Spondyloarthropathies That Mimic Ankylosing Spondylitis: A Narrative Review

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ABSTRACT: Ankylosing spondylitis is the most common type of seronegative inflammatory spondyloarthropathy often presenting with low back or neck pain, stiffness, kyphosis and fractures that are initially missed on presentation; however, there are other spondyloarthropathies that may present similarly making it a challenge to establish the correct diagnosis. Here, we will highlight the similarities and unique features of the epidemiology, pathophysiology, presentation, radiographic findings, and management of seronegative inflammatory and metabolic spondyloarthropathies as they affect the axial skeleton and mimic ankylosing spondylitis. Seronegative inflammatory spondyloarthropathies such as psoriatic arthritis, reactive arthritis, noninflammatory spondyloarthropathies such as diffuse idiopathic skeletal hyperostosis, and ochronotic arthritis resulting from alkaptonuria can affect the axial skeleton and present with symptoms similar those of ankylosing spondylitis. These similarities can create a challenge for providers as they attempt to identify a patient's condition. However, there are characteristic radiographic findings and laboratory tests that may help in the differential diagnosis. Axial presentations of seronegative inflammatory, non-inflammatory, and metabolic spondyloarthropathies occur more often than previously thought. Identification of their associated symptoms and radiographic findings are imperative to effectively diagnose and properly manage patients with these diseases.

KEYWORDS: Inflammatory, metabolic, spondyloarthropathies, back, neck pain

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Introduction

Spondyloarthropathies (SpA) encompasses a group of chronic, inflammatory autoimmune diseases including ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-related, and reactive arthritis (ReA). These are commonly referred to as "seronegative spondyloarthropathies" due to their frequently negative rheumatoid factor. With a prevalence of 1.3% to 1.7%, seronegative spondyloarthropathies affect the axial skeleton and should be included in the differential diagnoses of back and neck pain.[1-3]

Diffuse idiopathic skeletal hyperostosis (DISH) can present similarly to and may coexist with AS, presenting a diagnostic challenge.[4] Similarly, alkaptonuria, an autosomal recessive metabolic disorder, can present with back or neck pain. DISH and alkaptonuria should be recognized as a potential differential diagnosis in patients with neck and back pain.

Medical management of spondyloarthropathies has become increasingly effective and is now primarily aimed at limiting inflammation and overall disease severity. Patients with neurologic deficits, instability, or spine deformity, may require surgery. Satisfactory patient outcomes are more likely when providers have a thorough understanding of disease pathology and presentation. Diagnosing early and choosing appropriate treatment will help reduce future disease burden. The objective of the current study was to review the epidemiology, pathophysiology, presentation, and management of seronegative inflammatory and metabolic spondyloarthropathies that mimic ankylosing spondylitis.

Epidemiology

Prevalence of ankylosing spondylitis is between 0.2% and 0.5%, most commonly affecting young men, with a male to female ratio of 3:1.[1] Annual incidence is 0.5 to 14 per 100 000. IBD-associated axial arthritis, has a prevalence of 0.05% to 0.25% with a male to female ratio of 1:1. Axial involvement is present in 2% to 16% of IBD patients with a higher prevalence in Crohn's disease (CD) patients than in those with ulcerative colitis (UC). The prevalence of psoriasis ranges from 0.51% to 11.4% with psoriatic arthritis (PsA) occurring in about 25% of patients with psoriasis. A recent study demonstrated 12.5% of patients with PsA having axial symptoms with rates similar between men and women. ReA incidence is reported as 0.6 to 27 per 100 000 patients, and prevalence at 30 to 40 per 100 000 once again with axial involvement more common in men with a ratio of 1 to 3:1.[5] DISH incidence over the age of 50 is 25% in men and 15% in women. Ochronotic spondyloarthropathy is a spine disorder secondary to alkaptonuria with an incidence of 0.1 to 0.4 in 100 000 live births.

The prevalence of alkaptonuria is 0.4 to 1 per 100 000 with equal distribution between males and females.[6] These data are summarized in Table 1.

Pathophysiology

AS is characterized by enthesitis and with disease progression, ossification of the disk space anteriorly and facet joints posteriorly resulting in ankylosed bamboo spine and kyphosis. This

Table 1. Epidemiological data of spondyloarthropathies.

DISEASE	INCIDENCE (PER 100 000)	PREVALENCE (PER 100 000)	MALE:FEMALE
Ankylosing spondylitis	0.5-14	200-500	3:1
Enteropathic (IBD-associated) axial arthritis	unknown	50-250	1:1
Psoriatic arthritis	6.59	12.5	1:1
Reactive arthritis	0.6-27	30-40	1-3:1
Alkaptonuria (cause of ochronotic spondyloarthropathy)	0.1-0.4	0.4-1	1:1

Abbreviation: IBD, inflammatory bowel disease.

state of chronic inflammation, hypervascularization, and lack of mobility result in osteopenia, making the spine vulnerable to fracture with even minor injuries.[7,8] The hallmark of AS is sacroiliitis; from there, the disease typically proceeds cephalically. The pathogenesis of AS is poorly understood but is believed to involve a combination of genetic and environmental factors.

Several mechanisms have been proposed relating to new bone formation in AS. The Wnt pathway, known best for its organizing role in embryogenesis, is suggested to be involved in osteoblastogenesis based on evidence that gain of function mutations of low-density lipoprotein receptor-related protein 5 (LRP5), a component of a complex binded by Wnt proteins, leads to high bone density, while loss of function mutations lead to low bone density.[9,10] Furthermore, Wnt stimulates hypertrophic chondrocyte production.[11,12] Dickkoft-1 (Dkk-1), an inhibitor of the Wnt pathway, is thought to be dysfunctional in AS and is subsequently overexpressed when compared with healthy subjects.[13,14] Inflammatory cytokines IL-6 and IL-17A have been shown to suppress Dkk-1, providing further regulation of bone formation.

Human leukocyte antigen (HLA-B27) is strongly linked to disease susceptibility, and a close correlation exists between the frequency of this allele and the prevalence of AS in a given population. It is estimated that HLA-B27 contributes 20% to 50% of the genetic risk of AS, leaving room for other gene involvement. There are three leading theories on how HLA-B27 predisposes to inflammation, none of which sufficiently explain the pathogenesis which are (1) HLA-B27 presents certain peptides leading to a direct effect on the immune response, (2) HLA-B27 heavy chain misfolds and induces an unfolded protein response, and (3) HLA-B27 forms a cell-surface dimer that serves as a target for natural killer cells.

Three other potential candidates that contribute to the genetic risk of AS have emerged, including the IL-1 gene cluster, ARTS1, and the interleukin-23 receptor (IL-23R) gene. The association between IL-1 and AS is strong, but the overall attributed genetic risk is estimated at only 4% to 6%. When IL-1 inhibitors were used in studies it showed positive effects, but the results were minimal compared with tumor necrosis factor (TNF) antagonists.[15-17] Aminopeptidase regulator of TNRF1 shedding (ARTS1) gene may contribute up to 26% of the risk in developing AS, with loss of function genes potentially leading to proinflammatory effects. ARTS1 is also helpful for cleavage of peptides that will later be presented by MHC Class I HLA molecules.[18,19] One hypothesis of the pathophysiology of AS, though not fully supported, with regard to HLA-B27 is the presentation of an arthritogenic peptide. ARTS1 tailoring which peptides are eligible for presentation on MHC may support this hypothesis.

The IL-23/IL-17 axis has shown a role in the pathophysiology of AS and other spondyloarthropathies in several studies. IL-23 is produced from antigen-presenting cells that link adaptive to innate immunity. It is essential to the proliferation and terminal differentiation of CD4 + Th17 cells. EP4, a prostaglandin receptor, was found to be significantly overexpressed on Th17 cells in AS compared with healthy patients, patients with rheumatoid arthritis, and those with PsA indicating EP4 as a potential marker for disease activity. IL-23R is present on dendritic cells, macrophages, and Th17 cells which specifically produce IL-17, a cytokine that induces the production of IL-1, IL-6, and TNFα, and other proinflammatory chemokines. Polymorphisms in IL-23R are interestingly associated with both IBD and psoriasis as well, potentially explaining the increased risk of IBD and psoriasis in AS patients.

Gut dysbiosis, or the alteration of microbial species in the gut, can modulate disease pathogenesis in AS and other spondyloarthropathies with distinct microbiome profiles helping to differentiate diseases. Altered microbial metabolites and antigens which are readily transported across the intestinal barrier act on distal tissues providing a means of communication between gut and host cells, which a defective mucosal barrier or inflammation further propagates. Silent microscopic inflammation of the gut is present in up to 60% of AS patients. Recent studies have highlighted the gut-joint axis of inflammation in SpA. More than 50% of SpA patients with axial involvement have been shown to have gut inflammation.

Spondyloarthropathies are a well-known extra-intestinal manifestation of IBD. The pathophysiology of this linkage is poorly understood but is thought to involve the "gut synovial axis." The current model holds that immunological problems occur at the intestinal mucosa then spread to musculoskeletal sites.[20] There are two hypotheses on the connection between

intestinal inflammation and SpA. In one hypothesis, aEβ7 integrin expressed by intraepithelial T-cells in the intestinal mucosa bind to E-cadherin expressed by intestinal epithelium which leads to inflammation of the intestines. Patients with SpA have a nearly identical interaction leading to synovial inflammation and subsequent lymphocyte proliferation. These lymphocytes then depend on adhesion molecules such as vascular adhesion protein 1 (VAP-1) to translocate to the intestinal epithelium where they induce local macrophages to express the scavenger receptor CD163 which induces additional integrin binding leading to a cycle of inflammation. The significance of the CD163 receptor is that it is widely found in both intestinal mucosa as well as synovium. Lymphocytes and macrophages can translocate to the synovium leading to inflammation and resultant joint pathology. The second hypothesis involves a causal link between HLA-B27 and human β2 microglobulin. In this hypothesis, bacterial exposure of IBD patients lead to proliferation of lymphocytes causing widespread inflammation of the bowel and synovium. The mechanism proposed in this hypothesis remains unclear; however, this hypothesis relies on a bacterial trigger for IBD and SpA.

PsA is an immune-mediated disease that is influenced by genetic and environmental components. The pathogenesis is driven by the innate and adaptive immune system including infiltration of immune cells such as T-cells, dendritic cells, neutrophils, and macrophages. Activated T-cells can induce bone resorption and articular damage via RANK/RANK-L interactions which can also be triggered by IL-17. The pathophysiology of PsA also involves the IL-23/IL-17 axis. It has been demonstrated that IL-23 induced Th17 cytokines contribute to psoriatic plaque development, pannus formation, joint erosion, and new bone formation.

There are unique differences of gene expression in patients with PsA compared with those without. Some characteristically upregulated genes in the synovium include WNT3A, BMPR2, and TGFBR1, which contribute to bone erosion and new bone formation. PsA also presents with increased vascularity and skin inflammation more commonly than other types of arthritis. This is consistent with the upregulation of genes that control processes associated with angiogenesis and vascularization such as vascular endothelial growth factor (VEGF) and TBGB1 which in turn facilitate inflammation and joint damage.

HLA allotype susceptibility has also been hypothesized to contribute to the pathophysiology of PsA. Autoreactive T-cells induce inflammation after binding a self-peptide through MHC class I molecules. HLA allotypes such as HLA-B27, B8, and B39 demonstrated an increased frequency in patients with musculoskeletal manifestations of psoriasis as compared with patients with dermatologic manifestations alone. HLA-B39 is more associated with peripheral PsA, whereas HLA-B27 axial PsA. It is interesting to note that HLA-B27 prevalence is less in axial PsA compared with AS. The different phenotypic patterns of symptoms that occur in PsA patients may be explained by conferred susceptibility of certain haplotypes. Although traditionally characterized as a seronegative arthropathy, small subsets of patients do test positive for rheumatoid factor.

It has also been theorized that enthesitis can be the primary source of inflammation that propagates the synovitis in PsA. Tissue microtrauma due to mechanical stress is one theory for the upregulation of proinflammatory release of cytokines and immune mediators from entheseal organs, especially in genetically predisposed patients.

Gut dysbiosis may also be a mechanism of inflammation in patients with PsA. Decreased bacterial diversity in PsA patients compared with patients with only psoriasis has been observed.[21] Inflammatory bowel disease is also more prevalent in psoriasis patients than those without.[22]

ReA is defined as a sporadic, acute, sterile synovitis that arises as a sequela to remote infection. The location of infection plays little role but is typically of the gastrointestinal (GI) or genitourinary (GU) tracts. Notably, components of Gram-negative enteropathic bacteria have been identified in synovial fluid of patients with ReA, including *Yersinia, Salmonella, Chlamydia trachomatis*, and *Shigella*. Following primary infection, bacteria persist in lymph nodes where they interact with the immune system and gain access to joint spaces and tendinous structures. Once immunogens have accessed the synovium, there is a humoral immune response to the offending agents; they trigger a CD4 + dominant T-cell response with a predominance of the interferon (IFN-y) and IL2 cytokines. This leads to a synovial environment that promotes further inflammation and possible relapsing infection with arthritogenic bacteria. A strong association has also been shown with the HLA-B27 serology and subtypes in 50% to 90% of cases of ReA. B27 serotype associated ReA is heavily associated with spondyloarthrytides and represents a genetic connection to ReA. The qualities of B27 have been intensely studied, and it is thought to be due its role as a class I antigen. In this capacity, B27 exhibits molecular mimicry with some bacterial antigens and affects a CD4 + response resulting in inflammation. In addition, studies have shown suppression of Th1 cytokines essential for elimination of arthritogenic bacteria in B27 patients leading to predisposition of reinfection or protracted infection and subsequent inflammation.

DISH occurs when soft tissue is calcified and ossified, like AS, but is not inflammatory, though it can coexist with AS.[4] DISH diagnosis requires flowing anterolateral bony bridges of at least four contiguous vertebrae without sacroiliitis and extensive degenerative disk disease. Ochronotic spondyloarthropathy is a spine disorder secondary to alkaptonuria caused by a deficiency of homogentisic acid oxidase leading to abnormally high levels of homogentisic acid. The homogentisic acid precipitates in the articular cartilage as ochre-colored pigment

granules, and subsequently, the cartilage loses elasticity and becomes brittle, leading to calcification and eventual break down. Four progressive stages of ochronotic spondyloarthropathy have been described: an inflammatory stage (stage 1), the stage of early disk calcification (stage 2), the stage of fibrous ankylosis (stage 3), and the stage of bony ankylosis (stage 4), which is often similar to AS.

Presentation

The hallmark clinical presentation of AS is back, neck pain, morning stiffness, and gluteal pain due to sacroiliitis. As the disease reaches thoracic levels, motion at the costovertebral joints becomes limited, resulting in impaired pulmonary function. Patients with AS demonstrate kyphotic ankylosis of the spine and hip flexion contractures that result in loss of sagittal balance. Kyphotic cervical spine, when severe, results in chin-on-chest deformity that significantly impairs the visual field forward gaze angle and interferes with hygiene and swallowing.

Physical examination may demonstrate sacroiliac joint pain as assessed by Gaenslen or Patrick's Faber test. The extent of kyphotic cervical spine deformity and subsequent correction can be evaluated by chin-brow vertical angle. Chest expansion measured at fourth intercostal space (nipple line) typically is limited to < 2.5 cm after fusion of costovertebral joints. Spinal mobility can be evaluated by the modified Schober test. Enthesitis, dactylitis, and asymmetric peripheral arthritis are common symptoms found as well. Uveitis occurs in up to 50% of AS patients affecting males slightly more than females, typically sudden onset with a predilection for unilateral anterior inflammation and an excellent visual prognosis with recovery usually within 2 months. Patients with AS have an increased risk for IBD and psoriasis, 6.8% and 9.3%, respectively, compared with the general population of 0.01% to 0.5% for IBD and 0.3% to 2.5% for psoriasis. There is a definitive association of heart disease with AS with the three major categories being aortitis and aortic insufficiency, conduction disturbances of the AV node, and myocardial involvement with possible compromise of left ventricular function. Klingberg et. al found the prevalence of aortic regurgitation in AS patients be 18% where he further suggested electrocardiography be a routine part of AS management.

IBD-related spondyloarthritis shares the common presenting features of SpA such as inflammatory back pain, enthesitis, dactylitis, and ocular symptoms. As with AS, IBD-related spondyloarthritis pain can progress from the lumbar spine toward the cervical spine.[23] Although it may seem obvious that these patients should have symptoms of IBD, that is not necessarily the case. Extraintestinal manifestations such as axial spondylitis may precede the diagnosis of IBD by several years in up to 20% of patients. Axial disease activity is independent of IBD activity, whereas exacerbations of peripheral arthritis and IBD tend to coincide. Peripheral arthritis, when present, often affect the lower limbs. IBD is associated with a lower incidence of uveitis compared with AS with a prevalence in 2% to 5% of patients, more commonly in females. The phenotype of uveitis in IBD can differ from the phenotype of AS. Some patients will develop acute onset, unilateral, anterior uveitis, but about half will develop uveitis that is bilateral, sometimes posterior to the lens, and insidious in onset that tends to be more persistent. Other extra-articular manifestations include skin lesions such as erythema nodosum and pyoderma gangrenosum and less common features such as clubbing, periostitis, amyloidosis, and granulomatous disease of bone and joint.

Psoriasis presents with erythematous plaques with silver scales. PsA is characterized by pain and stiffness in multiple joints with the distal interphalangeal joint most commonly affected. Musculoskeletal manifestations of psoriasis typically manifest after dermatologic lesions have developed, with the minority of patients presenting initially with axial pain and stiffness. The higher incidence of cervical involvement, sparing thoracic, and lumbar spines in PsA helps distinguish psoriatic spondyloarthropathy from AS. Axial involvement in PsA can present diagnostic challenges, as some question remains as to whether axial PsA is better described as two simultaneous diseases: psoriasis and AS. Michelena et al[24] found that axial PsA has unique clinical manifestations and is largely HLA-B27 negative when compared with combined AS and psoriasis, suggesting that axial PsA is a distinct disease. Patients with axial PsA tend to have higher presentations of IBD, nail onycholysis, enthesis, psoriasis, and tender joints on physical exam than those with peripheral PsA. Uveitis is less common in PsA compared with AS, affecting around 7% of patients. Those patients who have axial PsA and uveitis were more like to be B-27 positive males. Uveitis presents very similarly to the IBD phenotype with about half of cases having a more insidious and persistent course. Dactylitis is more commonly seen in axial PsA compared with AS and may be an additional tool in helping to differentiate the diagnosis.

ReA is classically in a patient in their third decade of life who has symptomatic gastrointestinal or *C. trachomatis* infection. Following an interval of 1 to 2 weeks (or longer for *Chlamydia*) the patient will begin to exhibit musculoskeletal symptoms which typically includes lower extremity asymmetrical oligoarthritis in the large joints. Extraarticular manifestations include keratodermia blennorrhagica, bursitis, tendinitis, enthesitis, dactylitis, inflammatory low back pain, and erythema nodosum, which is frequently associated with *Yersinia* infection. In addition, eye disease is not unusual with conjunctivitis being especially common. Other ocular manifestations include anterior uveitis and circinate balanitis, which is particularly associated with Chlamydia.

Diagnosis of ReA is dependent upon diagnosis of preceding infection, but musculoskeletal complaints often appear after acute infection has resolved. Stool culture can detect antigens if acute infection persists; however, isolation of pathogen specific

Table 2. Signs and symptoms of seronegative spondyloarthropathies.

SIGN/SYMPTOM	ANKYLOSING SPONDYLITIS	IBD-ASSOCIATED AXIAL ARTHRITIS	PSORIATIC ARTHRITIS	REACTIVE ARTHRITIS	OCHRONOTIC SPONDYLOARTHRITIS
Enthesitis	Common	Common	Common	Common	Uncommon
Peripheral arthritis	Common; asymmetric	Common; lower limbs	Common	Common; asymmetric lower extremity	Common
HLA-B27	Associated	Associated	Associated	Associated	No association
Uveitis	Up to 50%	2%-5%	7%	Common	-
Skin/nail lesions	Uncommon	Erythema nodosum, pyoderma gangrenosum	Nail onycholysis	Erythema nodosum, keratodermia, blennorrhagica	Bluish or blackish discoloration of skin
Dactylitis	Uncommon	Uncommon	Common; more than AS	Common	-
IBD	Increased risk; 6.8%	Always	Common	Uncommon	-
Psoriasis	Increased risk; 9.3%	Uncommon	Always	Uncommon	-
Conjunctivitis	Uncommon	Uncommon	Uncommon	Common	-
Other	Decreased chest expansion, cardiovascular complication	-	Erythematous plaques	Bursitis	Sclera and ear cartilage discoloration, perspiration that stains clothing, urine when left standing in air turns dark brown/ black, kidney stones

Abbreviations: AS, ankylosing spondylitis; HLA-B27, Human leukocyte antigen; IBD, inflammatory bowel disease.

antibodies from the serum has proven to be a powerful tool in diagnosis. Enzyme-linked immunosorbent assay (ELISA) effectively detects pathogens such as Salmonella and Yersinia. The test of choice for *C. trachomatis* infection is nucleic acid amplification test (NAAT) in clean catch urine samples and should be followed by microimmunofluorescence (MIF) for definitive serological diagnosis. Shigella does not have a reliable serological test and is thus reliant on clinical diagnosis.

Due to the high connection with the HLA-B27 serotype, testing for B27 has been proposed; however, studies have shown a sensitivity of 50%, suggesting an unreliable test especially in patients who have a low post-test probability of ReA; thus HLA-B27 should not be used as a diagnostic tool. HLA-B27 is, however, associated with more severe symptoms and thus can suggest predisposition to chronic ReA.

DISH is commonly identified in adults over 50 and more often in men than women. Diabetes mellitus is strongly associated with DISH, and other risk factors include obesity and retinoid use. Contrary to previous lines of thought, DISH can include sacroiliac joint involvement. Radiographic findings may be helpful in distinguishing DISH, but the disease remains difficult to separate from AS, and in some instances appears simultaneously with AS.[25] Alkaptonuria usually becomes apparent in the third decade of life, as buildup of ochronotic pigment leads to eventual dark discoloration of sclera and ear cartilage. Often, perspiration can stain clothing of the affected patient. Patients present with pain and stiffness as the pigment accumulates in the large joints and spine with enthesitis also reported. Patients experience a loss of lumbar lordosis and limited mobility. Approximately half of affected patients will have a joint replacement surgery by 55 years of age. The disorder is classically characterized by the excretion of urine that initially appears normal but turns dark brown or black if left standing. The diagnosis of alkaptonuria can be confirmed by quantitative measurement of homogentisic acid in the urine.[26,27] Signs and symptoms of AS and its mimickers are highlighted in Table 2.

Radiographic Assessment

In AS, plain radiographic findings of bamboo spine appearance are due to fusion of the zygapophyseal joints and symmetric marginal syndesmophyte formation. Bridging syndesmophytes as well as complete sacroiliac joint ankylosis was more likely in AS when compared with axial PsA and may prove useful in differentiating the two more so than the unilateral asymmetrical grade of sacroiliitis. The intervertebral disk space is often comparatively preserved. Pathologic changes at the sacroiliac joint are common and result into fusion (Figure 1). Radiographic sacroiliitis is a later finding in the disease course and magnetic resonance imaging (MRI) may show signs of inflammation much earlier before there is radiographic evidence of damage.[28,29] The changes can be seen early in MRI scan as increased signal changes on T2 weighted images and as complete fusion on computed tomography (CT) scan at late stages of disease. Correlation between MRI inflammation and clinical disease

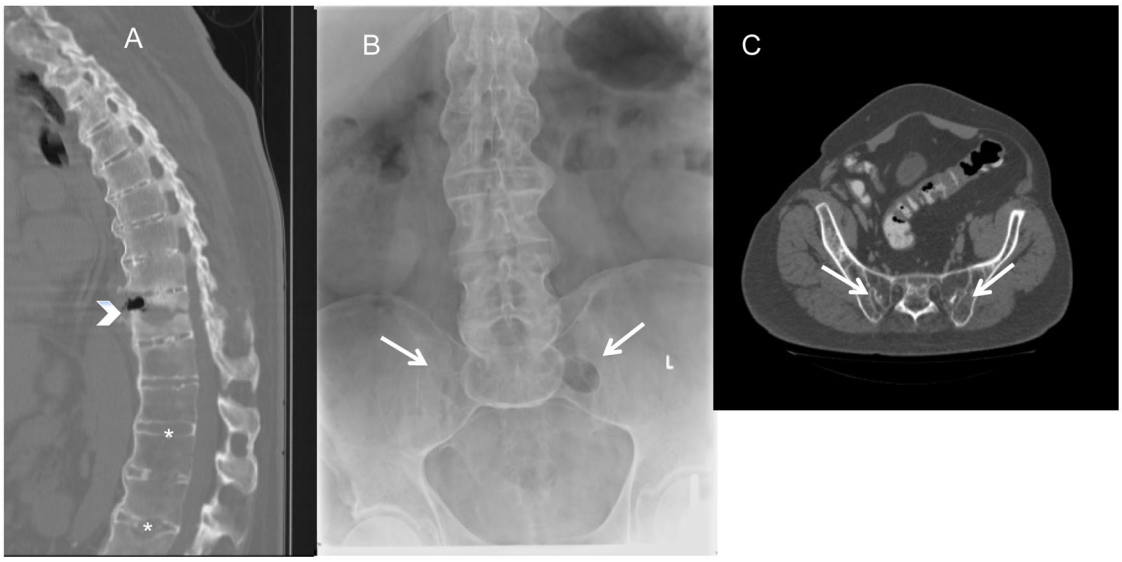

Figure 1. A 50-year-old man presented to the clinic with mid back pain that started three months ago after a fall off a ladder. CT scan midsagittal view (A) of the thoracic spine showing T10 hyperextension fracture nonunion (arrowhead). Plain radiograph anteroposterior view (B) of the lumbar spine showing bamboo spine, fusion of the sacroiliac joints (arrows). Both the CT and the plain radiograph showing preservation of the intervertebral disc space (stars). CT scan axial view (C) of the pelvis showing fusion of the sacroiliac joints (arrows).

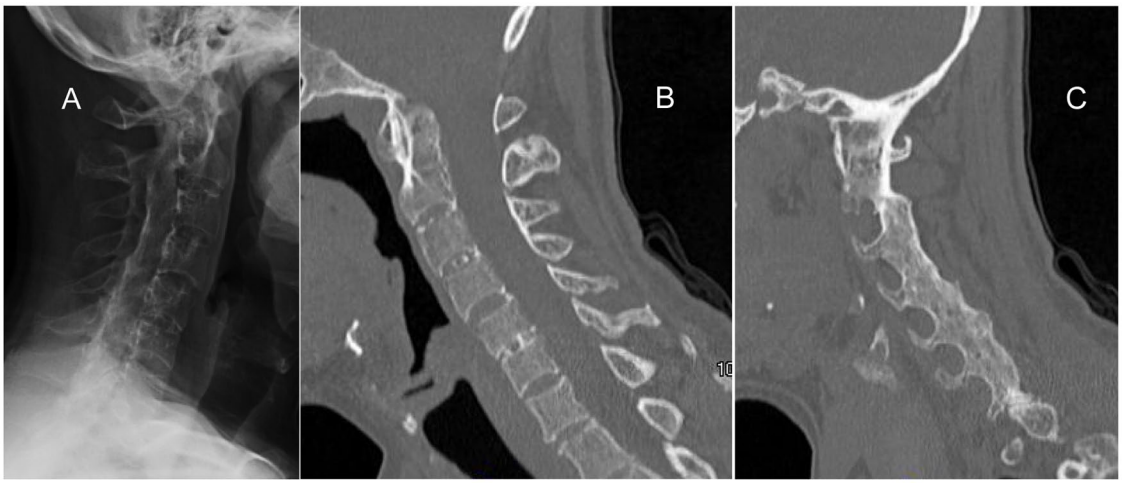

Figure 2. A 43-year-old man presented to the clinic with neck pain and stiffness. He denied any back pain. He had a long history of psoriasis with multiple peripheral joint pain and stiffness. Upright plain lateral radiograph (A), CT midsagittal (B) and parasagittal (C) images of the cervical spine.

activity are modest, but still plays an important role in early disease and determining appropriate treatment.

Radiographic imaging may be nonspecific in IBD-related spondyloarthropathy as it can present with sacroiliitis or AS, which are unlikely to indicate IBD as the contributor to symptoms. Radiography will indicate lack of erosion, osteoporosis, or joint narrowing. However, IBD patients with axial involvement have a higher prevalence (30.55%) of aseptic spondylodiscitis, also known as Andersson lesions (ALs), which occur earlier and are more commonly asymptomatic when compared with those with AS106 or PsA.[30]

In PsA, plain radiographic findings of the hand interphalangeal joints show both erosive changes and new bone formation, giving the classic pencil-in-cup deformity. The most common spine imaging changes found in PsA is cervical apophyseal joint ankylosis without anterior or posterior ligamentous calcification (Figure 2). The localization of changes to the cervical spine and lack of ligamentous calcification helps to differentiate between PsA and AS. Unilateral sacroiliitis with bulky paramarginal and vertical syndesmophytes can also be used to differentiate PsA from AS which typically involves bilateral inflammation without paramarginal syndesmophytes.

In ReA, plain radiographic features are similar to those in PsA. These features include signs of joint inflammation, periostitis, bony proliferation and enthesitis. It is possible to have these features in a unilateral or bilateral pattern with the lower extremity more commonly involved. Sausage digits, pencil-in-cup deformities as well as ivory phalanx in the feet are possible.

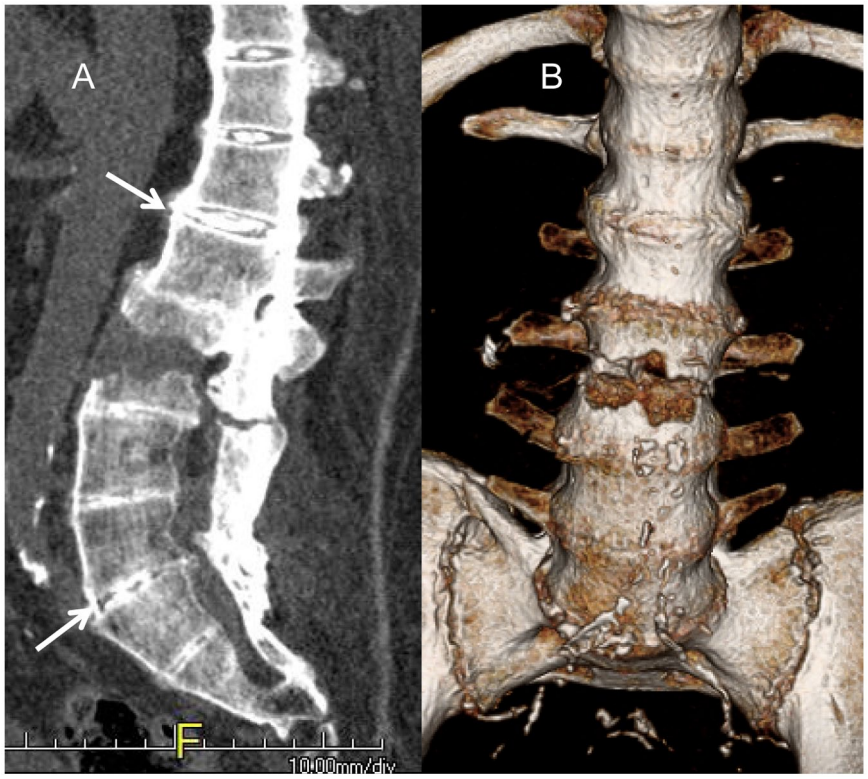

Figure 3. A 68-year-old man presented to the emergency department with severe low back pain after a fall in the shower. He had a long history of alkaptonuria and ochronosis with joint replacements of bilateral hips, knees, and the left shoulder. CT midsagittal (A) and (B) coronal images showing complete ankylosing of the facet joints, calcification of the intervertebral disc as well as anterior and posterior ligaments, with three columns unstable hyperextension injury of L3. The sacroiliac joints are not fused which differentiates ochronotic spondyloarthropathy from ankylosing spondylitis.

Due to the similarity in radiographic findings, a good clinical history is paramount in differentiating between psoriatic and reactive arthritis. Features that will provide the most differentiation include sex, age and distribution of arthritis.

Distinction of DISH from AS radiographically can be challenging as DISH is a lesser-studied disease. Radiographic findings involve anterior longitudinal ligament calcification; whiskering enthesopathy of the iliac crest, ischial tuberosities, and greater and lesser trochanters; and periarticular hyperostosis in the hands, elbows, knees, and quadriceps tendon insertion. Because spinal symptoms are uncommon in patients, X-rays are important for diagnosis.[31] MRI can reveal subchondral bone marrow edema, fat metaplasia, subchondral sclerosis, entheseal, para- and intra-articular bridging. Ghossan et al[25] recommend a collegial meeting for analysis of cases where DISH and AS are both plausible diagnoses. Two characteristic radiographic features differentiate alkaptonuria from AS. In alkaptonuria, the intervertebral disks are calcified, and sacroiliac joints are not fused (Figure 3). This is in contrast to AS where the intervertebral disk space is preserved, and sacroiliac joints are fused (Figure 1).

Management

Treatment of patients with inflammatory spondyloarthropathy must be individualized based on type of disease, presence of extra-articular manifestations and disease activity. Non pharmacological treatment in addition to pharmacological treatment provides the best outcomes. Physical therapy and exercise programs are recommended to all patients to decrease stiffness, improve pain and function. An important lifestyle modification to recommend is smoking cessation as smoking is associated with increased disease activity, although quitting has not shown to benefit signs and symptoms of patients to date. In general, there is a role for non-steroidal anti-inflammatory drugs (NSAIDs) in treatment of inflammatory and metabolic spondyloarthropathy. There is conflicting evidence of whether continuous NSAIDS reduce structural damage in the spine vs on-demand use only. At this time the recommendation is that NSAIDs should only be prescribed if the patient is symptomatic to avoid long-term risks of NSAID use and not for a possible protective effect. Local injection of glucocorticoids may be used but great evidence is lacking. Short-term high dose systemic steroids might be useful in some patients, but long-term use is not recommended regardless of dosing. In general, traditional non-biologic disease-modifying antirheumatic drugs (DMARDs such as sulfasalazine, methotrexate, leflunomide, or penicillamine) are ineffective for most patients with axial disease but have efficacy in those with peripheral arthritis or IBD. Biologics such as anti-TNF agents (infliximab, adalimumab, etanercept, certulizumab, and golimumab) are now considered the standard of care for patients with inflammatory spondyloarthropathy after inadequate response to conventional treatment with NSAIDs and non-pharmacological management. Those

with axial spondyloarthropathy and IBD are less likely to benefit from etancercept as it lacks efficacy in treating IBD. More recently, secukinumab, an IL-17A inhibitor monoclonal antibody has been approved for treatment of AS and PsA. It should also be avoided in patients with IBD as it resulted in more adverse events and was not efficacious in those with Crohn's disease. IL-23 inhibitors, such as ustekinumab and risankizumab, have not demonstrated efficacy in the treatment of axial spondylarthritis in current studies. Newer research has demonstrated that JAK inhibitors, such as tofacitinib, filgotinib, and upadacitinib have reduced active inflammation and improved clinical efficacy and may be an emerging therapy for those with axial spondylarthritis. Unlike SpA, DISH does not respond to NSAIDs and the treatment options are limited to treating symptoms and surgery.[25,31] Surgical interventions can correct deformities in selected patients with severe spinal disease, such as severe cervical kyphosis that interferes with forward vision. Fusion of the atlantoaxial joint is needed in patients with evidence of instability, severe pain or neurological dysfunction. Total hip arthroplasty, as hip involvement is frequent in this population, and corrective osteotomy are also possible surgical interventions that may help with disabling deformities and pain.

Limitations and Future Directions

Limitations of the literature accessed for this review include that of many other narrative reviews in that our findings are based on the paucity of published literature on these topics. The pathophysiology of most of these diseases have not been fully elucidated which will require further investigations. Gut dysbiosis is also an emerging concept that needs additional studies to determine the significance within these diseases. Newer therapies such as JAK inhibitors need to be studied with randomized controlled trials comparing their efficacies to other treatment options in axial spondyloarthropathies.

Conclusions

Identifying spinal involvement of spondyloarthropathies remains a challenge. They affect the axial skeleton more often than previously thought and as a result, should be included in the differential diagnosis for patients presenting with back and neck pain. The axial presentations of these diseases have subtle distinctions that need to be detected early to minimize time to proper diagnosis. CT and MRI are being used more frequently to track early stage and progression of the diseases. It is essential for the spinal surgeon to appreciate the pathophysiological, clinical, and radiographical nuances of the axial arthropathies caused by these diseases to effectively manage symptoms and choose appropriate treatment.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

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Author Contributions

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