



## Educational Case

### Educational case: Osteoarthritis

Jonathan Light, MS<sup>a</sup>, Harrison Klause, MD<sup>b</sup>, Richard M. Conran, MD, PhD, JD<sup>c,\*</sup>

<sup>a</sup> School of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

<sup>b</sup> Department of Radiology, Eastern Virginia Medical School, USA

<sup>c</sup> Department of Pathology & Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA



The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme>.<sup>1</sup>

**Keywords:** Pathology competencies, Organ system pathology, Musculoskeletal, Arthritis, Osteoarthritis, Rheumatoid arthritis, Adults

#### Primary objective

Objective MS2.7: Arthritis. Compare and contrast rheumatoid and osteoarthritis including the etiology, pathogenesis, and morphology of each.

Competency 2: Organ System Pathology; Topic: MS: Musculoskeletal System; Learning Goal 2: Nonneoplastic Disorders of the Musculoskeletal System.

#### Patient presentation

The patient is a pleasant 60-year-old previously healthy woman who presents to the clinic with intermittent back pain, a painful right knee, and painful hands. She states that her right knee and hands are stiff for 30 min in the morning and resolve with activity. Her knee and hand pain are exacerbated by movement throughout the day but are relieved completely with rest. She states that bearing weight on her right knee has been more painful recently (mornings and evenings, 7 days per week) with the pain reaching a maximum of 7/10 compared with 4/10 previously, but the pain has slowly progressed for the past 24 months. In addition, she states she has had the pain in her hands and wrists for 2 or more years. She does not report a history of crystal-induced arthritis, such as gout or pseudogout, or Lyme disease. Surgical history includes bilateral endoscopic carpal tunnel release (ECTR) 1 year ago with persistent pain and tingling in her hands and wrists, cholecystectomy 10 years ago and an appendectomy as a child, but no joint surgeries or trauma. Her last menstrual period was 10 years ago. She has self-treated

her musculoskeletal pain intermittently with ibuprofen for temporary relief and manages hypertension with lisinopril. Family history includes her mother has seropositive rheumatoid arthritis (RA), and her father has hypertension. Social history is negative for alcohol, tobacco, or recreational drug use. She was an equestrian until 5 years ago. She reports no recent sexual activity or history of a sexually transmitted infection. The patient has not changed her diet in the past 5 years, and her weight has been stable. On review of systems, she does not report night sweats, recent fevers, cough, headache, skin changes, or redness of her face or extremities, or other problems except for back, hand, and knee pain.

#### Diagnostic findings, Part 1

The patient's height is 67 inches, and she weighs 155 pounds. Body mass index is 24.3 kg/m<sup>2</sup>. Her vital signs are blood pressure 132/78 mmHg, heart rate 100 beats per minute, respiratory rate 12 breaths per minute, and temperature 98.2 °F. On physical examination (PE), her skin shows hypertrophic scarring of the ventral wrists at the ECTR surgical sites; there is no visible malar rash or target lesion. Head, ears, eyes, neck, and throat examination is unremarkable. The mucous membranes are moist, and she has a healthy dentition. The thyroid gland is normal in size and consistency, and cervical lymph nodes are regular. Cardiac examination demonstrates a regular rate and rhythm, with no gallops, rubs, or murmurs, and the lungs are clear to auscultation, with no wheezing, egophony, or crackles. Her abdominal examination is benign as there is no organomegaly or palpable masses; visible well-healed scars are evident from her previous appendectomy and cholecystectomy. Her

\* Corresponding author. Eastern Virginia Medical School, Pathology & Anatomy, 700 West Olney Road, Norfolk, VA, 23507, USA.

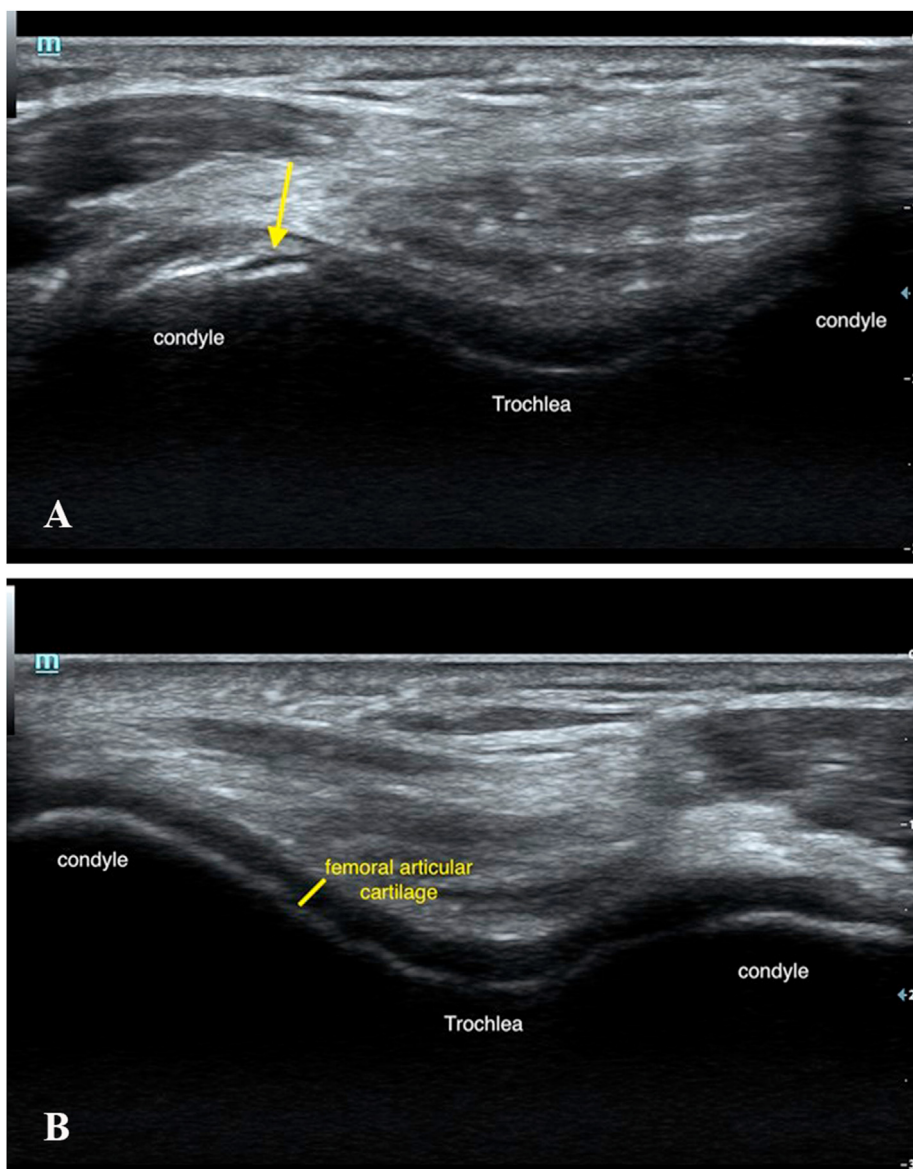
E-mail address: [conranrm@evms.edu](mailto:conranrm@evms.edu) (R.M. Conran).

musculoskeletal examination shows a medial bony irregularity and mild tenderness to palpation of the right patellofemoral joint and mild tenderness of the contralateral knee joint medially. The first carpometacarpal joint of both hands is tender to palpation. The hands and wrists demonstrate no erythema or warmth; however, some tenderness to palpation of the patient's ECTR scars is demonstrated. Tinel test (tapping over the affected median nerve elicits paresthesia of the palmar and distal first three-and-half digits) is positive bilaterally. Heberden's (distal interphalangeal [DIP] joint swelling) and Bouchard's (proximal interphalangeal [PIP] joint swelling) nodes are evident on the first, second, and third digits. The patient has mild tenderness to palpation over the lumbar back, with no obvious deformities; flexion and extension are limited due to pain, and there is no scoliosis or kyphosis. The right knee joint has varus deformity and exhibits crepitus with a limited range of motion (ROM); strength of 5/5. The right knee has no erythema or warmth but a mild effusion. The right hip strength is 5/5 and elicits no pain on palpation or movement. The straight leg raise test is normal bilaterally.

**Questions/discussion points, Part 1**

**What is the differential diagnosis for polyarticular joint pain?**

In general, different causes of polyarticular joint pain include infectious arthritis, osteoarthritis (OA), RA, crystal-induced arthritis, Lyme disease, hemochromatosis, and systemic lupus erythematosus (SLE). The absence of malar rash argues against SLE (sensitivity 57%, specificity 96%).<sup>2</sup> While the classic bull's eye lesion (circular target-like rash) supports a Lyme disease diagnosis, the rash may not always be present. Furthermore, five joints or fewer are affected simultaneously in a patient with Lyme disease, and the usual joints involved are knees, shoulder, elbow, wrist, or ankle.<sup>3</sup> Cancer metastasis could affect several joints but would typically be associated with unexplained weight loss, night sweats, or history of infections. A patient with hemochromatosis may have joint pain but may also have cirrhosis, heart failure, and bronzing of the skin.



**Fig. 1.** Ultrasound of the knee. A. The scan shows joint margin destruction (arrow) suggestive of osteoarthritic change. The patient's knee is in the flexed position and the probe in the transverse approach. B. The scan is from a different patient that demonstrates the normal femoral cartilage (anechoic-dark) contour with uniform thickness for comparison. The patient's knee is in the flexed position and the probe in the transverse approach.

### What is the next step in the management of the patient in the clinical vignette?

The clinician should order conventional radiographs of the lumbar spine, bilateral hands, wrists, and right knee. OA and RA have distinct findings on conventional radiographs.<sup>4</sup> While OA is possible based on a history of chronic joint pain without relapsing episodes and the PE findings, bilateral wrist pain is not characteristic of OA.<sup>5,6</sup> PIP and DIP joint involvement, however, is common in OA. Typically, DIP joint sparing occurs in RA.<sup>6</sup> The American College of Rheumatologists (ACR) recommends imaging studies when the patient has decreased joint function, such as limited ROM.<sup>7</sup> If OA is high on the differential diagnosis, a conventional radiograph would yield any necessary information to make the diagnosis. Ultrasound is considered first for the patient due to being a portable, nonradiation study, with potential to identify specific joint pathologies. However, patients with severe joint disease may not be able to flex the knee enough to allow optimal visualization using ultrasound. The patient has a limited ROM, so conventional radiographs are necessary even if ultrasound identifies joint pathology.

Ultrasound is a cost-effective, noninvasive, specialized imaging technique used in cases of gout, OA, and RA.<sup>8</sup> In gout, the presence of the “snowstorm” sign appears due to uric acid crystal foci (hyperechoic) within the synovial fluid (hypoechoic). The clinician writing the ultrasound report should be specific when noting snowstorm sign of the affected joint in gout since snowstorm sign is also used in the ultrasonography of molar pregnancy. Ultrasound in OA is useful for detecting joint space narrowing and has a high sensitivity for demonstrating subchondral cysts or tendon or ligament damage surrounding the affected knee.<sup>4</sup> In RA, ultrasound may demonstrate acute synovial inflammation and tenosynovial effusion, sometimes in the setting of a subclinical presentation.<sup>9</sup> Therefore, ultrasound may be used to identify joint pathology and predict disease progression, also help with treatment. For patients with RA, ultrasound may improve early diagnosis and management during the ‘window of opportunity’ (before disease progression establishes significant damage to bone, cartilage, and tendon).<sup>9</sup> Furthermore, ultrasound has utility of being able to identify normal nerve and vessel architecture within the wrist. Therefore, ultrasound images of the patient's wrists are obtained to identify possible postoperative hypertrophic scar tissue causing traction or compression of her median nerve as a cause of her bilateral wrist pain based on a positive Tinel test on PE.

### Diagnostic findings, Part 2

Imaging of the hand and knee were obtained (Figs. 1–5).

### Questions/discussion points, Part 2

#### What is seen in the ultrasound scan of the knee?

Fig. 1A is an ultrasound scan of a knee from a patient with a similar clinical presentation of knee pain, demonstrating joint margin destruction, suggesting osteoarthritic change. The patient's knee is in the flexed position, and the probe is in the transverse approach. Artifact versus osteoarthritic change was considered due to sound passing through two adjacent surfaces with different echogenicities but repeat images from different approaches combined with the clinical presentation were consistent with joint pathology. Documentation of ultrasound findings should include a written description of the findings and images added to the patient's chart. Fig. 1B is an ultrasound scan of the knee from a patient that demonstrates the normal femoral cartilage (anechoic-dark) contour and uniform thickness for comparison. The patient's knee is in the flexed position, and the probe is in the transverse approach. The patient's ultrasound examination is clinically insufficient for diagnosis due to the limited ROM of her right knee, so conventional radiographs are obtained.

Additionally, ultrasonography of the patient's bilateral wrists demonstrates preservation of normal nerve architecture; however, no transverse carpal ligaments are identified, which is expected after CTR. The median nerve is observed bilaterally with some surrounding inflammation and compression by overlying tissue (presumably scar tissue). Snowstorm sign is not evident on any of the patient's joint ultrasounds; therefore, gout is less likely.

#### What is seen in the radiographs of the hand and knee?

Fig. 2 is a conventional anteroposterior (AP) radiograph of the right hand demonstrating advanced findings of RA characterized in this image by ankylosis of the carpal bones, juxta-articular osteoporosis, marked erosions and subchondral cysts along the radiocarpal, ulnocarpal, first carpometacarpal, metacarpophalangeal, and PIP joints with relative sparing of the DIP joints. Fig. 3 is a conventional oblique radiograph of the right hand, which demonstrates degenerative OA characterized by marginal osteophyte formation, joint space narrowing, and subchondral sclerosis in a distribution involving the first carpometacarpal joint, proximal and DIP joints, most conspicuous at the first interphalangeal, second and third distal phalangeal joints. Fig. 4A–B are conventional oblique and lateral radiographs of the right knee, which demonstrate advanced tricompartmental OA, characterized by marked joint space narrowing and osteophyte formation, most conspicuous in the medial and patellofemoral compartments. Fig. 5 is a lateral radiograph of the lumbar spine that demonstrates multilevel degenerative changes of the thoracolumbar spine, characterized by disc space narrowing and end-

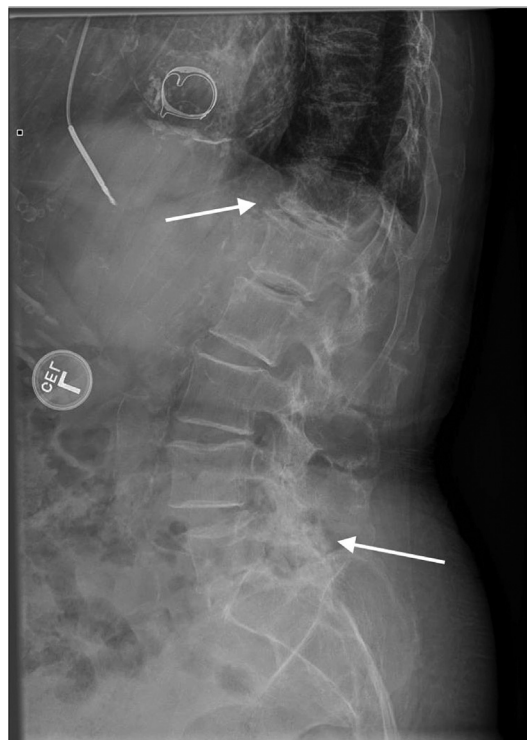


Fig. 2. Right hand rheumatoid arthritis: Conventional anteroposterior (AP) radiograph of the right hand demonstrates advanced findings of rheumatoid arthritis characterized in this case by ankylosis of the carpal bones, juxta-articular osteoporosis, marked erosions, and subchondral cysts (arrow) along the radiocarpal, ulnocarpal, first carpometacarpal, metacarpophalangeal, and proximal interphalangeal joints with relative sparing of the distal interphalangeal joints.

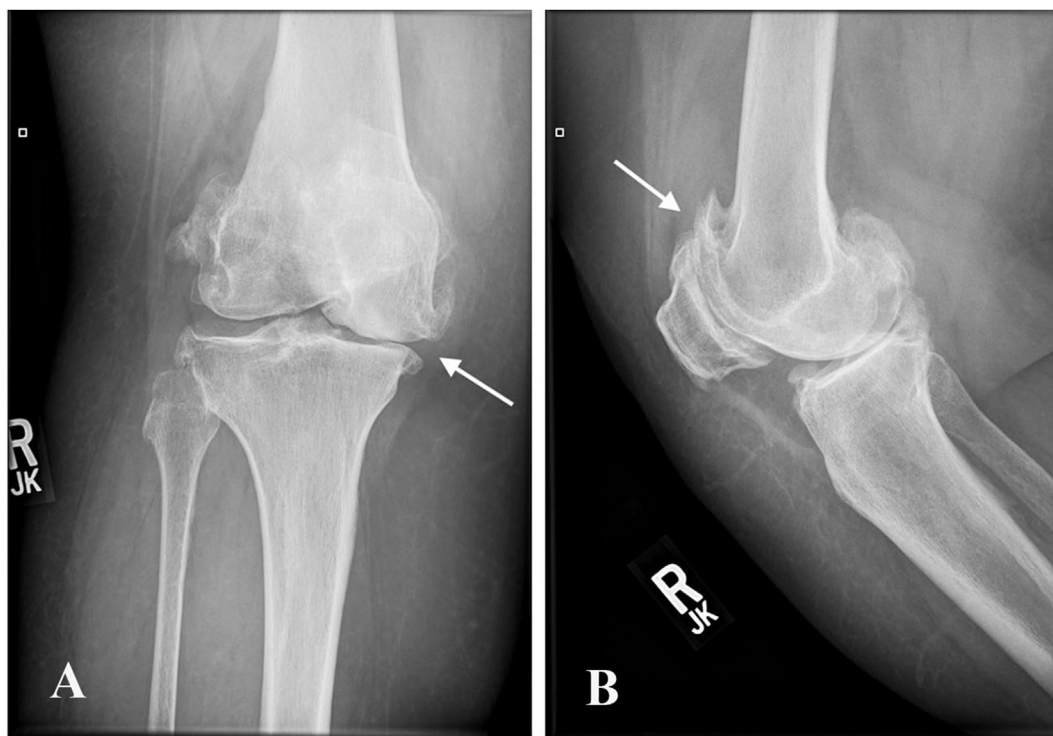


**Fig. 3.** Right hand osteoarthritis: Oblique radiograph of the right hand demonstrates degenerative osteoarthritis characterized by marginal osteophyte formation, joint space narrowing, and subchondral sclerosis in a distribution involving the first carpometacarpal joint, proximal, and distal interphalangeal joints, most conspicuous at the first interphalangeal, second (arrow), and third distal phalangeal joints.

plate osteophyte formation, most conspicuously evident at T12-L1, as well as facet arthropathy at the lower lumbar spine with associated retrolisthesis (a posterior slippage of the vertebra; the opposite of spondylolisthesis).



**Fig. 5.** Lateral radiograph of the lumbar spine demonstrates multilevel degenerative changes of the thoracolumbar spine, characterized by disc space narrowing and end-plate osteophyte formation, most conspicuously evident at T12-L1 (arrow), as well as facet arthropathy at the lower lumbar spine (arrow) with associated retrolisthesis.



**Fig. 4.** Right knee osteoarthritis: Oblique (A) and lateral (B) radiographs of the right knee demonstrate advanced tricompartmental osteoarthritis, characterized by marked joint space narrowing and osteophyte formation, most conspicuous in the medial and patellofemoral compartments (arrow).



**Which figure, Fig. 2 or Fig. 3, best matches the clinical findings for the patient in the clinical vignette and why?**

Fig. 2 demonstrates carpal bone ankylosis, potentially consistent with wrist pain, whereas Fig. 3 shows no carpal bone involvement. Fig. 3 demonstrates PIP and DIP joint involvement and involvement of the first carpometacarpal joint of both hands, which align with the PE findings. Fig. 3 is consistent with the patient's clinical presentation.

**Discuss a possible cause of the Patient's wrist pain based on her past medical history**

The patient's past medical history reveals ECTR. Carpal tunnel release may be surgically performed endoscopically or by the open technique (OCTR). ECTR is considered minimally invasive surgery. With ECTR, there is a 1.45% rate of transient neuropraxias compared to just 0.25% with the OCTR technique.<sup>10</sup> Neuropraxia may be due to iatrogenic injury and is a cause of postoperative symptoms such as paresthesia or motor weakness secondary to CTR; however, these symptoms are usually transient rather than persistent. Furthermore, ECTR has a significantly better outcome in terms of reducing trauma to nerves, arteries, or tendons compared to OCTR, 0.49% compared to 0.19%, respectively.<sup>10</sup> The outcomes of both ECTR and OCTR are generally good with a relatively low risk of injury.<sup>10</sup> Other studies have shown that ECTR and OCTR have comparable outcomes with lower incidences of scar associated post-operative complications in ECTR.<sup>11</sup> Sensitivity caused by scar tissue formation postoperatively is a significant consideration for the patient's wrist pain based on her ultrasound examination results and past medical history.

**Which laboratory tests are needed to support osteoarthritis versus rheumatoid arthritis?**

The most likely diagnoses based on history, clinical presentation, and imaging are OA and RA. Additionally, the patient's family history is seropositive for RA supporting the possibility of RA.

When there is a concern for RA, screening rheumatoid factor (RF) antibody, anti-citrullinated protein antibody (ACPA), and routine lab work is indicated, including complete blood cell counts (CBC), comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).<sup>5</sup> The ACR advises against ordering routine lab arthritis panels for patients with joint pain. The diagnosis of OA is

primarily clinical, based on history (joint stiffness for 30 min or less in the morning) and PE (joint crepitus and tenderness).<sup>12</sup> The ACR and European Alliance of Associations for Rheumatology (EULAR) have essential diagnostic criteria for knee OA,<sup>12</sup> which should be utilized by the clinician as there are no laboratory tests to diagnose OA.

The role of CBC in the patient's assessment is to screen for infection or malignancy. In the setting of infection as the cause of the patient's joint pain, leukocytosis would be evident (white blood cell count greater than 11,000 per mm<sup>3</sup>).<sup>13</sup> Low white blood cell count (<4500/mm<sup>3</sup>)<sup>14</sup> could indicate an autoimmune condition such as RA. CBC has less diagnostic utility in OA since OA is neither infectious nor autoimmune. ESR is a measure of inflammation, which is represented by an increased mass of clumped proteins and erythrocytes in the bottom of the laboratory centrifuge tube. ESR may be elevated in the setting of RA. CRP is a routinely used serum marker ordered by the clinician when there is concern for RA based on the clinical presentation and patient history. In patients with RA, there is a significant relationship between CRP levels and tissue inflammation scores from patient's knee synovium samples.<sup>15</sup> CRP levels may remain elevated chronically in patients with RA.<sup>15</sup> However, CRP levels are sometimes found to be significantly elevated in patients with OA.<sup>16</sup>

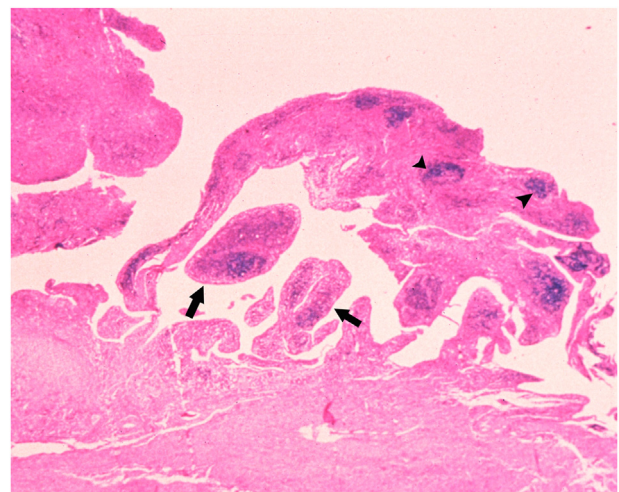
As many as 50–80% of patients with RA have autoantibodies.<sup>17</sup> RA autoantibodies target the Fc portion of other IgG antibodies and are termed rheumatoid factor (RF).<sup>18</sup> ACPAs target proteins that contain citrulline and are prevalent in patients with RA.<sup>18</sup> However, RF or ACPAs may be measured in healthy individuals including those with OA.<sup>18</sup> RF and ACPAs have a sensitivity of 69% and 67% for patients with RA, while the specificity for RA is 85% and 95%, respectively.<sup>18</sup> The ACR/EULAR criteria for patients with RA heavily weigh RF and ACPAs for meeting diagnostic criteria. If the patient is negative for both RF and ACPA, zero criteria points are met, but if the patient is low or high positive for RF or ACPAs, two or three criteria points are assigned, respectively.<sup>19</sup> Therefore, patients who are ACPA seronegative require 10 or more joints to be affected to meet the criteria and those seropositive for ACPA still fulfill the criteria with only a single joint affected. Abnormal ESR or CRP meets one criteria point only, which supports the importance of the laboratory results (RF or ACPA seropositivity) in RA.<sup>19</sup>

### Diagnostic findings, Part 3

A CBC, CMP, ESR, CRP, and RF were obtained. The laboratory test results were within the normal range. The RF was seronegative.



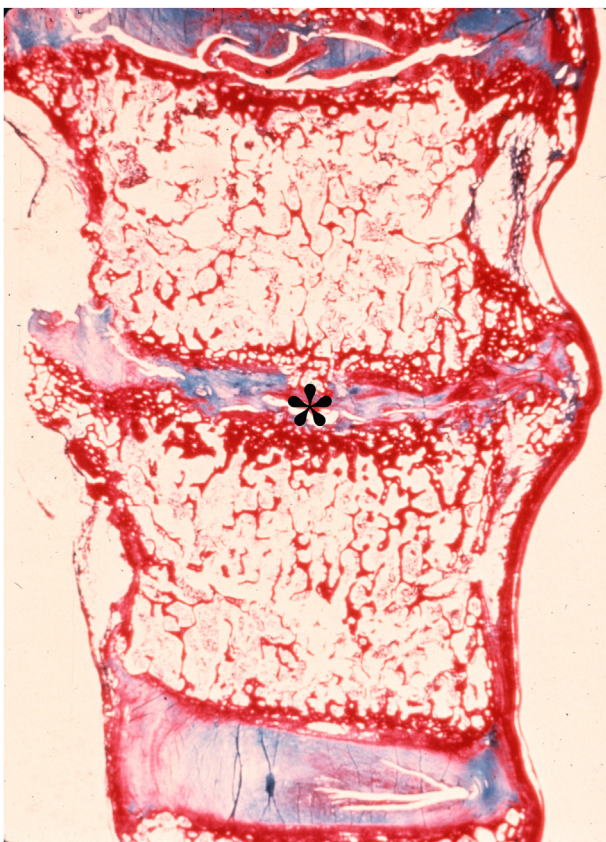
**Fig. 6.** Rheumatoid arthritis. The hyperplastic synovium shows numerous finger-like villous projection that replaced the joint space.



**Fig. 7.** Rheumatoid arthritis. The synovium shows hyperplasia with villous formation (arrows). Lymphoid aggregates are seen in the villi (arrowheads) (H&E, low magnification).

**Table 1**  
Osteoarthritis (OA) versus rheumatoid arthritis (RA).

	OA	RA
Demographics	- 50 years age <sup>6</sup> - Women (knees and hands); men (hips) <sup>6</sup>	- Second to fourth decades <sup>6</sup> - Women three times more common than men <sup>6</sup>
Clinical signs	- Morning stiffness <sup>6</sup> - Deep achy pain with limited ROM <sup>6</sup> - Crepitus <sup>6</sup> - Heberden's nodes <sup>6</sup> - Bouchard's nodes <sup>5</sup> - Sparing of wrists, elbows, and shoulders <sup>6</sup> - No specific biomarker for diagnosis and prognosis <sup>25</sup>	- Malaise, fatigue, generalized musculoskeletal aches <sup>6</sup> - Symmetric joint involvement <sup>6</sup> - Small joints affected first <sup>6</sup> - Symptoms begin in the hands and feet, then wrists, ankles, elbows, and knees - MCP joints, PIP joints, wrist joints, and fifth MTP <sup>8</sup> - RF <sup>6</sup> - ACPAs <sup>6</sup> - Elevated ESR and CRP <sup>15</sup> - Synovitis and tenosynovitis <sup>8,9</sup> - Joint erosions (91.4% of patients) <sup>8</sup> - Synovial proliferation and pannus in RA distribution <sup>8</sup> - Pannus <sup>5</sup> - Bony ankylosis <sup>6</sup> - Erosions <sup>6</sup> - Subchondral cysts <sup>6</sup> - Sparing of the distal interphalangeal joints <sup>6</sup> - Synovial cell proliferation <sup>6</sup> - Inflammation (lymphoid follicles) <sup>6</sup> - Increased vascularity <sup>6</sup> - Fibrin exudate on joint surfaces <sup>6</sup> - Subchondral bone resorption <sup>6</sup> - Pannus <sup>6</sup> - Fibrous ankylosis <sup>6</sup> - Bone ankylosis <sup>6</sup> - Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, and biologics such as etanercept, and adalimumab <sup>27</sup> - Viscosupplementation <sup>27</sup>
Laboratory value findings		
Ultrasound signs	- Synovial cysts <sup>4</sup> - Synovitis and effusion <sup>25</sup> - Joint erosions (70.0% of patients) <sup>8</sup>	
Radiographic signs	- Marginal osteophyte <sup>5</sup> - Joint space narrowing <sup>6</sup> - Subchondral sclerosis <sup>6</sup> - Subchondral cyst <sup>6</sup>	
Morphology	- Loose bodies <sup>6</sup> - Bone eburnation <sup>6</sup> - Marginal osteophytes <sup>6</sup> - Few inflammatory cells <sup>6</sup>	
Pharmacotherapy	- NSAIDs <sup>26</sup> - Oral acetaminophen <sup>26</sup> - Intra-articular corticosteroid injections <sup>26</sup> - HA viscosupplementation (subset of patients) <sup>26</sup>	



**Fig. 8.** Section of vertebral column from a patient with osteoarthritis. Notice the intervertebral disc in the center of the image (\*) shows severe degenerative changes (Masson, low magnification).

### Questions/discussion points, Part 3

#### **What is the most likely diagnosis based on the clinical, imaging, and lab findings?**

The patient has conventional radiographs that are consistent with OA, not RA. DIP joints are spared in RA. Additionally, there is limited ROM of the right knee and back on clinical examination, joint space narrowing and osteophytes on imaging (right knee and lumbar back), and a seronegative RF lab result. The presence of Bouchard's nodes and Heberden's nodes further supports OA as the diagnosis.

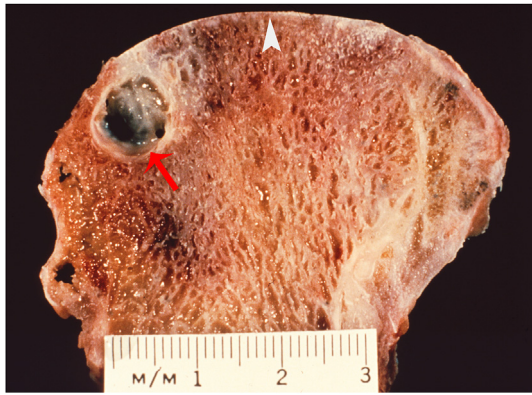
#### **What are the diagnostic criteria for OA of the knee?**

The EULAR recommendations require the following symptoms: knee pain, no early morning stiffness (EMS) or EMS  $\leq 30$  min, and functional limitation. The required clinical signs include crepitus, restricted ROM, bone enlargement, joint margin tenderness, and no palpable warmth. The ACR diagnostic criteria are that the individual must have knee pain and any three or more of the following: no EMS or EMS  $\leq 30$  min, crepitus, bone enlargement, joint margin tenderness, and no palpable warmth. The patient in the clinical vignette per the EULAR and ACR criteria meets the diagnostic requirements for knee OA.

#### **Discuss the epidemiology of OA and RA**

OA is the leading cause of joint disease worldwide.<sup>20</sup> Some estimates are that OA affects 10% of men and 18% of women over the age of 60.<sup>20</sup> The leading risk factor for OA is age<sup>20</sup>; the prevalence increases exponentially after the age of 50.<sup>6</sup> Several nonhereditary possible contributions increase the risk of OA development, including systemic, biomechanics, and past injury. Genetics also plays a crucial role with at least 11 loci known.<sup>20</sup> As many as 14 million people in the United States have OA of the knee, roughly half are under 65.<sup>21</sup> Additionally, concomitant hand and knee OA more often affect women than men.<sup>6,22</sup>





**Fig. 9.** Osteoarthritis. The gross image of the femoral head demonstrates erosion of the articular surface (arrowhead) with subchondral cyst (red arrow).

OA of the knee is clinically more common than the hip and hand.<sup>12</sup> OA accounts for an increased number of hospitalizations compared to RA.<sup>22</sup>

RA is a chronic autoimmune disorder, which principally affects the joints. The incidence of RA is 0.5%–1.0%,<sup>19</sup> with an evident increase in the northern hemisphere from the south to north and rural to urban areas.<sup>23</sup> RA affects twice as many women as men, and the peak age is 50 years.<sup>19</sup> Positive family history for RA is significant clinically as there is a three to five times increased likelihood of developing RA when the family history is positive.<sup>23</sup> There is a 40%–65% heritability seen for seropositive RA.<sup>23</sup> In seropositive RA, there are autoantibodies, including RF, ACPA, anti-carbamylated (anti-CarP) antibodies, and anti-acetylated protein antibodies.<sup>19</sup>

#### **What is the pathogenesis of OA and RA?**

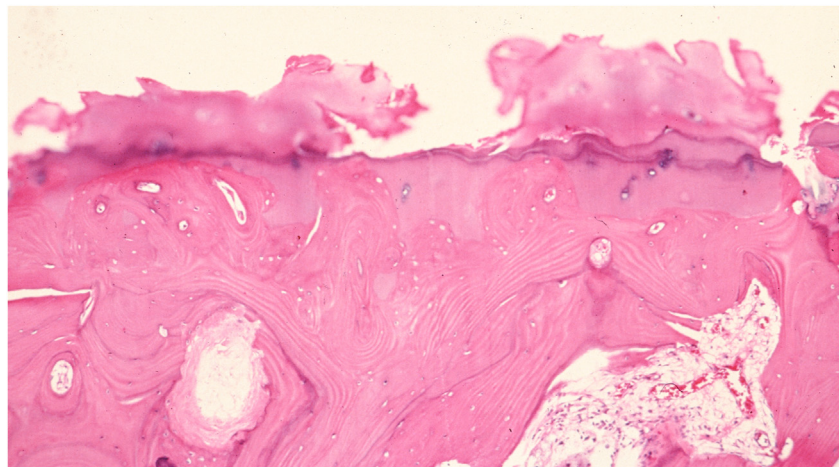
OA is a degenerative joint disease primarily affecting the articular cartilage of weight-bearing joints such as the hips, knees, spine, and fingers.<sup>6,24</sup> The pathogenesis of OA involves the entire joint: cartilage, subchondral bone, and soft tissues, including the synovium.<sup>12</sup> In OA, cartilage integrity is lost predominantly by biomechanical stress; however, genetic influences may result in early chondrocyte injury and disordered matrix repair.<sup>6</sup> There is an uneven balance in the repair mechanism. Proliferating chondrocytes synthesize matrix proteoglycans, but the degradation rate exceeds production in OA.<sup>6</sup> Diminishment of proteoglycans permits more water to interact with the collagen, causing swelling of the cartilage.<sup>24</sup> Additionally, chondrocytes secrete matrix

metalloproteinases (MMPs), which break down the extracellular matrix type II collagen.<sup>6</sup> Chondrocytes and the adjacent synovium release soluble factors and pro-inflammatory cytokines, including transforming growth factor-beta (TGF- $\beta$ ), which stimulates the production of MMPs.<sup>6</sup> Other important modulators are tumor necrosis factor-alpha (TNF- $\alpha$ ), prostaglandins (PGE<sub>2</sub>), and nitric oxide, which all contribute to disease.<sup>24</sup> Eventually, chondrocyte depletion and irreversible matrix degradation occur in advanced OA.<sup>6</sup> Additional changes to the surrounding structures include meniscal degeneration, sclerosis of the underlying bone, osteophyte expansion at the joint margin, weakness of the surrounding joint muscles, ligamentous injury, and synovitis.<sup>5</sup> Genetics contribute to the development of OA via mutations in the COL2A1 gene, responsible for producing type II collagen, the main component of articular cartilage.<sup>24</sup>

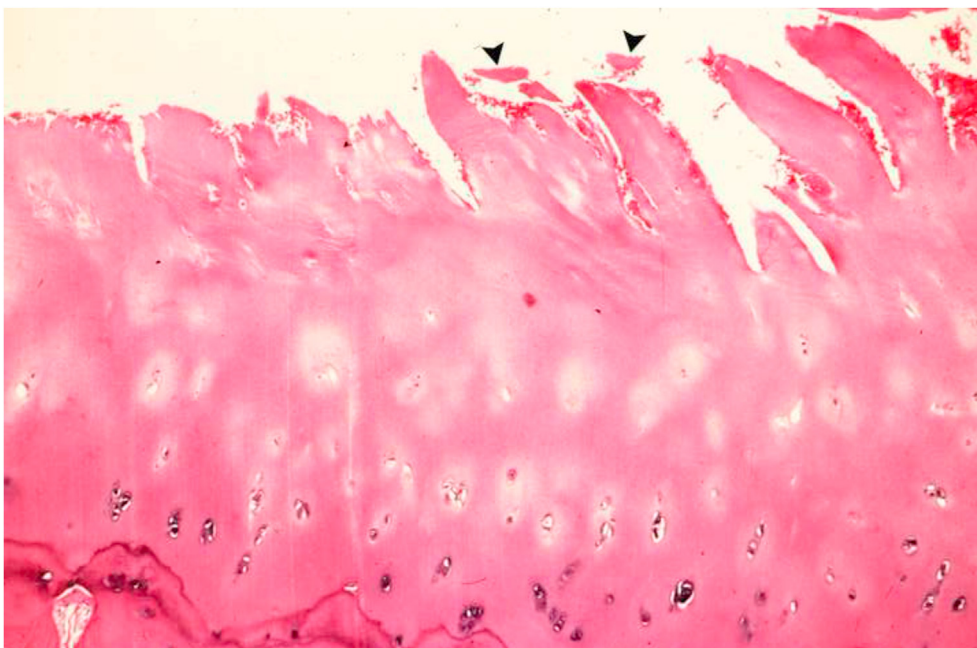
RA is a chronic autoimmune disorder primarily affecting the joints. T-helper CD4<sup>+</sup> cells are principally responsible for the pathogenesis of RA.<sup>6</sup> The central cytokines involved in RA are interferon-gamma (IFN- $\gamma$ ), interleukin-17 (IL-17), IL-1, tumor necrosis factor (TNF), and receptor activator of nuclear factor kappa-B ligand (RANKL); TNF is the most important cytokine involved in RA pathogenesis.<sup>6</sup> These cytokines potentiate the inflammatory response. Antibodies directed against self-antigens lead to the pathologic changes seen in RA.<sup>6</sup> Some autoantibodies are directed against self-citrullinated peptides (ACPAs) in up to 70% of RA patients<sup>6</sup> and can include IgM, IgA, or IgG antibody classes.<sup>23</sup> In citrullination, arginine within a peptide is post-translationally modified to citrulline. Complement activation via the classic and alternative pathways by ACPAs leads to reduced complement levels and increased complement cleavage products within the synovial fluid of individuals with RA.<sup>17</sup> Many proteins within the joints are affected by citrullination, including within the hyaline cartilage, fibrinogen, type II collagen, the intermediate filament protein vimentin, and  $\alpha$ -enolase, the glycolytic enzyme.<sup>6</sup> Additional autoantibodies present in up to 80% of RA patients are pentameric anti-IgM and dimeric anti-IgA, which target the Fc heavy chains of IgG; these two autoantibodies against Fc $\gamma$  are called RF.<sup>6</sup> Genetics and environmental influences also contribute to RA development.<sup>6</sup> The HLA-DR4 allele is detected in roughly 50% of individuals with ACPA-positive RA.<sup>6</sup> Environmental factors including smoking and periodontal disease are implicated in RA pathogenesis due to increasing citrullination of self-peptides.<sup>6</sup>

#### **Compare and contrast the clinical findings in OA and RA**

Joint involvement differs between OA and RA. While “joint mice” occur in OA, pannus (inflammatory synovium which migrates to the surface of the articular cartilage) formation and ankylosis (fibrous fusion of the joint) occur in RA.<sup>24</sup> Pannus formation in joints of individuals with



**Fig. 10.** Fragmented articular surface in osteoarthritis. The articular surface of bone in this image shows fragmentation of the articular surface, referred to as “fibrillation.”



**Fig. 11.** Low-power photograph showing fragmentation of the articular cartilage. Small fragments of cartilage may become detached and form loose bodies (“joint mice”) within the joint space (arrowheads).

RA occurs due to proliferation of synovial cells, inflammation (often with lymphoid aggregates, which are not observed in OA), angiogenesis, fibrin-laden exudate on articular joint surfaces, and subchondral bone resorption (Figs. 6 and 7).<sup>6</sup> Joint loss in RA is characteristically juxta-articular, occurring on both sides of the joint.<sup>24</sup> Fissuring, eburnation, marginal joint osteophytes, and subchondral cysts are common findings in OA. Furthermore, extraskeletal manifestations of RA are rheumatoid nodules, which have a core of fibrinoid necrosis with palisading macrophages, surrounded by plasma cells and lymphocytes.<sup>24</sup> Rheumatoid nodules are characteristic of RA and present in the skin of the elbow and leg, areas that experience high pressure and these lesions are firm, mobile, rubbery, and sometimes tender.<sup>24</sup> However, the patient in the clinical vignette has a normal skin exam. Table 1<sup>4-6,8,9,15,25-27</sup> summarizes findings in OA and RA.

#### Diagnostic findings, Part 4

Fig. 8 is a section of lumbosacral spine obtained at autopsy from a patient with OA. Fig. 9 is an image of a bisected femoral head submitted for pathological examination from a patient with OA.

#### Questions/discussion points, Part 4

##### *Describe the findings in the lumbosacral spine and femoral head*

Fig. 8, a resection of the lumbosacral spine from another patient with OA progression at autopsy, shows narrowing of the joint space between two vertebral bodies secondary to degeneration of the intervertebral (IV) disc; marginal osteophytes surrounding the IV discs is evident.

The bisected femoral head from a patient with a similar bone morbidity caused by OA as the patient demonstrates erosion of the articular surface with a subchondral cyst on gross examination (Fig. 9). The femoral head shows fibrillation, surface cracks in the articular cartilage, a feature characteristic of OA on microscopic examination (Fig. 10). Loose bodies, dislodged fragments of articular cartilage, flake off the fibrillated surface into the joint space (referred to as joint mice) with progression of the OA (Fig. 11).

#### *What are the gross and histomorphologic findings of OA?*

The histomorphometry of early OA is the loss of surface proteoglycans from the hyaline cartilage, which results in a decreased metachromatic staining.<sup>24</sup> Clusters of proliferating chondrocytes surrounded by basophilic staining matrix (territorial matrix) further characterize early OA.<sup>6,24</sup> Some chondrocytes die, leaving empty lacunae within the cartilage.<sup>24</sup> Several years later, OA may progress to fibrillations or cracks in the articular cartilage, which parallel its long axis.<sup>24</sup> Disease advances and fibrillations become oriented more perpendicular to the articular cartilage's long axis, in line with the type II collagen fibers within the cartilage matrix.<sup>24</sup> These defects in the articular cartilage become filled with synovial fluid.<sup>24</sup> Additionally, subchondral cysts develop secondary to synovial fluid within subchondral irregularities or bone fractures.<sup>6</sup> Chondrocytes eventually drop out, and entire cartilage units become detached, forming loose bodies,<sup>6</sup> also called joint mice.<sup>28</sup> This leads to nonuniform articular cartilage with erosion points and enhanced thickness of subchondral bone.<sup>29</sup> Subchondral bone is exposed and burnished by articulation with the opposing bone, such as the tibia plateau and femoral condyle, causing eburnation.<sup>6</sup> Osteophytes (bone spurs) occur at the joint margin<sup>29</sup> capped by articular hyaline cartilage and fibrocartilage, which slowly ossify.<sup>6</sup>

Osteophytes are palpable at the PIP joints (Bouchard's nodes) and DIP joints (Heberden's nodes) in the patient in the clinical vignette; sometimes osteophytes are palpable at the knee joint. The patient in the clinical vignette has a palpable deformity of the medial right knee. Based on the clinical presentation and imaging, the bone deformity seen in this patient's right knee is consistent with an osteophyte. Additionally, the patient has a varus knee, causing increased medial joint cartilage damage, seen on clinical examination, imaging, and histology.

#### *What are the costs associated with OA?*

OA's healthcare costs in high-income countries are substantial, accounting for 1–2.5% of their gross domestic product.<sup>12</sup> Total hip and total knee replacements account for a majority of these costs.<sup>12</sup> However, the cost for the individual with OA, such as loss of personal savings due to



decreased work, combined with national costs, exceeds direct healthcare costs.<sup>12</sup> The personal medical expenditure costs for the individual with OA was \$2117 (CI 95%, \$1268–2966) more than the average person, totaling \$139.8 billion nationally in 2013.<sup>30</sup> Ambulatory care followed by prescriptions and inpatient hospital stay accounts for the three most significant expenditures in order from greatest to least.<sup>30</sup> OA was the second most expensive condition treated in United States hospitals in 2017.<sup>31</sup>

### What are current treatment options for OA?

Treatment for OA initially is nonpharmacologic. The ACR/Arthritis Foundation Guideline recommends first trying the “physical, psychosocial, and mind-body approaches” to managing OA of the knee.<sup>32</sup> For example, yoga, balance training, cognitive behavioral therapy (CBT), Tai Chi, weight loss, self-efficacy programs, or exercise are recommended for treating knee OA (KOA).<sup>32</sup> The patient in the clinical vignette may be offered a cane and instructed to unload the weight on her right knee by utilizing the cane in her left hand although her back pain may increase fall risk.<sup>26</sup> The clinician may refer the patient to a physical therapist (PT).<sup>33</sup> Additionally, a randomized trial demonstrated that an over-the-counter neoprene sleeve provided patients with symptomatic pain relief, particularly those with varus deformity of the knee secondary to OA.<sup>33</sup> Topical analgesics such as capsaicin is a first-line pharmacologic approach to avoid gastrointestinal toxicities caused by oral nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>33</sup> The patient in the clinical vignette is given a neoprene sleeve and referred for physical therapy. NSAID therapy is also recommended if the topical analgesic fails to provide pain relief. While controversial, viscosupplementation using intra-articular hyaluronans (HAs) offers another treatment option. HA is a principle component of synovial fluid that is diluted in OA.<sup>34</sup> Some studies have shown that intra-articular HA injection is equally or more effective than NSAIDs or intra-articular corticosteroids for pain relief and functional improvement.<sup>34</sup> Because viscosupplementations have different chemical properties, cross-linking mechanisms, and formulations, the results of these studies may only apply to a subset of patients with symptomatic OA.<sup>26,34</sup> The use of oral narcotics such as tramadol are not recommended for individuals with OA of the knee.<sup>26</sup>

### Teaching points

- Osteoarthritis (OA) is the most common joint disease worldwide, affecting more women than men.
- Clinical examination of the osteoarthritic joint demonstrates mild tenderness, limited range of motion, and joint enlargement without effusion.
- OA is primarily caused by biomechanical stress injuring the articular cartilage.
- OA is characterized by increased joint cartilage degeneration and an unequal repair mechanism.
- Wrist pain is uncommon in OA but is common in RA.
- Joint stiffness in the morning for 30 min or less and joint pain worse with activity and better with rest is typical of OA.
- Distal interphalangeal (DIP) sparing occurs in rheumatoid arthritis (RA), whereas DIP, PIP, and first MCP hand joints are most affected in OA.
- Joint mice are loose bodies, dislodged fragments of articular cartilage, that flake off the fibrillated surface into the joint space, seen in OA.
- RA is a chronic autoimmune disease primarily affecting joints.
- RF is comprised of anti-IgM and anti-IgA against Fcγ. RF and ACPA seropositivity facilitate the diagnosis in RA patients based on ACR and EULAR guidelines.
- Pannus, ankylosis, and rheumatoid nodule are common in RA. Few inflammatory cells are demonstrated on histology in OA.
- Pannus is characterized by an inflammatory synovium which migrates to the surface of the articular cartilage with subchondral bone involvement.

- Rheumatoid nodules have a core of fibrinoid necrosis with palisading macrophages, surrounded by lymphocytes and plasma cells. Rheumatoid nodules are characteristic of RA and present in the skin of the elbow and leg, areas that experience high pressure and these lesions are firm, mobile, rubbery, and sometimes tender. Extraskelletal manifestations are common in RA but not OA.
- The principal cell involved in RA pathogenesis is the T-helper cell. TNF is the most important mediator of RA pathogenesis.
- First-line treatment for OA involving the knee is a topical analgesic as well as nonpharmacologic management. Oral NSAIDs if tolerated are recommended to treat OA of the knee. Oral narcotics (tramadol) are not recommended for osteoarthritis of the knee. Viscosupplementation may be used for a subset of patients with symptomatic osteoarthritis of the knee.

### Author's note

Figs. 6–11 were obtained during the scope of US government employment for Dr. Conran.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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