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Inflammatory and Dysplastic Lesions Involving the Spine

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Fibrous dysplasia

Pathophysiology and genetics

Fibrous dysplasia (FD) is a disease of the bone marrow stromal cell (BMSC) [1,2]. BMSCs form the structural framework in which hematopoiesis occurs, containing multipotent stem cells that can differentiate into osteoblasts, osteocytes, chondrocytes, and bone marrow adipocytes among others [3]. In FD, BMSCs begin their differentiation along the osteogenic lineage, but differentiation is arrested, giving rise to the fibro-osseous masses of tissue causing the disease.

The molecular basis of the disease involves activating mutations in the GNAS gene. GNAS codes for the α-subunit of the signaling G protein, Gsa [4,5]. Gsa is central in the cell signaling pathway that leads to the generation of the intracellular second-messenger cyclic adenosine monophosphate (cAMP) and activation of mutations resulting in ligand-independent cAMP/protein kinase A signaling. cAMP is involved in the signal transduction from multiple cell surface receptors, including parathyroid hormone (PTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and others. All the mutations in Gsa that have been identified in association with FD are at the 201Arg position. In greater than 95% of the cases, arginine is replaced by cysteine or histidine (R201C or R201H). These mutations result in inhibition of the intrinsic guanosine triphosphatase (GTPase) activity of Gsa protein, and it is this aspect that leads to constitutive ligand-independent generation of intracellular cAMP [5]. The result of these mutations is that BMSCs harboring the Gsa mutation are under constant PTH stimulation, analogous to the bone disease in hyperparathyroidism. The defect in Gsa also explains the molecular etiology of the associated extraskeletal manifestations, including café-au-lait spots (constitutive melanocyte-simulating hormone signaling in skin melanocytes), precocious puberty (ovarian FSH signaling), and hyperthyroidism (thyroid TSH signaling) among others.

FD is a genetic disease, yet there has never been a well-documented case of vertical transmission from parent to offspring. The observation that FD is not inherited, combined with the observation that the bone disease often tends to involve one side of the skeleton, has led to the generally accepted hypothesis that FD is the result of somatic mutations that occur at some early stage

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of embryonic development. What follows from this hypothesis is that in patients who have McCune-Albright syndrome (MAS; a sporadic disorder associated with a GNAS1 gene mutation and characterized by FD, café-au-lait spots, premature puberty, and abnormal skin pigmentation), in whom tissues derived from all three germ layers are involved (bone/mesoderm, skin/ectoderm, and various endocrine tissues/endoderm), the mutation that gives rise to this phenotype must have occurred early in development at the inner cell mass stage. For disease that is isolated to the skeleton but involves craniofacial and long bones, the mutation must have arisen later in development in the mesectoderm, because the craniofacial bones are of neuroectodermal origin and the long bones are of mesodermal origin [6]. Thus, the phenotype and extent of skeletal involvement are dictated by the developmental stage and location in the developing organism in which the mutation occurs.

Presentation and diagnosis

Most children who have FD present for medical evaluation because of a fracture through an FD lesion, a limp, or an incidentally discovered lesion when radiographs are obtained for another reason. The radiographic appearance of FD can appear markedly different depending on the age of the patient. The radiographs in extremely young children (<2 years of age) often lack the classic ''ground-glass'' appearance and have more of a streaked heterogeneous appearance, occasionally mistaken for enchondromatosis. With maturity, lesions become more lytic and develop a ground-glass appearance, and with age, the lesions tend to become sclerotic at their edges [6,7].

Adult patients who have FD typically present with a limp or a fracture [8]. The radiograph usually reveals a lytic ground-glass lesion consistent with FD. If there is doubt regarding the diagnosis, CT is useful for demonstrating the medullary-based fibro-osseous nature and MRI is useful for identifying/excluding fluid-filled non-FD cystic lesions. To determine the extent of disease, a technetium bone scan or a skeletal survey should be performed [9]. A bone scan is more sensitive than CT or plain films in detecting skull, spine, and rib lesions and in detecting early preclinical long bone lesions, but it is less useful than CT or MRI for operative planning on the spine. By the age of 8 to 10 years, most lesions (craniofacial and long bones) have already been established and are detectable by bone scan.

Clinical examination of the patient suspected of having FD should include examination for scoliosis, neurologic deficit, increased intracranial pressure from calvarial bone (hypertrophy), limb deformity, pelvic obliquity, and facial asymmetry [10]. Laboratory panels should include serum electrolytes and bone formation markers, such as alkaline phosphatase, bone-specific alkaline phosphatase, and osteocalcin, and serum and urine markers for bone resorption, such as N-telopeptide of collagen, pyridinium cross-links, and deoxypyridinoline cross-links [11–13]. In general, all markers of bone metabolism are elevated in FD in parallel, relative to disease activity, and no specific assay is superior to another to assess disease severity or prognosis. Markers may be normal in cases of mild disease or in older patients who have ''burnt-out'' disease, however [14].

Spinal manifestations and treatment

The involvement of the spine in patients who have FD was thought to be an uncommon problem, mostly reported in case reports. Current data indicate that it is more common than previously thought, however, and scoliosis has recently been added to the constellation of findings that make up the disease.

Scoliosis can be difficult to assess clinically in patients who have FD because they can have lower extremity deformities causing limb length discrepancies or pelvic deformities causing pelvic obliquity. Thus, scoliosis may be attributed to secondary compensation and not correctly identified as a primary disorder. In a study of 62 patients who had polyostic fibrous dysplasia (PFD), lesions in the spine were identified in 63% of the study group and scoliosis was identified in 40% to 52% of the patients [15]. There was also a statistically significant association between the lesions in the spine and the level at which the curve occurred, suggesting that the FD was causative. The location of café-au-lait spots and other areas of bone involvement (eg, pelvis, ribs) did not correlate with the scoliosis.

The care of scoliosis in children involves identification and aggressive monitoring. The role of bracing in adolescents with scoliosis and FD is unclear and may need to be individualized to the patient [16]. Patients with rib or pelvic involvement may not be able to fit adequately in a brace, although this is a valid option for patients with only spinal lesions. Data exist on patients with large curves who have undergone successful

posterior spinal fusions with no evidence of difficulty with fusion or loss of fixation in up to 22 years of follow-up [17]. Because the etiology of the curve in FD is the deformity caused by bone, which is more plastic in nature, it is unclear whether curve progression abates in adolescents or continues into adulthood [18]. The finding that certain patients who have FD develop pulmonary symptoms after childhood (and growth plate closure) provides evidence that curves may continue into adulthood, however.

Treatment

Early nonsurgical treatment of FD includes glucocorticoids, calcitonin, and external beam radiation [19]. None of these treatments have been definitively proved effective, and radiation predisposes FD to malignant transformation. The only medications that have shown any efficacy in the treatment of FD are (paradoxically) bisphosphonates [20]. Although FD is a disease of the osteoblast, bisphosphonates, which inhibit osteoclasts, are advocated for two reasons. First, lesion expansion is mediated by osteoclastic resorption of adjacent normal bone; bisphosphonates would inhibit this process, impeding lesion expansion. Second, FD is a "high-turnover" bone disease, sometimes with dramatic elevations in markers of bone turnover and occasionally with evidence of increased numbers of osteoclasts in FD lesions [6,21]. Bisphosphonate use has been postulated to inhibit these processes. The first report of bisphosphonates in FD was by Liens and colleagues [22]; in that study, nine patients who had FD were treated with high-dose intravenous pamidronate. These investigators subsequently increased the size of the group and reported good long-term pain outcomes and decreases in markers of bone metabolism [23].

Absolute surgical indications for the treatment of FD are lacking. An individual surgeon's experience is limited by the rarity and spectrum of severity found in this disorder. Failed surgical management is often related to loss of fixation, with cutout of metal devices [24]. Thus, before surgical intervention, it is important to evaluate and treat associated endocrinopathies, particularly hyperparathyroidism and phosphate wasting, which can further weaken already osteomalacic bone [25]. Further caution should be given in the panostotic form of the disorder, in which there is no normal bone for fixation to gain purchase. In some patients, no amount of surgical intervention can prevent progression of disease and the need for assisted ambulation.

Eosinophilic granuloma

Pathophysiology

Eosinophilic granuloma (EG) is a subset of histiocytosis X and is sometimes referred to as Langerhans cell granulomatosis (LCG) based on its pathogenic characteristics. LCG also includes Letterer-Siwe disease and Hand-Schuller-Christian disease. LCG is usually multifocal, involving the bones, skin, mucosal membrane, lymph nodes, pituitary gland, liver, and lung, alone or in various combinations. EG is characterized by a single or multiple skeletal lesions, and it predominantly affects children, adolescents, or young adults. Any bone can be involved, but the most common sites include the skull, mandible, spine, ribs, and long bones. Symptoms include localized pain, tenderness, swelling, fever, and leukocytosis. Lesions usually begin to regress after approximately 3 months, but they may take longer [26].

The distinctive morphologic lesions of the entire group of LCG disorders consist of expanding erosive accumulations of histiocytes, usually within the medullary cavity. Microscopically, proliferation of foamy and vacuolated histiocytes is associated with a variable admixture of neutrophils, eosinophils, lymphocytes, and plasma cells. The concentration of eosinophilic infiltrate varies from scattered mature cells to sheet-like masses of cells. Occasionally, areas of bone necrosis may interrupt the cellular infiltrate. The foamy cells may also be amassed in clumps; however, because these clumps represent phagocytosis of lipid debris, they are of no clinical significance [27,28].

Any bone can be involved in LCG, but the calvarium, ribs, and femur are particularly common sites. Solitary lesions are more common than multiple ones. When the lesions are multiple, new osseous lesions occur within 1 to 2 years; the condition is still classified as LCG [27,28]. Additional LCG of bone occurring as long as 4 years after initial diagnosis should be interpreted as a localized form of EG [29–32]. This differentiation is important because focal disease has a more favorable prognosis than that of the multifocal disseminated form, which involves organs other than the skeletal system. Similar lesions may occur within the lungs, skin, and stomach as a unifocal lesion or as part of multifocal disease.

Lung involvement occurs in 20% of patients who have EG and in an older group (20–40 years of age). Lung involvement also has a strong association with smoking. Diffuse pulmonary infiltrates may be a manifestation of a covert osseous EG. Monostotic disease involves 50% to 75% of patients [33]. Skull involvement is seen in 50% of patients. Rarely, the growing epiphysis may be involved with EG, in which transphyseal extension can be demonstrated in most patients by the radiologic and histopathologic findings [34].

Presentation and diagnosis

Most patients are asymptomatic, and the diagnosis is based on radiographic demonstration of a destructive bone lesion arising from the marrow cavity with characteristic morphologic findings. Localized bone pain and focal tenderness may occur as a result of bone erosion and, rarely, a pathologic fracture. A swelling or mass may be palpable at the site of osseous involvement. Rarely, children may present with fever and leukocytosis. Involvement of the mastoid process may appear with intractable otitis media and chronic discharge. Mandibular involvement may present with gingival and continuous soft tissue swelling [26]. Severe spinal involvement can result in deformity, back pain, and occasional neurologic deficit [35,36].

Plain radiography is the mainstay in the diagnosis of LCG, although a specific diagnosis cannot always be made without bone biopsy, because children and adolescents are subject to skeletal neoplasms. Radionuclide study, CT, MRI, and, occasionally, angiography are complementary examinations. Any or all may be used to arrive at a diagnosis [37,38].

Spinal manifestation and treatment

Vertebral destruction in LCG may lead to flattening of the vertebral body, which is termed *vertebra plana*, and is much more common in children than in adults, primarily in the dorsal spine. Although associated kyphosis has not been described, scoliosis can occur [39]. LCG can also produce expansile lytic lesions of the vertebral bodies and the posterior vertebral elements [40,41]. Involvement of the second cervical vertebra is an extremely rare occurrence; however, when it occurs, it may cause atlantoaxial instability [42,43].

It is important to note that a wide variety of bone lesions may mimic EG; these include infections, traumatic lesions, and neoplasms [44]. A false-negative diagnosis of EG is exceptional when plain radiographic findings are used, although difficulty may be encountered with lesions in areas with more complex anatomy, such as the posterior elements of the vertebral bodies. In these cases, conventional tomography or CT may prove useful. With radionuclide scanning, the false-negative rate is 30% [38].

Treatment

Percutaneous biopsy for tissue analysis to aid in the diagnosis of indeterminate metastatic disease is often performed. Needle biopsy for tissue sampling in primary osseous neoplasms is more controversial but may prove diagnostic in patients with inflammatory bone lesions and EG, with a diagnostic yield ranging from 50% to 94% in malignant bone lesions and less in benign disease. The prognosis is most often excellent, with spontaneous resolution by fibrosis occurring within 1 to 2 years. Alternatively, curettage, excision, or local irradiation leads to cure.

Ostegenesis imperfecta

Pathophysiology

Osteogenesis imperfecta (OI) is an autosomal dominant condition characterized by a mutation in or absence of collagen production, thus yielding weakened bones. Bone homeostasis is a complex process. Intact bone is able to sense its mechanical environment and initiate a new round of bone formation when damaged or weakened bone is encountered. This fundamental principle of bone biology is continuously called on in OI because the matrix that is produced is never able to support the load placed on the skeleton, resulting in bone fragility and fractures [45].

Bone of a patient who has OI reveals a state of high turnover characterized by increased numbers of osteoblasts and osteocytes [46] and an increased number of osteoclasts. Dynamic labeling shows increased numbers of double-labeled surfaces with a reduced mineral apposition rate [47].

Presentation and diagnosis

Clinical features depend on the type of OI, but bone fragility with multiple fractures and bony deformities is a hallmark of all types. The major presenting signs and symptoms of OI include blue

sclerae, hearing loss, tooth abnormalities (dentinogenesis imperfecta [DI]), joint laxity, and abnormal skin texture (smooth thin skin) [48]. Other features common to multiple OI types include bleeding diathesis (easy bruising) and respiratory distress [49]. OI is classified into four distinct types (Table 1). A fifth category has been added to include a group of individuals with osteoporosis, interosseous membrane ossification of the forearms and legs, and a high frequency of hypertrophic calluses.

Type I is the prototypical and most common form of OI and has the best prognosis. The mode of inheritance is autosomal dominant. Its clinical distinguishing features are blue sclerae at all ages and presenile conductive hearing loss or a family history of hearing loss. Bone fragility is mild, with minimal bony deformities. The stature of patients who have this form is often normal or near normal. Ligamentous hyperlaxity, resulting in joint hypermobility or subluxation, is common. Approximately 20% of patients have kyphoscoliosis [49]. DI is present in some families but not in others. Therefore, type I OI is subclassified into patients who do not have DI (type IA, more common) and those who do have DI (type IB, rare). Some have suggested that these two subgroups are biochemically distinct and that individuals with OI type IB, whose bodies make structurally abnormal collagen, are more similar to those with OI type IV than to those with other types of OI, including type IA.

Type II is the most severe form of OI, characterized by extreme bone fragility leading to intrauterine or early infant death, with only rare exceptions. The cause of death is most often respiratory failure. The mode of inheritance is autosomal recessive. The sclerae are blue or occasionally black. Clinically distinguishing features include intrauterine growth retardation, thin and beaded ribs, crumpled long bones, and limited cranial or facial bone ossification. Limbs are short, curved, and angulated [48]. Type II OI can be further subdivided into types IIA, IIB, and IIC on the basis of radiographic features of the long bones and ribs. Although patients who have type IIA or IIC uniformly die in the perinatal period, those who have type IIB survive into early childhood in rare cases.

Table 1
Osteogenesis imperfecta I subtypes (diagnostic criteria)

I	Most common, mildest form, autosomal dominant inheritance, blue sclerae, hearing loss, few fractures, modest deformities, stature nearly normal, ~20% with scoliosis
II	Most severe form, autosomal recessive, typically terminal (secondary to lung underdevelopment caused by rib fractures), blue or black sclerae
III	Most severe nonlethal form, autosomal recessive, white sclerae, triangular face, barrel-shaped ribcage, severe bone fragility, and osteopenia yielding frequent fractures, progressive deformities, short stature, and scoliosis
IV	Autosomal dominant, white sclerae, short stature, skeletal deformities, less severe than type III

Type III is the next most severe form of OI and is the most severe form for children surviving beyond the perinatal period. Its hallmark features are severe bone fragility and osteopenia, which are progressively deforming. The mode of inheritance is thought to be autosomal recessive. Multiple fractures and progressive deformity affect the long bones, skull, and spine, and are often present at birth. Postnatal growth failure is severe. Kyphoscoliosis is common. Sclerae are normal. This form is most familiar to radiologists and spine surgeons because children who have type III OI tend to have severe dwarfism attributable to spinal compression fractures, limb deformities, and disruption of growth plates (Fig. 1) [50].

Type IV OI is distinguished from the other forms by the slightly increased, although still variable, severity of bone fragility and by the presence of normal sclerae. The mode of inheritance is autosomal dominant. Mild to moderate bony deformity of the long bones and spine is present, with a variable frequency of fractures. Basilar impression of the skull with consequent brain stem compression is common and reported in 70% of patients. Hearing loss is also noted, as is DI, yielding further subclassifications: IVA (without DI) and IVB (with DI).

The preferred examination during an initial investigation of OI is plain radiography, because most imaging characteristics of OI are visible on plain radiographs [51]. MRI plays an adjunct problem-solving role in assessing for associated complications, such as basilar invagination [52].

Molecular techniques have recently played an increasing role in the diagnosis of OI. It has been estimated that greater than 90% of patients who have OI have a mutation in the gene coding for type I procollagen (COL1A1 and COL1A2). Almost 300 different mutations have been

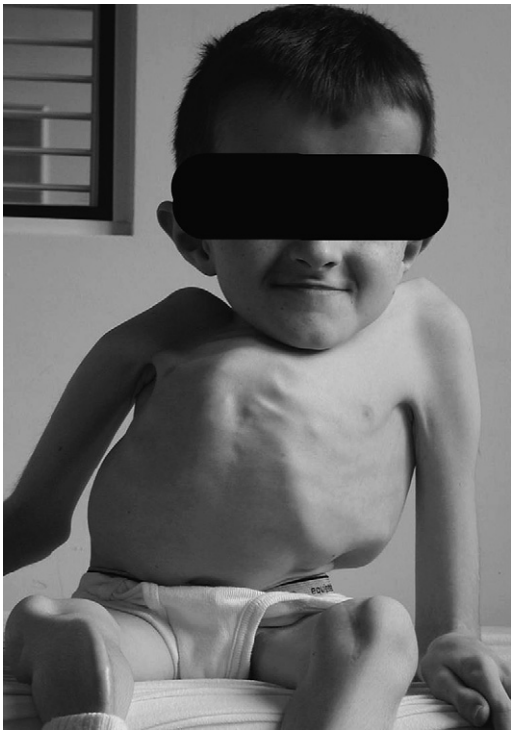

Fig. 1. Characteristic appearance of a patient who has type III OI exhibiting dwarfism and limb deformities secondary to the hallmark progressive disruption of growth plates, bone fragility, and osteopenia.

reported in the Human Type I Collagen Mutation Database, testifying to the high allelic heterogeneity of the disease [53]. The high rate of new private mutations, with virtually no recurrent hot spot, is common also to other collagen disorders (attributable to defects in type II, III, and V collagens, respectively) and represents a major obstacle in the development of efficient molecular diagnostic protocols. Although the diagnosis is still based on clinical and radiologic findings, there is a growing demand for molecular studies (ie, identification of the causal mutation) [53]. Prenatal diagnosis, however, is mostly sought by healthy parents who have had a severely affected child (OI type II or III). A prenatal screening on DNA from a chorionic villus sample is feasible only when the causal mutation in the affected sibling has been characterized.

Spinal manifestations and treatment

OI presents a variety of clinical and surgical problems to the spine surgeon. The mechanism of production of spinal deformities in OI follows logically from the softness or brittleness of the bone [52]. Vertebral collapse with compression fractures is commonly seen. The pressure of the elastic nucleus pulposus on the soft vertebral bodies causes the vertebrae to become biconcave (codfish vertebrae). Microfractures near the vertebral growth plates may cause interference with their growth, causing deformity. Curvatures of the spine are augmented because of laxity of the spinal ligaments, although vertebral compression may also play a role. Whatever the cause, a patient who has severe OI is prone to severe spinal deformity [54,55].

With the increasing longevity of patients who have the disease, more cases of spinal deformity, with its accompanying complications (back pain, respiratory distress, and nerve root compression) are to be expected. Pulmonary function studies performed in 11 patients who had OI revealed that the spirometric deficits correlated well with severity of kyphoscoliosis [54,55].

Children who have DI also have a predilection for scoliosis. Overall, in children who have OI, the incidence and severity of scoliosis increase with the severity and type of disease and age [56]. The most recent cross-sectional study on the prevalence of scoliosis in the OI population was published by Karbowski and colleagues [57]. They found scoliosis in 75% of 102 patients between 3 and 71 years of age. In 20 patients, the severity of scoliosis was greater than 40°, whereas 56 patients had scoliotic angles of less than 40°. Twenty-six patients did not have scoliosis.

The pathogenesis of scoliosis in patients who have OI is not precisely known. Most likely, the primary triggering factors are vertebral microfractures caused by bone fragility and injury to vertebral growth plates. Secondary factors, such as ligamentous laxity, limb length inequality, pelvic obliquity, and intervertebral disc abnormalities, may contribute to continuous progression of the scoliotic curve. Conversely, some studies refute ligamentous laxity as a contributing factor in the pathogenesis of these spine deformities [58,59]. Vertebral body shape was identified by Ishikawa and colleagues [60] as a predictor of spinal deformity, identifying four types on lateral roentgenograms: biconcave, flattened, wedged, and unclassifiable. In their study of 44 patients who had OI, these investigators concluded that in the presence of six biconcave vertebrae or more before puberty, severe scoliosis ($>50°$) was likely to develop [60].

Thoracic and lumbar vertebrae often have a "codfish" appearance. Repeated compression microfractures produce codfish vertebrae, which reveal osteoporosis, reduced height, biconcave shape, and adjacent biconvex discs. As a rule, the natural history of scoliosis in patients who have OI includes curve progression. This progression was detailed by Hanscom and Bloom [51] using radiographic criteria to identify six grades (A–F) of the disease. Patients who had type A disease had a mild form of OI, and their scoliosis progression could be halted by arthrodesis of the spine, whereas patients who had grade F disease had a severe form that is incompatible with survival. Patients who had type B, C, D, and E grades almost always developed progression of scoliosis, with results of spine arthrodesis variable at best (Fig. 2).

Treatment

Treatment of scoliosis can be nonoperative or operative, the latter of which is particularly difficult secondary to the patient's short stature and deformity of thoracic cage, ribs, and vertebrae. Bony anatomic structures are fragile and soft, thus complicating adequate transmission of corrective forces and conventional spinal orthosis with the currently available instrumentation. Nonoperative treatment of scoliosis in OI has included observation and brace treatment. Monitoring of spine status in all children who have OI is mandatory because progression of spine deformity is likely to occur. Orthotic treatment is almost always ineffective [59,61]. The soft cast brace could be indicated in a relatively limited group of patients who have OI and scoliosis and also have spinal pain or sitting discomfort with a Cobb angle less than 30° and are younger than 9 years of age [62,63]. In patients who have thoracic scoliosis great than 60°, vital capacity is often impaired in addition to restrictive pulmonary disease [64]. Surgery is indicated when spinal deformity is progressive and causing pain, the principal goals of which are to maximize function and minimize deformity and disability. Unfortunately, surgical options currently available for these patients are far from ideal.

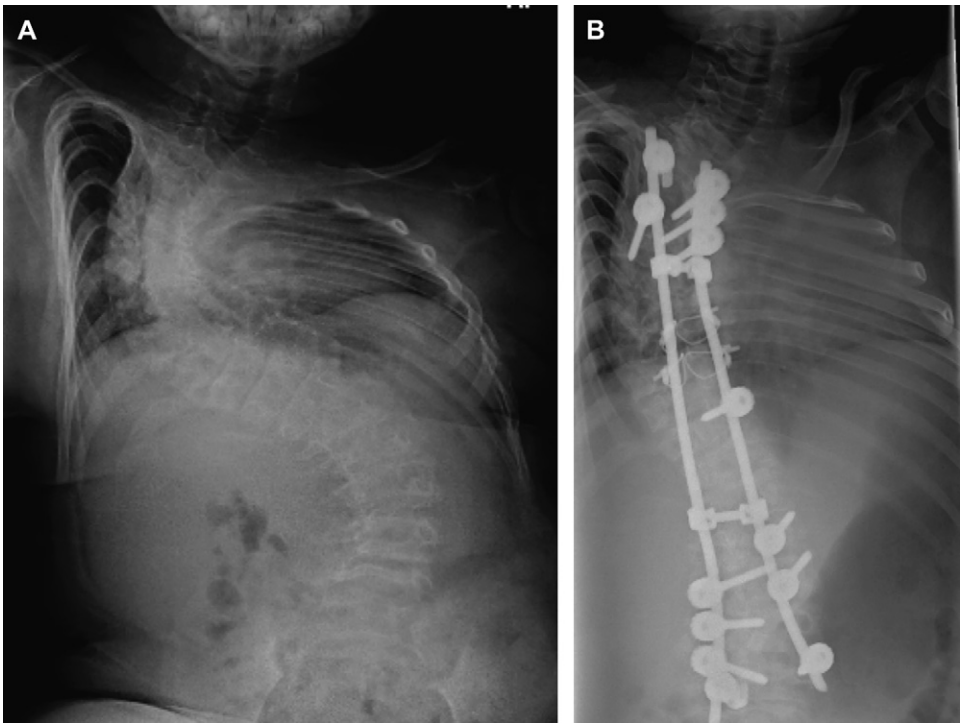

Fig. 2. OI results from microfractures near the vertebral growth plates yielding vertebral compression and spinal ligament laxity. (*A*) It ultimately results in severe scoliotic deformities of the spinal axis, as is depicted in this preoperative coronal plain film in a patient who has type III OI. (*B*) Postoperative anteroposterior radiograph after thoracolumbar correction and fusion.

Conventional methods of scoliosis correction with Harrington rods are minimally helpful because of the fragile vertebrae where hooks are placed. Consequently, methylmethacrylate has been used as an adjunct for better and safer hook purchase [65]. Luque segmental instrumentation is also an option, but special caution should be taken when tightening wires to the lamina [66]. More modern techniques include use of Smith-Peterson and pedicle-subtraction osteotomies for correction, but few long-term studies exist on their clinical effectiveness [66]. As a general rule of thumb, however, if progression of the scoliotic curve reaches a Cobb angle of 35° to 40°, early spine fusion, regardless of technique, is generally accepted provided that no medical contraindication exists [67].

Complications of scoliosis surgery in patients who have OI are common and should be anticipated, especially in those with an associated kyphotic deformity, in which instability of the metal implant is likely to occur [67]. In a series of 60 patients who had OI and were surgically treated for scoliosis, Yong-Hing and MacEwan [68] reported 33 complications in 20 patients, including but not limited to Harrington hooks being cut out during or after surgery (10 patients), excessive blood loss (>2.5 L, 9 patients), and pseudarthrosis (5 patients). Of note, children treated with bisphosphonates may have better bone stock and less fragile vertebrae, and thus have fewer complications and instrumentation failures.

Basilar impression in osteogenesis imperfecta

Basilar impression in patients who have OI is slowly progressive and has potentially serious complications, although it may remain asymptomatic [69]. Basilar impression denotes elevation of the floor of the posterior cranial fossa, including medial migration of occipital condyles and infolding of the margins of the foramen magnum. Basilar invagination denotes cephalad migration of upper cervical vertebrae into this cranial depression (Fig. 3) [70,71]. Before 1993, the frequency of basilar impression with neurologic complication was traditionally thought to be rare in patients who have OI. In a large clinical screening study, including 87 patients who had OI, Sillence [72,73] reported an overall frequency of basilar impression of 25% in these patients. He found that basilar impression occurred at the highest frequency, 71% (10 of 14 patients) in OI type IVB and that 50% of these patients had neurologic signs of compression of posterior fossa structures [72]. In another study, basilar impression was found in 17% of 47 patients who had type III OI [49]. Sawin and Menezes [69] reported basilar impression in 18 patients with the following distributions: 10 who had type III, 6 who had type IV, and 2 who had type I.

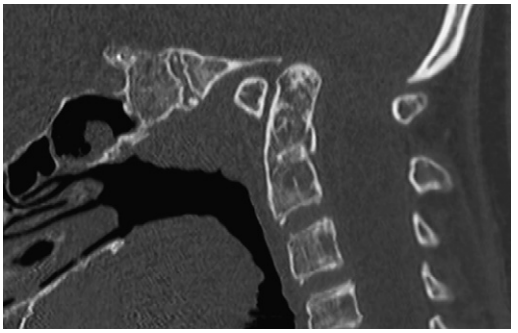

Fig. 3. Basilar invagination has been reported in nearly 25% of all cases with OI, half of which manifest with neurologic signs from compression of posterior fossa structures.

The clinical symptoms in patients who have basilar impression are usually slow to develop. Radiologic features may be present for several years before progression of neurologic signs. Sillence and colleagues [73] found that basilar impression was radiologically present long before puberty, with the youngest subject being 2 years of age. Neurologic signs may be present before symptoms, which include (1) nystagmus, (2) facial spasms, (3) nerve paresis, (4) pyramidal tract signs, (5) proprioceptive deficits, and (6) papilledema in cases of hydrocephalus. Conversely, neurologic symptoms may develop later, including (1) headache (neck and occiput), which is worse with movement, coughing, sneezing, or straining; (2) trigeminal neuralgia; (3) imbalance; (4) weakness in arms and legs; and (5) bladder disorders. The catastrophic consequences of basilar impression include brain stem compression, tetraplegia, respiratory arrest, and sudden death [74].

Ossification of the posterior longitudinal ligament

Pathophysiology

Collagen and elastin fibers are densely concentrated centrally in the posterior longitudinal ligament (PLL), beginning at the clivus and extending to the sacrum. This ligament is widest

at the disc spaces and narrowest at the midvertebral levels. It is approximately 1 to 2 mm thick centrally and thins out laterally. Initial hypertrophy of the PLL attributable to fibroblastic hyperplasia is followed by increased collagen deposition. Progressive mineralization and cartilaginous in-growth form ossification centers that eventually mature into haversian canals.

The ossification potential of the PLL has been well documented in Japan and the United States [75,76]. In Japan, immunohistochemical evaluation of PLL cells obtained from anterior cervical surgery revealed "upregulation of proliferating cell nuclear antigen" [77]. In the United States, Epstein and colleagues [75] showed that osteocalcin synthesis occurs in patients who have radiographically confirmed ossification of the posterior longitudinal ligament (OPLL) and confirmed its absence in spondylotic tissues.

A genetic locus for OPLL is most likely located close to the human leukocyte antigen (HLA) site on chromosome 6-p [54,55]. Patients who have diffuse idiopathic skeletal hyperostosis (DISH), half of whom have OPLL, test positive for HLA antigen [78]. An autosomal dominant mode of OPLL inheritance is frequently inferred because one quarter of the siblings of patients who have OPLL manifest the disease and demonstrate two concurrent strands of HLA. Other genetically modulated factors, including increased concentrations of growth hormone receptors, activins, and the bone morphogenetic proteins BamHI 10/10 kb and *Hin*dIII 19/19 kb, were also found in patients who had OPLL [79,80].

Presentation and diagnosis

One quarter of Japanese patients who have cervical myelopathy exhibit OPLL [81]. Neural injury occurring in the presence of OPLL stems from direct mechanical or indirect ischemic compromise. Cervical OPLL has been found to occur twice as often in men compared with women [81–84].

Patients who have early OPLL typically present in their mid-40s with radiculopathy or mild myelopathy. Those with more mature OPLL usually become symptomatic in their mid-50s with moderate to severe myelopathy. Although symptoms are usually gradual in onset, 10% may precipitously develop myelopathy after mild trauma, and many new deficits may prove irreversible despite surgical decompression [85].

Imaging of OPLL starts with plain films. Absolute cervical stenosis (canal diameter <10 mm) and relative cervical stenosis (canal diameter of 10–13 mm) predispose patients who have OPLL to developing more severe deficits earlier in the clinical course. When the "occupancy ratio" is greater than 40%, as defined by the thickness of OPLL divided by the canal diameter, the risk for symptomatic myelopathy increases. MRI is useful in the identification of early OPLL [86]. The ligaments appear slightly hyperintense on MRI without contrast administration and inhomogeneously enhance with gadopentetate-dimeglumine (Gd-DTPA) administration compared with disc herniations, which are uniformly hypointense. Between 30% and 60% of patients who have OPLL have accompanying disc protrusions [87].

Early OPLL originates opposite multiple interspaces, which may be visualized on transaxial, coronal, and sagittal MRI studies. These examinations provide an overview extending from the cervicomedullary junction through the cervicothoracic junction. Mature OPLL appears densely hypointense on T1- and T2-weighted MRI studies, which demonstrate hyperintense foci within the ossified ligament indicating foci of active bone marrow production in mature haversian canals in 50% of patients who have continuous OPLL [87]. Greater detail of intrinsic changes in the cord may be seen on T2-weighted MRI studies; hyperintense foci reflecting edema, myelomalacia, or gliosis may also be seen. These factors constitute poor prognostic indicators for patients who have spondylotic myelopathy compared with OPLL-related myelopathy [87]. Enhanced MRI studies may differentiate postoperative scarring from disc intrusions and may also confirm the adequacy of postoperative decompression. Accompanying vascular anomalies are readily revealed by magnetic resonance angiography.

Early OPLL may contain punctate ossification or pearls of ossification on CT studies, and these centers may progressively coalesce as maturation occurs [64]. The four types of OPLL include (1) the segmental form (39%) found posterior to the vertebral bodies but not spanning the disc spaces; (2) the continuous form (27%) extending posterior to two or more vertebral bodies, including the disc spaces; (3) the mixed form (29%), including continuous and segmental elements (Fig. 4); and (4) the localized form (5%) located posterior to the disc spaces with some rostral and caudal retrovertebral extension (Table 2) [88].

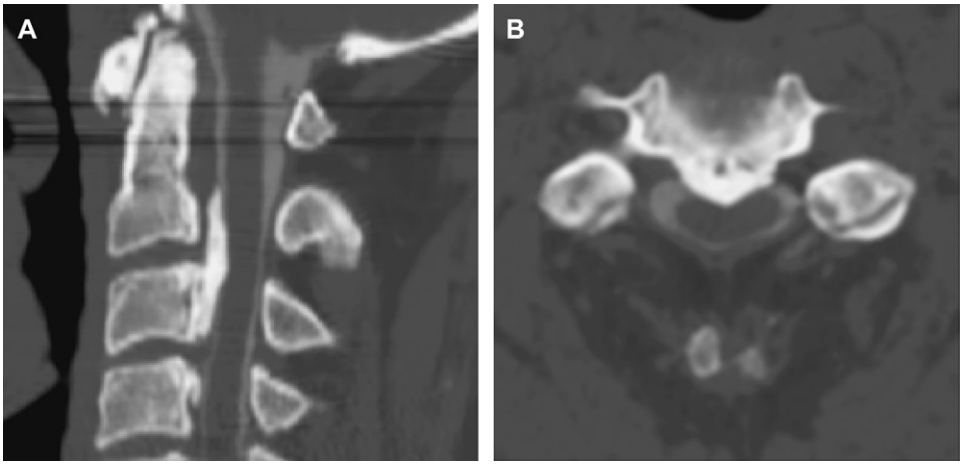

Fig. 4. Sagittal (*A*) and axial (*B*) CT scans reveal continuous segmental OPLL at C2 to C3 (with en bloc ossification of dura at C3).

Reconstructed two-dimensional (2D) and three-dimensional (3D) CT and myelo-CT scans provide greater detail of compressive changes in the spinal cord attributable to ventral OPLL, whereas dynamic studies often reveal ventral intrusion from kyphosis or dorsal compromise resulting from ossification of the yellow ligament, facet arthropathy, or laminar shingling [75,81–84]. Postoperative myelo-CT studies can be obtained to document further whether the cord has been adequately decompressed [85].

Fusion is typically documented on radiographic studies, wherein trabeculation and the lack of osseous lucency may be confirmed at the graft–vertebral body interface. Dynamic radiographs confirm the absence of motion, ideally less than 1 mm between the tips of contiguous spinous processes, and lack of subluxation or translation. Also, 2D CT studies may provide a third criterion for fusion after allograft fibula strut placement by documenting cephalad and caudad bone ingrowth into the central fibular canal. In one series in 18 patients undergoing anterior cervical fusion at an average of three levels, bone ingrowth was shown in 94% of patients 3 to 6 months after surgery at a rate of 1.5 to 3.5 mm cephalad and 2.1 to 4.6 mm caudad [89]. Ossification of the PLL extending through the dura is rarely seen in the North American population. When it occurs, dural ossification was subdivided into three categories according to shape by Mizuno and colleagues [88]: (1) isolated ossification; (2) double-layered ossification (which is associated with a dural defect); and (3) en bloc ossification, based on its relation to the dura mater.

Table 2
Ossified posterior longitudinal ligament subtypes

Type	Frequency (%)	Location of ossified ligament
Segmental	39	OPLL behind the vertebral body, each segment separated by uninvolved disc space
Continuous	27	OPLL extends behind several vertebrae, including disc spaces
Mixed	29	Contains elements of continuous and segmental subtypes
Localized	5	OPLL limited to the ligament behind the disc space

Abbreviation: OPLL, ossified posterior longitudinal ligament.

DISH, which is characterized by ossification along the ventral aspect of the cervical vertebrae, is found in 15% to 30% of adults older than 65 years of age [90]. OPLL has been found to accompany DISH in up to 50% of cases [91]. Although DISH often becomes extensive, it rarely produces dysphagia, and careful diagnostic consideration should be given to other causes before considering resection with its attendant morbidity [91].

Spinal manifestations and treatment

Most older patients (>65 years of age) who have asymptomatic OPLL and significant medical comorbidities are followed conservatively,

because prophylactic surgery in this age group plays a minimal role. For those who have rapidly progressive myelopathy and comorbidities, including cardiovascular disease, chronic obstructive pulmonary disease, diabetes, and peripheral vascular disease, nonsurgical management is often considered, because the risks for perioperative morbidity and mortality are elevated. In a series by Saunders and colleagues [92], 3 of 31 postoperative deaths occurred in patients older than 70 years of age who had significant cardiovascular comorbidities. Patients who have severe longstanding myelopathy and increased cord signals on T2-weighted MRI, reflecting myelomalacia (apoptosis) and cord atrophy, are also poor candidates for surgery. Alternatively, those patients younger than 65 years of age, without fixed deficits or major comorbidities, should be considered candidates for prophylactic surgery in the face of CT- or MRI-documented severe compromise of the spinal canal. Surgery performed in these cases, before even minor cervical trauma, may avoid future quadriparesis or quadriplegia [93].

Early studies indicated that direct anterior resection of OPLL results in improved postoperative outcomes [27,28]. In a study by Fessler and colleagues [94], Nurick grades improved in 86% of cases after anterior surgical approaches. These patients improved an average of 1.24 Nurick grades, whereas those undergoing laminectomy improved only 0.07 Nurick grades. More recently, however, several series have demonstrated equivalent results with regard to neurologic status when laminoplasty and anterior decompression are compared, with a lower complication rate with laminoplasty [94,95].

For patients who have OPLL causing myelopathy and who have maintained cervical lordosis, it is the authors' preference to perform a laminoplasty or a laminectomy with fusion to allow for dorsal decompression of the spinal cord. For those who have cervical kyphosis, dorsal decompression does not allow the thecal sac to "float away" from the OPLL. For these patients, the authors prefer direct anterior decompression with corpectomy at one or more levels, followed by anterior spinal fusion.

Ossification of ligamentum flavum

Pathogenesis

The pathogenesis of ossification of ligamentum flavum (OLF) remains uncertain. The higher prevalence in Japan implicates genetic or environmental factors [96]. Patients who have OLF have a higher frequency of non–insulin-dependent diabetes [97], obesity, hyperinsulinism, hemochromatosis, and calcium metabolism abnormalities. Thoracic OLF typically occurs at T9 to T12; this region is particularly prone to degenerative processes [98,99]. Otani and colleagues [97] noted a high incidence in cases with thoracic hyperkyphosis and suggested that the altered mechanical stresses as a consequence of this predispose to the development of OLF. Recent studies have revealed that fibronectin, bone morphogenic proteins, and transforming growth factor-β may play an important role in the development of ossification of the spinal ligaments [96].

Presentation and diagnosis

OLF predominantly affects middle-aged men with a male/female ratio of approximately 2.7:1 [100]. The clinical course is characterized by progressive myelopathy. The most common symptoms are altered gait, weakness, and numbness in the lower limbs, and signs include spastic paraparesis with hyperreflexia; upgoing plantars, clonus, and sensory deficits mainly involving deep sensation; and proprioception [100]. Sphincter disturbance and radicular symptoms are rare.

The combination of MRI and CT is required for the precise diagnosis of OLF [101]. MRI accurately delineates the location and extent of spinal cord compression in several planes but has difficulty in differentiating between an ossified and hypertrophied ligament. CT scanning best demonstrates the increased density of the ossific changes (Fig. 5A). Plain spinal radiographs may show beak-like bone projections from the apophyseal joints into the spinal canal on the lateral views.

Age-related enlargement of the ligamenta flava is common. Ono and colleagues [96] reported that ossification of the spinal ligaments have the following characteristics: (1) ectopic bone formation within the ligaments; (2) tissue hyperplasia and cellular proliferation; (3) before ossification, sequential occurrence of fibrocartilaginous cellular proliferation followed by calcification and tissue resorption with vascular ingrowth; and (4) specific site of predilection, often occurring in combination with senile ankylosing vertebral hyperostosis or DISH [96].

Spinal manifestations and treatment

The surgical procedure most commonly performed in patients who have OLF is a laminectomy

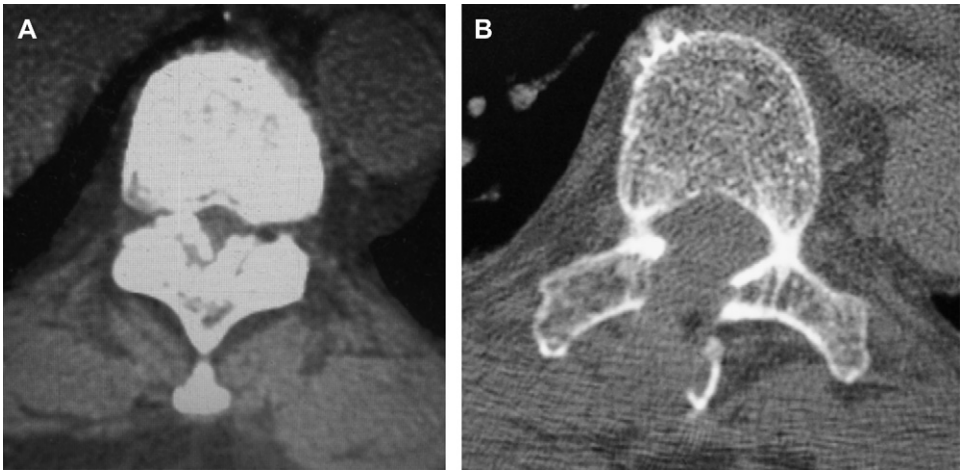

Fig. 5. (*A*) Preoperative axial CT scan demonstrates the increased density of the ossification changes present in a patient who has thoracic OLF. (*B*) Postoperative axial CT scan after minimally invasive laminectomy and removal of OLF demonstrates adequate surgical decompression of ossified ligamentum with restoration of normal spinal canal caliber.

with removal of ossified ligaments (Fig. 5B) [102]. Others, like Okada and colleagues [96], recommend decompression by laminoplasty. This may provide better stability in patients who have extensive lesions and may reduce the incidence of postoperative kyphosis and restenosis secondary to scar tissue. Medial facetectomy with or without supplemental internal fixation can be performed if degenerative hypertrophy of the articular masses is present [102]. The prognosis depends not only on the extent of the lesions but on the time to diagnosis and treatment, and the clinical outcome is usually favorable if early surgical decompression is performed [101]. Regular follow-up is necessary because recurrence or development of ossification at other levels has been reported [102].

Rheumatoid pseudotumor (inflammatory pseudotumor)

Pathophysiology

Rheumatoid arthritis (RA) is a chronic multisystemic disease of unknown cause. The characteristic feature is persistent inflammatory synovitis usually involving peripheral joints in a symmetric distribution. Synovial inflammation causes cartilage destruction and bone erosion with subsequent joint deformity. The axial skeleton, with the exception of the cervical spine, is affected later and less frequently [103,104].

Microvascular injury and an increase in the number of synovial lining cells seem to be the earliest histologic abnormalities in rheumatoid synovitis. The etiology of these features is unknown. As the disease progresses, the synovium becomes edematous and protrudes into the joint cavity as villous projections [105–107]. The synovium in joints expresses an antigen that triggers the production of rheumatoid factor (RhF), an immunoglobulin M directed against autologous immunoglobulin G. This interaction is mediated by polymorphonuclear leukocyte infiltration, complement activation, and immune complex formation and leads to the propagation of a chronic inflammatory response. Lymphokines and other inflammatory mediators initiate an aggressive cascade that culminates in synovial joint destruction with the laying down of pannus. Eventually, the chronic inflammation results in the formation of granulation tissue at the midline retro-odontoid space, compressing the brain stem and cervical cord (“pseudotumoral pannus”), as is shown in Fig. 6 [106]. In RA, multiple alterations of ligaments and bones at the craniovertebral junction (CVJ) are responsible for an occipitoatlantoaxial dislocation (“cranial settling”) [103].

Physiologically, the panus seen in RA describes the granulation tissue that is formed within the synovium by proliferating fibroblasts and inflammatory cells. Mediators of joint destruction include phospholipase A_2, prostaglandin E_2, and plasminogen activators. Class II molecules are involved in antigen–T-cell interaction.

Presentation and diagnosis

RA activity in the cervical spine begins early, with 83% of patients in prospective studies

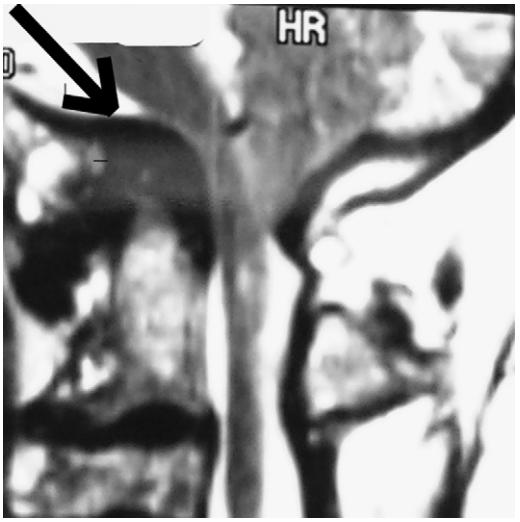

Fig. 6. Sagittal T2-weighted MRI of a rheumatoid patient who has pannus (*arrow*) surrounding the dens.

developing anterior atlantoaxial subluxation within 2 years of disease onset. Activity in the cervical spine progresses clinically and radiologically in tandem with peripheral joint involvement. The severity of peripheral erosive damage is strongly correlated with the degree of structural damage in the cervical spine. Signs and symptoms of spinal involvement include neck pain, myelopathy, weakness, ligamentous instability, and cranial neuropathy [103].

The mainstay of imaging the rheumatoid spine remains plain radiography. Flexion/extension views are necessary to assess the level of involvement and any evidence of instability. The need for further imaging by means of CT, MRI, or myelography may also be assessed during radiography. Only half of patients with radiographic evidence of atlantoaxial instability are actually symptomatic. The role of plain radiography is to establish whether there are risk factors for cord compression [108].

Instability is defined as an anterior atlantodental interval (ADI) of greater than 2.5 mm in adults. This distance is measured as the interosseous distance between the posterior aspect of the arch of the atlas and the anterior aspect of the odontoid process. The point of measurement of the joint is a subject of debate (the inferior point is the most popular). There is a slight variation in normal measurements between men and women. More importantly, it should be noted that an ADI of less than 2.5 mm, which changes considerably on flexion and extension, may also be abnormal. An ADI of 3 to 6 mm indicates early instability and implies transverse ligament damage. An ADI of greater than 6 mm indicates that the alar ligaments are also damaged. Some investigators consider an ADI of greater than 9 mm to be an indication for surgical stabilization [106].

Recent literature suggests that the posterior atlantodental interval (PADI) is a better method of assessing atlantoaxial instability because the PADI directly measures the spinal canal, and therefore shows how much is narrowed by the subluxation. The PADI is the distance between the posterior surface of the odontoid and the anterior margin of the posterior ring of the atlas. At all cervical spinal levels, the cord requires a minimum canal width of 10 mm; the cerebrospinal fluid (CSF) requires 2 mm, and the dura requires 2 mm. Therefore, a minimum PADI of 14 mm is required to avoid cord compression. The normal spinal canal measures 17 to 29 mm at C1.

The predictive value of the PADI has been found to have a 97% correlation with neurologic deficits in patients with value of less than 14 mm on pain radiographs [109]. Also, neurologic recovery from surgery was unlikely if the PADI decreased to less than 10 mm, whereas complete motor recovery occurred if surgery was performed while the PADI was greater than 14 mm.

Surgical treatment

As the name implies, on neuroimaging studies, it may be difficult to differentiate rheumatoid pseudotumor from a tumor, occasionally necessitating a biopsy to establish the correct diagnosis. Once confirmed, posterior decompressive surgery and craniovertebral fixation are the treatments of choice, because the pannus typically resorbs spontaneously after stabilization and fixation.

Summary

Dysplastic lesions of the spinal column remain a challenging group of disorders to diagnose and treat, with highly variable clinical presentations, disease locations, and associated systemic disease processes. With continued advances in diagnostic imaging modalities and evidence-based treatment algorithms, we can hope to refine and improve the surgical decision-making process further so as to minimize the pain, scoliosis, myelopathy, and

weakness attributable to these varying disease entities.

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