18

Toll-Like Receptors: At the Intersection of Osteoarthritis Pathology and Pain

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1. Introduction

Osteoarthritis (OA) is a common chronic joint disease projected to affect an astounding 18% of the population in the western world by the year 2020 (Lawrence et al., 1998). In addition, it has a cost of $15.5 billion per year in the US alone, taking into account the accompanying disability and social consequences (Yelin and Callahan, 1995). Current hypotheses of OA pathology and OA pain tend to be exclusive to either. Here we present a hypothesis that is an attempt to identify a common aetiology for both.

2. OA pathology

The features of OA constitute a group of conditions that are diagnosed upon common pathological and radiological characteristics (Felson et al., 1997) and are believed to be caused by material failure of the cartilage network leading to tissue breakdown (Poole, 1999) or by injury of chondrocytes with increased degradative responses (Aigner and Kim, 2002).

3. OA pain

Pain has been defined as the primary symptom of OA (Creamer, 2000). Physicians typically rely on scores of pain and measures of joint function to make treatment decisions for OA (Swagerty, Jr. and Hellinger, 2001), as pain rather than joint pathology is more pronounced in this disorder.

4. Immunologic mechanisms in OA

OA has been considered to primarily affect cartilage and bone. However, there is increasing awareness that all tissues of the synovial joint, including synovium, ligaments and nerve terminals, are likely affected by this complex disease. Moreover, OA has been described as a non-inflammatory degenerative condition that is characterized by the imbalance of articular cartilage degradation and repair. Traumatic injury of the joint, either acute sport injuries or chronic aging accumulation is the leading cause of this imbalance. But genetic factors also play a role in some OA. Surprisingly, C-reactive protein (CRP), a systemic marker of inflammation, is increased in serum in OA patients at early phases (Saxne et al.,

2003b;Sowers et al., 2002) although it has been suggested that inflammation is actually related to complication by crystalline arthritis (Rothschild and Martin, 2006). This suggests the presence of low-grade inflammation at early stages of the disease process.

Recently, the research of the genetic linkages and the innate immune activation in OA further supports a possible pathogenic role of inflammation and a "chronic wound repair" type of immunologic mechanisms in OA (Kato et al., 2004;Scanzello et al., 2008). There have been reports about linkages between HLA haplotypes and OA, including the linkages of HLA-Cw1, 4, 10 (Wakitani et al., 2001), HLA B35-DQ1, B40-DQ1, DR2-DQ1 (Merlotti et al., 2003), HLA DR2, DR4 (Riyazi et al., 2003). These HLAs are polymorphologic molecules presenting antigens to T cells, which supports a role of immune activation at the onset of OA.

Synovial inflammation is milder than in rheumatoid arthritis (RA). Despite this, cellular infiltration of activated lymphocytes and neo-vascularisation are documented in many advanced OA, as well as patients at early stages (Walsh et al., 2007;Pearle et al., 2007;Saito et al., 2002;Saxne et al., 2003a). The severity of synovial inflammation defined by MRI is correlated with pain intensities in OA patients (Hill et al., 2007). Synovitis seen under arthroscopy is associated with cartilage degradation (Ayral et al., 2005).

Increased levels of immunoglobulins have been reported in OA. Jasin reported IgM and IgG levels in OA cartilage tissue are three times more than in normal cartilage tissue (Jasin, 1985). This suggests that antibodies are synthesized within the affected joint by infiltrating immune cells or that the cartilage is more permeable to immunoglobulins.

5. Toll-like receptors (TLRs)

TLRs are a group of pattern recognition receptors (Barton and Medzhitov, 2002), which gate the immune response. Up to now, a total of 13 TLRs have been identified -TLR1 to TLR10 in human; TLR1 to TLR13 (except TLR10) in murine (Beutler, 2005). A highly specific pattern governs the TLR recognition of various microbial ligands. Each of these TLRs responds only to a limited number of microbial ligands summarized in Table 1 of Akira and Takeda (2004).

TLRs adopt either the myeloid differentiation primary response gene 88 (MyD88)-dependent or MyD88-independent pathway following activation. TLR signalling pathways lead to the production of several critical transcription factors, including NF-κB, interferon regulatory factor (IRF) and activator protein-1 (AP-1). Three most common TLR-mediated signalling pathways are the MyD88-dependent and MyD88-independent release of NF-κB, and the MyD88-independent production of IRF. Each of TLRs seems to recruit different subsequent signalling pathways (Akira and Takeda, 2004). But detailed information remains unclear to us.

Mollen et al. (2006) proposed the theory of "TLRs and danger signalling": During tissue stress or injury, a variety of damage-associated molecules are actively secreted by stressed cells, passively released from necrotic cells, or originally from the degradation of the extracellular matrix. These damage-associated molecular patterns are recognized by TLRs in a similar manner as that of exogenous pathogen-associated molecular patterns.

A long list of damage-associated molecules have been proposed as putative endogenous TLR ligands (Beg, 2002), including hyaluronan, heparin sulphate, fibrinogen, high-mobility group protein (HMGB1), HSP 60, host mRNA, host chromatin and small ribonucleoprotein particles as well. Therefore, TLRs seem to be critical players in determining the nature of tissue injure, and initiating corresponding signalling pathways that result in distinct forms of pain.

Increasing evidence supports TLR4 as the main TLR sensing tissue damage in that it responds to a couple of endogenous ligands, such as HSP 60, fibrinogen, heparin sulphate and hyaluronan (Johnson et al., 2002;Ohashi et al., 2000;Smiley et al., 2001;Taylor et al., 2004a;Termeer et al., 2002). TLR4-dependent signalling pathway has been linked to sterile inflammation resulted from various neural and non-neural tissue injuries. Studies reveal that the production of inflammatory cytokines is compromised during tissue injuries in C3H/HeJ strain mice featured with TLR4 mutation - reduced TNF level in would incision (Bettinger et al., 1994); low circulating IL-6 in hemorrhagic shock (Prince et al., 2006); and decreased IL-1β expression at the nerve stump in sciatic nerve lesion (Boivin et al., 2007). As a consequence, the overall inflammatory response in TLR4-deficient animals is attenuated. Evidence includes reduced accumulation and activation of macrophages in injured nerve tissue (Boivin et al., 2007); less severe systemic inflammatory response (e.g. lower hepatic IL-6 level, less liver injury) after bilateral femur fracture with soft tissue crush injury (Levy et al., 2006).

TLR2 was implicated in the pathogenesis of arthritis (Cho et al., 2007). TLR2, IL-8, and vascular endothelial growth factor (VEGF) were upregulated in arthritic joints in human synovial tissue culture, which was block by anti-TLR2 antibodies. Interestingly, HMGB1 was up-regulated at the same time frame in arthritic joints in human (Kokkola et al., 2002;Taniguchi et al., 2003). HMGB1 has been proposed as the primary putative endogenous TLR2 ligand (Park et al., 2004;van Beijnum et al., 2008;Yu et al., 2006). Although there is no direct evidence for the involvement of HMGB1-TLR2-mediated pathway in arthritis, some results favour the notion. Park et al. (2006) showed the protein-protein interaction between HMGB1 and TLR2 was functional in term of initiating intracellular signal transductions. Yu et al. (2006) demonstrated that anti-TLR2 antibody blocked HMGB1-induced TLR2-dependent IL-8 release in HEK cells.

TLR3 and TLR9 are known to recognize microbial nucleic acids. However, host nucleic acids are also capable of initiating immune response via TLR activation - chromatin can induce the production of anti-DNA antibodies via a TLR9-dependent mechanism (Leadbetter et al., 2002). In Alzheimer's patients, TLR3 expression was identified in brains without previous viral infection (Jackson et al., 2006). The up-regulation of TLR3 expression might partly be explained by the finding that RNA is a constituent in senile plaques (Marcinkiewicz, 2002). The inflammatory nature of the disease may result from TLR3 activation by host RNA. Necrotic cells resulted from various processes including tissue injuries release host nucleic acids. Kariko et al. (2004) demonstrated that it was RNA released from necrotic cells that led to TLR3-dependent release of TNF-α. Necrotic cell lysates lost the capability to stimulate TNF-α release once they were pretreated with Benzonase, a potent and nonspecific nuclease that degrades all RNA into oligomers of 2–5 nucleotides in length.

6. TLR pathways in OA pathology

Age and joint trauma are two risk factors for the development and progression of OA. Endogenous damage-associated molecules, including hyaluronan, fibronectin, have been identified in OA in response to initial tissue injury. Hyaluronan is highly viscous polysaccharide found in the extracellular matrix, and is a major component of synovial fluid and cartilage, which plays an important role in the lubrication and shock absorption for the joint tissue. Its molecular weight/length is reduced in exercise and joint injury (Brown et al., 2007). In OA, both of the concentration and molecular weight of hyaluronan are reduced (Dahl et al., 1985). Hyaluronan fragments of specific sizes have been shown to promote

angiogenesis and have immune regulatory effects mediated by the TLR-4 receptor (Taylor et al., 2004b). However, TLR-4 responses initiated by bacterial product lipopolysaccharide (LPS) and endogenous product hyaluronan are different, due to the recruitment of different accessory molecules, CD14 for the LPS-TLR-4 response and CD44 for the hyaluronan-TLR-4 response (Taylor et al., 2007). Fibronectin is another extracellular matrix component affected by both age and tissue injury, and the presence of fibronectin and a specific isoform containing the B sequence, Ed-B fibronectin, in osteoarthritic cartilage but not in normal cartilage has led to the suggestion that the isoform might play a role in extracellular matrix remodelling (Chevalier et al., 1996). In addition to the traditional integrin-mediated pathways, certain splice variants of fibronectin are also capable of activating a TLR-4 dependant pathway (Lasarte et al., 2007;Gondokaryono et al., 2007;Okamura et al., 2001).

Although TLRs are constitutively expressed on immune cells, the expression of TLR can be induced on other cell types as a result of IL-1 stimulation or TLR-4 activation (Matsumura et al., 2003;Kim et al., 2006;Ojaniemi et al., 2006). Radstake et al. (2004) reported the expression of TLR-2 and TLR-4 in osteoarthritic synovial membrane. Moreover, cultured synovial cells and chondrocytes from OA subjects show responsiveness to TLR-4 agonist LPS and TLR-2 agonist peptidoglycan (Kim et al., 2006;Kyburz et al., 2003;Ozawa et al., 2007). TLR-4 deficiency rescues cartilage and bone erosion in arthritis, while TLR-2 deficiency promotes the disease severity (Abdollahi-Roodsaz et al., 2008).

Activation of TLR-2 and TLR-4 recruits downstream adaptors such as MyD88 and Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP), and ultimately leads to the activation of various transcription factors including IRFs, AP-1, and NF-κB. All TLR pathways are capable of activating NF-κB, and recent evidence suggests a role of NF-κB in OA. The activation of NF-κB requires the degradation of IκB bounding to it. Amos et al. (2006) showed that inhibiting NF-κB via over-expressing IκBα inhibited the production of many inflammatory and destructive mediators in OA, including TNF-α, IL-6, IL-8, oncostatin M, and metaloproteinase (MMP)-1, 3, 9, 13. The Bondeson group further showed that several MMPs and aggrecanases such as a disintegrin and metalloprotease with thrombospondin motifs 4 and 5 (ADAMTS 4, 5) are NF-κB dependent (Bondeson et al., 2007). MMP-1 and MMP-13 are capable of cleaving collagen type II, and MMP-3 cleaves other components of extracellular matrix, such as fibronectin and laminin (Yoshihara et al., 2000). ADAMTS4 and ADAMTS5 work together to cleave aggregating proteoglycan aggrecan in cartilage (Song et al., 2007;Lohmander et al., 1993). Chen et al. (2008) reported the suppression of early surgically induced OA, such as minimized synovitis and articular cartilage damage, by intra-articular delivery of NF-κBp65 specific siRNA NF-kB.

Several autoantibodies against degradative products of cartilage tissues have been identified in OA, in both humans and other animal species. These include antibodies against collagen 2 (Jasin, 1985;Niebauer et al., 1987;Osborne et al., 1995), cartilage link protein (Guerassimov et al., 1998), G1 domain proteoglycan aggrecan (Niebauer et al., 1987), cartilage intermediate layer protein (Tsuruha et al., 2001), human chondrocyte gp-39 homologous, YKL-39 (Tsuruha et al., 2002), and osteopontin (Sakata et al., 2001). Collagen II has been indentified as one of the major autoantigens in human and other animal models of RA, but much remains to be known about the autoantigen(s) driving the synovitis in OA. MyD88 dependent TLR signalling is critical for the induction of adaptive immune responses, including B-cell activation and antibody production (for review see Pasare and Medzhitov, 2005). Stimulating TLRs on B cells can result in polyclonal activation and production of low-

affinity immunoglobulin M (IgM) antibodies, which may be one of mechanisms producing autoreactive antibodies (Iwasaki and Medzhitov, 2004).

7. TLR bridges traumatic injury and OA pain

Chronic pain can arise from a wide variety of causes - arthritis pain, low back pain, migraine, cancer pain, post-herpetic neuralgia, diabetic neuropathy, and others. Currently, chronic pain is explained more or less on the basis of structural abnormalities, such as osteoarthritis or herniated disk (Omoigui, 2007a). Chronic pain has not been able to be classified into well mechanism-based entities. To distinguish inflammatory pain from neuropathic pain is the best attempt so far. Hawker et al. (2008) revealed two distinct types of OA pain: an early predictable dull, aching, throbbing "background" pain and an unpredictable short episode of intense pain that develops later (Hawker et al., 2008). During the progression of OA, pain evolves from the "background" pain that is use-related in early OA (Kidd, 2006), to unpredictable short episodes of intense pain on top of the "background" pain in advanced OA (Hawker et al., 2008). However, the nature of the pain in OA still remains unclear (Hunter et al., 2008;Kidd, 2006;McDougall, 2006;Wu and Henry, 2010). Our poor understanding of chronic pain results in poor mechanism-based treatments, particularly for neuropathic pain (Gordon and Dahl, 2004;Colombo et al., 2006;Jackson, 2006;Rice and Hill, 2006;Dworkin et al., 2007).

One critical fact about chronic pain is that its nature is determined shortly after the initial insult. For example, nerve section induces neuropathic pain only, but never inflammatory pain, no matter how complicated the subsequent cytokine cascade is. Different types of tissue injury are associated with distinct forms of chronic pain. TLRs likely play an important role in the "judgment of pain" in various tissue injuries, as they are the most important interface initiating the release of cytokines following cellular response to distinct pathogen- or damage-associated molecular patterns, and they have limited yet highly specific subtypes associated with distinct intracellular signalling pathways.

The notion that inflammatory mechanisms are underlying all pain syndromes was recently proposed in two review papers (Moalem et al., 2005;Omoigui, 2007b). Alteration of the chemical environment surrounding sensory neurons changes nociception (Clatworthy et al., 1995) demonstrated that the development of the thermal hyperalgesia was tightly governed by peri-axonal inflammation. These findings lead to a re-examination of the significance of the accumulation of immune cells and inflammatory factors in nerve injuries. Cytokines likely play critical roles in the above processes. TNF-α, IL-1 and IL-6 have been shown to induced hyperalgesia if injected peripherally into the paw (Cunha et al., 1992;Ferreira et al., 1988), which can be blocked by the application of antibodies against each of these cytokines (Cunha et al., 1992;Schafers et al., 2001;Sommer et al., 1999). A second line of evidence is from inflammatory models of neuropathic pain. Those models are able to mimic neuropathic type of pain by means that are unlikely to injure sensory axons. Neuropathic pain can be induced by placing chromic gut thread next to sciatic nerve (Maves et al., 1993), by cutting ventral roots of spinal nerves which are motor efferents (Li et al., 2002;Sheth et al., 2002), by applying complete Freund's adjuvant (CFA) (Eliav et al., 1999) or zymosan (Chacur et al., 2001) around the intact sciatic nerve. Third line of evidence is from neurology clinics. Neurologists surprisingly found that pain is a common comorbidity in autoimmune diseases of nervous system: 65% of multiple sclerosis patients reported pain during the

course of their disease (Kerns et al., 2002); 70-90% of Guillain-Barre syndrome patients complained pain (Pentland and Donald, 1994;Moulin et al., 1997).

A sundry of signalling pathways – such as PKA, PKC, PKG, ERK, P38 MAPK, NF-κB and JAK/STAT have been implicated to be involved in the development of chronic pain (Hanada and Yoshimura, 2002;Ji and Woolf, 2001;Obata and Noguchi, 2004). Among them, NF-κB, JAK/STAT and MAPK pathways are of particular importance in chronic pain: NF-κB pathway is the most important cellular pathway responsible for the production of inflammatory cytokines (Nguyen et al., 2002); JAK/STAT pathway is the primary pathway responsible for cytokine receptor signalling (Ihle, 1995); and MAPKs play a pivotal role in transducing extracellular stimuli into intracellular posttranslational and transcriptional responses, and are hot topics in recent pain mechanism studies, particularly ERK and P38 (Ji and Suter, 2007;Ma and Quirion, 2005;Obata and Noguchi, 2004). TLR signalling pathways have intensive crosstalk with the above mentioned pain-related pathways.

TLR and NF-κB pathway - Different adaptor molecules recruited by different TLRs result in differences in NF-κB activation. TLR signalling via the MyD88-dependent pathway leads to the early phase release of NF-κB. During TLR2 or TLR4 signalling, TIRAP/MAL is recruited to TIR domain, and then MyD88, whereas during TLR5, TLR7 or TLR9 signalling, MyD88 is recruited to TIR domain. Activation of MyD88-independent pathway downstream of TLR3 or TLR4 accounts for the late phase release of NF-κB, where TRIF is the key adaptor recruited.

TLR and IFN-JAK-STAT pathway – Type I IFNs previously were found mainly due to the activation of the MyD88-independent pathway which triggers the expression of IFN-β and chemokine genes (Sakaguchi et al., 2003). Recruitment of MyD88 by TLR7, TLR8 or TLR9 also results in the release of different set of type I IFNs, including both IFN-α and IFN-β species. (Honda et al., 2004;Takaoka and Yanai, 2006). The activation of IFN-receptors by Type I IFNs is an important mechanism linking TLR pathway and the JAK-STAT pathway (Akira and Takeda, 2004;Kawai and Akira, 2005), as the JAK-STAT pathway is one of the best characterized IFN-signalling pathways (Stark et al., 1998).

TLR and MAPK pathway - TGF-β–activated protein kinase 1 (TAK1) is a member of the MAP3K family, which is a key regulator of MAP kinase activity (Yamaguchi et al., 1995). TAK1 can be activated by TLR3 or TLR4 signalling via the MyD88-independent pathway. Moreover, another MAP3K, MEKK3 could be activated via the MyD88-dependent pathway. TLR4 but not TLR9 signalling via MEKK3 induced the activation of JNK/P38 but not ERK, suggesting differential activation of MAPKs during TLR signalling (Huang et al., 2004).

Accumulating evidence shows that TLRs are involved in chronic pain determination, likely at the level of primary sensory neurons. Dorsal root ganglion (DRG) neurons are located at the first stop of the sensory pathway. Different types of pain seem to affect different subgroups of DRG neurons. TLRs are constitutively expressed in immune cells. However, TLR expression is also found in CNS and PNS - in microglia, astrocytes (Bsibsi et al., 2002) and sensory ganglia neurons (Wadachi and Hargreaves, 2006). In polyarthritis models induced by CFA injection (Djouhri and Lawson, 1999;Xu et al., 2000), only A δ neurons and C neurons were significantly altered in electrophysiological properties, with C neurons the more severely altered. In complete sciatic nerve transection model (Abdulla and Smith, 2001), partial sciatic nerve transection model (Liu and Eisenach, 2005), or lumbar spinal nerve transection models (Kim et al., 1998;Liu et al., 2000;Ma et al., 2003;Sapunar et al., 2005;Stebbing et al., 1999), changes in A type neurons were common, even in the large size

neurons. In some studies (Abdulla and Smith, 2001;Kim et al., 1998;Ma et al., 2003), changes in C neurons were also reported, but are less prominent than those in A neurons. Therefore, it seems that there are distinct changes in subgroups of DRG neurons in various chronic pain models resulted from different mechanisms, which can be regarded as pain manifestation at the neuronal level. Several TLRs have clearly established their correlation with hyperalgesia or allodynia. Compared with wild type mice, TLR2 knock-out mice showed reduced mechanical allodynia and thermal hyperalgesia after spinal nerve axotomy (Kim et al., 2007). Intrathecal administration of TLR3 antisense oligodeoxynucleotide (ODN) suppressed the spinal nerve ligation-induced tactile allodynia, whereas intrathecal injection of TLR3 agonist induced behavioural changes similar to the nerve-injury induced sensory hypersensitivity (Obata et al., 2008). TLR4 knock-out mice and the rats treated with TLR4 antisense ODN both showed significantly attenuated mechanical allodynia and thermal hyperalgesia in L5 spinal nerve transection (Tanga et al., 2005). TLR activation in microglia in spinal cord was proven to play a critical role in spinal nerve axotomy-induced sensory hypersensitivity (Kim et al., 2007;Tanga et al., 2005;Obata et al., 2008).

8. Conclusion

We propose a novel concept regarding the mechanism underlying the pain in OA induced by traumatic injuries. Following an initial trauma to the joint, two distinct yet interacting processes are initiated. One is neural injury of joint afferents and ensuing maladaptive changes of the nervous system, which results in pain in OA. The other is the cartilage degradation and bony changes in the joint, which generates characteristic pathology in OA. These two processes are likely initiated by damage-associated molecules produced during the initial joint injury, such as hyaluronan, fibronectin and proteoglycan aggrecan, mediated by pattern-recognition receptors like the TLRs. The TLR-dependent pathways lead to the activation of NF-$_K$B and downstream transcription factors to produce various inflammatory and destructive mediators and autoantibodies. Thus, various downstream pathways, such as the MMP-mediated, ADAMITS-mediated, MAPK-mediated, are activated to generate a spectrum of osteoarthritic changes, both functional (pain) and structural (deficit in cartilage and bone deformity). TLRs, maybe other pattern-recognition receptors, are at the intersection of OA pathology and pain.

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10. List of abbreviations

AP-1, **A**ctivator **P**rotein-1; **CFA**, **C**omplete **F**reund's **A**djuvant; **CRP**, **C**-**R**eactive **P**rotein; **DRG**, **D**orsal **R**oot **G**anglion; **HMGB**, **H**igh-**M**obility **G**roup **P**rotein; **IRF**, **I**nterferon **R**egulatory **F**actor; **LPS**, **L**ipo**p**oly**s**accharide; **MyD88**, **My**eloid **D**ifferentiation Primary Response Gene **88**; **OA**, **O**steo**a**rthritis; **ODN**, **O**ligo**d**eoxy**n**ucleotide; **RA**, **R**heumatoid **A**rthritis; **TAK1**, **T**ransforming Growth Factor (TGF)-β–**A**ctivated Protein **K**inase 1; **TIRAP**,

Toll-**I**nterleukin 1 **R**eceptor (TIR) Domain Containing **A**daptor **P**rotein; **TLR**, **T**oll-**l**ike **R**eceptor ; **VEGF**, **V**ascular **E**ndothelial **G**rowth **F**actor

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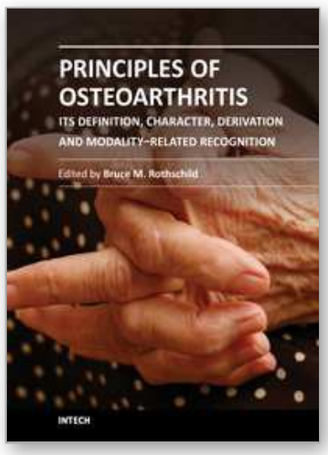

Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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