16. MRI confirmed osteitis of sacroiliac joints bilaterally, with small erosions noted on T1 weighted imaging. Plain radiographs of the sacroiliac joints confirmed bilateral Grade 1 sacroiliitis.

After screening investigations, Rebecca was started on a TNF inhibitor within a clinical trial. Marked improvement occurred within six weeks, with eventual resolution of pain. Her fatigue improved markedly and the abdominal symptoms resolved.

After five years, she continues treatment with an ongoing excellent response. Attempts to withdraw treatment on two occasions have resulted in disease flare.

Important points:
This patient has a number of atypical features: female, intermittent significant symptoms, *HLA-B27* negative and low-level elevation of ESR and CRP, and minimal X-ray changes. The clinical features of inflammatory lower back pain are present on history and the investigations are supportive. Many patients with axial spondyloarthropathy have low-grade IBD that is subclinical.

Summary

Ankylosing spondylitis needs to be considered in patients with lower back pain for longer than three months, with onset of symptoms less than 45 years.

Plain X-rays and blood investigations may be normal during initial assessment. These do not rule out the diagnosis.

Treatment with TNF inhibition dramatically alters the outcome for these patients.

Online resources

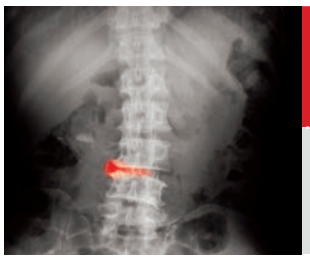
Back in Focus (UK site)
www.axialspabackinfocus.co.uk

Arthritis Australia
www.arthritisaustralia.com.au

Don't Turn Your Back On It
http://bit.ly/1oZIYCf

References and further reading

Available on request from howtotreat@cirrusmedia.com.au



How to Treat Quiz

Ankylosing spondylitis/ spondyloarthritis — 22 July 2016

INSTRUCTIONS
Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ
www.australiandoctor.com.au/education/how-to-treat

1. Which THREE are common features of spondyloarthritis?
a) Axial skeletal involvement
b) Tenosynovitis
c) Bilateral, symmetrical peripheral joint swelling
d) Extra-articular features, such as uveitis

2. Which TWO statements regarding the nature of the arthropathies are correct?
a) Ankylosing spondylitis manifests with primarily axial involvement, with peripheral arthritis occurring in the hips and shoulders.
b) Psoriatic arthritis manifests with primarily axial involvement, with peripheral arthritis occurring in the hips and shoulders.
c) Reactive arthritis commonly manifests with predominantly peripheral symptoms, with axial symptoms less common.
d) Non-radiographic spondyloarthropathy has features of sacroiliitis on X-ray but no MRI features consistent with sacroiliitis or spinal inflammatory disease.

3. Which THREE statements regarding the epidemiology of ankylosing spondylitis are correct?
a) The prevalence of ankylosing spondylitis is the same in those of European and Asian descent.
b) The prevalence of ankylosing spondylitis is the same in those of European and African descent.
c) Males are more affected than females.
d) The average delay from onset of symptoms to diagnosis is 8-11 years.

4. Which TWO statements regarding the aetiology of ankylosing spondylitis are correct?
a) The cause of ankylosing spondylitis is well described, and the condition occurs with higher frequency within families.
b) *HLA-B27* occurs in 90% of patients with ankylosing spondylitis and may have a direct etipathogenetic role via interleukin 23 (IL-23) signalling.
c) Environmental factors associated with greater severity of disease are living under/ near power lines and exposure to lead.
d) The exact triggers for ankylosing spondylitis in individuals remain undetermined, but putative mechanisms include alterations in the gut microbiome and mechanical entheseal stress.

5. Which THREE features increase the suspicion of ankylosing spondylitis?
a) Family history of ankylosing spondylitis
b) Other features of spondyloarthritis
c) Dramatic response to NSAIDs
d) Older than 45

6. Which TWO statements regarding the investigation and diagnosis of ankylosing spondylitis are correct?
a) Diagnosis is made on clinical examination (inability to flex the lumbar spine), supported by the history of back pain for longer than three months
b) A positive *HLA-B27*, in conjunction with a history of lower back pain, is sufficient to confirm the diagnosis of ankylosing spondylitis.
c) A negative radiograph does not rule out the diagnosis of ankylosing spondylitis.
d) For diagnostic purposes, a plain anteroposterior pelvic X-ray is optimal.

7. Which THREE statements regarding the investigation and diagnosis of ankylosing spondylitis are correct?
a) CT and bone scan provide useful information about grading the severity of ankylosing spondylitis.
b) MRI will assess active inflammation of the sacroiliac joints and spine.
c) Measurement of ESR and CRP is useful in assessing disease activity and forms part of the baseline assessment once the diagnosis of ankylosing spondylitis has been established.
d) The Bath Ankylosing Spondylitis Disease Activity Index is a tool used by rheumatologists to assist in assessing clinical activity.

8. Which TWO statements regarding the management of ankylosing spondylitis are correct?
a) Patient education and support are vital in the management of ankylosing spondylitis.
b) NSAIDs are the mainstay of therapy and can safely be used long term for pain relief.
c) Non-response to TNF inhibitors in patients with osteo-proliferation is unusual.
d) The response to TNF inhibition is generally short-lived, with most patients ceasing the medication within 18 months.

9. Which THREE statements regarding the management of ankylosing spondylitis are correct?
a) Anti-TNF therapy results in a dramatic response, with reduction and resolution of multiple symptoms.
b) Adverse effects associated with TNF inhibitors are common.
c) There are currently five anti-TNF therapies licensed for use in Australia for the treatment of ankylosing spondylitis.
d) The most common adverse effect is injection site reaction for subcutaneous agents, which manifests as an erythematous area at the site of injection.

10. Which TWO statements are correct?
a) The objective of treatment is to achieve a state of minimal or no axial and peripheral joint symptoms, stable measures of spinal mobility and optimal functional status.
b) Once patients with ankylosing spondylitis have been symptom-free for six months, medication with drawl can be considered.
c) In the Assessment of SpondyloArthritis–endorsed recommendation for early referral of patients suspected of having axial spondyloarthritis by their GP, the most important factor is identifying the patient with inflammatory lower back pain.
d) Any patient with lower back pain for longer than three months should be referred to a rheumatologist.

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Claire Berman**
Email: **claire.berman@cirrusmedia.com.au**

NEXT WEEK

Next week's How to Treat discusses the conditions to exclude when evaluating the red, painful and swollen knee. Of all the possible causes of a red, hot and swollen knee, septic arthritis must not be overlooked. The author is **Associate Professor Mark Arnold**, associate dean and head of school, School of Rural Health, Sydney Medical School, University of Sydney, NSW.