CLINICAL PRACTICE

*Exercises in Clinical Reasoning***More than Skin Deep**

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In this series, a clinician extemporaneously discussed the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (italics) is integrated throughout the discussion.

Clinical Information: A 53-year-old Puerto Rican woman presented to the Emergency Department with facial swelling, erythema, pain and high fever of 3 weeks duration. The swelling was first localized to the left cheek, then spread to involve the right side of her face, including the right lower eyelid. She had a severe headache, dizziness, photophobia, diplopia, and pain with extraocular movement. She denied any preceding skin eruption, breakdown or facial trauma.

Clinician. Periorbital and facial edema accompanied by fever, pain and localized erythema is most commonly associated with infection. Infections of the facial tissues and orbital region may arise from streptococcal and staphylococcal organisms, or less commonly, from atypical pathogens, including actinomycosis or mycobacteria, in the context of a penetrating injury or underlying immunosuppression. An intrathoracic malignancy associated with a superior vena cava syndrome, angioedema, or rheumatologic disorder may produce orbital swelling, and need be considered. Other less common non-infectious etiologies of periorbital edema include anasarca arising from nephrotic syndrome, cirrhosis, congestive heart failure and protein-losing enteropathy.

Diagnostic Reasoning. Problem representation is the way in which salient features of a case are summarized, and is

used to formulate a differential diagnosis. In this case, the problem representation is a 53-year-old female with subacute facial edema and fever.

The patient reported being in good health until a year earlier, when she developed intense episodes of generalized pruritus, occurring three times weekly over 8 months, without associated rash or wheal. The pruritus resolved spontaneously. No new medications were prescribed during that time.

The sustained period of pruritus might signal a systemic disorder, particularly a malignancy, specifically Hodgkin's disease, non-Hodgkin's lymphoma, polycythemia rubra vera, or a paraproteinemic state. These disorders, along with biliary obstruction, may be associated with pruritus. Perhaps immunosuppression from an occult malignancy could enhance susceptibility to a facial infection, or produce a locally infiltrative process.

Her family history was significant only for coronary artery disease and hypercholesterolemia. She had three healthy adult children, worked as a legal assistant and was in a monogamous heterosexual relationship. She denied alcohol, tobacco, or illicit drug use. Originally from Puerto Rico, she immigrated to the East Coast of the United States at age 33. There was no foreign travel, environmental or animal exposures.

The patient's temperature was 38.2 °C (100.8 °F), and she had a heart rate of 68 beats per minute, blood pressure of 91/57 mmHg, respiratory rate of 15 breaths per minute and oxygen saturation of 94 % while breathing ambient air. Physical examination demonstrated prominent periorbital, non-pitting, firm edema with distinct subcutaneous nodules, more prominently affecting the right face, involving the right upper and lower eyelids, impairing full opening of the right eye. Mild hyperemia of the conjunctivae was localized to the left eye. Pupils were equal and reactive to light. There was no thyromegaly or cervical lymphadenopathy. Oropharynx revealed normal healthy dentition. Tongue was midline and mobile. Oral and buccal mucosa were pink and moist. Uvula was midline. The floor of mouth showed no mass upon palpation. The lungs were clear to auscultation; the first and second heart sounds were normal, with regular rhythm, and without murmurs, rubs or gallops. Her abdomen was soft without organo-

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megaly. Extremities were notable for 2+ pulses. There were no rashes on the trunk or extremities, and no joint tenderness or effusion was present.

Given the prominent periorbital sites of facial induration, the photophobia and pain with eye movement, ophthalmologic evaluation is appropriate. Photophobia raises concern for uveitis or scleritis, with possible ocular involvement in a multisystem disease. Orbital imaging may define ocular muscle inflammation or infiltration, as a potential cause of pain with extraocular motion.

Bedside ophthalmologic consultation was pursued, revealing normal visual acuity and extraocular movements. There was no proptosis or facial droop. Dilated eye exam revealed flat optic nerve heads, bilaterally, with a normal cup-to-disc ratio, normal macula, and normal caliber retinal vessels, without evidence of ocular inflammation.

Comprehensive metabolic panel was within normal limits, except for a mild elevation in alkaline phosphatase of 165 U/L (normal range [NR] 30–120). Protein and albumin were 7.0 and 3.9 g/dL, respectively, without evidence of a gamma gap. The white blood cell count was 10,630 cells/mm³ with 81 % neutrophils; hemoglobin and hematocrit were 12.6 and 38.3 %, respectively, with a platelet count of 355,000; ESR was elevated at 99 mm/hr (NR 4–30) and CRP was 12.0 mg/dL (NR 0–0.5). Urinalysis was normal. Chest x-ray demonstrated normal heart size, without infiltrate, effusion, or mediastinal enlargement. Computed tomography of the face and orbits, with intravenous contrast, demonstrated diffuse edema and stranding affecting the periorbital, premaxillary and submandibular soft tissues, consistent with facial and periorbital cellulitis with mild extension to the posterior septal fat (Fig. 1). The extraocular

muscles were unremarkable. There was no orbital pseudotumor or evidence of sinus disease.

Most notable are the patient's facial exam and elevated inflammatory markers. Periorbital and orbital cellulitis are common causes of inflammatory changes near the eye. Periorbital cellulitis, also called preseptal cellulitis, is a localizing infection to the soft tissues anterior to the septum. The septum is a thin, fibrous membrane that separates superficial and deep ocular structures. Orbital cellulitis is defined by extension of infection posterior to the septum. Symptoms include proptosis, ophthalmoplegia and diplopia due to involvement of the orbital muscles and fat. Orbital cellulitis is highly morbid, so it is important to rule out and treat early with broad-spectrum antibiotics. Complications include subperiosteal and orbital abscesses, meningitis and septic cavernous sinus thrombosis. If a patient fails to improve, further investigation with lumbar puncture and additional imaging should be pursued.

Whereas the differential diagnosis remains quite broad, the clinician is faced with a need to prioritize the diagnostic work-up and empiric therapeutic interventions. Specifically, the clinician grapples with the sense of urgency to identify acute infectious disorders, that if unrecognized and left untreated, could have devastating consequences, with possible extension to the central nervous system, producing a meningitis. When this consideration weighs sufficiently heavily on the clinician's thought process, the threshold is met to pursue examination of the cerebrospinal fluid. Antimicrobial therapy, to prevent infectious complications, is promptly implemented.

Treatment with intravenous vancomycin, cefepime and metronidazole for periorbital cellulitis was initiated. Given the persistent headache, high fever and photophobia, lumbar puncture was performed and was unremarkable, yielding 1 WBC/mm³. Cerebrospinal fluid [CSF] protein and glucose were 14 mg/dL and 73 mg/dL, respectively; immunologic studies were negative for enterovirus, cryptococcus, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, and varicella zoster virus.

The patient initially defervesced after 48 h of intravenous antibiotics, but the periorbital and facial swelling only minimally improved. Thereafter, during the first week of hospitalization, facial induration and erythema waxed and waned in intensity over the malar surface of both cheeks, extending to the jaw line, infraorbital margins and to the nasal arch and glabella. The fever recurred with a peak value of 39 °C [102.2 °F], with persistently negative blood cultures.

With only short-lived therapeutic benefit from broad-spectrum antibacterial medications, recurrence of fever and unchanged facial induration, efforts to consider alternate etiologic processes need be revisited. Laboratory work-up to assess for other causes of fever, including infectious, malignant or rheumatologic causes, would be helpful. One would ascertain whether blood, urine and cerebrospinal fluid samples

Figure 1. Facial computed tomography (CT) scan of the orbit, with intravenous contrast, demonstrating diffuse edema and stranding affecting the periorbital, premaxillary and submandibular soft tissues.

show growth of bacterial or other infectious organisms. The facial and orbital tissues could be re-imaged to determine if the indurated sites have responded to empiric antibiotic treatment and receded, versus advanced in distribution.

Tuberculin skin testing was negative. MRI/MRA imaging of the brain and orbits with gadolinium demonstrated extensive bilateral facial and superior orbital inflammatory changes, with post-septal involvement along the inferior aspect of the orbits; there was no evidence of cavernous sinus thrombosis. Negative serologic studies included antinuclear antibody, rheumatoid factor, Jo-1, Ro, La, and Scl-70 antibodies. C-antineutrophil cytoplasmic antibody [ANCA] titer was borderline positive at 1:10; proteinase-3 was weakly positive at 24.8 units. LDH was minimally elevated at 246 U/L (NR 122–220). In addition, the prior CSF, blood, and urine cultures returned negative for bacterial, mycobacterial, and fungal organisms.

Having considered each of the posited disease processes, which can be discarded and which ought to be further investigated? An acute bacterial process seems less tenable. In the presence of an immunosuppressed state, fungal processes still need be considered. The lack of orbital bone inflammation (e.g. osteitis) or erosive features, based on the computed tomography (CT) imaging of the orbits [Fig. 1] and follow-up MRI 1 week later, diminish evidence for Wegener's granulomatosis. Importantly, sinus opacification or pulmonary parenchymal involvement on the admission chest x-ray, nor glomerulonephritis or aseptic meningitis are absent, otherwise characteristic of Wegener's inflammation. A broad-based serologic search for autoimmune rheumatologic disorders, including systemic lupus erythematosus, rheumatoid arthritis, anti-synthetase syndrome, scleroderma and ANCA-associated vasculitis is unrevealing. Further consideration to a possible occult malignancy, particularly of a lymphoproliferative variety, that may contribute to fever and infiltration of facial soft tissues and pruritis seems warranted. A simple and fundamental method to accrue more relevant insight into the disease process might be gleaned by revisiting the clinical history.

After recognizing that the patient's progress has plateaued, the clinician realizes he/she needs to change gears to broaden the differential. The initial approach emphasized an urgency to identify and treat an acute life threatening illness; attention is now turned to a more subacute elusive process. Either a new strategy or modification of the existing evaluative strategy is necessary to re-energize the patient's work-up, one that will re-examine the clinical course and expand the explanations being considered. Such an approach is incumbent upon the clinician after recognizing an impasse in clinical progress, to avoid getting 'stuck in neutral.'

Six weeks prior to admission, the patient had noted unilateral right ankle pain and swelling. Similar symptoms

affected the left ankle shortly thereafter. An evaluation at an Urgent Care Facility yielded a diagnosis of Achilles tendonitis. A ten-day course of prednisone, beginning at 30 mg daily, resulted in complete resolution of these symptoms. However, 1 week later, she noted malaise, fever ranging from 37.8 °C – 40 °C (100 °F - 104 °F), chills, anorexia, and the onset of facial swelling and erythema. At an outside Emergency Department, an allergic reaction was diagnosed and a 5-day course of 60 mg daily prednisone prescribed. Her facial swelling initially improved, but recurred at the end of the steroid course.

One well-recognized challenge in clinical reasoning—applicable here to the detection of ankle pain and swelling—is the diagnostic tension created by the opposing positions of Occam's razor versus Hickam's dictum. Occam's razor denotes a principle that advances a single unifying diagnosis over multiple concomitant diagnoses to explain a patient's course; otherwise stated, Occam (a 14th century Franciscan friar) explicated that among competing hypotheses, the simplest explanation be favored. In contrast, the principle of Hickam's dictum (attributed to Dr. John B. Hickam, Chair of the Department of Medicine at the University of Indiana from 1958 to 1970), states that multiple different explanations may account for a patient's various symptoms. Moreover, the coexistence of several common disorders, on a probability basis, is more likely than the emergence of a rare single-unifying multisystem disease. Presently, ankle joint pain is uncovered that closely preceded in time the onset of facial pain and induration. The clinician ponders whether the musculoskeletal system is similarly involved in a single multisystem disease, as Occam's razor might advocate. Alternately, might the ankle pain and swelling have been true, true and unrelated, as proponents of Hickam's dictum would argue?

In addition to the invoked diagnosis of Achilles tendinitis, the ankle process might have been an ankle arthritis or peri-arthritis. Lower extremity arthritis and arthralgias may occur with occult vasculitis. Additional rheumatic etiologies to consider in the differential diagnosis of ankle pain and swelling include inflammatory bowel disease-associated arthritis, reactive arthritis, psoriatic arthritis and rheumatoid arthritis. Moreover, inflammation in and around the ankle joint is well described as ankle peri-arthritis in the context of Lofgren's syndrome, a variant of sarcoidosis.⁵ Ankle region inflammation may also be observed with disseminated infections, including disseminated mycobacterial or fungal disorders and endocarditis.

By returning to the bedside, additional valuable clinical information has been gleaned, and an effective lateral thinking strategy adopted, by which the differential diagnosis of further alternatives has been expanded. To provide structure for continued hypothesis generation, the clinician separates his/her thought process into two main categories: malignant and rheumatologic.

The detection of a new element in the patient's history raises a key question—is the ankle process of 6 weeks prior to hospitalization, the smoking gun, an indispensable clue that might unravel the entire case, or simply a red herring? The history of ankle region inflammation, including the therapeutic response to corticosteroid medication, raises suspicion for a possible diagnosis of sarcoidosis. However, the prior history of pruritis still lends credibility to the notion of an occult lymphoma. Further radiologic evaluation of the chest, abdomen and pelvis seems warranted to evaluate for possible adenopathy or occult mass lesion.

CT scan of the chest, abdomen and pelvis demonstrated extensive mediastinal lymphadenopathy with paratracheal, hilar and subcarinal lymph nodes measuring up to 1.7 cm (Fig. 2). Minimal right lower lobe scarring and trace bilateral pleural effusions were present. Abdomen and pelvis images were unremarkable.

Prominent mediastinal adenopathy may be seen in neoplastic, inflammatory and infectious disorders. Specifically, mediastinal lymphadenopathy may be observed with Hodgkin's and non-Hodgkin's lymphoma, sarcoidosis, Wegener's granulomatosis and other rheumatologic disorders, and with disseminated tuberculosis and mycoses.

Deep skin biopsy of the indurated facial tissue revealed a lobular mixed inflammatory infiltrate of lymphocytes, histiocytes, neutrophils, and eosinophils with scant multinucleation of histiocytes within the subcutaneous fat, consistent with a panniculitis (Fig. 3). Special stains were negative for organisms; a malignant infiltrate was not detected.

Adenopathy together with histologic evidence of a facial panniculitis is an uncommon phenotype, which continues to raise consideration for both sarcoidosis and lymphoma as the underlying disease process. The prior

Figure 2. CT scan of the chest, revealing extensive mediastinal lymphadenopathy (red arrows).

Figure 3. Deep skin biopsy (with arrows) depicting a lobular mixed inflammatory infiltrate composed of lymphocytes, histiocytes, neutrophils, and eosinophils with scant multinucleation of histiocytes within the subcutaneous fat, consistent with a panniculitis.

history of ankle peri-arthritis supports a diagnosis of sarcoidosis. However, the antecedent history of generalized pruritis may still augur the presence of an occult malignancy. Further, pruritis and elevated alkaline phosphatase may be explained by the early phase of chronic cholestasis, rarely seen in sarcoidosis. Pursuit of histologic clarification is warranted.

Endobronchial ultrasound-guided transbronchial needle aspiration of a right paratracheal lymph node yielded predominantly blood, minimal lymphoid tissue, and inconclusive cytopathology. Subsequent mediastinoscopy with lymph node biopsy demonstrated multiple noncaseating granulomas, distortion of lymph node architecture, and no evidence of lymphoma (Fig. 4), furnishing strong histologic support for a diagnosis of sarcoidosis. Special

Figure 4. Histologic examination of mediastinal node with evidence of multiple noncaseating granulomas (indicated by arrows), with distortion of lymph node architecture, and no evidence of lymphoma.

stains for fungus and acid fast bacteria were negative. Immunohistochemical stains for CD20 and CD3 showed a normal distribution of B and T cells, respectively. Given these pathologic findings, a diagnosis of sarcoidosis was deemed most likely. She began treatment with 40 mg of daily prednisone, and 200 mg of hydroxychloroquine twice daily. During most of the subsequent 6-month period she was maintained on 20 mg of daily prednisone, with additional use of intralesional triamcinolone and oral minocycline. At dermatology follow-up 8 months into this regimen, her facial process was described as being substantially less indurated.

DISCUSSION

In the present case, confronted with a woman presenting with facial swelling, indurated skin and a high spiking fever, the reflexive response was to quickly entertain an infectious process, and to intervene without delay with potent broad-spectrum antimicrobial therapy. Realizing the potentially catastrophic consequences from uncontrolled extension of a bacterial facial infection into the central nervous system, the appropriate response was neuroradiology imaging and prompt initiation of antibiotic treatment.

When the initial diagnostic formulation became increasingly less tenable, with waning clinical support, particularly the lack of a therapeutic response, a number of factors further compounded the situation, and impaired forward movement. First, the disease phenotype was an entity the treating physician had not previously encountered, and neither prior didactic nor clinical experience had prepared him/her for what to do next in this particular set of clinical circumstances. Second, there is a tendency to only modestly modify an existing treatment regimen (e.g. the combination of antibiotic medications) as one assesses, and then reassesses, for a therapeutic response, rather than initiate an entirely new approach. The third factor is inertia. It takes significant effort to go back to the beginning and revisit the entirety of the History of the Present Illness to seek out clues that may have previously gone unrecognized, yielding new insight into the disease process.

This process of lateral thinking prompts the clinician to go back to the drawing board and the pivotal question, "What else might this be?"² This effort revealed the onset of first unilateral, then bilateral, ankle pain and swelling, at the outset of the illness, 6 weeks prior to the hospitalization and 3 weeks prior to the facial swelling. As a general principle, even when history-taking and examination are comprehensive, an impasse in clinical progress still necessitates a return to the drawing board, on a piece of paper or literally on the board in the house-staff work room, to tally up the elements of the history, examination, laboratory and radiologic data, as measured by the support they furnish to the differential diagnosis. In addition, an additional option during a clinical

impasse is to explore the input of a consultant previously uninvolved with the case, to bring a fresh set of hands (and eyes and ears) to re-evaluate the patient from scratch.

What each of the above proposed solutions has in common is a concerted effort to undertake renewed lateral thinking.² This problem solving strategy involves the clinician taking a step back and asking him/herself what may have been overlooked or previously considered unrelated. In simple terms, an effective lateral thinking strategy poses the fundamental question: "What am I missing?" The renewed effort to dig deeper, to gather additional elements of the patient history, revisit the examination, and refocus the diagnostic search, ultimately proved to be vitally important to untangle this patient's course.

CLINICAL TEACHING POINTS

1. Sarcoidosis is a multisystem disease of unknown etiology with histopathologic evidence of noncaseating epithelioid granulomas in one or more affected organs.⁴
2. Exclusion of alternate causes of granulomatous inflammation, such as infectious (e.g. tuberculosis, disseminated mycosis), malignant (e.g. lymphoma) or other rheumatic etiologies (e.g. granulomatous vasculitis), is a prerequisite to the diagnosis of sarcoidosis.
3. Sarcoidosis commonly affects the lungs, skin and eyes. Cutaneous manifestations include erythema nodosum, lupus pernio, and sarcoid-associated panniculitis affecting the extremities, hands and face.^{1,3,4}
4. Lofgren's syndrome, with its classic triad of hilar adenopathy, erythema nodosum and periarticular ankle inflammation or Heerfordt's syndrome, with uveitis, parotitis, fever, and facial nerve palsy⁵ are distinct syndromes that should heighten a clinician's suspicion for sarcoidosis.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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REFERENCES

1. **Ahmed I, Harshad SR.** Subcutaneous sarcoidosis: is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? *J Am Acad Dermatol.* 2006;54:55-60.
2. **Croskerry P.** The importance of cognitive errors in diagnosis and strategies to minimize them. *Acad Med.* 2003;78:775-80.
3. **Fernandez-Faith E, McDonnell J.** Cutaneous sarcoidosis: differential diagnosis. *Clin Dermatol.* 2007;25:276-87.
4. **Iannuzzi MC, Rybicki BA, Teirstein AS.** Sarcoidosis. *N Engl J Med.* 2007;357:2153-65.
5. **Lofgren S.** Primary pulmonary sarcoidosis. I. Early signs and symptoms. *Acta Med Scand.* 1953;145:424-31.