Occam’s Razor versus Saint’s Triad

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A 60-year-old woman with a history of radiologically confirmed seronegative rheumatoid arthritis presented to the emergency department with a 10-day history of worsening dyspnea on exertion, nonproductive cough, and subjective fever and a 7-day history of pain in the right leg and buttock, which limited her mobility. There was no sputum production, orthopnea, paroxysmal nocturnal dyspnea, or pleuritic chest pain.

I would start creating my differential diagnosis by taking into account the relatively short time course of the symptoms and the clinical context in which they developed. Given the patient’s underlying disease, I am considering several complications of rheumatoid arthritis (although they are unlikely, given her seronegative status), such as parenchymal and distal-airway disease (interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, or constrictive bronchiolitis), pleural effusion, or pericardial effusion. Other diseases associated with pulmonary complications and arthritis, such as Wegener’s granulomatosis and systemic lupus erythematosus, should also be considered. In addition, she may have a pulmonary infection, particularly if she is receiving immunosuppressive therapy for her underlying rheumatic disease. The leg and buttock pain sounds like sciatica, but other possible explanations include her underlying arthritis, septic arthritis of the hip, or even deep venous thrombosis, which could be complicated by pulmonary embolism.

The patient had been evaluated at her local clinic a few days earlier. A chest radiograph and an ultrasound examination of her right leg showed no abnormalities. An antihistamine for presumed allergic rhinitis was prescribed. Her dyspnea progressed, and on the morning of admission, the patient was seen by her rheumatologist and was found to have a fever, tachypnea, and hypoxemia.

The initially normal chest radiograph was obtained early in the course of her illness and does not dissuade me from considering a process involving the pulmonary parenchyma, which might appear later as radiographic changes. I would focus on four main categories of disease at this point: a primary infectious process within the lungs (particularly if she is receiving immunosuppressive medication); an infection elsewhere (which perhaps would account for her leg and buttock pain) with a secondary process involving the lungs, such as bacteremia or acute respiratory distress syndrome; a noninfectious inflammatory process that may be associated with fever, such as bronchiolitis obliterans with organizing pneumonia, pulmonary embolic disease (despite the absence of abnormalities on the ultrasound examination of the leg), systemic lupus erythematosus, or Wegener’s granulomatosis; and drug toxicity, depending on the pharmacologic treatment of her rheumatologic disease. The normal chest radiograph rules out a clinically
significant pleural effusion. I do not believe that allergic rhinitis explains her presentation, because this diagnosis should neither cause dyspnea nor be associated with fever.

The patient's history included the CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), right-knee arthroplasty, right-hip arthroplasty with postoperative deep venous thrombosis five years previously, and hypothyroidism. The patient had been in a monogamous relationship for the past 30 years. She occasionally drank alcohol and reported that she did not use tobacco or illicit drugs. Her inflammatory arthritis was being treated with 5 mg of prednisone taken once a day (for the past 10 years), 25 mg of methotrexate administered subcutaneously once a week (for the past 11 months), and 300 mg of infliximab administered intravenously every 8 weeks (for the past 4 months). Her status with respect to tuberculin skin testing was unknown. Additional medications included levothyroxine, hydrocodone, acetaminophen, and alendronate (to prevent osteoporosis); she also took a folic acid supplement.

The CREST syndrome is associated with pathologic changes in the pulmonary vasculature similar to those in primary pulmonary hypertension, but the fever and the tempo of the presentation in this case argue against that diagnosis. The patient does have prosthetic material from her orthopedic procedures, and the possibility of infection originating in one of these areas remains in the differential diagnosis. Perhaps the most important additional information is that she was receiving drugs that are immunosuppressive, at least one of which (methotrexate) is also associated with inflammatory complications involving the pulmonary parenchyma.

Although her dose of prednisone is relatively low, she is also receiving infliximab in addition to the methotrexate and therefore should be considered immunosuppressed. Imunosuppression places her at risk both for common types of bacterial pneumonia and for infection with a variety of opportunistic pathogens, such as pneumocystis, viruses, fungi, and mycobacteria. A particular concern with the use of infliximab, which is a functional tumor necrosis factor α antagonist, is the development of mycobacterial disease. Since fever accompanies her respiratory symptoms, an opportunistic infection involving the lungs must be considered seriously.

The patient was alert but in moderate respiratory distress. Her temperature was 38.3°C, her heart rate was 82 beats per minute, her blood pressure was 130/72 mm Hg, her respiratory rate was 24 breaths per minute, and her oxygen saturation was 75 percent while she was breathing room air. She was using accessory muscles to breathe. Auscultation revealed crackles in the lower lung fields and dullness to percussion at the bases. There was no pleural friction rub. Cardiovascular examination showed a normal first heart sound but a prominent pulmonic second sound, with no audible murmur of tricuspid insufficiency. The neck veins were not elevated. She had hypertrophic changes of the metacarpal–phalangeal and proximal interphalangeal joints, with bilateral ulnar deviation. There were multiple cutaneous telangiectasias on the face and arms but no rash or nodules. Examination of the right hip showed no acetabular tenderness or edema and revealed a normal range of motion. There was no calf tenderness or edema.

Particularly intriguing in this case is the combination of the dramatically low oxygen saturation and the presence of a prominent pulmonic second sound on cardiac examination. The patient's hypoxemia could contribute to reactive pulmonary vasoconstriction, further complicating the underlying pulmonary vascular disease due to the CREST syndrome. Alternatively, considering her severe hypoxemia along with the prominent second pulmonic sound, I would be concerned about right-to-left intracardiac shunting, perhaps through a patent foramen ovale. Although we generally like to invoke Occam's razor, for some patients we cannot follow the rule of diagnostic parsimony. In this case, I could easily envision an opportunistic pulmonary infection being responsible for the fever, crackles, hypoxemia, and worsening pulmonary hypertension, which is then complicated by right-to-left intracardiac shunting and further deterioration in oxygenation.

The white-cell count was 8000 per cubic millimeter with a normal differential count, the hematocrit was 35 percent, the platelet count was 142,000 per cubic millimeter, the partial-thromboplastin time was 30 seconds (normal range, 19 to 30), and the international normalized ratio for the prothrombin time was 0.9. The serum aspartate aminotransferase level was 107 U per liter, the alanine aminotransferase level was 55 U per liter, the bicarbonate
level was 19 mmol per liter, the C-reactive protein level was 12.4 mg per deciliter (normal range, 0.020 to 0.800), and the lactate dehydrogenase level was 1142 U per liter (normal range, 104 to 236). The serum levels of alkaline phosphatase, direct and indirect bilirubin, glucose, creatinine, and urea nitrogen were normal. Arterial-blood gas analysis on 15 liters of oxygen delivered by a face mask showed that the partial pressure of oxygen was 230 mm Hg, the partial pressure of carbon dioxide was 29 mm Hg, and the pH was 7.45. The patient’s chest radiograph revealed patchy infiltrates scattered throughout both lungs. Her electrocardiogram was normal.

The slightly elevated levels of aminotransferases may reflect an early toxic effect of methotrexate on the liver, although a nonspecific response to a systemic infection is also possible. The patient’s acid–base status suggests a mixed metabolic acidosis and respiratory alkalosis. The elevated level of C-reactive protein indicates the presence of inflammation, infection, or both; her underlying rheumatic disease alone might explain this, or there may be an additional contributory process. The pulmonary infiltrates are also nonspecific, reflecting either an inflammatory or an infectious process. I remain most concerned about an opportunistic pulmonary infection (especially tuberculosis, given the treatment with infliximab), an infection complicating a joint prosthesis (with secondary pulmonary manifestations due to septic emboli or the acute respiratory distress syndrome), or a noninfectious inflammatory process, such as methotrexate-associated pneumonitis or bronchiolitis obliterans with organizing pneumonia.

Sputum cultures for bacteria were obtained, and empirical antibiotic therapy with levofloxacin, intravenous trimethoprim–sulfamethoxazole, and corticosteroids was begun. Although empirical antibiotic therapy for pneumocystis pneumonia or community-acquired pneumonia is reasonable, the patient should simultaneously undergo further diagnostic testing, since there are a number of other important possibilities under consideration. I have four key diagnostic questions at this point. Does the patient have an infection involving a prosthetic joint? Does she have thromboembolic disease? Does she have an opportunistic pulmonary infection? Does she have intracardiac right-to-left shunting (presumably through a patent foramen ovale)? Because there may be more than one process present, I favor investigating these diagnostic questions in parallel, beginning with an evaluation for possible thromboembolic disease and opportunistic pulmonary infection.

Spiral computed tomography (CT) of the chest (Fig. 1) showed large emboli in the right main pulmonary artery, right segmental pulmonary arteries, and left subsegmental arteries. The CT scan also showed extensive, peripheral, patchy ground-glass infiltrates (Fig. 2).

Although I have mentioned deep venous thrombosis as a potential cause of the leg and buttock pain, I am surprised by the diagnosis of extensive pulmonary thromboembolic disease. The additional finding of patchy ground-glass infiltrates is probably not related to the thromboembolic disease, and I remain concerned about another coexisting process, particularly an opportunistic infection. Given the need for anticoagulation and the likelihood of pulmonary hypertension, I would not want to perform a transbronchial biopsy. Rather, I would try to identify an opportunistic pathogen — particularly pneumocystis, given the appearance of the CT scan, or mycobacterium, given the use of infliximab — in induced sputum or bronchoalveolar-lavage fluid.

The patient received an intravenous bolus of unfractionated heparin followed by a continuous infusion of unfractionated heparin. Her clinical status re-
The patient was soon discharged from the hospital while taking an oral corticosteroid (the dose of which was to be tapered), trimethoprim–sulfamethoxazole, and warfarin. After completing treatment for P. carinii pneumonia, the patient continued to take trimethoprim–sulfamethoxazole for prophylaxis. She was contacted five months after hospitalization and reported no breathing difficulties.

This case illustrates two important points that come up relatively frequently in puzzling clinical problems. First, diagnostic parsimony is a worthwhile goal, but it is one that cannot always be achieved. Second, pulmonary embolic disease remains one of the most challenging diagnoses to make clinically, and objective confirmation of the presence or absence of thromboembolism is important whenever the diagnosis is considered.

Pluralitas non est ponenda sine necessitate.
— William of Occam, 14th century

“What on earth is Saint’s Triad?” So asked C.F.M. Saint several decades ago about his own eponym. Saint, a South African surgeon, emphasized the importance of considering the possibility of multiple separate diseases in a patient whenever his or her history and the results of the physical examination were atypical of any single condition. The triad that bears his name is the association of hiatal hernia, gallbladder disease, and diverticulosis. There is no pathophysiological basis for the coexistence of these three diseases; that, perhaps, was his point. Saint emphasized that more than one disease may be responsible for a patient’s clinical signs and symptoms. This is, in fact, the same point made by the apocryphal Hickam, credited with Hickam’s dictum: “A patient can have as many diagnoses as he darn well pleases.” Because physicians are seeing an increasing number of patients with a multitude of acute and chronic illnesses, the views of Saint and Hickam warrant consideration in the practice of modern medicine. Neither name, however, is as well known as that of William Osler, who is credited with applying the teaching of Occam to clinical medicine.

In the 14th century, William of Occam stated, “Plurality must not be posited without necessity.” A subsequent version of this statement was expressed as “Among competing hypotheses, favor the simplest one” — hence the term “Occam’s razor.” As the discussant points out, parsimony of diagnosis is an important standard in modern medicine; however, this principle can fail us. As the population continues to age — and as diagnostic studies increase in number and sophistication — the dulling of Occam’s razor is certain to continue. Indeed, this patient’s dyspnea had two distinct causes: pulmonary embolism and P. carinii pneumonia.

Why Hickam’s dictum in this particular case? This patient’s inflammatory arthritis required that she receive immunosuppressive therapy to control her symptoms. Chronic immunosuppression then placed her at increased risk for an opportunistic infection. P. carinii pneumonia then led to shortness of breath, fever, and lethargy that may have prompted her to reduce her physical activity, a change that, in turn, may have predisposed her to the development
of venous thromboembolism. Though only a hypothesis, this line of reasoning provides one explanation for her risks of multiple, seemingly unrelated diseases.

How should we balance the competing philosophies of Occam and Saint in the modern era? As people live longer and as the prevalence of disease increases, physicians must anticipate the greater likelihood of multiple diagnoses. A recent population-based study concluded that in patients 65 years of age or older who have chronic medical diseases and receive prescription medications free of charge, additional unrelated disorders are undertreated, as compared with the same disorders in patients who do not have another underlying medical condition. An accompanying editorial suggested that this finding may be related to the application of Occam’s principle of parsimony by the health care providers. If physicians consider the tenets of Saint and Hickam as well, patients may receive better care.

Although the view of Saint is useful for complicated medical cases, can the diagnostic parsimony that medicine has adhered to for so many years be abandoned? Will physicians err by assigning, for example, separate diagnoses of arthritis, dermatitis, and kidney disease to a patient who has systemic lupus erythematosus? It is clear that in patient care we cannot embrace either principle exclusively; rather, we should keep the views of both Occam and Saint in mind.

Supported by a Career Development Award from the Health Services Research and Development Program of the Department of Veterans Affairs and a Patient Safety Developmental Center Grant (P20-HS11540) from the Agency for Healthcare Research and Quality (both to Dr. Saint).

REFERENCES