Pyrexia of unknown origin?
Think still

Lawrence Owino Okong’o,
Mmed (UoN); Mphil. (UCT).
Lecturer, Department of Paediatrics and Child Health,
University of Nairobi. Paediatrician/ Rheumatologist.
DISCLAIMER

The presentation has been supported by ROCHE.
Case presentation

• FM, 4 years old Female. Admitted on 12-2-2018 with 6 months history of:
  • General malaise,
  • Pain and swelling of knee, ankle, elbow joints
  • Recurrent fever.
• Admitted at a peripheral facility 1 month earlier with febrile illness and treated for malaria and antibiotics (ceftriaxone) with minimal improvement.
• FSH: Older of 2 siblings, other (male) alive and well.
  • Family history unremarkable.
Admission physical exam findings

• Febrile T= 37.6C; Sick looking. Generalized lymphadenopathy 1-2cm, discrete. Mild pallor.
• Abdomen: generalized distension. Liver 6cm BCM.
• RS: Tachypnoeic RR= 36; With flaring alar nasi and lower chest indrawing. Vessicular breath sounds. No added sounds and good air entry.
• ENT: No Ear or pharyngeal/ tonsillar inflammation.
• CVS: Tachycardia 124/min. Normal heart sounds/ no added sounds.
INVESTIGATIONS

• Blood, urine, stool, CSF cultures – negative.
• HIV? – Negative
• In view of persistent fever spikes and arthritis?
  • Rickettsia and Brucella serology: both negative.
• Malaria antigen test and film: negative.
• Leishmania IgG (21/3/18) = Neg
• ASOT was +; but RF negative.
Tuberculosis or no tuberculosis?

- Mantoux – Negative (0 mm).
- Quantiferon: positive
- LN Biopsy: reactive. No granuloma. Negative ZN for AAFBs.
# Laboratory investigations

<table>
<thead>
<tr>
<th></th>
<th>23/3/18</th>
<th>16-3-18</th>
<th>10/3/18</th>
<th>4/3/18</th>
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<tbody>
<tr>
<td>CRP (&lt;10)</td>
<td>24</td>
<td></td>
<td>244</td>
<td>59.6</td>
<td>0</td>
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<tr>
<td>WBC</td>
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<td></td>
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<td>573</td>
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<tr>
<td>Neutr</td>
<td>68.8%</td>
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<tr>
<td>ESR (0-20) mm/hr</td>
<td></td>
<td>80</td>
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### Laboratory investigations

<table>
<thead>
<tr>
<th>Date</th>
<th>1/3/18</th>
</tr>
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<tbody>
<tr>
<td>Rapid salmonella Ag</td>
<td>Neg</td>
</tr>
<tr>
<td>ASOT (21/2/18)</td>
<td>Neg</td>
</tr>
<tr>
<td>LNode</td>
<td>Dermatopathic changes. No granuloma, no malignancy. ZN negative for AAFBs.</td>
</tr>
<tr>
<td>Blood, urine, stool, CSF M/C/S</td>
<td>Repeatedly negative</td>
</tr>
<tr>
<td>BMA (21/2/18)</td>
<td>No features of malignancy.</td>
</tr>
<tr>
<td>INR</td>
<td>1.38 (0.9-1.3)</td>
</tr>
</tbody>
</table>
Working diagnoses

• 1. Septicemia
• 2. Tuberculosis.
TREATMENT
Rheumatology review 10/3/2018

• Noted history of fever on and off x2/12; alternate with periods of normal temp.
• Child very sick during spikes and generally well in between.
• History of associated joint pain and swelling.
• Had erythematous pruritic rash, most notable at height of fever spikes. Managed previously as allergy.
• Exam: Irritable, afebrile. Generalized lymphadenopathy.
• Abdomen distended with liver 6cm and spleen 2cm BCM.
• MSS: mild-mod wasting. Small effusion right knee.
• Skin: Generalized erythematous rash with scaling/ desquamation. No gottron’s, no malar rash.
Progress

- During admission, developed **severe anaemia** and required **transfusion** in both instances.

- Post discharge:
  - The child continued to run daily fevers and complained of knee pain.
  - Two weeks after discharge noted recurrence of the erythematous rash, generalized in face, trunk and limbs.
  - Examination revealed slight knee effusion.
## Laboratory investigations

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<td></td>
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<tr>
<td>LDH (125-220)</td>
<td>1017</td>
<td>4880</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (11-300 ng/ml)</td>
<td>1140</td>
<td>40405</td>
<td></td>
<td></td>
<td>&lt;1200</td>
<td></td>
</tr>
<tr>
<td>Uric acid (149-506umol/l)</td>
<td>458</td>
<td>608</td>
<td></td>
<td></td>
<td>551</td>
<td></td>
</tr>
<tr>
<td>ESR (0-20) mm/hr</td>
<td>62</td>
<td></td>
<td>80</td>
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<td>80</td>
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</table>
Impression: Systemic JIA

• Based on:
  • quotidian fever,
  • rash,
  • arthritis,
  • poor response to antibiotics,
  • hepatosplenomegaly,
  • lymphadenopathy.

• Investigations:
  • ESR, CRP raised.
  • Ferritin markedly raised.
  • LDH, Uric acid elevated.

• Cardiology review and repeat ECHO – normal CVS exam.

• Repeat evaluation by haematologist in view of anaemia and high Uric/LDH:
  • No features suggestive of malignancy.
SYSTEMIC JIA
Introduction

• Juvenile Idiopathic Arthritis (JIA) refers to a heterogeneous group of chronic inflammatory diseases that share the common feature of arthritis of unknown origin occurring before the age of sixteen.

• JIA is the most common chronic rheumatic disease of childhood with prevalence estimated at 1:1000 for children under 16 years old.

## Pathogenesis

<table>
<thead>
<tr>
<th></th>
<th>SoJIA</th>
<th>Oligo/PolyArthritis</th>
<th>ERA</th>
</tr>
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<tbody>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>Neg</td>
<td>+ve in &lt;25%</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Neg</td>
<td>+ve in 50-85%</td>
<td></td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Polymorphisms in genes coding IL6, Macrophage inhibitory factor.</td>
<td>HLA associations observed:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Poly - HLA-DR4</td>
<td>HLA B27 +ve 80-90% pts with ank spondylitis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oligo - HLA-A, HLA-B, &amp; HLA-DR</td>
<td>Polymorphisms in TNF, IL1 genes.</td>
</tr>
<tr>
<td><strong>Environment</strong></td>
<td>Seasonal pattern suggests viral aetiology.</td>
<td>Infectious agents esp virus may play a role.</td>
<td>May be triggered by infectious in the GIT and GUT.</td>
</tr>
</tbody>
</table>

SoJIA: Background, epidemiology and pathogenesis

- Is a type of JIA associated with systemic inflammation.
- It is currently considered to be an autoinflammatory syndrome.
- The disorder was named after Sir George Frederic Still who first described it in 1896.
- Pathogenesis of SoJIA:
  - Triggers are unknown but infections suspected.
  - Contrasted to autoimmune diseases, in auto-inflammation, **monocytes** and **neutrophils** rather than lymphocytes are the main effector cells.
  - They manifest with recurrent fever and inflammation in joints, skin, GIT, eyes.
  - They are associated with gene mutations with SoJIA associated with polymorphisms in genes encoding **IL-6**, **IL-10**, **TNF** and **IL-1**.
SoJIA2: Back ground, epidemiology and pathogenesis

• Innate immunity cells such as monocytes and neutrophils are expanded in number.

• There is also upregulation of innate immunity receptors such as TLR-5.

• JIA prevalence is estimated at 1:1000 for children under 16 years old; with SoJIA accounting for about 10% (30-50% in some series).

• In our setting, SoJIA accounts for about 16% of JIA cases.** (unpublished)
SoJIA
## SoJIA Diagnostic criteria - ILAR

<table>
<thead>
<tr>
<th>ILAR CRITERIA</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fever of at least 2 weeks plus</td>
<td>☒</td>
</tr>
<tr>
<td>2. Arthritis in at least one joint plus</td>
<td>☒</td>
</tr>
<tr>
<td>3. One or more of the following</td>
<td>☒</td>
</tr>
<tr>
<td>- Erythematous rash.</td>
<td></td>
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<tr>
<td>- Generalized lymph node enlargement.</td>
<td>☒</td>
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<tr>
<td>- Hepatomegally/ splenomegaly.</td>
<td>☒</td>
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<tr>
<td>- Serositis.</td>
<td></td>
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<tr>
<td>4. Exclusions</td>
<td></td>
</tr>
<tr>
<td>- Psoriasis, presence of RF.</td>
<td>☒</td>
</tr>
<tr>
<td>- Ank. spondylitis, enthesitis or Arthritis in HLA B27+ male &gt; 6 yrs</td>
<td>☒</td>
</tr>
</tbody>
</table>

Petty et al. J Rheumatol. 2004
sJIA: Quotidian fever, Rash

Photo Courtesy Prof. Scott rheumatology database UCT
Treatment and Outcome of SoJIA.
Outcomes 1: JIA is a chronic disease
Outcome 2: When do we stop therapy?

Criteria for inactive disease

• NO joints with active arthritis
• *NO fever, rash, serositis.*
• NO active uveitis.
• Normal CRP and ESR.
• NO disease activity on the physician's global assessment of disease activity

• **Clinical remission on medication:** inactive disease =/> 6 months while on medication.
• **Clinical remission off medication:** inactive disease =/> 12 months while the patient is off all medication.

Outcome 3: Disease and treatment related damage
MACROPHAGE ACTIVATION SYNDROME (MAS) ASSOCIATED WITH SoJIA

• MAS is an acquired form of hemophagocytic lymphohistiocytosis (HLH).

• MAS is a potentially fatal condition that is characterized by:
  • persistent fever, .... (CF Quotidian fever of SoJIA).
  • Cytopenias ....... (Falling Hb, Falling Platelets, Falling ESR).
  • liver abnormalities .... (Including very high ferritin),
  • coagulopathy and
  • central nervous system dysfunction.
  • Well-differentiated macrophages with hemophagocytic activity are the pathologic hallmark of MAS (these may be seen in splenic aspirates/ BMA)
MAS ASSOCIATED WITH sJIA

• Approximately 10% of patients with sJIA are diagnosed with MAS.

• However, in as many as 50% of patients with active sJIA, MAS is evident in bone marrow aspirates.

• Management of HLH:

<table>
<thead>
<tr>
<th>MAS classification criteria</th>
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<tr>
<td>Ferritin ng/ml</td>
<td>&gt;684</td>
</tr>
<tr>
<td>Platelet u/L</td>
<td>&lt;=181</td>
</tr>
<tr>
<td>AST u/L</td>
<td>&gt;48</td>
</tr>
<tr>
<td>TGs mg/dl</td>
<td>&gt;156</td>
</tr>
<tr>
<td>Fibrinogen mg/dl</td>
<td>&gt;360</td>
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</table>
SoJIA Management in Kenya

• Access to biologics is limited.
• Most of our patients thus have to contend with the relatively high adverse effect profile of NSAIDs and steroids.
• However, IL-6 receptor blockers (Actemra) is locally available and may be accessed in Kenyatta National Hospital.
• IL1 antagonist Anakinra is not yet available locally.
• There is some support from NHIF for biologics if appropriately motivated for.
Your QUESTIONS
My Quizz
Anti-nuclear Abs are positive in most children with systemic JIA. True or false?
False,
It’s auto-inflammatory.
Rheumatoid factor is positive in most children with systemic JIA. True or false?
False,
It’s auto-inflammatory not autoimmune.
Evanescent rash of SoJIA is rarely observed in Africans due to dark skin. True or false?
False,

It’s often easily visualized especially at the height of fever. And most Africans are brown anyway!!.
Which wrist is affected in this child with JIA? Why?
Right.

Increased bone age in affected joint due to inflammation (vascular proliferation)
Biologic therapy for systemic JIA targets which two cytokines? Name the biologics.
IL-1: Anakinra,
IL-6: Tocilizumab (Actemra)
Falling ESR and Platelets may be an indicator of good response to therapy in children with systemic JIA.

True or false?
True.
However if associated with rising Ferritin, stabilization of rash and fever, liver and CNS dysfunction then it may be indicative of MAS.
Summary

• SoJIA is a subtype of JIA manifesting with quotidian fever, evanescent rash, arthritis and other systemic manifestations.

• It is an important differential in a patient with fever for whom an infectious origin has not been found.

• Safe and efficacious treatment agents including biologics exist for disease control.

• Untreated, the disease manifests severe early articular damage and complications such as MAS and anaemia.
THANK YOU
FOR GRACING THIS SESSION.