KIKUCHI FUJIMOTO DISEASE AND LUPUS: A Combination for catastrophe

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Case History

❑Patient Details:

- XYZ
- 24 year, Female
- Resident of Delhi

❑Chief complaints:

- Fever x 15 days
- Neck swelling x 12 days
- Rashes over cheeks and hands x 10 days
- Oral ulcers x 10 days

History of Presenting Illness

- **Fever x 15 days**
  - High grade (2-3 spikes/day, non documented)
  - Associated with myalgia, polyarthralgia
  - Not associated with night sweats, nausea, vomiting, diarrhea, cough, abdominal pain, headache, fowl smelling vaginal discharge

- **Neck Swelling x 12 days**
  - Multiple small nodular swelling on both the side of the neck- (?Lymph nodes)
  - Associated with throat pain initially and difficulty swallowing- (?Tonsillitis)
  - No history of redness and pus discharge over the swelling
  - No history of hoarseness and breathing difficulty

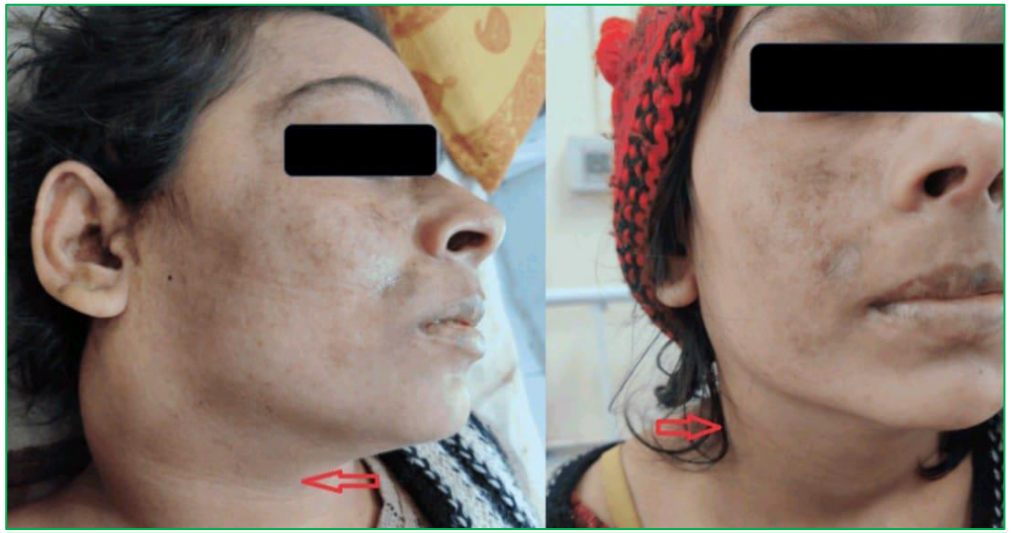

Figure1: Characteristic rash and bull neck enlargement of lymph nodes on the left with resolution of symptoms post treatment on the right image

❑ Rashes over cheeks and Bilateral hands x 12 days

- Characteristic malar rash
- sparing the nasolabial folds seen
- Maculopapular rashes on bilateral hands
- Sometimes pruritic
- Not associated with any drug exposure, recent infections.

❑ Oral ulcers x 10 days

- Painful

❑ History of joint pains, hair loss, easy fatiguability, irregular menstrual cycles, decreased apetitie present

❑ No history of photosensitivity, abdominal pain, decrease urine output, recurrent infections, recent travel, animal/pet exposure, recreative substance abuse

❑ Past history

- No history of similar illness in the past
- No prior history of any comorbidities (DM, HTN, Thyroid, Aasthma, Allergies, CKD)

❑ Family History

- No history of similar illness in any family members

❑ Treatment History

- No history of past admissions
- No history of any long term treatment for similar illness

❑ Personal History

- History of loss of apetite x 15 days
- Bowel, Bladder, Sleep habits are normal
- No addictions
- Irregular menstrual cycles present

On Examination

- Conscious, oriented to time, place, person
- VITALS: BP-116/74
  - PR-88/min, normal character
  - RR- 14/min , regular
  - Spo2- 97% On room air
  - Temp- 101.F

General physical Examination

- Pallor + (mild)
- Oral examination- posterior pharyngeal wall congestion present
- No icterus, clubbing, cyanosis, pedal edema present
- Bilaterally enlarged cervical lymph nodes present (3x 4 cm, level 1,2 ,3)
- Bilateral axillary lymph nodes enlarged (2x3 cm)
- LN were nodular, firm, non matted, mild tenderness
- Multiple erythematous, non tender, maculo papular lesions over B/L arms

Systemic Examination

- P/A- soft, non tender
- Hepatomegaly of 16 cm elicited
- CNS- No FND, motor, sensory and cerebellar examinations normal
- CVS- S1 and S2 normal, No murmur appreciated
- R/S- B/L air entry+, NVBS, No adventitious sounds present

ROUTINE INVESTIGATIONS

- Blood investigations revealed anemia, leukopenia and mild transaminitis.
- Urine R/M: 2 + Moderately increased proteinuria
- CXR- Normal
- ECG- Normal
- ABG- No acid-base abnormality noted .

	18/9/2022	3/10/20
Hb	10.1	11.7
HCT	35.4	36.3
Platelet count	1.5 L	1.69 L
TLC	2900	2540
DLC	N54/L40	N53/L31
Urea	12	11
Creatinine	0.59	0.5
Ca	9.2	8
PO_4	3.1	4
Uric Acid	4.4	3.8
Na+	142	139
K+	3.7	4.4
Bil	0.6	0.3
Total protein	7.8	6.9
Albumin/ Globulin	3.9	3.6/3.3
ALP	3.8	69
SGOT/SGPT	166/114	281/149

SUMMARY

- 24 year old female, with no prior comorbidities, presented with chief complains
- Fever x 15 days
- Neck swelling x 12 days
- Rashes over cheeks and hands x 10 days
- Oral ulcers x 10 days
- Generalised lymphadenopathy
- Hepatomegaly
- Investigations s/o Leukopenia, anemia, transaminitis
- Urine R/M s/o – proteinuria (?UTI ?Glomerulonephritis)

- **PROVISIONAL DIAGNOSIS:** **FEVER WITH LYMPHADENOPATHY**
- **DIFFERENTIAL DIAGNOSIS:**
  Tuberculosis
  Viral ilnessess- Infectious Mononnucleosis
  SLE
  Lymphoma
  Sarcoidosis
  HLH
  Histoplasmosis

FURTHER WORKUP

Fewer Workup

LAB PARAMETER	VALUE	INTERPRETATION
Blood Culture-Aerobic and Fungal	Sterile	
Urine Culture	Sterile	
Malaria QBC	Negative	
Typhidot IgM	Negative	
TB quantiferon gold Assay	Negative	
Viral Makers- Hep B,C and HIV	Negative	
Lymph Node FNAC for Gene Xpert	M tb not detected	
Peripheral smear	Leukopenia, Atypical cells present	?Viral infection
EBV and CMV PCR	Negative	
Serum ACE	60	Normal

LAB PARAMETER	VALUE	INTERPRETATION
ESR	90	High
CRP	1.9mg/dL	HIGH
CK	190	NORMAL
LDH	1066	HIGH
Ferritin	1564	HIGH

LAB PARAMETER	VALUE	INTERPRETATION
Total Cholesterol	42	Normal
Triglycerides	189	Borderline High
LDL-C	Zero	
HDL	21	Low

❑Urine Analysis:

- Urine ACR- 307
- Urine C/S- sterile
- Urine active sediment- None

❑ULTRASOUND- NECK s/o:

- Enlarged necrotic lymph nodes in anterior and posterior triangles
- Largest measuring 3.3 x 5.1cm

❑CECT of neck, thorax, abdomen s/o:

- Multiple heterogenously enhancing necrotic bilateral cervical and axillary lymph nodes alongside serous cavity effusions

❑Immunological workup:

IMMUNOLOGICAL PARAMETER	RESULT
ANA	POSITIVE (Homogenous pattern1:640)
Anti dsDNA	Positive
Anti Smith/ Ant-ribosomal P Ab	Positive
C3	42 (Low)
C4	6 (Low)
Anti LKM1/ASMA	Negative
ANCA	Negative
Anti Thyroglobulin	Negative

Workup for SLE

Entry criteria fulfilled with a score > 10

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Workup for HLH

- Not satisfying 5/8 criteria for HLH

The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below) Fever Splenomegaly Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood) Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk) Platelets <100 × 10^9/L Neutrophils <1.0 × 10^9/L Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL) Fibrinogen ≤1.5 g/L Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy. Low or no NK cell activity (according to local laboratory reference) Ferritin ≥500 μg/L sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

❑ Bone Marrow Biopsy studies-

- Peripheral blood flow cytometry- No clonal B lymphoid population seen
- Bone Marrow aspirate-
  - Cellular reactive bone marrow with a normal M:E ratio
  - No morphological evidence of lymphoma infiltrate on multiple smear examined
- Bone marrow Biopsy-
  - Adequate bone marrow biopsy with overall cellularity 75-80%
  - All marrow components including erythroid, maturing myeloids and megakaryocytes are well represented
  - There are no lymphoid aggregates

❑ Excisional lymph node biopsy-

- Focal necrosis in cortical and paracortical areas with marked karyorrhexis and proliferation od distinctive crescentric histiocytes and plasmacytoid monocytes, which are characteristics of KFD, with an absence of neutrophils and plasma cells was seen
- Immunohistochemical staining showed CD 68 positive histiocytes and CD 8 positive T cells

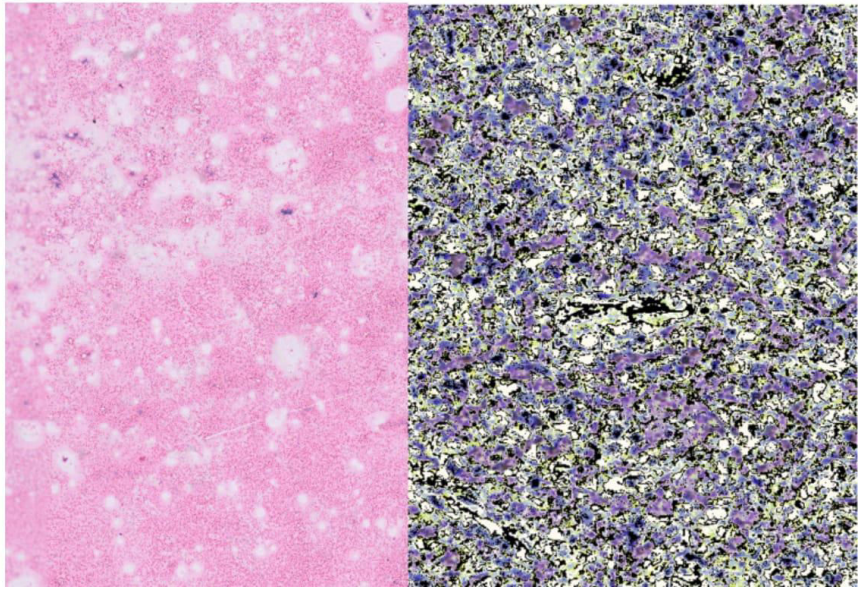

FIGURE 2 : FNAC of the node illustrating (left) proliferation intercurrent necrosis, and numerous apoptotic cells, (right)- IHC demonstrating cd68 reactive histiocytes.

KIKUCHI FUJIMOTO DISEASE

❑ INTRODUCTION

- Also known as Histiocytic Necrotizing Lymphadenitis
- Rare entity of unknown cause
- Pathogenesis- Unknown
- Clinical presentation, course and histologic changes suggest T cells and histiocyte response to an infectious agent (Most accepted hypothesis- Viral-autoimmune origin)
- Inciting Agent-
  - Post Infectious-EBV, HHV6, HIV, Hep B, Parvovirus, Paramyxovirus, Parainfluenza virus, Yersinia, Toxoplasma

- Autoimmune-KFD has been reported to simultaneously occur or follow SLE.
- Other autoimmune diseases (Still's disease, Sjogren's syndrome, polymyositis, and rheumatoid arthritis)have rarely been reported to be associated with KFD
- One Ultrastructural study proposed that kikuchi reflects a self limited, SLE like autoimmune condition caused by virus infected transformed lymphocytes.

KIKUCHI FUJIMOTO DISEASE

Epidemiology

- Young women > men (1:4 M:F)
- Mean Age of presentation 30 years
- More common in Asians

Clinical Features

- Most common- Fever with cervical lymphadenopathy(Usually Painful) in a previously healthy young woman
- Lymphadenopathy (100 percent)
- Fever (35 percent)
- Rash (10 percent)
- Arthritis (7 percent)
- Fatigue (7 percent)
- Hepatosplenomegaly (3 percent)

Atypical/ Uncommon Presentation

- Rigors, myalgia, arthralgia, and chest and abdominal pain
- Night sweats, nausea, vomiting, diarrhoea, and weight loss-more prominent in patients with extranodal disease
- Several reports of disease limited to the mediastinum, with no cervical involvement

❑RASH IN KIKUCHI

- Transient skin rashes similar to rubella or drug-induced eruptions may be seen in sick patients
- Occasionally, the rash is pruritic
- Some reports describe skin manifestations in up to 40 percent of patients, including facial erythema; erythematous macules, patches, papules, or plaques; lichen planus
- The presence of a malar "butterfly rash" should raise the diagnosis of SLE which has been associated with Kikuchi disease

❑LYMPH NODE IN KIKUCHI

- Lymph node involvement is usually cervical and localized in Kikuchi disease.
- Extensive node involvement can occur-axillary, epitrochlear, mediastinal, mesenteric, inguinal, intraparotid, iliac, retrocrural, celiac, and peripancreatic nodes.
- Size-Moderately enlarged (1 to 2 cm in diameter) but occasionally are much larger (≤7 cm)
- LN firm, smooth, discrete, and mobile
- Often associated with dull or acute pain

Other manifestations in KIKUCHI	
Aseptic meningitis	Polymyositis
Acute cerebellar symptoms with tremor and ataxia	HLH
Optic neuritis, Panuveitis, bilateral papillary conjunctivitis	Autoimmune hepatitis
Thyroiditis	Brachial Neuritis
Parotid enlargement	Peripheral Neuropathy
Pleural effusion, pulmonary infiltrates	Acute Renal Failure
Symmetrical polyarthritis	APLA with multiorgan failure

Lab Parameters In KIKUCHI

- Majority of patients have a normal complete blood count, although leukopenia has been reported in up to 43 percent.
- Atypical lymphocytes (25 % cases) .
- Other reported findings include thrombocytopenia, pancytopenia, and, in those with severe disease, anemia of chronic disease.
- ESR can be normal but was elevated to more than 60 mm/hour in 70 percent of patients in one series.
- Other nonspecific findings can include mildly abnormal liver function tests and elevated serum lactate dehydrogenase.
- Macrophage activation syndrome was described in 30 percent of a series of hospitalized patients, associated with longer hospital stays and increased late glucocorticoid use.

❑ Bone Marrow Studies

- An increase in macrophages without atypical cells is the most frequent finding.

❑ SEROLOGY

- Antinuclear antibodies (ANA), rheumatoid factor, and lupus erythematosus preparations are generally negative
- Some patients initially diagnosed with KFD have subsequently developed SLE, and an ANA test should be performed in patients with suspected Kikuchi syndrome who have features suggestive of SLE in order to exclude this diagnosis.
- Transient rise in anti-DNA and antiribonuclear protein antibody levels has been reported.
- Serology for Epstein-Barr virus, cytomegalovirus, HIV, toxoplasmosis, Y. enterocolitica, cat scratch disease is often performed since these infections are considered in the differential diagnosis of fever and lymphadenopathy.

Final Diagnosis: KIKUCHI FUJIMOTO DISEASE with SLE

❑ TREATMENT

- Self limiting disease lasting for months with simple and conservative measures.
- No proven and effective treatment for KFD as of now.
- Symptomatic measures aimed to relieve local and systemic complaints with analgesics, antipyretics and NSAIDS given to alleviate node tenderness and fewer
- Patients with severe and recurrent symptoms may be managed with hydroxychloroquine (HCQ), corticosteroids and Anakinara (recombinant human interleukin 1 receptor anatagonist)
- Our patient was managed by glucocorticoid therapy with HCQ. She responded well to the treatment with resolution of symptoms, and the remaining hospital course was uneventful.
- She is still under follow up with no recurrence of the disease till date.

CONCLUSION

- Kikuchi disease is an uncommon, self- limiting disease with an excellent prognosis when identified and managed appropriately.
- Not always does SLE or KFD precedes each other, sometimes they co present.
- Awareness of the disease among clinicians is exceedingly important, when a patient with fewer and lymphadenopathy comes, to prevent any misdiagnosis and inappropriate treatment in an otherwise benign disease.
- Long term follow-up is required to survey the possibility of relapse or development of SLE or other lympho-proliferative diseases later in life.


Thank You

THANKYOU