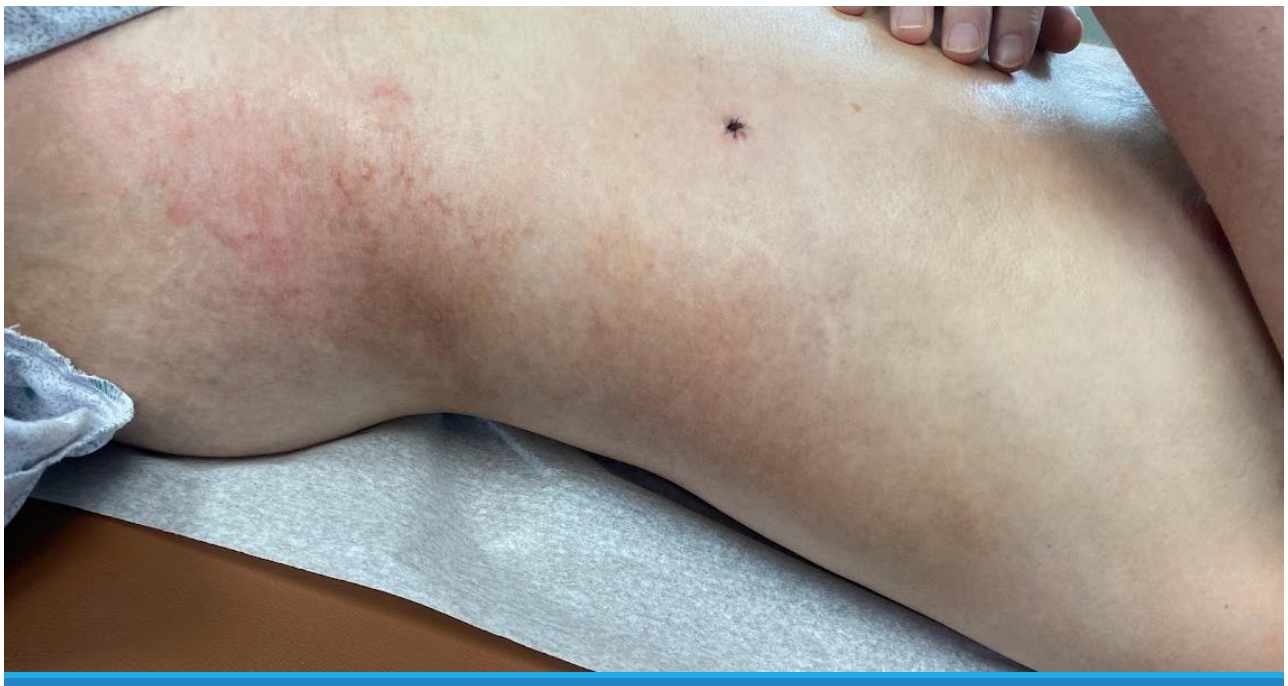
Eosinophilic Fasciitis involving the trunk—crucial clues to distinguish from scleredema and scleroderma

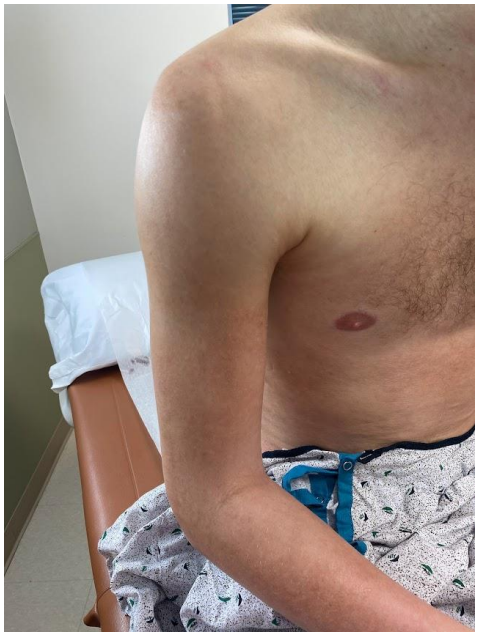
ANNIE JIN, MD PGY4

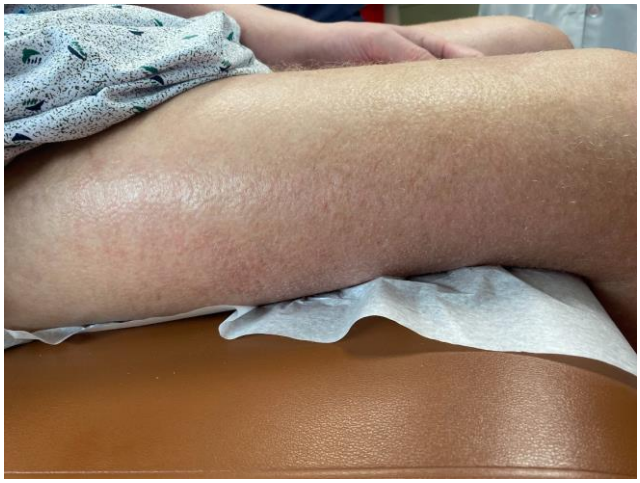
TEMPLE UNIVERSITY LEWIS KATZ SCHOOL OF MEDICINE

1

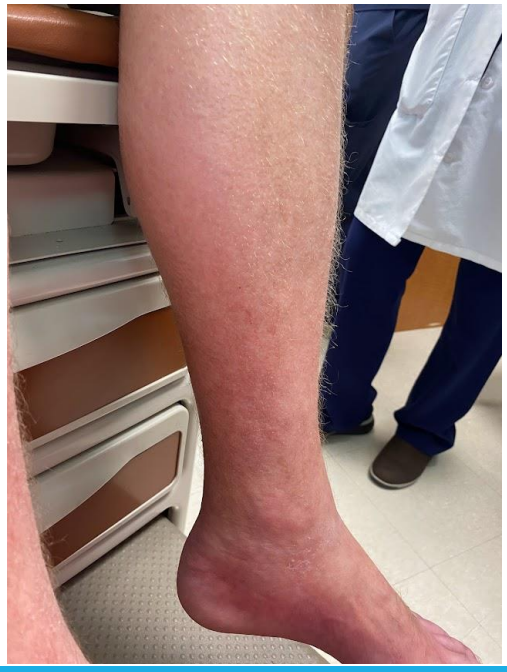


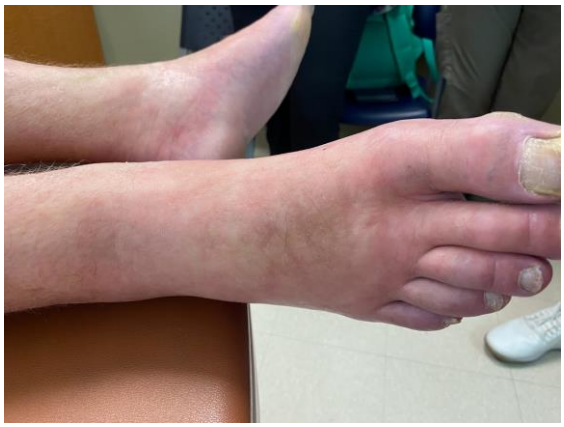
2



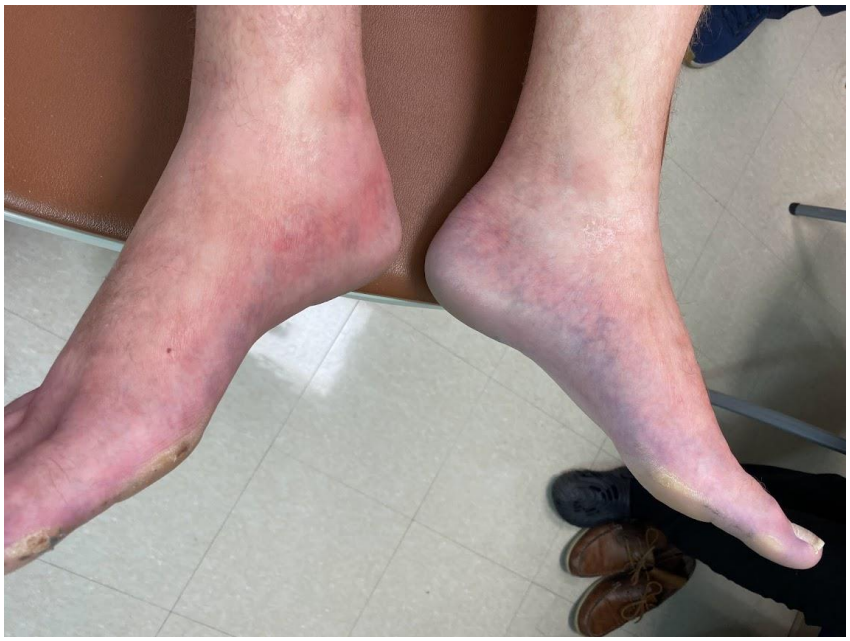


3

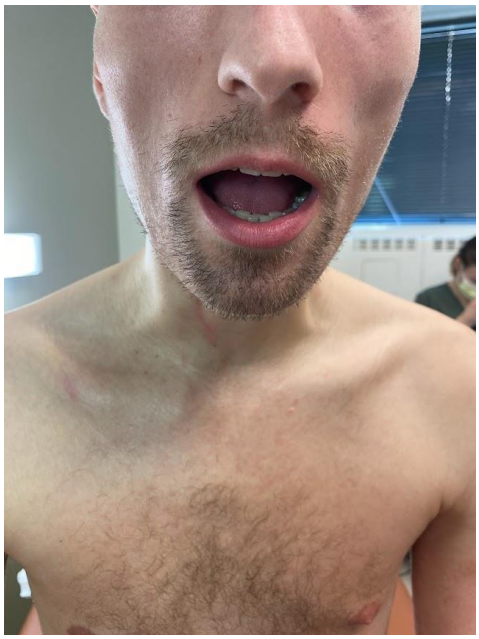




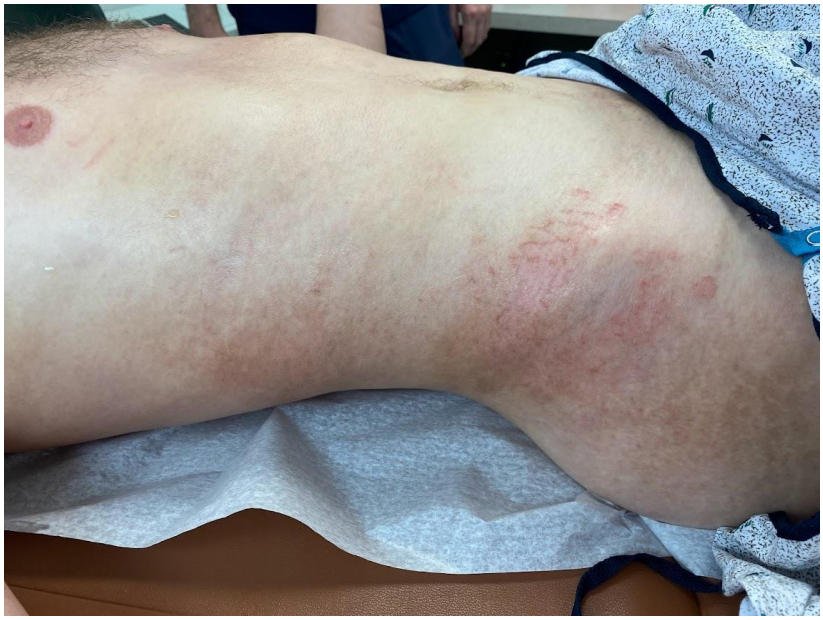
4



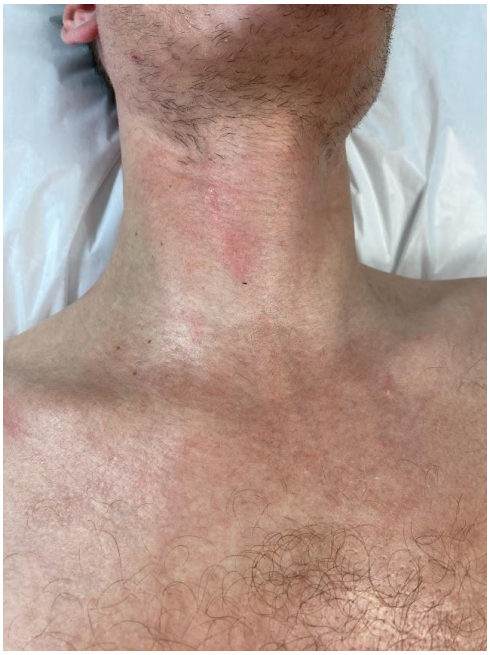
5



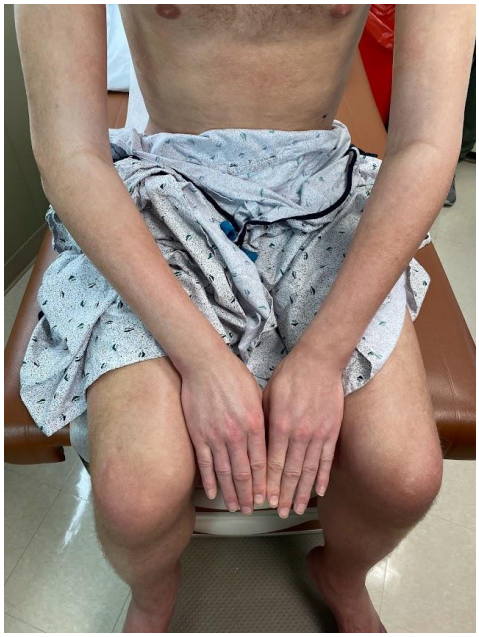
6



7



8



9

Clinical history

5/31/23 – Patient is a surgery resident who presents to our clinic as a return patient (previously seen for unrelated conditions) for **widespread thickening of skin – worse on legs, abdomen and arms.**

- Treated for *viral infection* in **January with gradual worsening of thickened, dry, swollen skin since then and rapidly progressing in the past few weeks**

6/1/23 –

- **EBV infection in December**, which was treated
- Admitted **early Feb 2023 with diffuse swelling, dyspnea and decreased exercise tolerance**
  - Extensive work-up – PET scan, labs. Remarkable for **elevated eosinophil count** with **slightly elevated ESR**, **positive p-ANCA** and negative ANA.
  - Started on steroids, with decrease in eosinophils and **discharged with diagnoses of anasarca, eosinophilia, and esophageal wall thickening. Prednisone** was down-titrated to **current dose of 20 mg** to keep eosinophil count down

10

Clinical history cont.

6/1

- **Three weeks ago**, he started with a **new rash, swelling, and tightening on his lower extremities, hips, and on his arms.** It also involved his **dorsal feet.**
- He's noted that he **feels his range of motion is also more limited**
- He feels like he **can't open his mouth as wide as he used to when eating certain foods**, like a sandwich.
- Over the **last month, median nerve tingling and numbness with extension of fingers**
- He notes that he **runs a marathon approximately yearly**, but **runs about 8 miles every day** and **lifts weights**

Brother has T1DM

No family history of autoimmune disorder.

11

Treatment 5/31

Plan

1. Eosinophilic fasciitis (Shulman syndrome)
Acute condition worsening

Procedure:
4-mm punch biopsy, closed with 3-0 nylon
Indication - for histopathologic confirmation
Area (L abd) was cleaned with alcohol.
1% lidocaine (2 mL) was injected subcutaneously to anesthetize the area
Explained recurrence and scarring. Consent given.
Verbal informed consent is being obtained due to COVID-19 restrictions; the nature of the procedure and the risks/benefits/alternatives/recuperative process to the treatment/procedure/surgery were discussed; all questions were answered; and the patient/legally authorized representation have consented to the procedure/treatment/surgery.

Patient is currently on prednisone managed by hematology.
Patient may need more aggressive therapy, especially if diagnosis and biopsy are most consistent with scleroderma, to prevent further rapid progression.

Continue prednisone. Will add methotrexate and IVIg.

12

Treatment 6/1

1. **Eosinophilic fasciitis**
-Discussed etiology with patient
-Will continue predisone 60mg at present and start methotrexate
-Start methotrexate 2.5mg, take 15mg on same day every 7 days; SER including cytopenias, elevated LFTs, and increased risk of infections
-Start folate 1mg on the other non-methotrexate days
-Stop bactrim
-IVIG 500mg/kg daily x 4 days, each month; SER, including anaphylaxis, headache, hypertension, immune suppression, inability to get new vaccines.
-Patient will discuss IL-5 inhibitor, benralizumab, with Dr. Criner
-MRI of lower left extremity
-Recommended OTC moisturizer (e.g. Cerave, Aveeno, Eucerin, Vaseline etc) and the importance of using soaps and cleansers with low pH (Eucerin, Cerave, etc)
-Start clobetasol 0.05% ointment; apply to affected area(s) at body twice daily for 2 weeks, then only on the weekends; SER including atrophy, striae, thinning of the skin, dyschromia, and hypopigmentation
-Start triamcinolone 0.1% ointment; apply to affected area(s) at body twice daily for 2 weeks, then only on the weekends; SER including atrophy, striae, thinning of the skin, dyschromia, and hypopigmentation

13

Labs, testing, and imaging

- 4 mm punch biopsy was obtained from the left abdomen
  - On histopathology, changes were consistent with **morphea**
- **MRI** of left femur: diffuse thickening and enhancement of deep intermuscular fascia and fascia encasing the musculature—seen with stated clinical history of eosinophilic fasciitis
- Absolute eosinophil count of 5.9 K/mm^3 on 12/13/22 (range: 0.0 to 0.5 K/mm^3), 5.3 K/mm^3 on 2/3/23
- ESR of 17 mm/hr on 4/6/23 (range: 0-15 mm/hr)
- p-ANCA 1:320
- PR3: 2.9 (range 0-0.9)
- IgE - 612 IU/mL (range 0-180 IU/mL)
- ANA was negative

14

Labs cont.

Component Ref Range & Units	9 mo ago	
Epstein Barr Virus Viral Capsid Antigen Antibody IgM 0.0 - 35.9 U/mL	66.0 ^	
Comment:		Negative <36.0 Equivocal 36.0 - 43.9 Positive >43.9
EBV VCA IgG 0.0 - 17.9 U/mL	>600.0 ^	
Comment:		Negative <18.0 Equivocal 18.0 - 21.9 Positive >21.9
Epstein Barr Virus Nuclear Antigen Antibody IgG 0.0 - 17.9 U/mL	298.0 ^	
Comment:		Negative <18.0 Equivocal 18.0 - 21.9 Positive >21.9

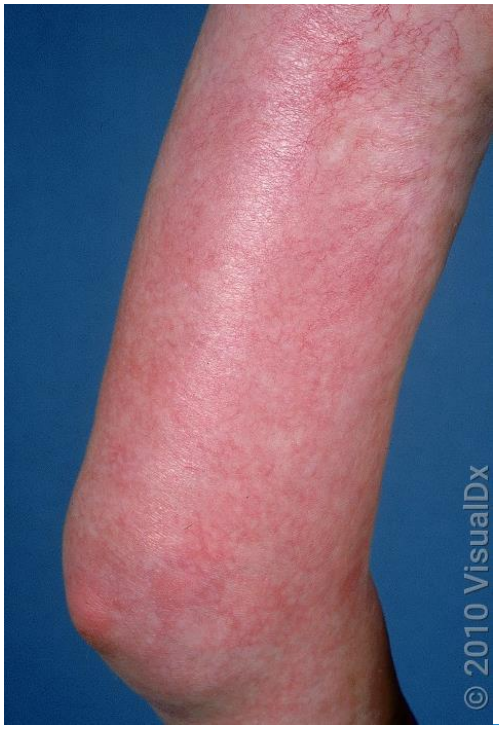
15

1 month follow-up 6/30

1. Shulman Syndrome
-patient with worsening stiffness after dec prednisone, plan to inc to 40mg daily with appropriate ppx (alendronate, vit D, calcium carbonate)
-continue methotrexate, repeat labs as below
-IVIG, dec to 2 days dosing period as 4 days is disruptive to patient, discussed possible worsening headaches
-RTC in 4 weeks

Physical therapy was also started

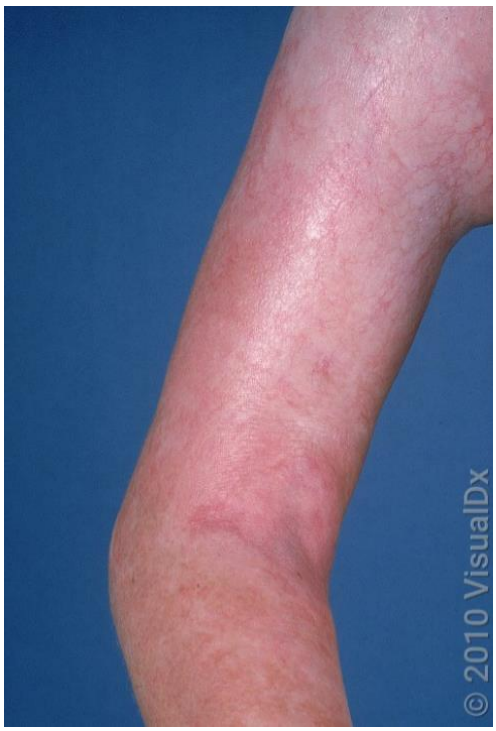
16



Eosinophilic fasciitis (Shulman disease): Etiology

- Rare, fibrosing disorder with unknown etiology
- Possible triggers or factors associated with EF:
- **Strenuous exercise**
- Initiation of hemodialysis
- Infection with *Borrelia burgdorferi*
- Chronic GVHD
- Exposure to certain medications including statins, phenytoin, ramipril, subQ heparin, immune checkpoint inhibitor therapy (nivolumab and pembrolizumab)
- Autoimmune diseases including thyroid disease, primary biliary cirrhosis, SLE, and Sjögren's disease
- **Association with hematologic disorders – up to 10% of patients** (aplastic anemia, acquired amegakaryocytic thrombocytopenia, myeloproliferative disorders, myelodysplastic syndromes, lymphoma, lymphocytic and eosinophilic leukemia, multiple myeloma, paroxysmal nocturnal hemoglobinuria)

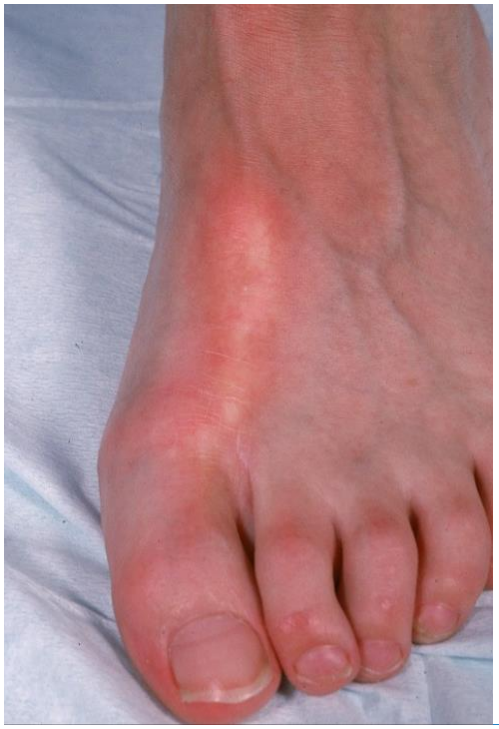
17



Eosinophilic fasciitis: Clinical presentation

- Early phase: limb or trunk erythema and nonpitting edema
- Later phase: collagenous thickening of subcutaneous fascia
- Eosinophilia is a prominent laboratory finding in the early phase, although not always present in active early cases and less prominent in later stages
- Bilateral symmetric induration of skin and deeper perimuscular fascial planes (although unilateral can occur)
- Typically, acute onset
  - Erythema, swelling, induration of the extremities that is accompanied by peripheral blood eosinophilia
  - Subacute course may also occur
  - ***Thickening and hide-bound quality*** of affected skin is ***similar to scleroderma-spectrum disorders***

18



Clinical features

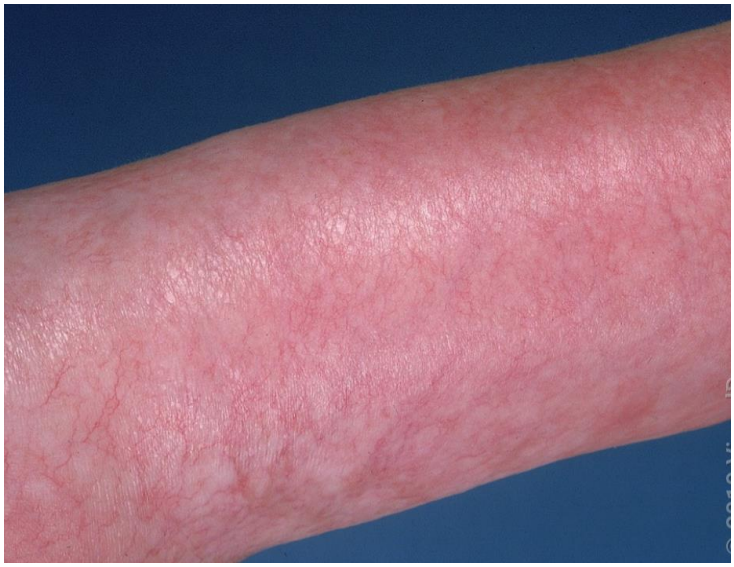
- Although early edematous phase can be indistinguishable from early sclerodermatous skin changes, the irregular, woody, peau d'orange texture of established EF is distinct from the smooth, shiny skin surface seen in patients with systemic sclerosis
- Most commonly occurs on extremities, neck and trunk*
- Scleroderma of the fingers (sclerodactyly), the hallmark of systemic sclerosis, is absent in EF*
- Skin of hands and feet is generally spared*

19

Groove sign

- Affected skin becomes taut and adherent to underlying tissues with an overlying peau d'orange quality to the surface.
- The groove sign is seen with *elevation of the affected limb*
- Elevation *reduces the distending venous pressure*, causes *visible indentation along the course of the superficial veins*

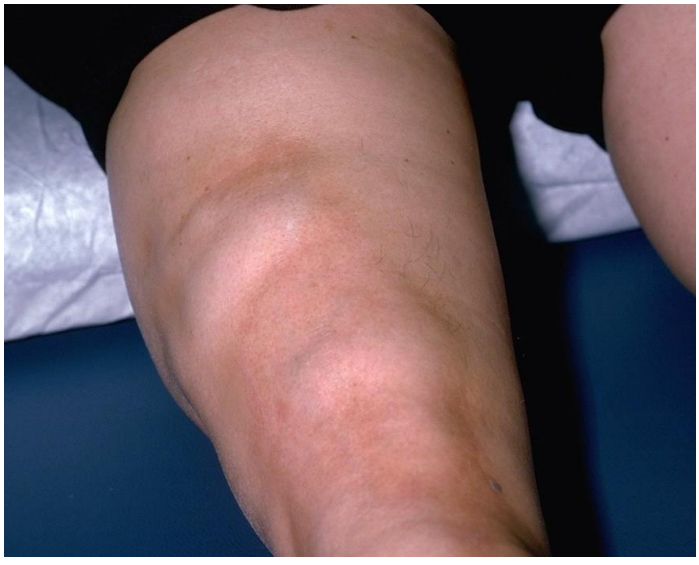
20



Other symptoms and signs

- **Arthritis**
  - **40%** had arthritis in one study of 52 patients with EF
  - Tends to involve areas adjacent to fasciitis
  - Joint contractures may develop*, sometimes in the absence of typical skin involvement
- **Myalgias and myositis** – muscle pain and weakness are common
  - Deep skin and fascial involvement merging into perimyositis may occur, however inflammatory myositis is uncommon.
- **Neuropathies** – carpal tunnel syndrome has been commonly described – 23% in one series of 52 patients
- **Visceral involvement** – rarely present. Occasional cases of pleural effusion, pericarditis, and renal involvement have been described

21



Lab findings

- Majority have peripheral blood eosinophilia early in disease
  - Peripheral eosinophilia is transient and **does not correlate with disease severity**
- Over 50% of patients have elevated ESR, CRP (C-reactive protein) and a polyclonal hypergammaglobulinemia
- ANA have not been reported to be present in EF with any consistency
- Serum levels of CK (creatinine kinase) are typically normal (as in our patient), even in patients with myalgia

22

Diagnosis

- **Suspected in patients with erythema, swelling, induration of the extremities that is accompanied by peripheral eosinophilia.**
- Skin changes typically spare the fingers, hands, and feet, and evidence of systemic involvement is usually absent
- Absence of history of Raynaud phenomenon helps distinguish EF from systemic sclerosis
- In most cases, the diagnosis of **EF is confirmed with full thickness skin-to-muscle biopsy**.
- **MRI can also be used to demonstrate fasciitis**, especially in atypical cases (fasciitis without clinically evident skin changes)
- **Careful review of CBC to determine whether further hematologic investigations are warranted**

23

Differential diagnosis

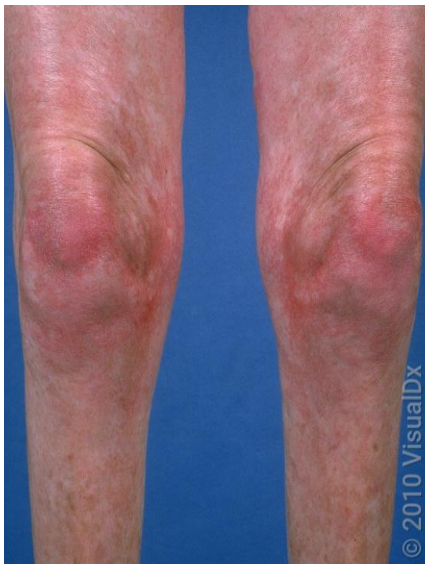
- Localized scleroderma (morphea)
  - Slowly progressive course and are not associated with significant eosinophilia
- Systemic sclerosis
  - Can be difficult to distinguish from EF
  - **Absence of Raynaud phenomenon** favors a diagnosis of EF –vast majority of patients with limited and diffuse systemic sclerosis have or develop Raynaud phenomenon at or near the time of the earliest skin changes
  - **Nailfold capillaries typically normal** in EF (dilated capillary loops, microhemorrhages, and avascular areas observed by capillaroscopy are seen in systemic sclerosis)
  - EF: **Digital pitting is absent, and fingers, feet and face are spared in EF***
  - **Internal organ involvement** (pulmonary fibrosis, pulmonary hypertension, renal crisis) is frequent in systemic sclerosis but **typically absent in EF**
  - EF is **only rarely associated with ANA** or systemic sclerosis-specific antibodies
- Scleredema
  - Diffuse skin induration without serum autoantibodies or evidence of inflammation on skin biopsy is typical of scleredema

24

Treatment

- **Peau d'orange** and **trunk involvement** are **poor prognostic factors** in EF (Shulman disease) – retrospective study in 27 French centers of 119 patients with EF (1992 to 2018)
- **Systemic glucocorticoids** are mainstay of treatment (usually 1mg/kg per day) – majority of patients (75%) respond and ~50% of patients can achieve remission with glucocorticoids
  - Often rapid resolution of peripheral blood eosinophilia and normalization of ESR
  - Doses slowly reduced as the affected skin softens, which can take weeks to months, generally lags behind the resolution of eosinophilia
  - Prevention of glucocorticoid-induced osteoporosis and prophylaxis against *Pneumocystis jirovecii* (PJP)
- Treatment for associated hematologic disorder (up to 10% of patients)
- **Methotrexate** 15 to 25mg/week
  - Usual duration of therapy once remission is achieved is 4-6 months
- Mycophenolate or hydroxychloroquine – however limited data supporting the use of either agent
- **Physical therapy** for preventing the development of joint contractures

25



Treatments cont.

- Other therapies are based on case series or anecdotal reports
  - Tocilizumab, baricitinib, sulfasalazine, azathioprine, infliximab, rituximab, IVIG, dapsone, cyclosporine, UVA1 phototherapy, PUVA, antithymocyte globulin
  - Some patients with refractory disease have reported to respond to treatment with IL-5 antibody reslizumab

26

References

- Zuelgaray E, Chevret S, Jachiet M, et al, Trunk involvement and peau d'orange aspect are poor prognostic factors in eosinophilic fasciitis (Shulman disease): A multicenter retrospective study of 119 patients. J Am Acad Dermatol. 2023 Jan;88(1):160-163. doi: 10.1016/j.jaad.2020.11.009. Epub 2020 Nov 12. PMID: 33188872.
- Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? Trans Assoc Am Physicians. 1975;88:70-86. PMID: 1224441.
- Falanga V, Medsger TA Jr. Frequency, levels, and significance of blood eosinophilia in systemic sclerosis, localized scleroderma, and eosinophilic fasciitis. J Am Acad Dermatol. 1987 Oct;17(4):648-56. doi: 10.1016/s0190-9622(87)70251-5. PMID: 3668010.
- Pinal-Fernandez I, Selva-O' Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. Autoimmun Rev. 2014 Apr-May;13(4-5):379-82. doi: 10.1016/j.autrev.2014.01.019. Epub 2014 Jan 11. PMID: 24424187.
- Lakhanpal S, Ginsburg WW, Michet CJ, Doyle JA, Moore SB. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum. 1988 May;17(4):221-31. doi: 10.1016/0049-0172(88)90008-x. PMID: 3232080.
- VisualDx for several clinical photos