CLINICAL PRACTICE

Exercises in Clinical Reasoning

Keeping a Flexible Differential Diagnosis: an Exercise in Clinical Reasoning

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In this series a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (**bold**). Additional commentary on the diagnostic reasoning process (*italic*) is interspersed throughout the discussion.

A **57-year-old woman with type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), smoking-related interstitial lung disease (ILD), and fibromyalgia presented to clinic with progressive, intractable lower back and neck pain. For decades, she suffered from widespread joint pain, but recently her neck pain and lower back pain were most bothersome. Her pain was constant, worsened with activity, and not alleviated with rest. She denied fevers, night sweats, chills, and weight loss. She had no focal weakness, paresthesia, urinary retention, or fecal incontinence. She had no morning stiffness or recent joint swelling.**

Worsening symptoms in a patient with long-standing pain might represent progression of an underlying chronic disorder, or a new—and possibly unrelated—process. For example, she may have a progressively worsening spinal deformity such as scoliosis or kyphosis that is now causing spinal cord or nerve root compression. On the other hand, she may have developed a new infection or malignancy that has no relation to an existing problem.

Her age and progressive pain prompt consideration of rheumatologic, degenerative, infectious, and malignant conditions. Worsened pain with activity decreases the likelihood of an inflammatory process such as rheumatoid arthritis (RA) or the inflammatory spondyloarthropathies. Further, while RA may affect the cervical spine, it rarely causes lower back pain. Conversely, inflammatory spondyloarthropathies tend to cause lumbar spinal and sacroiliac pain but usually spare the neck. The lack of weakness and normal bowel and bladder function argue against cauda equina syndrome or myelopathy.

Cognitive flexibility has been variably defined in the clinical reasoning and psychology literature.[1–5] While it is unclear if flexibility is a distinct cognitive skill or simply a modifying property of other cognitive processes,[1] maintaining flexibility in clinical problem-solving has been associated with diagnostic expertise.[2, 3] Flexibility is observed in clinicians who fluidly move between intuition and analytical thinking.[5] In addition, flexible diagnosticians tend to (1) use a more responsive mode of questioning during the patient interview, (2) reorganize their working differential diagnosis throughout the encounter, and (3) interpret clinical data from multiple perspectives.[2]

The discussant applies flexibility by exploring a seemingly chronic problem in a new light. The clinician first separates the patient's presentation into one of two broad categories, progression of a hitherto undiagnosed systemic disease or an entirely new problem. This primitive categorization of potential explanations for the patient's concerns represents an early mental sorting process that can be refined and reprioritized. Viewing the case through these two frames preserves open-mindedness and avoids premature closure. The flexible diagnostician can subsequently toggle between these frames to build a broader differential diagnosis as the case unfolds.

Her back pain began in her teens when she was diagnosed with scoliosis. Since her early twenties, she experienced diffuse arthralgias and intermittent periods of joint swelling, particularly in her ankles, wrists, and toes. She previously consulted with various specialists and had been diagnosed with "degenerative arthritis," osteopenia, and fibromyalgia. Her back pain did not improve with non-steroidal anti-inflammatory medications, epidural steroid injections, or radiofrequency ablation of the lumbar spinal nerve roots.

Previous laboratory testing included a normal serum creatinine, complete blood count, erythrocyte sedimentation rate, serum protein electrophoresis, and urinalysis. Titers

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of rheumatoid factor, antinuclear antibodies, SS-A and SS-B antibodies, antineutrophil cytoplasmic antibodies, *Borrelia burgdorferi* IgM and IgG antibodies, and rapid plasmin reagin were all negative or within normal ranges. MRI studies of her cervical, thoracic, and lumbar spine revealed multilevel degenerative disc disease and neural foraminal narrowing without evidence of cord pathology or nerve root compression.

Her self-reported history of scoliosis would provide a possible anatomic explanation for her chronic neck and back pain but was not corroborated by imaging. Her multilevel degenerative disc disease at least provides a partial explanation for her chronic pain. However, more intriguing are the symptoms that again raise concern for a systemic inflammatory disorder: long-standing, relapsing-remitting small joint swelling and pain. This pattern of small joint arthritis can be seen in RA or lupus, infectious diseases such as Lyme disease or mycobacterial infection, and crystalline synovitis; only RA would have such a protracted time course. The patient's previous laboratory testing argues against some of these conditions but does not completely exclude them. While degenerative disc disease is often considered a "wear-and-tear" phenomenon of aging, degenerative changes in other joints should not be presumed idiopathic; these changes may be sequelae of inflammatory arthritis.

The discussant's frame of "long-standing and relapsing-remitting small joint swelling and pain" prioritized a systemic inflammatory process. From this frame, the clinician then activates various illness scripts. Experienced diagnosticians evaluate diagnostic likelihoods by comparing the patient's presentation against their own illness scripts. These scripts evolve and become more elaborately structured and clinically relevant with experience.[6, 7]

Accordingly, both knowledge and experience are important ingredients for the flexible problem-solver. The discussant had likely encountered atypical presentations of rheumatoid arthritis or Lyme disease. With richer and more comprehensive illness scripts, the expert diagnostician views these scripts as malleable and tolerates unexpected findings.[1, 5] *Here, the clinician understands the limitations of diagnostic tests and still activates the illness scripts for rheumatologic diseases and infectious arthritides despite a myriad of negative test results. This tolerance in script matching and flexibility in script selection typify diagnostic expertise.*

On review of systems, she endorsed fatigue and a depressed mood. Her fatigue was post-exertional and often accompanied by orthostatic lightheadedness. She also had frequent headaches and a history of chronic abdominal pain accompanied by alternating periods of diarrhea and constipation. More recently, she had developed dyspnea on exertion, which led to a diagnosis of COPD and ILD. Her social history included a 30 pack-year history of smoking and rare alcohol use. She had previously worked as a graphic designer but was no longer working due to her pain and fatigue.

Chronic fatigue is commonly seen in systemic inflammatory disorders and cancer but would be less common in degenerative disorders such as osteoarthritis. Orthostasis commonly results from hypovolemia, medication side-effects, and autonomic insufficiency. However, orthostatic hypotension is unexpected in the context of many systemic inflammatory disorders that have been considered; it may hint at a cardiovascular disorder, such as an infiltrative cardiomyopathy, or it may be related to dysautonomia. Her intermittent diarrhea may be caused by inflammatory bowel disease with spondyloarthritis. Celiac disease may also manifest with gastrointestinal and musculoskeletal symptoms. While rare, Whipple disease could also account for her diarrhea and small joint arthritis. Her ILD could be associated with rheumatoid arthritis, dermatomyositis, scleroderma, or sarcoidosis. It would be premature to dismiss any elements in her review of systems at this point.

The discussant recognizes the challenge of a "pan-positive review of systems." To safeguard against dismissal of relevant information, the discussant uses a "try it on" strategy. Here, the discussant regroups salient features—such as "joint pain with orthostasis," "joint pain with diarrhea," and "joint pain with ILD"—in search of a unifying diagnosis. While this process is effort-laden and time-consuming, the discussant's flexibility increases the likelihood of finding a matching illness script. Using this strategy would be inefficient and impractical for straightforward cases, such as uncomplicated urinary tract infections or viral respiratory illness. However, when the symptoms are progressive and suggest multisystem involvement, or when no disease immediately comes to mind, such flexibility may help determine which complaints to acknowledge and which to dismiss.

Throughout the interview, the patient fixated on labeling her myriad symptoms as "inflammatory." Her symptoms seemingly worsened after undergoing vaginal sling surgery for uterine prolapse 5 years ago; she attributed these symptoms, particularly her worsening joint pain, to an immune-mediated reaction to the mesh implant.

The patient's concern that her systemic symptoms may be related to a surgical implant is understandable. It is human nature to seek connections between events, and patients might mistakenly, but logically, attribute new symptoms to an antecedent medical procedure. Her worsened symptoms after surgery are likely coincidental as there is no plausible physiologic connection. It would still be prudent to search for potential reactions to her specific implant using resources from the Food and Drug Administration (FDA).

Colonoscopy was normal, and fluoroscopic defecography demonstrated severe pelvic floor descent. Chest CT revealed a pattern consistent with respiratory bronchiolitis interstitial

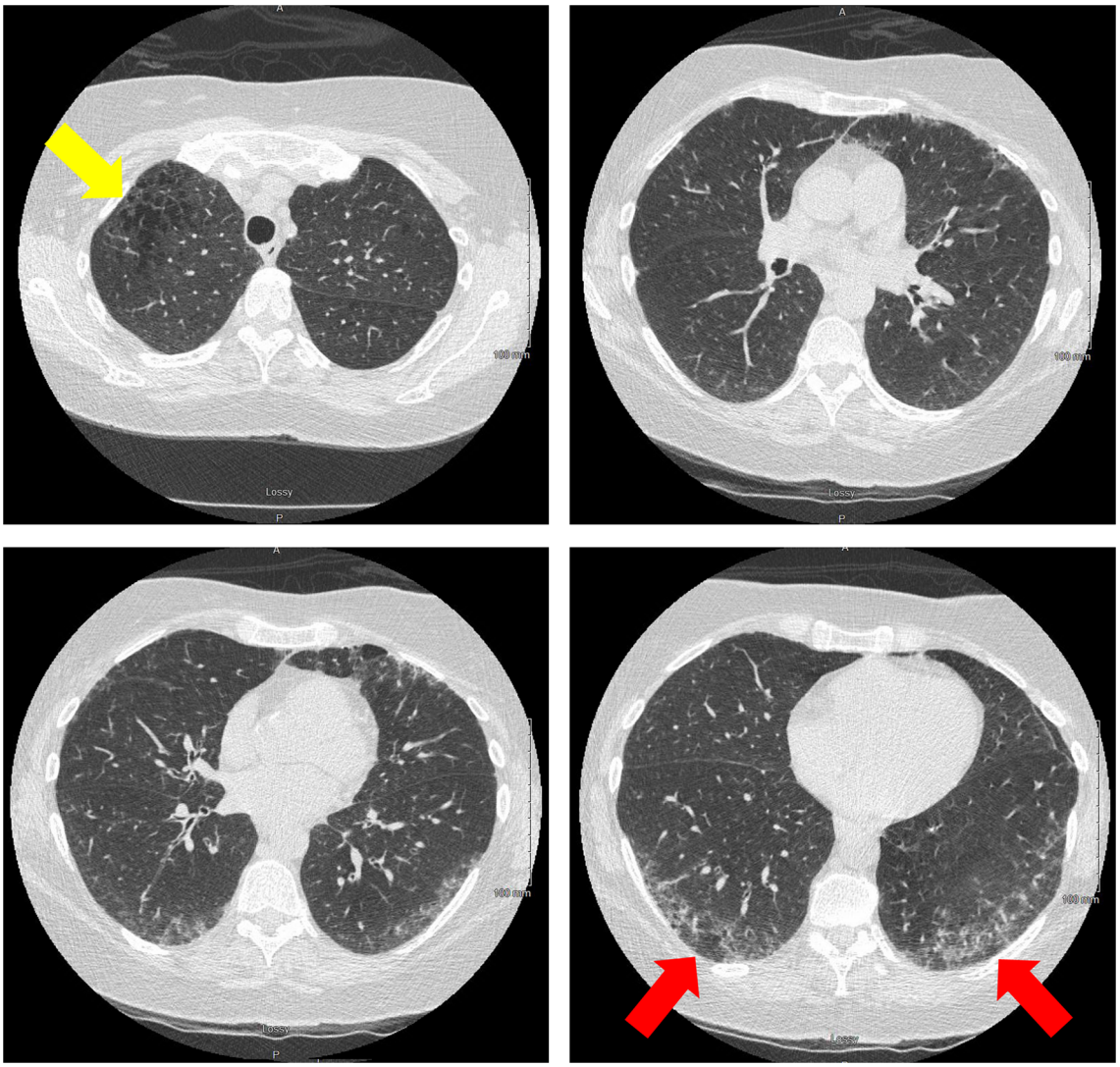

Figure 1 Chest CT demonstrating apical emphysematous change (yellow arrow) and peripheral ground glass attenuation and subpleural intralobular interstitial thickening (red arrows).

lung disease (Fig. 1). Pulmonary function tests demonstrated mild obstruction. She was advised to quit smoking and use bronchodilator therapy. After the patient's surgical mesh eroded through her vaginal wall—a known complication previously reported to the FDA—she had the mesh removed. Postoperatively, she had significant vaginal prolapse and a rectocele, but her joint symptoms did not improve. Notably, her family history included "early onset" degenerative arthritis in her mother and her mother's siblings. Her two daughters also suffered musculoskeletal maladies including both having been born with "bow deformities" of the legs, which ultimately required leg bracing.

This patient has had a number of medical problems that, when evaluated independently, seem unrelated. Taken together, however, these findings suggest an inherited connective tissue disorder (CTD), particularly given the life-long nature of her problems and her family history. Inherited connective tissue disorders are uncommon conditions that are usually related to mutations in the genes coding for key proteins in connective tissue matrix and include the Ehlers-Danlos syndromes (EDS), Marfan syndrome, and osteogenesis imperfecta. Evaluation for an inherited CTD begins with a focused history, inquiring about repeated atypical or low-impact injuries such as dislocations, fractures, or repeated-use injuries. Patients should also be asked about a history of excessive flexibility. Family history is important as many of the hereditary CTDs are inherited in an autosomal dominant pattern, and a family history of early degenerative arthritis and injuries is common. The prominent musculoskeletal symptoms in this patient and her family raise concern for EDS more than another CTD; Marfan syndrome (and related conditions) has a unique phenotype including significant height, arachnodactyly, lens dislocations, and aortic disorders. Osteogenesis imperfecta can have varied presentation but most prominently features multiple fractures early in life. Because several forms of EDS can also involve the cardiovascular system, clinicians should also inquire about a family history

of intracerebral hemorrhage, spontaneous aortic or arterial dissection, or premature valvular disease. Because of the critical nature of connective tissue in the extracellular matrix, inherited CTDs can affect myriad organ systems. It is conceivable that this patient's vaginal prolapse, gastrointestinal symptoms, and interstitial lung disease could all be accounted for by defects in collagen synthesis.

Additional history revealed that she was born with high arches in her feet. Since childhood, she had been prone to finger and toe dislocation and minor fractures and had dislocated her shoulder at age 8. She was unable to keep up with peers during rope-climbing exercises or push-ups due to apprehension of dislocating her shoulder again. She had dermatologic problems in the past including blistering and easy bruising, oral sores, and premature graying of her hair.

This patient has overlapping features of EDS subtypes with features of hypermobility as evidenced by repeated joint subluxation, skin hyperextensibility and fragility, and perhaps even vascular fragility given her easy bruising. Thus, it is especially important to evaluate for vascular EDS, a condition associated with life-threatening vascular dissections and a markedly reduced life expectancy. Referral should be made to a genetics specialist for genetic testing and counseling. Physical examination should focus on cardiovascular, dermatologic, and musculoskeletal evaluations with special attention to a formal hypermobility scale, such as the Beighton scale (Table 1). This validated scale evaluates for hypermobility in the hands, elbows, knees, and spine. A total of 9 points is possible, and generally, a cutoff of 5 is used for hypermobility. The patient has already undergone an appropriate evaluation for other potential causes of arthritis. An echocardiogram should be performed to evaluate for mitral and aortic valvulopathies that could suggest certain EDS subtypes.

On examination, blood pressure was 101/63 mmHg and pulse rate of 79 bpm while supine; blood pressure was 78/46 mmHg with heart rate 104 bpm after 1 min of standing. She had significant kyphosis but no obvious scoliosis. There was no evidence of active tenosynovitis in her hands, knees, or feet. Her Beighton score was 5 out of 9 on initial evaluation; 2 points for the ability to hyperextend each fifth finger, to flex the thumb to each forearm, and to touch the floor with hands flat on the floor. However, the patient recalled that she had been able to voluntarily hyperextend her knee and elbow in her youth. She also demonstrated a unique ability to fold her hands into a praying position behind her back (Fig. 2).

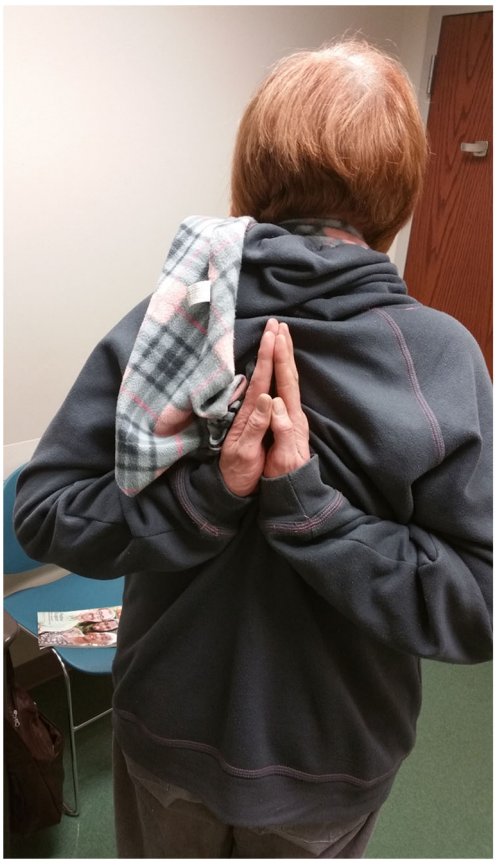

Figure 2 Patient demonstrating ability to hold hands in praying position behind her back.

This physical examination is clearly consistent with hypermobility and its long-term complications. Her only moderately elevated Beighton score for hypermobility reflects long-term sequelae of hypermobility, including osteoarthritis, kyphosis, and tendonopathy. If she were evaluated earlier in her life, her score likely would have been higher. Her lack of inflammation on examination is reassuring, as its presence would repudiate

Table 1 Beighton scale used for diagnosing hypermobility. A score of 5 or greater affirms joint hypermobility [8]

Joint/structure(s) tested	Finding of hypermobility	Scoring
Metacarpal-phalangeal joint of 5th finger	Ability to hyperextend 5th finger beyond 90° relative to dorsum of hand	1 point per hand (up to 2 points)
Thumb	Ability to passively touch thumb to ipsilateral forearm	1 point per thumb (up to 2 points)
Elbow	Hyperextension of elbow beyond 10°	1 point per elbow (up to 2 points)
Knee	With knees locked and standing upright, hyperextension of knee beyond 10°	1 point per knee (up to 2 points)
Waist and spine	With knees locked and feet together, ability to place palms of both hands on the floor	1 point

the working diagnosis of EDS. Her borderline orthostatic hypotension and tachycardia point to a lack of adequate autonomic compensation for changes in body position. Orthostatic hypotension is a common, although incompletely understood, finding in EDS.

The discussant acknowledges data points that are less supportive of the working diagnosis of EDS, namely the equivocal Beighton score, and remains open to considering alternative hypotheses in mentioning joint inflammation. Avoiding concrete interpretation of clinical data aligns with the discussant's flexible activation of illness scripts.

She was advised that she had joint hypermobility (JH), which was most likely secondary to the hypermobile subtype of EDS. Tilt table testing revealed dysautonomia. After consultation with two geneticists, she was diagnosed clinically with EDS, hypermobile subtype. At these clinic visits, her Beighton score was 7 out of 9. Given that her family history also contained mitral valve prolapse and aortic aneurysms in first- and second-degree relatives, she underwent TAADNext (Ambry Genetics, Viejo, CA) testing, which is a 22-gene panel that includes *COL5A1*, *COL5A2*, and *COL3A1*. The panel was negative for a known genetic mutation implicated in connective tissue disorders. Nonetheless, she was advised that her family is afflicted by an autosomal dominant connective tissue disorder that clinically fits with hypermobile EDS.

DISCUSSION

Experts view cognitive flexibility as important in developing diagnostic expertise,[2, 3, 9] but the term flexibility has been variably defined. Flexibility has been described as a dynamic property of cognition that reflects the mind's tolerance to alternative views or categorizations.[5] The contemporary psychology literature contains other descriptors of cognitive flexibility including the abilities to shift between mental tasks, control mental resources, or maintain a wide perspective.[1] Maintaining multiple representations of knowledge translates to diagnostic expertise,[10] and deliberately gaining knowledge and experience likely contribute to developing flexible thinking.[1, 5] The relevance of cognitive flexibility is perhaps best encapsulated by F. Scott Fitzgerald: "The test of a first-rate intelligence is the ability to hold two opposed ideas in the mind at the same time, and still retain the ability to function."[11]

The extent to which flexibility is actually controlled by conscious thought is unclear.[1, 3]

Nevertheless, as evidenced by this case, staying flexible can be an active decision manifesting in three practical strategies. First, clinicians can maintain open-mindedness in considering new diagnostic possibilities, even for patients who seemingly have undergone exhaustive evaluations. Second, clinicians should explore how various combinations of symptoms and signs activate different illness scripts. In this case, the ultimate fit was found with the combination of "joint pain" and "strong family history of joint problems." Finally, clinicians should avoid thinking in absolutes. For example, diagnostic labels may be incorrect, or test results may be false positives or negatives. Recognizing these limitations, as well as the limitations and failings of one's own knowledge, allows for more diverse interpretations of the same clinical data.

This case also highlights the importance of flexibility in assessing patients with complex histories and multiple complaints. Often, these patients carry previous diagnostic labels, and it is tempting to accept these labels without skepticism. The intentional act of reconsidering alternative diagnoses is rooted in the tenets of flexible thinking. While there is substantial debate about using strategies to avoid unwanted effects of cognitive biases, being intentionally flexible, curious, and skeptical when faced with such patients may be an effective means to reduce diagnostic errors.

CLINICAL TEACHING POINTS

- Chronic musculoskeletal pain has myriad causes. A widespread distribution of non-inflammatory arthritis accompanied by a history of joint subluxation should prompt clinicians to think of joint hypermobility (JH). Common extra-articular manifestations of JH-related disorders include dysautonomia, functional gastrointestinal disorders, pelvic floor dysfunction, and psychological distress.[12, 13]
- Patients with JH often suffer widespread chronic pain[13, 14] and are often are labeled as having fibromyalgia or non-specific chronic pain syndromes.[14, 15] Accordingly, patients with JH may experience frustrating delays in diagnosis or misdiagnosis, lengthy diagnostic evaluations focused on isolated symptoms, and an overall poor understanding of their disorder among clinicians.[12, 16]
- The Ehlers-Danlos syndromes (EDS) represent a group of quintessential inherited connective tissue disorders that characteristically include prominent JH. EDS subtypes are categorized further by their clinical features and associated genetic markers.[8] Clinicians should consider one of the EDS subtypes when patients have JH, skin hyperextensibility, spontaneous arterial rupture or dissection, multiple hernias, rectal or uterine prolapse, mitral valve prolapse, and/or aortic root dilation.[8] While uncommon, various respiratory disorders including recurrent pneumothorax and bullous emphysema have also been reported in association with EDS.[17, 18]
- Hypermobile EDS follows an autosomal dominant inheritance pattern, but the precise genetic basis of the hypermobile subtype remains unknown.[8] When any form of EDS is suspected, referral to a genetic specialist should be considered.

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