13 Degenerative Disk Disease

Chelsea Frost, Lawal A. Labaran, and Hamid Hassanzadeh

Abstract

Intervertebral disks (IVDs) are essential components of spinal stability. Degeneration of IVDs is associated with structural failure and can lead to chronic back pain. IVDs have three main components: the nucleus pulposus (NP), annulus fibrosus (AF), and endplates (EPs), each with unique biochemical compositions that suit them for their respective roles. The NP helps to maintain IVD height and distribute loading forces, the AF contains the NP and maintains its pressurization, while the EP serves as a growth plate for vertebral bodies during childhood. Although disk degeneration has an assumed association with chronic low back pain, a clear causal relationship has not been established. The etiology of disk degeneration is a combination of genetic (various gene polymorphisms) and environmental factors (such as obesity and smoking). Disk degeneration begins with degradation of proteoglycans, resulting in disk dehydration and impaired ability to resist loading forces. Excessive stress in turn leads to the production of several inflammatory mediators and catabolic factors, further contributing to the degenerative cascade. MRI is the imaging modality of choice to evaluate suspected disk degeneration, although there is a high incidence of asymptomatic patients with radiographic disc degeneration. There are several potential treatments that are being developed with the potential to manage disk degeneration. These include biomolecular interventions and injection of protein solutions, cell implantation via gene-based therapy, and tissue engineering that can create implantable IVD material. These therapies have been studied to a relatively limited extent and have several potential drawbacks that should be considered.

Keywords: intervertebral disk, degeneration, chronic low back pain, interventions

13.1 Introduction

Intervertebral disks (IVDs) are fibrocartilaginous pads that resist compression while also allowing limited flexibility, spreading the load evenly across the vertebral bodies even when flexed.[1] Degeneration of IVD is associated with structural failure and commonly associated with chronic low back pain. Low back pain is the second leading cause of visits to a physician (second to upper respiratory problems), the most common cause of work-related disability in people under 45 years of age, and the most expensive cause of work-related disability. Up to 80% of the population is affected at some point in life, and 1 to 2% of the U.S. adult population are disabled because of low back pain.[2,3,4] The estimated annual direct medical cost was $315.4 billion from 2012 to 2014, while the indirect cost equated to about $264 million lost workdays in 2014–2015.[5]

Various factors have been implicated in the etiology of lumbar degenerative disk disease, and understanding these processes is crucial in the clinical management of this disease in terms of current and future therapies. This chapter will explore the basic disk anatomy, etiologic factors associated, pathophysiology of disk degeneration, and the current therapies being researched.

13.2 Disk Anatomy and Physiology

The IVD has three main components: a composite structure of gelatinous proteoglycan-rich nucleus pulposus (NP), a collagen-rich annulus fibrosus (AF) that surrounds the NP, and the cartilaginous endplates (EPs) that separate the NP and AF from the adjacent vertebral bones.[6] The NP consists of a proteoglycan and water gel held loosely together by an irregular network of collagen type II fibers and elastin fibers. Aggrecan is the predominant proteoglycan that has a high anionic glycosaminoglycan component that leads to the highly hydrated nature of the NP and helps maintain IVD height and distribute loading across EPs.[7,8] The AF consists of 15 to 25 lamellae composed primarily of collagen type I fibers. These collagen fibers are parallel within each lamellae and perpendicular between adjacent lamellae, thus creating the tensile strength of the AF.[9] The function of the AF is to contain the NP and maintain its pressurization under compressive loads. The EP is a thin, horizontal layer of hyaline cartilage that serves as a growth plate for vertebral bodies in childhood.[9]

Up until about 5 years of age, vascular channels that deliver nutrients throughout the IVD traverse the EPs; however, by adulthood, the EPs are avascular and the NP is 8 mm away from the nearest blood supply.[10,11] As blood vessels are restricted to the outermost aspects of the annulus, cell nutrition is delivered via diffusion for small molecules and bulk fluid flow for larger molecules.[10,12] The NP exhibits a low oxygen tension state that leads to anaerobic metabolism, resulting in a high lactic acid concentration and low pH. Based on in vitro studies, a chronic lack of oxygen can result in NP cells becoming dormant, whereas a chronic lack of glucose can kill them. Thus, this low oxygen microenvironment can negatively impact cellular function and the disk's ability to recover from any metabolic or mechanical injury.[9,12]

13.3 Etiology of Degenerative Disk Disease and Low Back Pain

It is understood that the socioeconomic impacts of lower back pain are enormous. However, while there is an assumed association between degenerative disk disease and lower back pain, there has yet to be a causal relationship formally established and a specific etiology is still to be determined.[13] There have been several studies examining asymptomatic patients with lumbar magnetic resonance imaging (MRI) demonstrating degenerative disk disease.[14,15,16,17] Based on conventional thinking, if degenerative disk disease were a predominant factor in the etiology of low back pain, then it would be uncommon in the asymptomatic patient.

There have been studies showing pain provocation associated with relatively innocuous mechanical stimulation of the outer

posterior annulus and EP. The posterior annulus is supplied by the sinuvertebral nerve, a mixed autonomic and somatic nerve. Nociceptive fibers normally penetrate the outermost 1 to 3 mm of the annulus, but have been reported to progress toward the NP of severely disrupted disks.[18,19] Painful disks are always structurally disrupted and appear to become sensitized to mechanical loading. Based on animal studies, contact with the NP can lower nerve stimulation thresholds and therefore result in painful stimuli.[18,20,21,22] Disk features most closely associated with pain include prolapse, disk narrowing, and radial fissures, especially when they reach the disk exterior and "leak," and internal collapse of the AF. EP fractures and disk bulging have a variable relationship with the painful sensation of low back pain.[17,23,24,25]

Various factors, both genetic and environmental, play a role in disk degeneration. As one ages, there is a decrease in nutrient supply, which negatively impacts the ability of the IVD to adequately respond to increased load or injury. Structural damage accrued over time will further propagate the degenerative cycle.[26] However, genetics may play a larger role than both inadequate nutrition and mechanical injury, and twin studies have noted a 70% genetic contribution to an individual's risk.[27,28] Polymorphisms are in the various genes for catabolism that can contribute to IVD degradation. Any increases in the inflammatory cascade can cause the polymorphisms to affect the balance between anabolic and catabolic mediators. Polymorphisms within interleukin-1 (IL-1), IL-6, and cyclooxygenase-2 (COX-2) have been associated with degenerative disk disease, and COX-2 specifically has been thought to contribute to the pain cascade.[29,30,31]

Environmental factors also play a role in the degeneration of IVD. It was previously believed that repetitive physical loading was a major risk factor; however, twin studies have shown that this only plays a minor role in degeneration.[32] Obesity has been implicated as a risk factor, with recent studies indicating a body mass index (BMI) > 25 kg/m^2 as an independent risk factor for radiographic findings and obesity at a young age as a strong risk factor for an increased number of degenerated disks.[33] Other studies indicate obesity increases IL-6 levels and thus the catabolic pathway leading to degeneration.[34] Cigarette smoking is the only chemical exposure that has been associated with disk degeneration as it is assumed to limit blood flow to vertebral EPs. An animal model showed increased production and release of proinflammatory cytokines with resultant chondrocyte decomposition.[35] Regardless of the etiology, the end result is degradation of the disk.

13.4 Pathophysiology

The functionality of the IVD depends largely on the extracellular matrix (ECM), a dynamic network of structural proteins that contributes to the IVD's ability to resist mechanical loading and tensile forces as well as the necessary environment for cell maintenance and survival.[36] The ECM is composed of macromolecules consisting of collagens, proteoglycans, and glycoproteins. Collagen is organized into fibrillar networks to provide the tensile strength, and elastin provides the needed elasticity to prevent delamination and help the lamellar recover after tensile loads.[37,38,39,40] Proteoglycans are negatively charged and enable for the IVD to remain hydrated. By attracting and retaining water, it allows a swelling pressure to develop and resist compression from axial loading. The glycoproteins provide structural support and help fine-tune tissue functionality as well as organize and assemble the ECM.[36] The IVD is also largely composed of water, and the concentration varies based on age, location in the disk, and body position.[41,42] The most hydrated area is the central region of the disk, the NP. In infancy, the water content of the NP is as high as 90% and subsequently falls to around 80% in the nondegenerate disk of an adult,[43] while the water content is around 65% in the outer AF.

The most important early change is the degradation of proteoglycans, including aggrecan, which leads to dehydration of the IVD and subsequent structural damage.[44] The AF must now resist compressive forces directly, which causes it to become stiff and weak, and propagates the degenerative pathway. Excessive stress causes production of inflammatory mediators and increases the number of catabolic factors. Degeneration also results in disorganization and destruction of the collagen matrix, which affects the mechanics of the disk and increases the risk of herniation and major annular tears.[45,46]

Various imaging modalities continue to be developed to better evaluate disk degeneration, and MRI is considered the modality of choice.[47] Based on MRI analyses, dehydration of the NP is indicative of IVD degeneration that progressively worsens and can be associated with tears within the AF or EP. These MRI changes are thought to be caused by failure of the tissue structures from ECM alterations. Tears in the AF may occur due to disruptions of organized collagen networks or mineralization of the EP, which, in turn, affects the nutrient supply and causes early cellular senescence or cell death.[36] Contrast enhancement for CT or MRI rapidly diffuses in a degenerated disk and will appear brighter due to the lower concentration of proteoglycans.[48] Magnetic resonance spectroscopy (MRS) is able to detect the metabolite concentration of a tissue. This modality can noninvasively detect the amount of lactic acid in the IVD, which increases in the degenerating disk.[48]

However, it is important to clinically correlate radiographic findings as many patients can be asymptomatic. In one MRI study of asymptomatic patients, 52% had a disk bulge on imaging, 27% with a protrusion, and 1% with extrusion.[17] Another study noted 24% of 300 myelograms performed on asymptomatic patients showed an abnormality of the lumbar disk.[49]

13.5 Advancements in Treatment

The increased burden associated with lower back pain has led to a greater need for understanding and improving existing treatment strategies. As such, animal models, both in vivo and in vitro, have been developed. In vitro models allow for a greater understanding of specific pathways and components of IVD degeneration, while in vivo models more accurately replicate the inherently complex process.[50] The mouse lumbar IVD most closely matches the human IVD.[51] Understanding the differences and similarities of animal models to the human IVD allows the implementation of interventions to better translate these findings to clinical therapies.

The amount of degeneration present in the IVD also provides an insight into the disk's biology at that time and determines

what interventions are available. In earlier stages, biomolecular interventions could rebalance anabolic and catabolic pathways in the degenerative cascade.[18,50] Protein solutions can be injected directly into IVD in order to stimulate cell growth and/or anabolic responses with the goal of reversing the degenerative cascade and further degeneration.[52] Prior studies have shown the IVD responding to exogenous growth factors.[53,54] There have been various in vivo studies that have shown increased proteoglycan content of the NP, increased disk height, and improved MRI findings.[55,56,57,58] However, these interventions currently are limited by the short duration of its therapeutic benefits. The delivery method for therapeutic proteins involves puncturing the AF, which, in turn, can generate a catabolic cascade that has previously been shown to cause an acceleration of disk degeneration in a 10-year follow-up of patients undergoing discography.[59,60] Previous attempts have been made to repair the AF with suturing and anuloplasty on in vivo models; however, these techniques failed to improve tensile strength.[61,62] New modalities are being studied and developed, which, in time, could have great potential in conjunction with other modalities at clinically managing degenerative disk disease.

Intermediate stages of degeneration, characterized with less active and rapidly disappearing viable cells, allow for cell implantation via gene-based therapy in order to repopulate the disk and are based on inducing changes to the intradiscal gene expression.[50] Genes are delivered via vector and are either injected directly or transduced into the cell. Currently, viral vectors are being utilized as nonviral vectors are still in development.[63] The biggest drawback to using viral vectors is the potential for mutagenesis leading to malignancies, as with retrovirus vectors, or immune responses, as with adenovirus vectors. There is also a large expense associated with the preparation and the still unknown risks to patients.

Tissue engineering can be utilized in advanced stages to mimic the native disk[50] as there is little potential for reversal of damage via the other two therapies. Introducing a substitute for the damaged disk can function as a scaffold to maintain the disk integrity, and physical conditioning of the cells should also be performed.[64,65,66] With the current advancements in technology, tissue-engineered whole-implantable IVD has been created that allow both AF and NP composites to replace the degenerated disk. Its use has been successfully demonstrated in animal models with similar properties to the native disk in both biomechanical and biochemical testing.[67,68] These disk analogs can autonomously regenerate disk morphology and functionality after implantation; however, more studies are needed as there have only been two translational studies performed so far.[53]

13.6 Conclusion

Spinal disorders continue to be a challenge in both health care and for society. The increasing knowledge of the anatomy and pathophysiology of the IVD has already allowed for the development of therapies based on the level of disk degeneration. More advancements are being investigated, which will further shape the management and treatments for degenerative disk disease and lower back pain.

13.7 Tips and Pearls

- IVDs are important contributors to spinal stability, and degeneration can lead to structural failure and chronic low back pain.
- Disk degeneration is caused by underlying genetic factors, including gene polymorphisms that regulate metabolic and inflammatory pathways.
- Disk degeneration is also caused by environmental factors such as obesity and smoking.
- Treatment of disk disease is dependent upon the degree of degeneration present. Current and future options include injections of protein solutions, gene therapy to modify cell proliferation, and tissue implantation.

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14 Spinal Inflammatory Arthritides

Evan D. Sheha, Sapan D. Gandhi, and Nicholas U. Ahn

Abstract

The spinal inflammatory arthritides encompass a group of rheumatologic diseases in which axial back pain and stiffness are a common feature of the disease process. The most common diagnoses in which spondyloarthritis (SpA) occurs include ankylosing spondylitis, reactive arthritis, psoriatic arthritis and rheumatoid arthritis. One hallmark of spondyloarthropathies is the development of symptomatic sacroiliitis, which, along with the presence of the HLA-B27 antigen, is one of the key diagnostic features of SpA. It is important to note that SpA is a clinical diagnosis co-incident with other autoimmune mediated diseases rather than a distinct disease process. Additionally, as with all rheumatologic diseases, there is a spectrum of disease severity, and as such not all patients with the above diseases will develop symptomatic axial arthritis. The aim of this chapter is to define the features of SpA common to each disease process and review the available medical and surgical options used in its treatment.

Keywords: spondyloarthritis rheumatologic disease, sacroiliits, ankylosing spondylitis, rheumatoid arthritis

14.1 Introduction

The spinal inflammatory arthritides, or spondyloarthritides, encompass a group of diagnoses characterized by an inflammatory arthritis of the axial spine. This chronic inflammation, termed axial spondyloarthritis (SpA) describes a commonality between an interrelated group of rheumatic diseases and exists on a spectrum of severity ranging from mild to severe chronic back pain and stiffness, typically manifesting as night pain and morning stiffness that improve with mobilization.[1] While axial inflammation is most common, affecting joints of the spine, pelvis, and rib cage, the spondyloarthritides may occasionally present with primarily peripheral inflammation. Since its recognition as a distinct clinical entity in the early 1970s, various criteria have been developed and modified over the intervening decades to aid in the categorization and definition of SpA, although, in brief, this clinical entity is defined by the Assessment of SpondyloArthritis International Society (ASAS) as chronic back pain (> 3 months) in patients younger than 45 years of age with sacroiliitis on imaging or the presence of HLA-B27 combined with additional clinical features consistent with an inflammatory disease process including inflammatory back pain or arthritis, enthesitis, elevated inflammatory markers, and family history, among others.[2,3] As such, SpA exists as the primary spine-related disease process that is present in, and helps define, the spinal inflammatory arthritides detailed below.

14.2 Ankylosing Spondylitis

Ankylosing spondylitis (AS) is perhaps the most widely recognized and well known of the spondyloarthropathies, characterized by early-onset sacroiliitis, which is considered the hallmark of this disorder.[4] First described in the late 16th century, AS was the first of the spondyloarthropathies to be studied and clinically defined—likely due to its unique clinical phenotype—and by the mid-1900s the notable similarities between AS and similar disease processes such as psoriatic arthritis (PsA) and reactive arthritis laid the grounds for Moll et al to classify the spondyloarthropathies as a distinct clinical entity.[4,5]

As one of the spondyloarthropathies, the clinical presentation of AS follows similar patterns, although with disease-specific manifestations. Patients typically begin to exhibit symptoms in late adolescence or early adulthood; onset in patients older than 45 years is rare. Common symptoms include chronic low back pain and stiffness early in the disease process. The onset is insidious, with morning stiffness and occasional night pain predominating, which improve with exercise but not rest.[1] Chest pain from costosternal stiffness may be seen along with inflammation of the joints of the axial spine including diskovertebral, apophyseal, costovertebral, and costotransverse joints. Progressive ankylosis of the spine may ultimately affect global sagittal balance with loss of lumbar lordosis, increased thoracic kyphosis, and cervicothoracic kyphosis resulting in the stooped posture, positive sagittal balance, and the chin-on-chest deformity seen in late-stage AS.[6,7] Eye involvement (iritis or, specifically, *anterior* uveitis) is the most common extra-articular manifestation of AS, presenting as monocular eye pain with photophobia and blurred vision.[8] Other organ systems are affected as a result of a generalized inflammatory process, which places patients with AS at higher risk of cardiomyopathies, valvular heart disease, gastrointestinal inflammatory disorders such as Crohn's disease or ulcerative colitis (which often occurs coincidentally), conduction abnormalities, and lung parenchymal abnormalities.[9,10,11] A large proportion of patients with AS are osteopenic or osteoporotic, which in combination with spinal ankylosis places them at an increased risk of clinically significant spinal fractures with minimal trauma.[12,13]

The typical early clinical manifestation and radiographic change associated with AS is sacroiliitis, noted first on plain radiographs as blurring of the margins of the sacroiliac (SI) joint, typically at the distal third, which may subsequently progress to joint erosion, bony sclerosis, and ultimately complete ankylosis.[14] However, it should be noted that according to the ASAS criteria, radiographic changes of the SI joint are not necessary for the diagnosis as prospective studies have demonstrated that only approximately 60% of patients with AS will develop radiographically detectable SI joint arthritis within 10 years of diagnosis.[14,15] Given the oblique orientation of the SI joints and the limited reliability of diagnosing SI joint arthritis on plain radiographs, magnetic resonance imaging (MRI) has been increasingly used to aid in the diagnosis. Short tau inversion recovery (STIR) and contrast-enhanced MRI sequences demonstrating capsulitis and bone marrow edema around the SI joint have been useful in aiding early diagnosis and are included as a modality for diagnosing SpA and AS, specifically, as outlined by the ASAS.[2,16] With regard to the remainder of the spine, vertebral inflammatory arthrosis presents with early radiographic changes of enthesopathy between vertebral segments. Inflammation in the superficial

anulus results in squaring of the vertebrae. As the enthesopathy progresses, bridging calcification between vertebral segments results in fused marginal syndesmophytes, which create the appearance of the "bamboo spine"—pathognomonic for axial SpA—on plain radiographs.

AS has a well-described association with HLA-B27, a surface antigen encoded by the major histocompatibility complex, and is found in up to 90% of patients with AS; however, the basis for this association remains unclear.[17] Advances in genomics have led to the discovery of a number of additional genes that interact with HLA-B27 and may influence the likelihood of developing AS and other similar autoimmune disorders including Crohn's disease, or ulcerative colitis, and the spondyloarthropathies in general.[18]

Initial treatment is typically focused on symptomatic relief with nonsteroidal anti-inflammatory drugs (NSAIDs), which remain the first-line treatment modality in AS. Physical therapy regimens focusing on maintenance of mobility and postural support are important adjuncts to early medical treatment with the goal of maintaining spine flexibility and overall mobility. If symptoms persist despite adequate treatment with NSAIDs, tumor necrosis factor (TNF) inhibitors have shown excellent efficacy in treating the symptoms of AS, occasionally resulting in complete remission of symptoms, although the increased risk of infection or activation of latent disease should be considered and ruled out when necessary.[19] SI joint corticosteroid injections may be considered, although systemic long-term glucocorticoids are generally contraindicated in light of their detrimental effects on bone turnover, especially given the high proportion of patients with baseline osteopenia and/or osteoporosis and the increased risk of spinal fracture in this population.

Individuals with AS who suffer from progressive thoracolumbar kyphosis resulting in the inability to maintain upright posture without significant excess energy expenditure, or chin-on-chest deformity secondary to fused cervical kyphosis, may ultimately require surgery to address their deformity and improve health-related quality of life. The surgical treatment of this disorder has classically been the correction of the deformity with restoration of sagittal balance through a posterior-based osteotomy. Smith-Petersen described the original posterior-based osteotomy, which bears his name (SPO) for treatment of the fused spine in rheumatoid arthritis (RA). In his technique, the spinous processes, facets, and ligamentum were excised prior to "raising and the head and foot of the operating table very slowly" and essentially cracking open the anterior spine through a fulcrum in the middle third of the spine, resulting ultimately in an anterior opening wedge osteotomy to restore lordosis.[20] This approach has fallen out of favor for large deformities requiring greater degrees of correction given the risk of damage to anterior structures—most specifically, and catastrophically, the great vessels—when the anterior cortex is cracked open.[21] Furthermore, higher degrees of correction require multiple osteotomy sites as the amount of correction through a single SPO is limited, adding further morbidity to the procedure. More recently, the posterior-based, closing wedge pedicle subtraction osteotomy has gained favor as a method to restore sagittal balance for large deformities with a high positive sagittal vertical axis, although at the risk of increased blood loss and need for additional, robust fixation.[22] Such osteotomies are usually performed at the L3 level where greater space is afforded by the caudal roots, although a more distal osteotomy may provide a greater degree of correction. Careful attention should be paid to the possibility of dural kinking, which is better tolerated at more distal levels, as is retraction of the thecal sac at levels distal to the conus medullaris. Severe cervical or cervicothoracic kyphosis may result in a chin-on-chest deformity, which severely restricts horizontal gaze, impacting patient quality of life and the ability to perform activities of daily living.[23] In cases of isolated severe cervical kyphosis and ankylosis, which is not better addressed through a distal osteotomy to address global sagittal imbalance, osteotomy options are typically posteriorly based and occur at the cervicothoracic junction. Cervical osteotomies in AS include the opening wedge osteotomy at C7–T1, first described for treatment of cervical kyphosis in AS by Urist in 1958, C7 pedicle subtraction osteotomy, or combined anterior release and posterior closing wedge osteotomies, although it should be noted that these operations carry a high risk of complications and postoperative morbidity, including dysphagia, neurologic complications, and pseudarthrosis.[24,25,26] Patients with AS who have spinal fractures or are suspected of having spinal fractures should be evaluated and treated aggressively given the risk of shearing mechanisms in unstable fractures, nondisplaced fractures that may progress if inadequately treated, and the associated increased risk of serious neurologic and vascular complications.[27,28] Advanced imaging, including computed tomography (CT) to better characterize fracture patterns and MRI to evaluate for nondisplaced fractures and associated soft-tissue injuries including epidural hematoma, are recommended in most cases, especially when fractures occur or are suspected at the cervicothoracic junction where evaluation with plain radiographs is limited. Erring on the side of surgical stabilization with long segment stabilization and the use of postoperative bracing can help offset the risk of failure in patients with poor bone quality, or late displacement in those treated nonsurgically.[29,30]

14.3 Reactive Arthritis

Reactive arthritis is a form of SpA typically resulting from a gastrointestinal or urinary tract infection, and classically presenting as the triad of conjunctivitis/uveitis, urethritis, and oligoarthritis occurring within 4 weeks of exposure.[31] Formerly known as Reiter's syndrome, this clinical entity has been most commonly associated with sexually transmitted disease (namely Chlamydial infections although others have been implicated), while postdysentery reactive arthritis may result after *Salmonella*, *Shigella*, and *Campylobacter*—among other—gastrointestinal infections.[32] Additionally, atypical infections (respiratory, dental, and ophthalmologic infections) have been implicated in the development of reactive arthritis.[33] Despite this association, in up to 50% of cases of reactive arthritis, no infection or bacteriologic etiology is identified.[34] The association with HLA-B27 is similarly less clear in reactive arthritis than in AS, where up to 90% of patients are HLA-B27 positive.[35] There is, however, some suggestion that HLA-B27 may predispose patients to a more severe clinical phenotype and development of SpA.[33,36]

Apart from the classic clinical manifestations, which include large joint oligoarthritis and enthesitis, aphthous ulcers, and gastrointestinal and genitourinary symptoms, patients frequently suffer from sacroiliitis and inflammatory low back pain typical of SpA.[34] The clinical course is variable, as patients may fully recover, relapse, or develop long-term SpA.[33] Treatment is typically

directed at addressing symptoms, with NSAIDs as the first-line treatment for both symptom management and potentially in prevention of syndesmophytes, although DMARDs, corticosteroids, broad-spectrum antibiotics, and TNF-alpha antagonists have also been used with varying degrees of effectiveness.[36]

14.4 Psoriatic Arthritis

PsA is an inflammatory arthritis in patients carrying a diagnosis of psoriasis who are seronegative for rheumatoid factor.[37] Specifically, PsA was defined initially by Moll and Wright based on a set of clinical criteria including skin or nail psoriasis, inflammatory arthropathies, or axial manifestations.[37,38] In the following years after its identification as a distinct clinical entity, the various diagnostic criteria used to define PsA have led to a wide range of reported epidemiologic incidence and prevalence, although pooled estimates show it to affect between 1 and 7% of patients with psoriasis and up to 30% of patients with severe dermatologic involvement.[39,40] Psoriasis is most commonly associated with its dermatologic manifestations, which typically take the form of well-demarcated erythematous papules or thick white and gray plaques (psoriasis vulgaris) on extensor surfaces, although more serious but rare forms of pustular psoriasis or erythrodermic psoriasis may be seen.[41] Nail pitting is a classic clinical finding in patients with PsA, with a lifetime incidence of 80 to 90% in patients with psoriasis and up to 90% in patients with PsA.[42] Additionally, nail separation from the bed can occur and a subungual hyperkeratosis may be confused with a fungal infection. The presence of typical dermatologic manifestations of psoriasis in combination with nail involvement in the patient presenting to a spine surgeon's office should raise suspicion for possible diagnosis of psoriasis, if one has not yet been established, and subsequent referral to rheumatology.

The manifestation of inflammatory arthropathy in patients with PsA most commonly affects peripheral joints, particularly the distal interphalangeal joints in a classic pencil-in-cup pattern, although arthritis mutilans—a destructive inflammatory arthritis of the interphalangeal joints resulting in shortening of the digits—is a rare manifestation in severe cases.[43] Dactylitis, tenosynovitis and enthesitis, and peripheral edema are also frequently seen.

Axial manifestations of PsA are less common and typically less severe, affecting up to 36% of patients with PsA; however, concurrent peripheral manifestations of PsA are common with only approximately 5% of patients presenting with isolated axial disease.[44] While the clinical presentation of axial arthritis secondary to PsA may mimic AS—presenting most commonly as low back or buttock pain or stiffness—axial pain in PsA is typically more mild or intermittent. Furthermore, radiographic features of axial PsA also differ from AS. Notable differences include asymmetric sacroiliitis, spondylitis without sacroiliitis, nonmarginal syndesmophytes similar to those seen in diffuse idiopathic skeletal hyperostosis, and frequent cervical spine involvement particularly at the zygapophyseal joints.[45,46,47,48,49] Risk factors for development of axial PsA include male sex, HLA-B*27, diffuse peripheral arthritis, elevated inflammatory markers, longer disease duration, and, generally speaking, a more severe presentation and higher disease burden.[50] In many cases, the axial manifestations of PsA may be clinically overshadowed by the peripheral joint involvement and systemic symptoms.

14.5 Rheumatoid Arthritis

RA is a systemic autoimmune disorder manifesting as a polyarticular inflammatory arthritis.[51] Spinal disorders in patients with RA most frequently involve the cervical spine. The development of a destructive, inflammatory pannus upper cervical synovial joints with coincident degradation of the cruciate, apical, and alar ligaments results in instability of the upper cervical spine. In advanced cases, subluxation of the upper cervical spine can result in both impingement on neural elements (myelopathy, radiculopathy) and in some cases vertebral artery insufficiency.

Patterns of cervical instability in rheumatoids include C1–C2 (atlantoaxial) subluxation, occipitocervical settling (basilar invagination), subaxial subluxation, and any combination of the above. Atlantoaxial subluxations predominantly occur at the C1–C2 level with anterior subluxation more common than posterior subluxation, particularly if the integrity of the upper cervical ligaments is affected, while basilar invagination is less common given the anatomy of the saddle joint providing inherent structural support at the occiput–C1 junction. Subaxial subluxation may also be seen, which typically presents as a multilevel, or "staircase," deformity. A number of measurements are used to quantify the degree of subaxial deformity in RA. An atlantodental interval (ADI), measured from the dens and the posterior border of the anterior arch of C1, on cervical flexion–extension radiographs of > 3.5 mm in adults indicates instability at this level, and an ADI > 10 mm typically denotes complete loss of integrity of the stabilizing ligamentous structures. Conversely, measurement of the space available for the cord, or posterior atlantodental interval (PADI), measures the distance from the posterior cortex of the dens to the anterior cortex of the posterior arch of the atlas. A PADI of < 14 mm in individuals with RA is similarly associated with increased risk of neurologic injury and in patients with RA is an absolute indication for surgical stabilization.[52] Rotatory subluxation, although less common in RA than anterior subluxation, can be evaluated via the open-mouth view.[53] Cranial settling, or basilar invagination, resulting from superior migration of the odontoid, is evaluated through a number of plain radiographic criteria including the Chamberlain, McGregor, and McRae lines, and the Ranawat criteria, among others. If there is clinical and radiographic suspicion for cervical spine instability, or the patient presents with neurologic deficits, advanced imaging with CT or MRI is indicated.[54]

Most frequently patients with cervical spine instability in RA present with symptoms of myelopathy. A thorough history and physical examination focusing on the signs and symptoms of cervical myelopathy should be conducted in all patients suspected of having cervical instability. Symptoms of myelopathy include difficulties with balance or ambulation and changes in fine motor function including difficulty manipulating shirt buttons or changes in handwriting, although it should be noted that peripheral joint involvement frequently seen in this disease may complicate the diagnosis.[53] The physical examination

should focus on evaluation of upper motor neuron myelopathy signs including positive Hoffmann's sign, Lhermitte's sign with neck hyperextension, generalized hyperreflexia, positive Babinski's reflex, and sustained ankle clonus. Additionally, occipitocervical instability may manifest as a posterior occipital headache, and patients with vertebrobasilar insufficiency may experience tinnitus, vertigo, and equilibrium difficulties.

Treatment in patients with cervical RA is conservative, typically involving use of nonsteroidal anti-inflammatory medications for symptom management as a first-line treatment, although these patients are frequently managed with systemic glucocorticoids, biologics, and disease-modifying antirheumatic drugs (DMARDs) at the direction of a rheumatologist.[51] Patients with cervical spine pain without neurologic deficits may be managed with a short period of immobilization in a cervical collar and addition of oral analgesics to their usual treatment regimen.

In those individuals with neurologic deficits attributable to cervical instability, surgery is indicated to address the unstable segments. Atlantoaxial subluxation, when reducible, can be reduced and stabilized via posterior surgery without decompression. Traditional posterior wiring techniques have been largely supplanted by screw and rod constructs and C1–C2 transarticular screw techniques.[55] In the cases where the subluxation is fixed, or large pannus formation precludes reduction or directly causes compression, as well as in cases of basilar invagination, an occipitocervical fusion with decompression via resection of the posterior arch of C1 is indicated.[56] Transoral and transnasal techniques for resection of the anterior pannus or the odontoid in cases of cord compression secondary to basilar invagination have also been described, although these are frequently performed in combination with posterior decompression and stabilization, especially in the presence of significant retrodental pannus or instability.[57,58] It is important to note that while patients with RA frequently exhibit cervical spine instability, not all will require surgery, which should be reserved for those meeting radiographic criteria for surgical intervention or demonstrating signs and symptoms of neural compromise.

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