An Elderly Man With Leg Pain And Anemia

SANA MAKHDUMI
RHEUMATOLOGY FELLOW
EMORY UNIVERSITY

Case Presentation

- 53 y/o white male with right lower extremity pain for three weeks
- Initially started as pain around his ankle followed by tightening of the muscles in right thigh and lower leg
- Denied h/o trauma
- Was seen by PCP who did blood work
- Was told that he had 'low blood counts'
- Started him on 'fluid pill' and pain medications
- Referred to Hematology

Case Presentation

- The pain progressed and started in left thigh also
- Two weeks later evaluated at Hematologist office
- Underwent bone marrow biopsy
- Over next week leg pain progressed rapidly to the point that patient was unable to ambulate , presented to ER
- Described feeling of weakness in thighs and legs

Case Presenatation

- In ER:
- Right leg tenderness> left
- Venous doppler US right LE was negtive for DVT
- Initial blood work revealed anemia
- Admitted for further evaluation
- Anemia workup; Hematology Consult
- Lower extremity pain with weakness; Rheumatology Consult

Past Medical History

- Hepatitis C (diagnosed 10 yrs back)
  -Treated with ribavarin and alpha-Interferon 2001-2002
  -Had relapse with worsening of viral loads and transamintis, treated again with alpha-IF, from May 2007- Sept 2009
  -Fatigue,arthralgias, depression 18 months into treatment
  -Continued therapy for additional 10 months
  -Liver biopsy Dec '09 – early cirrhosis
  -LFTS wnl, Viral load 100 IU/mL
  -Current illness February 2011

Hypothyroidism (diagnosed Nov 2008)
Patchy skin hypopigmentation, neck and hands (since 2009)
Blood transfusion 6 months ago in local ER (presented with dyspnea and fatigue)

- Medications:
  Levothyroxine 75 mcgs daily
  Lasix 40 mg daily
  Folic acid 1 mg daily
  Tramadol 50 mg , q8h prn

- FH: Father died of lung cancer age 60
  Mother died of MI at age 64
- SH: used to work as county Deputy Sheriff, quit since 03/2009
  No alcohol since 1990- prior to this only social
  Quit tabacco in 1991,
  Married living with spouse, one teenaged daughter

Review of systems

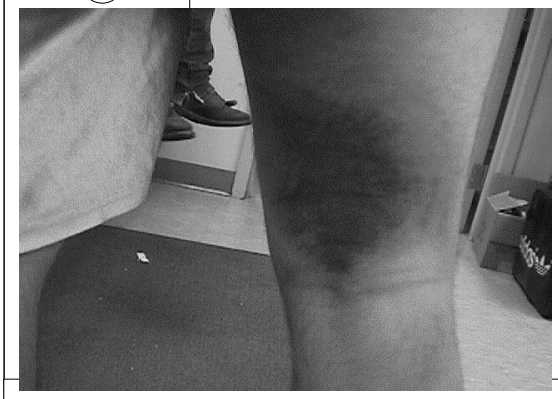
- Positive for worsening fatigue, Purplish discoloration of fingertips in cold, for past one month
- Arthralgias (hands, ankles, knees), decreased appetite, no weight loss, no heat or cold intolerance
- Denied sicca symptoms, reflux, photosensitivity, nasopharyngeal ulcers, rash, shortness of breath or hemoptysis
- Denied h/o serositis or blood clots in past, abdominal pain, bloody stools or hematuria

Physical Exam

- Middle aged white male in mild distress
- Vitals: T-38.1 , P-89, BP 150/82, RR-18, SaO2 100% RA
- Skin: Hypopigmented patches (vitiligo) over neck and hands
- Chest: CTAB
- CVS:S1,S2, regular
- P/A: liver span 11 cms, spleen tip not palpable, no fluid wave, BS +
- No stigmata of chronic liver disease

Physical Exam

- MSK: tenderness on dorsal/plantar flexion of bilateral ankles, no effusion, no muscle atrophy
- Neuro: UE bilateral 5/5 symmetric
  LE bilateral prox 3/5, distal 4/5
  Reflexes 1+ b/l
  Tone normal, sensations intact
  No fasciculations



Laboratory Data

- Cr 0.75, normal lytes
- T.Bili 2.5 direct bili 1.5
- Total protein 6
- Albumin 2.8
- AP 76
- ALT 14
- AST 27
- CPK 85
- TSH 3.39
- PT/INR/aPTT normal
- Urine analysis: no protein, no rbcs
- HIV ELISA negative

- Hb/Hct 8.3/24.4 (three months prior was 11/33.5)
- MCV 96
- Wbc 2.1 ,
  (59% N, 26% L, 10% M)
  Plt 122
  (3 months prior wbc 4.7 ;60%N, 29%L, Plts 156)

CRP 31.32 mg/L (0.3-8.00)
LDH 233 u/L (100-200)

Vitamin B12: 283 pg/mL
Folate 6.9 ng/mL
Iron, Ferritin, TIBC

In Summary

- 53 y/o CM with chronic HCV, with ongoing fatigue, 4 week h/o arthralgias, and Raynaud's phenomenon
- Bilateral thigh ,leg pain with weakness proximal>distal
- Ecchymosis on Right thigh posterior aspect
- Evidence of anemia requiring transfusion;hemolyis?
- Leukopenia with absolute lymphopenia

Working Diagnosis

- Hepatitis C relapse (Portal HTN, Hypersplenism)
- Autoimmune process (Lupus like disease, Polymyositis)
- Cryoglobulinemia (Hep C, lymphoproliferative disease)
- Coagulopathy (Acquired factor deficiency)
- Malignancy/paraneoplastic (Solid organ versus Hematological)
- Vasculitis (small to medium vessel)

Further Work up

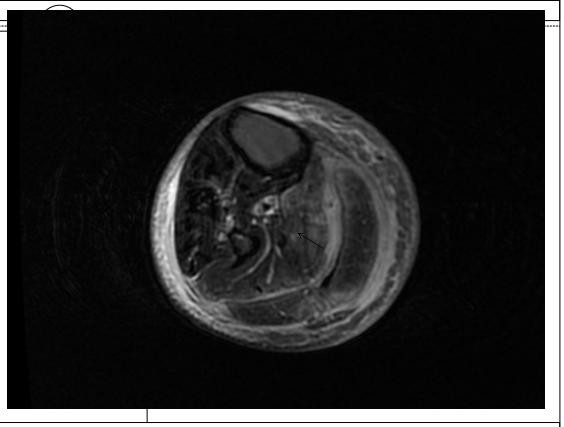
- Hepatitis C viral RNA PCR
- SPEP/ UPEP
- Hemolytic panel ,Bleeding time, Mixing study
- ANA profile
- ANCA
- Cryoglobulins, RF
- Abdominal ultrasound and AFP
- Complement levels
- MRI right thigh and leg

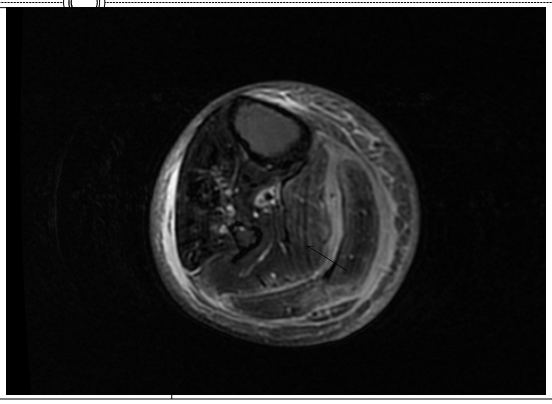
- Hep C RNA by PCR ; 50 IU/mL
- AFP<5 ng/ml
- Cryoglobulins negative
- Retic count 5.66 %
  Retic index 2.1 (>2)
  Haptoglobin 6 mg/dl(27-139)
  Bleeding time ; within normal
- C3, C4 normal
- Direct antiglobulin test weakly positive
- SPEP: Low albumin, other protein fractions are normal, no paraprotein identified

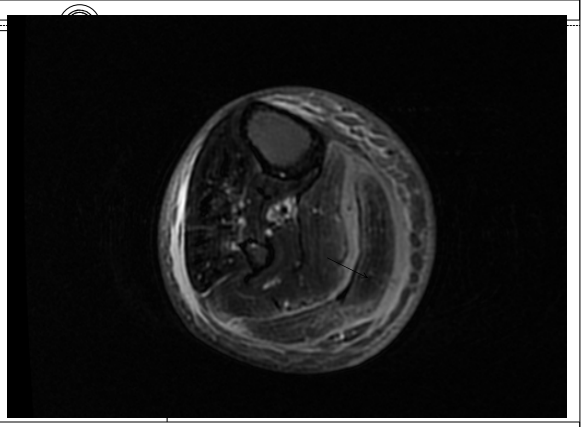
- Abdominal Ultrasound with doppler:
  -Coarse echotexture of liver compatible with early fibrosis, no focal lesions
  -No evidence of varices, spleenomegaly
  -Patent portal vein with normal portal pressures and flow direction

- Peripheral smear: Decreased red blood cells with marked anisocytosis, white cells and platelets morphologically unremarkable
- Bone marrow: Normocellular marrow with trilineal hematopoiesis and mild reactive erythroid hyperplasia
- Flow cytometry did not identify any unique cell populations

- ANA pending
- ANCA pending







MRI Right Thigh and Leg

- Nonspecific diffuse increased signal in quadriceps, gastronemius and soleus muscle possibly representing myositis
- Mild subcutaneous edema
- No abscess or focal fluid collection
- Normal bone marrow signal with no fracture or osteomyelitis

- Recent onset of Raynaud's, arthralgias, leucopenia, autoimmune hemolytic anemia, possible myositis
- Systemic autoimmune process; Lupus like disease
- Also had prior evidence of hypothyroidism and vitiligo

- Patient refused muscle biopsy
- Started on prednisone 30 mg po bid
- Improvement of muscle pain and weakness over next 48 hours , able to ambulate with PT on day 3 of prednisone therapy
- Blood counts remained stable

- ANA : 1:1240 (speckled)
- Anti-dsDNA : 40 IU/ml
- Anti-Smith : 12 Units
- Anti-SSA : 2.3 Units
- Anti-SSB: 3.8 Untis
- Anti-RNP: 132.1 Units
- Anti-Histone 0.4 units
- ANCA IgG <1:20

Interferon-alpha Induced Lupus Syndrome

Interferon-alpha Induced Autoimmunity

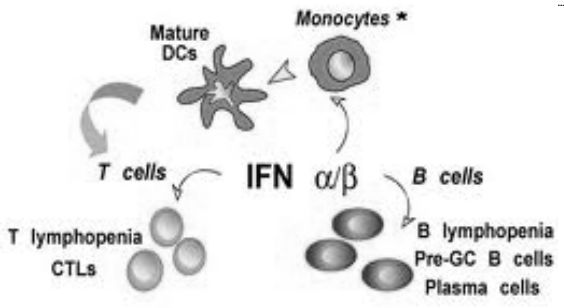
- In recent years there has been growing body of literature suggesting that exogenous IFN-α can induce severe systemic autoimmune disease in some individuals
- IFN-alpha is associated with new onset autoimmune disorders with a reported frequency of 4.3% to 18.5%
- Increase in titers of auto-antibodies can occur in upto 50% of treated indiviuals

Autoimmune manifestations of IFN-α

- Well-studied autoimmune disorders are thyroid dysfuntion, Insulin dependent diabetes , and autoimmune hepatitis (anti-thyroid,anti-islet cell and anti-smooth muscle Ab)
- Cases of Lupus-like syndrome, hemolytic anemia, and immune-mediated thrombocytopenia have been well described in literature; case reports

Proposed Mechanism

- IFN-α is a type I interferon that plays an important role in viral defense
- Physiologic functions of IFN-α include activation of dendritic cells and increased expression of major histocompatibility complex class I and II molecules, leading to increased antigen presentation
- Evidence suggests that IFN-α can bridge the innate and adaptive immune systems, and therefore can play an important role in self-tolerance and auto-immunity



IFN-alpha induced Lupus

- There are 25 cases of IFN-α therapy induced SLE or lupus-like syndrome reported in the English literature from 1990 to 2010
- Most data from patients with Hep C, Multiple Sclerosis or Myeloproliferative disorders

Incidence

- <1% of patients treated with IFN-alpha go on to develop clinical SLE, however a greater number of patients develop a "lupus-like" syndrome, meeting fewer than 4 of the 11 formal criteria for SLE

Clinical Onset

- On average, the time elapsed between initiation of IFN-alpha therapy and onset of lupus symptoms ranges between 2 weeks to 7 years
- In the majority of cases, SLE symptoms resolve after discontinuation of the alpha-IFN and a short course of immunosuppressive therapy
- Few cases were not reversible and were severe with life threatening leukopenia, and nephritis

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'*Interferon-alpha Induced Lupus in a Patient With Chronic Hepatitis C Virus' Rubina Rizvi, MD, Mehrnaz Hojjati, MD*

50 y/o male developed photosensitive malar rash, autoantibodies (dsDNA,SSA), 2 episodes of documented leukopenia and raynaud's ,one month after discontinuation of third cycle of pegylated IFN

Treated with HCQ and topical pimecrolimus

At week 8: Continued to have rash and low grade fatigue

Leukemia and Lymphoma

- March 2005; 46(3): 481 – 482
- *IFN- alpha Induced Lupus Nephritis in a patient with CML ; Goyal, Wadhwa et al*
- 29 y/o male in third year of therpay developed anasarca and nephrotic range proteinuria, renal biopsy WHO class 4 diffuse proliferative GN, positive ANA, anti-dsDNA
- Treated with pulse high dose steroids, patient developed pneumonia and died at week 4

Clinical Presentation

- Most cases of alpha-IFN induced Lupus syndrome have high ANA titers, arthralgia/arthritis, and lymphopenia
- Malar rash, nephritis, hypocomplementemia, and characteristic autoantibodies such as anti-dsDNA, anti-Ro, and anti-Smith
- Serositis is reported in 20% of the cases
- Unlike drug-induced lupus, these cases show a higher frequency of renal involvement and positive anti ds-DNA antibodies

Pathophysiology

- There has been an important proposed role for interferon-alpha in the immunopathogenesis of SLE
- Physiologic functions of IFN-alpha include stimulation of B-cells, activation of dendritic cells and enhanced expression of MHC
- It has been suggested that this along with impaired clearance of apoptotic cell debris in SLE patients can promote formation of immune complexes

Idiopathic SLE

- Approximately 50% of SLE patients show evidence of high serum IFN-α activity in large cross-sectional studies
- Could these patients represent a subgroup of Lupus patients who share a common pathogenesis related to alpha-IFN

IFN-α : A heritable risk factor for SLE?

- Study by Crow and Collegues (HSS);compared 266 patients with SLE and 405 of their healthy relatives, measured serum levels of IFN-alpha
- Abnormally high levels of serum IFN-α were frequently found in healthy first degree relatives of SLE patients
- However research showed that healthy family members with high levels of IFN-alpha did not develop auto antibodies or clinical disease

- *'Indiviuals with high levels of IFN maybe predisposed to SLE, but disease appears only when an environemntal factor triggers the immune system and causes production of damaging autoantibodies'* (Mary Crow MD; Two-Hit Model for developing Lupus, Rheum Dis Clin North Am, Feb 2010)
- Variable time onset of clinical activity in patients who have received IFN therapy

Which subset of patients are at risk?

- Studies of patients receiving IFN-α for hepatitis C; suggest that individuals with a positive antinuclear antibody test before therapy may be more likely to develop autoimmune complications while receiving IFN-α therapy
- There are also reports that IFN-α therapy worsens pre-existing autoimmunity
- Autoimmune disease is considered a relative contraindication to IFN-alpha treatment

Management

- In many instances, Lupus symptoms resolve within few weeks to months after discontinuation of IFN-alpha
- Symptoms persisting for an extended period may require treatment with appropriate immunosuppressive therapy, steroids, HCQ

Follow-up

- Our patient had been treated with IFN-alpha for HCV, subsequently developed cytopenias, raynaud's, arthralgias , myositis
- Positive ANA and ds-DNA ab
- 4/11 criteria for SLE
- He did well with improvement of muscle pain, some residual weakness, discharged home on day 7
- Slow taper of prednisone
- Active symptoms of fatigue and raynaud's

- Recently seen by GI (05/17/11), down to pred 5 mg daily with recurrence of bilateral thigh pain and weakness
- Increased prednisone to 30 mg bid
- Wbc 2.4, Hb 9.6, Plt 133k

In Conclusion

- Serious immunologic consequences can accompany IFN-alpha therapy
- The finding that an exogenously administered agent can induce a complex systemic human autoimmune disease is fascinating, even though it is a rare event
- Clinical symptoms may develop upto 7 years after initial exposure of IFN-alpha

- Most patients develop characteristic auto-antibodies
- Differs from drug-induced lupus with more renal involvement and anti ds-DNA
- Substantial need for careful monitoring of patients receiving IFN-alpha therapy

Targeting IFN-alpha; a promising therapy for SLE

- Much insight has been gained regarding IFN-alpha as a causal factor for SLE providing hope that there will have a better map of some of the early pathogenic events in SLE
- Anti-alpha- IFN antibody therapies are currently in early phase clinical trials in SLE
- These therapies may be directed preferentially at the "high IFN-*α*" subgroup of SLE patients
- Targeting IFN-alpha might be therapeutically efficacious in this subset of lupus patients

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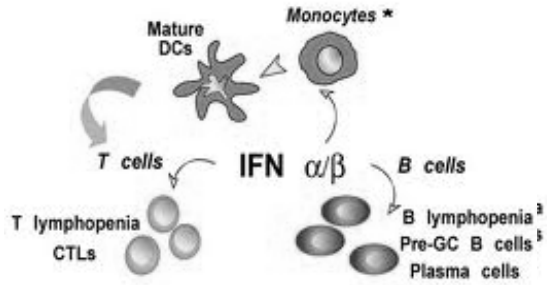
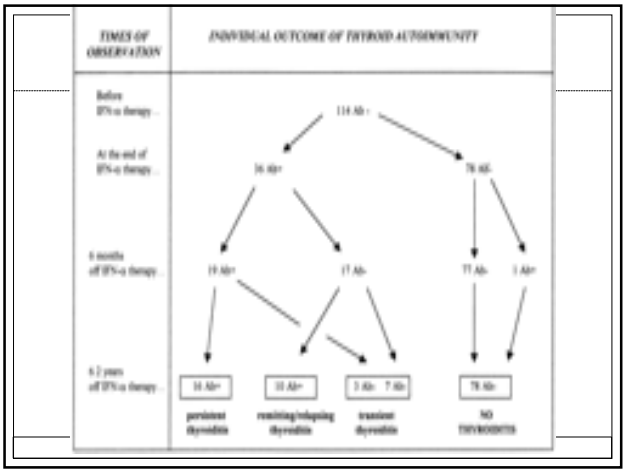
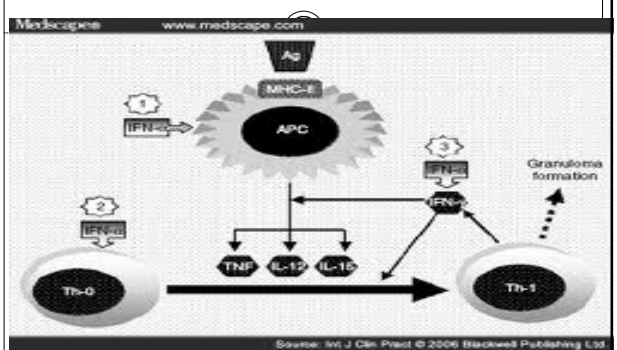
THANK YOU







- I DO NOT have any financial relationship to disclose