PATHOVIGNETTE RHEUM/IMMUNE

CC: " I have this rash, I'm so tired, and my joints ache"

History of present illness: Tabatha, a 38-year-old female patient, presents to the NP clinic complaining of a rash x 2 weeks. She reports that appears on her nose and cheeks and gets more pronounced when she is out in the sun. She reports it is painful and itchy at times. She also noticed that her hair has been falling out in patches. Other complaints include fatigue, and she needs at least one nap a day, usually in the afternoon. Initially she thought it was because she is a mother of 2 busy toddlers. She has some mild aches in her fingers and elbows, but she attributes it to "getting older". Her medical history is noncontributory as she has never been ill before but gets occasional aches and pains and heartburn. She medicates for these maladies by taking an occasional ibuprofen and antacid. She has no other prescription or OTC medications or supplements. She does not smoke or drink ETOH (never). Other ROS reveals a 10 lb. weight loss over the past few months (unintentional), some mild chest pains (these are intermittent and last for a few minutes), and a "little" shortness of breath (also intermittent and only last for a few minutes).

Medications: OTC ibuprofen and antacids (TUMS ®) as needed -not often, once, or twice every few months.

Allergies: none

PMHX: undiagnosed joint pains (played sports in high school), undiagnosed heartburn after certain foods (when she eats Mexican-style foods). G2P2, no complications w/ either pregnancy. Breastfed both infants x 1 year. Age of pregnancies 35, 37 -genetic testing performed and no issues.

Social: married, stay at home mother of 2 toddlers at home; nonsmoker, nondrinker, no illicit drugs. Went to college and has a Bachelor of Science in chemistry. Exercises as she can fit it in with 2 toddlers. Eats very healthy-almost "vegan" and organic foods only, adds occasional chicken or fish (1-2 times week). Drinks only water and caffeine intake is through tea-low, only one tea per day.

Family History: denies any known genetic issues in the family. MGM (66) alive, hypothyroidism; MGF (70) CHF, HTN, HLD; PGM (76) HTN, HLD, AFIB; PGF (DEC) pancreatic cancer, hyperthyroidism

PHYSICAL EXAM: VS: BP 112/70 HR: 79 RR 19/unlabored temp 37.8*

CONSTITUTIONAL: Well nourished, well-developed American Indian female with NAD. Appears tired and weak.

HEENT: PEERLA, EOM, no obvious papilledema, +anterior and posterior cervical lymphadenopathy; no thyromegaly, no sinus tenderness on maxillary sinuses B/L; no lesions or exudate

SKIN: rash noted on nasal bridge and cheeks; none on nasolabial folds; no other lesions or rashes noted on external skin.

CHEST: RRR s1s2 no MGR

RESP: Lungs CTA, non-labored w/ equal chest rise

ABDOMEN: NT/ND, BSX4 no palpable mass or organomegaly, no adiposity.

NEUROLOGIC: AAOx4, CNII-XII intact. Strength B/L U/L 5/5; DTR +2 symmetric no gait disturbance, heel to shin with no difficulty

PSYCHE: affect normal, interactive with good eye contact.

LABS/IMAGING:

MRI brain negative (no lesions, masses, or areas of infarct)

CRP 30; ESR 25; ANA 900:1 homogenous pattern, smith antigen +; U/A +proteinuria

Part #1: Read the Pathovignette and interpret all the high yield items within the brief that are important (s/sx, epidemiology, labs etc.), this will lead you to a diagnosis.

What do you think the diagnosis is? _____

Part #2 Now look up the disease/diagnosis (Emedicine, your book, etc.) Answer the questions below.

Etiology. What is the etiology of this presentation? What are ALL the associated etiologies with the disease?

Epidemiology. What characteristics are present with this presentation? What OTHER epidemiological characteristics are associated with this disease, meaning WHO ELSE would likely get it and at what prevalence/incidence?

Risk Factors. What risk factors are present in this presentation?

Classic Presentation. What clinical sign, symptoms and labs are present in this presentation? These are pertinent (+) positives. What clinical sign, symptoms and labs are NOT present but are associated with this disease presentation? These are pertinent (-) negatives.

Differential diagnosis. Choose 3 ***other*** diseases that could possibly present this way. Then you will decide how you can rule these in or out by interpreting labs, presenting symptoms or signs, or any other key presenting clues that lead to the other diagnosis.

DDX #1 _____(disease state)

I can rule this in/out by:

DDX #2 _____disease state)

I can rule this in/out by:

DDX #3_____(disease state)

I can rule this in/out by:

Pathophysiology. Describe how this disease starts at the cellular level and progresses to a disease state.

What are the mechanisms behind how this disease starts?

What cellular dysregulation or dysfunction is the basis for how this disease progresses?

What tissues are more likely to have evidence of immune complex deposition?

How do you tie the labs results in with the pathogenesis?

After you have answered all the questions, review your answers, and see if the case "makes sense" to you. The clues are very consistent with the expected diagnosis, and it should "make sense" after you complete all the steps. If you did not "get it" the diagnosis right (check the answer sheet), then

go back and critically analyze your thought process and see where you went wrong. Did you include the expected right diagnosis in your differential ?? If you did then you were on the right path, just a little off in interpreting the information. If you did not put it as the top differential, then your health detective skills (pathophysiology, etiology, epidemiology, risk factors, presentation, labs/imaging) need a little fine tuning. These cases are all "classic presentations" of the expected diagnosis with a few confounders. It should be an "easy" diagnosis by someone taking advanced pathophysiology. If you have issues, meet with the professor, and have a 1:1 session to work through any of the possible issues and complete one of these together.

DIAGNOSIS IS: SYSTEMIC LUPUS ERYTHEMOUS

ANSWERS AND RATIONALE W/ MEI SHEET (MINIMAL EXPECTED INFORMATION) FOR SYSTEMIC LUPUS ERYTHEMOUS PATHOVIGNETTE

The information below is the minimal expected information (MEI) you should memorize for SLE. This information should be easy to recall for a practicing NP. Fill in the blanks above with the information below and that is how you ANSWER ALL THE QUESTIONS. Additionally, within the case there are clues, below is a copy of the pathovignette with the high yield information highlighted, so you can figure out this case. For these cases (pathovignettes), there is no discussion of pharmacotherapeutics, they would be the focus of the pharmvignette.

1) SLE (SYSTEMIC LUPUS ERYTHEMATOUS)
    a) Define: Chronic systemic autoimmune dz
    b) antigen-driven immune-mediated disease
        i) characterized by: IgG antibodies to double-stranded (ds) DNA & nuclear proteins
        ii) Type III hypersensitivity reaction
        iii) 5-yr survival is >90%
        iv) renal failure, infection, and accelerated cv dz are often cause of death
2) Patho: autoantibodies cause a defect in apoptosis >>> that causes increased cell death = disturbance in immune tolerance/loss of tolerance (autoimmune). There is a redistribution of cellular antigens during necrosis/apoptosis, and this leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. ("Systemic Lupus Erythematosus (SLE): Practice Essentials …") Both central or peripheral tolerance is lost on self-reactive lymphocytes (Central tolerance (thymus)= t-cell apoptosis and bone marrow (BM) generation of regulatory T cells. Peripheral tolerance leads to anergy, or apoptosis of T/B cells. Autoimmunity is suppressed by regulatory T-cell and produce anti-inflammatory cytokines (IL-10 and TGF-b). Next, dysregulated lymphocytes target intracellular antigens. The apoptotic cell debris allows for the persistence of antigen and there is defective clearance. ("Systemic Lupus Erythematosus (SLE): Practice Essentials …") Also, there is immune complex production. T cells show defects in both signaling and effector function (they secrete less interleukin IL-2 and changes in the CD3 signaling subunits, CD8 cytotoxicity; T-regulatory, B-cell help; migration; and adhesion). Circulating immune complexes (IgG) that form with antigens in various tissues

or the direct effects of antibodies to cell surface components. Immune complexes form in microvasculature, leading to complement activation and inflammation. Antibody-antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed by demonstration of complexes of nuclear antigens such as DNA (=dsDNA), immunoglobulins, and complement proteins at these sites. ("Systemic Lupus Erythematosus (SLE): Practice Essentials ...") Helper (CD4+) T cells are increased. A lack of immune tolerance is observed in animal lupus models. Reports pointing to important roles of interferon-alpha, transcription factors, and signaling variations also point to a central role for neutrophils.

3) Etiology
    i) Unknown. Theories include ?hormonal factors, Drugs, Noninfectious/infectious, Viruses EBV
4) Risk factors
    i) Exposure to EBV, enterococcus gallinarum
    ii) Vitamin D def. pregnancy, silica dust, cigarette smoking, estrogen use in PMP (postmenopausal patient)
    iii) PROTECTIVE: breastfeeding,
5) Epidemiology
    i) Ages 15-45; 12: 1 female to male; after 45 y/o 2:1 ratio
        (1) >90% of cases occur in females-at childbearing age
        (2) Age of onset usually around 20-30 years (20% dx at these ages)
    ii) 1.5 million cases. Pooled prevalence per 72.8/100000 (five national lupus registries funded by the Centers for Disease Control and Prevention (CDC)
    iii) incidence estimates at roughly 5.1 per 100,000 person-years (95% CI 4.6 to 5.6) (five national lupus registries funded by the Centers for Disease Control and Prevention (CDC)
    iv) Ethnicity: Indigenous/Alaskan natives >>Hispanic >> Black >> Asian/ White
        (1) Severity of disease increases in Black and Asian descent
6) S/Sx (signs and symptoms *** classic presentation)
    i) Method: SLE has many s/sx, so an understanding of the clinical presentation is paramount to diagnosing the condition. The clinician should be familiar w/ the diagnostic criteria (EULAR) and recognize target organ damage for classification of this complex disease. If a patient is C/O at least 2 of these symptoms, then a workup is appropriate, ANA, and basic labs to prove any other possibilities (add to your differential possibilities)

ii) Rash ***(Malar rash- characterized by erythema over the cheeks and nasal bridge (but sparing the nasolabial folds), or Discoid rash- in sun-exposed areas but are plaque like in character, with follicular plugging and scarring.) w/ Photosensitivity (can be acute or chronic-may last 2 days)

iii) Fatigue/wt. loss or wt. changes/Fevers*** (lymphadenopathy may be found)

iv) Joint pain*** (arthralgias), muscle pain (myalgias) or arthritic pain (small joints of the hands, wrists, and knees (usually symmetrical, polyarticular). AVN (avascular necrosis seen in 44% of SLE R/T high dose steroid use)

v) Alopecia (patchy pattern of hair loss or present in temporal regions).

vi) Oral ulcers, any mucocutaneous manifestations (Raynaud phenomenon, Livedo reticularis, Panniculitis (lupus profundus), Bullous lesions, Vasculitic purpura, Telangiectasias, Urticaria

vii) Raynaud's' pleuritis, sicca (Sjogren's syndrome-dry mouth and dry eyes)

viii) Kidney^^^ (proteinuria, screat, urinary casts) most common visceral organ involved. +glomerular dz within 1 year, AKI and CKD may present with uremia and fluid overload. HTN or hematuria (think lupus nephritis); Edema (periorbital or peripheral regions), anasarca, and morning presacral edema upon arising from bed

ix) Neuropsychiatric -seizures and psychosis but also may include Acute confusional state, Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome), Anxiety disorder, Aseptic meningitis, Autonomic disorder, Cerebrovascular disease, Cognitive dysfunction, Cranial neuropathy, Demyelinating syndrome, HA, Mononeuropathy (single/multiplex), Mood disorders, Movement disorder (chorea), Myasthenia gravis, Myelopathy/Plexopathy, Polyneuropathy

x) Pulmonary manifestations- pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, and interstitial lung disease.

xi) Gastrointestinal- infectious causes (bacterial, viral [CMV]), nausea and dyspepsia

xii) Cardiac- pericarditis, vasculitis, myocarditis, heart failure, angina, CAD, antiphospholipid syndrome

xiii) Hematologic- leukopenia, lymphopenia, anemia, or thrombocytopenia, medication-related cytopenias. Immunosuppression may predispose persons with SLE to frequent infections

7) Differential Diagnosis

i) Method: Rule out drug-induced lupus (procainamide, isoniazid, and hydralazine most common, but include many others-see below). Lupus s/sx may coincide with other diseases, therefore ruling out other potential causes is paramount to making an astute diagnosis of SLE.

ii) Main (top10) DDX: Chronic Fatigue syndrome (r/o all other causes, diagnosis of exclusion); Behcet Syndrome (oral ulcers?, labs); dermatomyositis (r/o via rash specifics-Gottron's sign and muscle weakness); endocarditis (r/o ECG and CP); Fibromyalgia (r/o pain and clinical dx); HIV (r/o testing); hypothyroidism (r/o testing); IBD (r/u imaging and testing); Lyme disease (r/o serology and testing and HPI)

iii) Other DDX include Acute Pericarditis (CP presenting), antiphospholipid syndrome (thrombocytopenia presenting), autoimmune hepatobiliary disease, B-Cell Lymphoma (lymphadenopathy, cell dyscrasias presenting) FM (myalgias and arthralgias presenting)

8) Workup (see the TIMEOUT section)

i) Method: If a patient has C/O at least 2 of these symptoms, then a workup is appropriate, ANA is first initial testing ALONE, then if positive move on to basic labs to prove any other possibilities (add to your differential possibilities) and work up the rheum or connective tissue disorder. NP POV: if your patient is complaining of something work it up, you have a differential for a reason. If fatigue is a main complaint, that has such a wide etiology, so do not wait for a +ANA then do basics. Maybe they have anemia, or any of the other DDX, you could start working that up too. Do not go crazy as you need a reason to order labs, but within reason work it up.

ii) Labs

(1) CBC w/ diff (rule out anemia, eval for cytopenias)

(2) ESR, CRP (assess for inflammation-non-specific, if both severely elevated consider infectious process) ESR lags behind CRP-more of an acute phase reactant than ESR

(3) U/A(eval kidney), CMP-BUN/electrolyte/LFTs, spot protein/creatinine ratio, CKs, TSH (R/O thyroid); BC x2 (R/O endocarditis)

(4) PTT/Coags (check liver function and possible eval for Anti-phospholipid syndrome)

(5) complement levels -C3, C4, CH50, ANA (<320:1 is possible in normal population and non-specific, positive if 80:1, usually homogenous pattern- see below), dsDNA antibody (normal titre is 1:1 and correlates w/ disease activity), anti-Smith antibody; Anticardiolipin Antibody, Anti-ribonucleoprotein (Anti-RNP); Anti-Beta2-Glycoprotein1; Direct Coombs; RF and anticyclic citrullinated (anti-CCP R/O RA)

(6) Lyme serology, HIV serology

iii) Imaging/testing includes:

(1) ECG: R/O carditis

(2) X-rays-joints (little evidence of SLE); Chest Xray (assess for pleural effusion, PE, alveolar hemorrhage; monitor interstitial lung dz)

(3) CT SCAN- chest (assess for pleural effusion, PE, alveolar hemorrhage; monitor interstitial lung dz)

(4) MRI – brain (white matter changes, vasculitis, stroke. May be absent)

9) Prognosis/Complications

i) Highly variable disease pattern

(1) From benign to rapidly progressive disease

(2) Prognostic factors (EULAR)

(a) Clinical findings, diagnostic findings, immunologic results have certain indications if present (https://emedicine.medscape.com/article/332244-overview#a6)

(i) Clinical findings: neurologic, kidney, Skin lesions, arthritis, serositis,

(ii) Diagnostic study results: Anemia, thrombocytopenia, leukopenia, increased serum creatinine (sCreat) levels

(iii) Immunologic test results: Serum C3 and C4 concentration (which may be low), anti–double-stranded DNA (anti-dsDNA), anti-Ro/ Sjögren syndrome A (SSA), anti-La/Sjögren syndrome B (SSB), antiphospholipid (aPL), and anti-ribonucleoprotein (anti-RNP)

ii) Survival rates

(1) Reduced life expectancy 5yr./>90%; 10yr./ >90%; 15yr./ 80%

(a) Higher in those with mucocutaneous and MS issues

(b) Lower in those with kidney and CNS disease

(c) Mortality now R/T cardiovascular events or ADRs from immunosuppressive medications such a fatal infection from neutropenia.

(d) DM, HTN, HLD, bone issues, infections, and malignant comorbidities all increase mortality.

(2) Distinguish between disease activity and organ damage index

(a) Validated measure tools

(i) Systemic Lupus Activity Measure (SLAM)

(ii) SLEDAI

(iii) Lupus Activity Index (LAI)

(iv) European Consensus Lupus Activity Measurement (ECLAM)

(v) British Isles Lupus Activity Group (BILAG) Index

iii) Patient Education and Anticipatory Guidance

(1) Educate and inform on each medication, its' adherence, and ADRs; inform patient how to report/when to report r/t ADRs.

(2) Emphasize the importance of routine follow-up appointments for detection and control of SLE disease. Educate why and when to present to the clinic related to any new symptoms, including fever.

(3) Information, guidance, education, and prevention of heightened risks for infection.

(4) Information, guidance, education, and prevention of cardiovascular disease, HLD, BP goals for risk reduction of common comorbidities and complications.

(5) Educate on avoiding exposure to sunlight and UV light.

(6) Encourage vaccination, educate on non-live vaccines when disease state is stable.

(7) Offer and educate on smoking cessation (every visit if they smoke)

(8) For patients of childbearing potential, carefully plan pregnancies (inquire every visit for that population of childbearing ages).

TIMEOUT >>> UNDERSTANDING THE TESTING:

1. CBC count w/ differential -assess for leukopenia, lymphopenia, anemia, and thrombocytopenia.
2. Kidney Function-Urinalysis (U/A) and Creatinine assessment for kidney disease. Check LFTs which may be elevated (mild) in acute SLE. Creatine kinase levels may be elevated in myositis.
3. Serum antinuclear antibodies (ANAs). The antinuclear antibody (ANA) test can provide information about the type of autoimmune disease. ANA <320:1 is possible in normal population and non-specific, ANA is positive if >80:1 but considered a low titre. Can be elevated in any autoimmune disease and some infectious processes, such as hypothyroidism, RA. The pattern of the test can indicate the following:
    a. Homogeneous: the most common pattern, entire nucleus is stained with ANA, indicative of any autoimmune disease, but more specifically, lupus (systemic) or Sjögren's syndrome.
    b. Peripheral: exclusive to systemic lupus; the edges of the nucleus in a shaggy appearance are fluorescent. This pattern is almost exclusive to systemic lupus.
    c. Speckled: Fine, coarse speckles throughout the nucleus. may indicate various diseases, including lupus and Sjögren's syndrome.
    d. Centromere: staining is present along the chromosomes; may indicate scleroderma.
4. Immune- antibodies to (1) double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE. **(EULAR 6 points for one positive**)

5. Inflammatory markers- ESR and CRP (elevated). The level of ESR may not "fit" and relatively normal CRP level (if both are markedly elevated, suspect infectious process).
6. Complement (C3 and C4) levels are depressed in patients with active SLE as a result of consumption by immune complex–induced inflammation. **(Low C3 or Low C4 =2 pts/ Low C3 and Low C4 =EULAR 4 pts)**
7. Spot urine for protein/creatinine ratio. This will be used to eval and assess for any proteinuria, casts. Guidelines state (2019 ACR) >0.5 g/day spot protein/creatinine ratio greater than can substitute for the 24-hour protein measurement and that an active urinary sediment (defined as > 5 RBCs/hpf; > 5 WBCs/hpf; or cellular casts.

Medications that can impede Lupus testing or cause drug induced lupus: PTU and methimazole, griseofulvin, quinidine, primidone, phenytoin, methyldopa, penicillin, ethosuximide, chlorpromazine, mephenytoin, and carbamazepine

Notes	Autoantibody Tests for SLE	pts
Initial testing	***ANA:** Screening test; sensitivity 95%; not diagnostic without clinical features. Titer of at least 1:80	
Confirmatory testing	***Anti-dsDNA**: High specificity; sensitivity 70%; disease activity.	**6**
Confirmatory testing	***Anti-Sm:** Most specific antibody for SLE; only 30-40% sensitivity. SLE-specific antibodies	**6**
Neonatal Lupus	**Anti-SSA (Ro) or Anti-SSB (La):** associated with neonatal lupus	
Antiphospholipid antibodies	**Anticardiolipin:** screen for antiphospholipid antibody syndrome	**2**
Antiphospholipid antibodies	**Lupus anticoagulant:** Multiple tests (direct Russell viper venom test) to screen for inhibitors in the clotting cascade in antiphospholipid antibody syndrome	**2**
Drug-induced Lupus	**Anti-histone**: Drug-induced lupus (procainamide or hydralazine); p-ANCA–positive in minocycline-induced drug-induced lupus.	
	Direct Coombs test: + antibodies on RBCs	
	Anti-RNP: indicative of mixed connective-tissue disease/ overlap of scleroderma, SLE, and myositis.	

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CRP 30; ESR 25; ANA 300:1 homogenous pattern, smith antigen +; U/A +proteinuria

Contribute to the diagnosis -presentation clues

Contribute to the differential-possible other presentation clues

Protective clues for the diagnosis-risk reduction clues ??add to the differential

Resources used in making this pathovignette include:

Various sources are paraphrased and combined to provide most up to date information

Dipiro, T., & Talbert, R. (2019). Pharmacotherapy-A pathophysiological Approach 10th ed.

Epocrates (various topics)

FamilyPracticeNotebook.com (various topics)

https://fpnotebook.com/Rheum/Diffuse/SystmcLpsErythmts.htm

https://emedicine.medscape.com/article/332244-workup#c8

Up to date (various topics)

Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers -5th ed.