A 20-year-old lady with prolonged fever

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Miss W. J. a 20-year-old non-diabetic, normotensive, non alcoholic, non smoker, unmarried student, hailing from Chakaria, Coxs Bazar was admitted in CMCH on October 19 , 2023 with the complaints of –

1.Recurrent bouts of fever for one year

2.Generalized fatigue for two and half months

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- According to the statement of the patient, her illness started about one year back with recurrent febrile episodes . The fever was
  - high grade, intermittent, highest recorded temperature 102 °F
  - associated with chills but no rigors
  - with occasional evening rise and night sweats
  - without any focal symptom.

- The fever subsided completely with or without antipyretics after several hours.

- Initially, each febrile episode used to persist for 4-5 days, followed by afebrile periods of about a month. She took paracetamol as needed but did not seek any medical consultation.

- For the last 2 ½ months before presentation , the duration and intensity of fever increased (temperature often reached 104°F) .

- She also noticed progressive weakness, palpitation and chest discomfort while doing her daily activities. She took OPD consultation in a local hospital where she was found to be anemic and was referred to a medicine specialist.

- She reported unintentional weight loss of about 8 kgs in last one month.
- She denied any other symptoms suggestive of systemic rheumatic disease, any visible lumps, bleeding manifestations.
- She had no contact with known TB patients.
- She had no significant travel history.

- She was admitted in a private hospital in Chattogram about 2 months back. 2 units PCV were transfused and Rickettsial disease was diagnosed on the basis of serology. She was discharged with a 10-day course of Doxycycline and Cefixime and ANA (Hep-2) was requested. Clinical scenario remained unchanged.

- SLE was diagnosed on the basis of ANA (Hep-2) positivity and HCQ was started. She became afebrile and relatively well for next 1 month.

- 10 days before admission, she again became febrile (highest recorded temperature 106°F) with weakness so severe that she could not get up from bed without assistance.

- She was hospitalized again and was treated for sepsis with Piperacillin-Tazobacam for 7 days without any clinical improvement.

- Repeat ANA (Hep-2) came negative. CBC revealed pancytopenia and a bone marrow study was planned by a medical board. She was referred to CMCH for further evaluations.

- Patient got admitted in Medicine department of CMCH on 19th October, 2023. On the basis of clinical features and previous reports she was initially evaluated as a case of 'fever of unknown origin' .

- Physical examination revealed a severely ill febrile patient with moderate anemia, tachycardia, tachypnoea and moderate hepato-splenomegaly, without any palpable lymph nodes or bony tenderness.

- During her stay in CMCH
  - Fever escalated and she was treated with broad spectrum antibiotics and antifungal. Blood tests were repeated and bone marrow study was done.
  - 1 unit PCV and 1 unit apheretic platelet had to be transfused.
  - On the 8th day of admission, she developed jaundice which progressively deepened over the ensuing days and liver size increased.
  - She developed spontaneous bruises over her legs.

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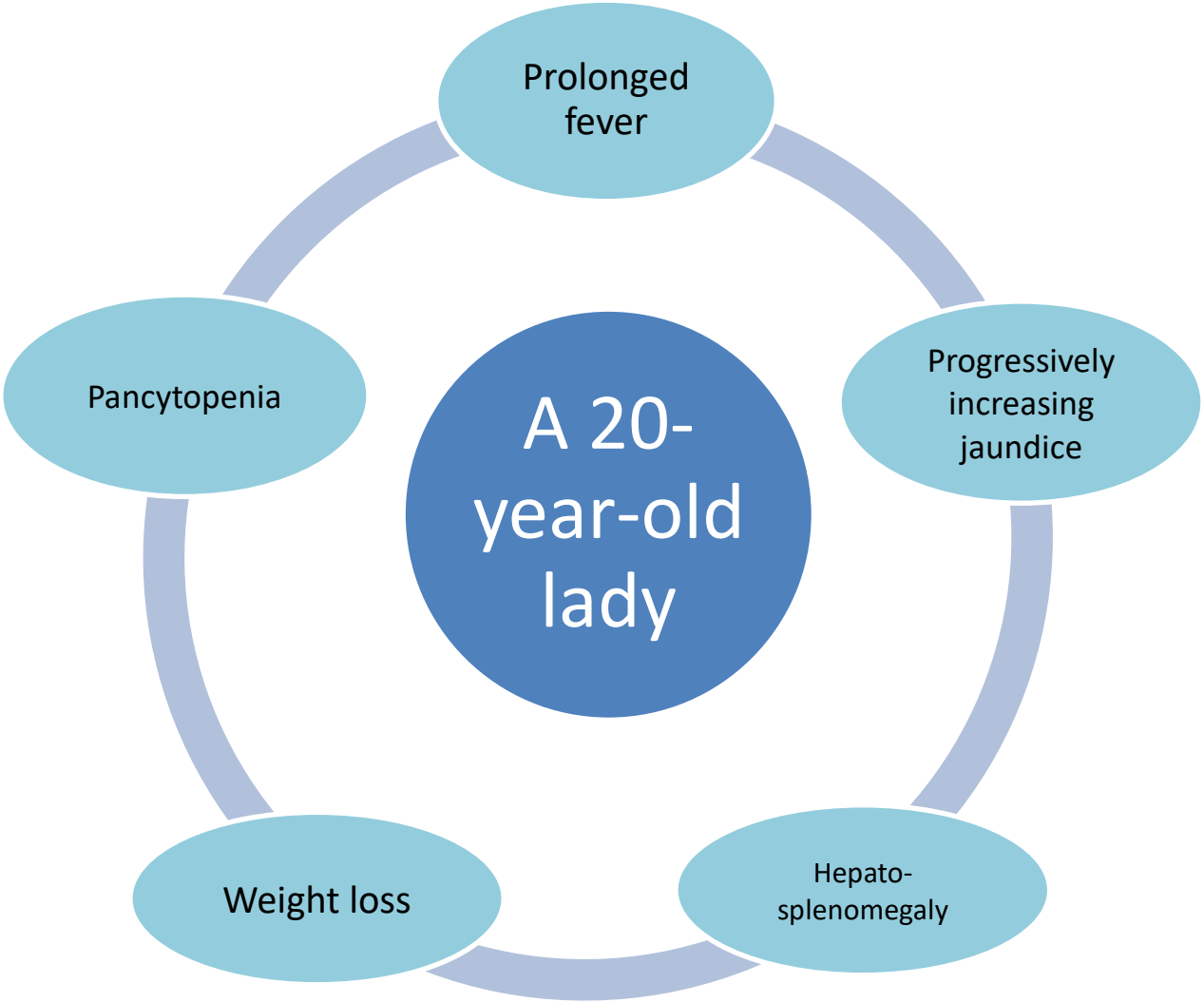
- Family history revealed , she had 4 brothers and 3 sisters. One of her elder sister died in 2016 at the age of 22 in BSMMU with a similar pattern of prolonged fever and repeated blood transfusions. She was diagnosed with a blood disorder and was started on chemotherapeutics but died several months after starting treatment.

Problem Lists



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PROVISIONAL DIAGNOSIS???

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Lymphoma with bone marrow infiltration with sepsis with MODS

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Differential Diagnoses

- Disseminated Tuberculosis
- Severe Systemic Lupus Erythematosus
- Hemophagocytic Lymphohistiocytosis (HLH)

Lab Investigations

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CBC

	Aug 8, 2023	Sep 14 2023	Oct 11 2023	Oct 13 2023	Oct 23 2023	Oct 28 2023	Oct 29 2023	Oct 31 2023	Nov 9 2023
ESR		18		18	99	23	22	22	
WBC	6700	7800	4800	2800	1840	1300	800	710	500
Neutrophil	41%	30%	42%	21%	40%	28%	22%	25.3%	25%
Lymphocytes	53%	64%	52%	73%	55%	64%	68%	62%	
Eosinophil				1%	0%	2%	2%	0%	
Platelets	155k	165k	70k	55k	21k	15k	11k	35k	5k
Hb	8.1	11.7	8.3	7.1	6.5	7.8	8.4	8.1	5.2
MCV	60.8	69.7	73.5	72.8	78.6	81	75	71.4	

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	Aug 8, 2023	Aug 31,2023	Oct 13 ,2023	Oct 20, 2023
PBF	Microcytic hypochromic anemia		Pancytopenia	Pancytopenia
Direct Coombs Test	Negative			
Triple Antigen test		P. OX2 1:640 P. OX19 1:640		
CRP	12 mg/l		78 mg/l	
Pro- Cal		0.06 ng/ml	1.18 ng/ml (Normal <0.5 ng/mL)	
S Creatinine	0.6 mg/dl		0.6 mg/l	
Urine R/M/E	No Pus cells, albumin nil, no RBC or RBC casts			

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	Aug 31,2023	Sep 9, 2023	Oct 12, 2023
ANA	Negative		
ANA (Hep-2)		Positve	Negative
Anti ds DNA	Negative		Negative
S. C3 ((N: 0.9-1.8)			0.69 g/L
S. C4 (N: 0.1-0.4)			0.12 g/l

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	Sep 2, 2023	Oct 11, 2023	Oct 22,2023
Blood for C/S	No growth	No growth	
MT	2 mm after 48 hours		Negative
NS1 For Dengue		Negative	Negative
Anti Dengue IgG,IgM		Negative	Negative
HBsAg, AntiHCV, HIV 1 & 2			Negative
ICT for Malaria			Negative
Anti Leishmania IgG,IgM			Negative

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	Aug 31 2023	Oct 12 2023	Oc 17 2023	Nov 2 2023	Nov 9 2023
S Bilirubin	0.91			9.93 mg/dl	
S ALT	16		148	405 U/L	
S AST				406 U/L	
S ALP				1870	
S LDH(U/L)	340	365	365		450
S Ferritin				13400 ng/mL	
Fibrinogen (NR: 2-4 g/L)			21	2.67 g/L	
Total Cholesterol			1.8	571 mg/dl	
Triglycerides				396 mg/dl	
LDL				327 mg/dl	

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Imaging

	August 31, 2023	Oct 14, 2023
USG W/A	Mild splenomegaly	hepatomegaly (15.85 cm) Moderate splenomegaly (18.38*10.33 cm) Multiple small lymph nodes (larger one 2.38* 1.82 cm) in the epigastric,pre and para-aortic region) Bilateral mild pleural effusion Mild ascites
Xray Chest P/A view	Normal	Normal
Echocardiography		Minimal pericardial effusion

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Bone Marrow Study (done on October 20,2023)

- Bone Marrow Aspiration :
    1. Dimorphic erythroid hyperplasia
    2. Markedly depressed granulopoiesis
    3. Frequent histiocytes with hemophagocytes
- Trephine Biopsy:
    - Plenty of histiocytes some of which show phagocytic content (Hemophagocytic Lymphohistiocytosis should be considered)

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Bone marrow trephine biopsy

Test	Value	Unit	Reference Range
HISTOPATHOLOGY NO: H23/1681 SPECIMEN: Bottle marked as bone marrow (trephine) biopsy. GROSS DESCRIPTION: The specimen received in formalin labelled with the patient's name and UHID number consisting of one linear grayish white soft to firm tissue, measuring about 1.3 cm in length. SECTION CODE: A1) 1x All embedded in one block. MICROSCOPIC DESCRIPTION: Sections prepared from the bone marrow biopsy specimen is approximately 80% cellular on average. Erythroid series demonstrate full range of maturation with erythroid hyperplasia, but myeloid series is depressed. Megakaryocytes are normal and adequate in number. There are plenty of histiocytes some of which show phagocytic content. Bony trabeculae are morphologically unremarkable. No atypical cell, parasite or granuloma is seen. DIAGNOSIS: Bone marrow (trephine) biopsy (Biopsy): Suggestive of secondary reactive marrow. COMMENT: As bone marrow shows a few histiocytes with ingested particles possibility of Hemophagocytic lymphohistiocytosis could be considered provided other relevant clinical and laboratory features are present. Please correlate with marrow aspiration and other biochemical findings.			

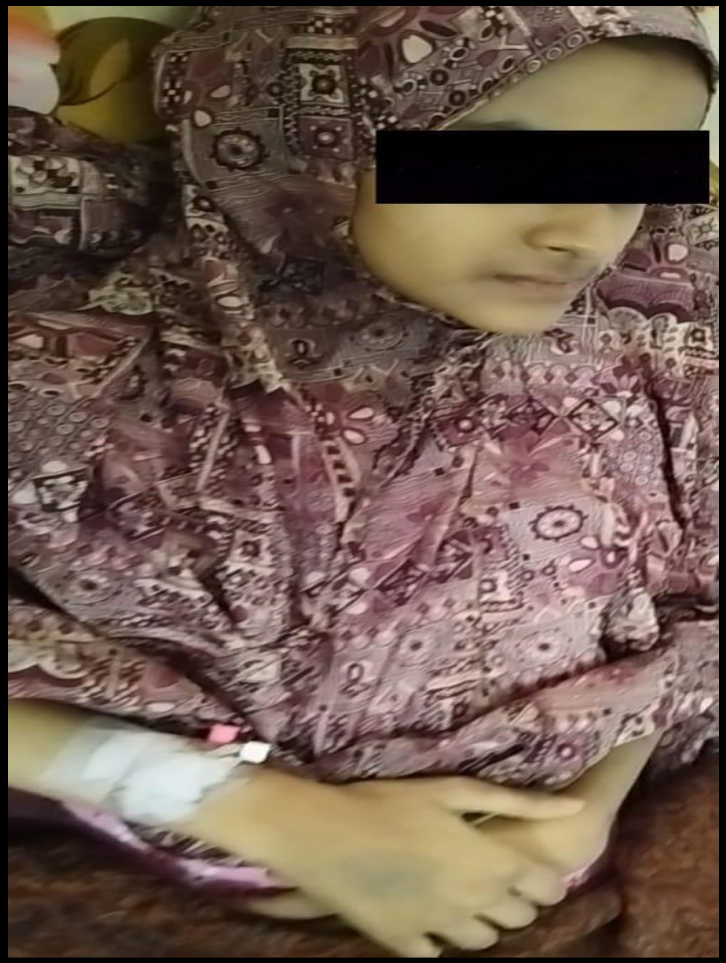
FINAL DIAGNOSIS

- Hemophagocytic Lymphohistiocytosis

? Familial Vs Secondary

Outcome

- Inj Dexamethasone was started and inj Etoposide was planned to be started but after repeated counselling she denied any further treatment with Etoposide and got discharged against medical advice.
- She died at home on November 18,2023.



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HLH-2004 diagnostic criteria

- 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 ,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
- Ferritin ≥500 µg/L
- sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL


THANK YOU!