18-12-2022
CPC

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Clinical Protocol for CPC

Mrs BK, 30 yr/ F	Unit: Internal Medicine	Clinical Discussant: Dr Mohan Kumar H
DOA: 09/06/2022	DOD: 16/06/2022	Pathologist: Dr Suvradeep

Presenting Complaints:

- Fever for ten days: documented up to 103°F, a/w chills
- Loose stools for eight days: 10-15 times /day, small volume, foul smelling, abdominal discomfort and tenesmus present
- Oral ulcers associated with throat pain for five days

No h/o jaundice, anorexia, loss of weight, hematemesis, melena
No h/o decreased urine output/ hematuria/ proteinuria/ dysuria
No h/o cough /shortness of breath /chest pain /palpitations
No h/o headache/ loss of consciousness/ dizziness, No other h/s/o a connective tissue disorder

Past history, **Personal and Family history:** Not Significant
Treatment history: For these above complaints, she visited a local hospital where she was started on iv antibiotics (ceftriaxone). Following initiating IV fluids/antibiotics, she noticed generalized swelling /redness over the arms, lower limbs and trunk. Subsequently, she was referred to PGI.

On examination:

The patient was alert, cooperative and conscious and oriented to time, place and person
BP – 100/70 mm Hg, **PR** – 120/min, **RR** – 18/min, **SpO_2**: 98% on room air **Temp:** Afebrile
Bilateral pitting pedal oedema up to the knee, generalized lymphadenopathy involving bilateral cervical, axillary and inguinal regions, maximum size 2x2 cm in the cervical region. No pallor, icterus, cyanosis and clubbing
Skin: Generalized erythema, palmoplantar hyperemia, oral ulcers, angular cheilitis
Abdomen: Soft, non-tender, liver palpable 3 cm below the right costal margin. Liver span 16 cm, tip of spleen palpable, bowel sounds normal. **Respiratory system:** B/L vesicular breath sounds heard **CVS:** S1/S2 normal, no S3/murmur **CNS** GCS – E4V5M6, Pupils B/L normal in size and reactive to light, No focal deficits.

INVESTIGATIONS:

Date	8/6/22	10/6/22	14/06/2022	16/6/22
Haemoglobin (g/dL)	9.9	9	7.6	8.2
Total Leucocyte count	33,200	32,100	29,400	73,800
Differential (N/L/M)	34/58/5	36/51/11	48/38/8	52/27/15
Platelet count (x10^3)	222	185	146	178
Sodium/Potassium	137/3.5	135/3.7	134/4.3	133/5.98
Urea/Creatinine	26/0.67	18/0.63	21/0.7	24/1.73
AST/ALT/Alkaline Phos	110/128/-	371/193/518	2491/599/720	36/1110/583
Bilirubin- Total/Direct	3.3/2.2	3.7/3 4	6.6/5.9	10.2/8.4
Total Protein/Albumin	4.4/2.2	4.8/2.0	6.0/1.6	7.2/1.8
Calcium/Phosphate	7.0/1.2			7.5/10.4
Coag (PT/PTI/INR/APTT)	45/30/3.14/40	65/21/4.5/45		71/19/4.9/102
Fibrinogen (g/L)		2.94		1.0
D dimer (ng/mL)		1002		1407
LDH (U/L)			1455	4301
CRP (mg/L)			163	112

ABG:

Date	8/6/22	15/6/22	16/6/22 (post-dialysis)
pH	7.406	7.24	6.706
pCO2	31	23	52.3
pO2	68.4	44	68
HCO3	19	9.9	6.4
Lactate	3.9	12.4	19.5

PBF (15/6/22) - Moderate anisopoikilocytosis. Normocytic normochromic red cells admixed with microcytes, macrocytes, ovalocytes and a few spherocytes. Leucoerythroblastic picture. Left shift is seen. Nucleated RBC- 4/100 WBCs, Myelocytes-2, N48 L28 M19 E3, Neutrophils show cytoplasmic vacuolations. Platelets adequate; few large forms and platelet clumps noted.

Malaria antigen Negative **IgM Dengue (sent twice)** Borderline
IgM Leptospira Negative
IgM Scrub Negative
Widal Test Negative
Hepatitis A / Hepatitis E antigen Negative
HIV / HBsAg/ Anti HCV – Negative
CMV IgM Reactive **CMV PCR** - Negative

Blood Culture Sterile
Procalcitonin: 3.72 ng/mL (16/06/2022)

Iron Profile (15/06/2022)
Serum Iron – 45 µg/dL **TIBC** – 153 µg/dL **Percentage saturation** – 29.3 % **Serum Ferritin** – 687 ng/mL
Ferritin 11,778 (15/06/2022)

Triglycerides 180 mg/dL
ANA – Negative (twice) **C3 -** 16 mg/dL **C4-** 13 mg/dL

Stool RME (twice) Pus cells +, no ova, cyst, atypical organism

USG Abdomen (8/6/22)
Liver - 18 cm, normal echotexture, outline normal, portal vein normal, spleen- 13.9 cm,
Right Kidney 9.5cm, Left Kidney 8cm – both showing normal echogenicity, with normal CMD

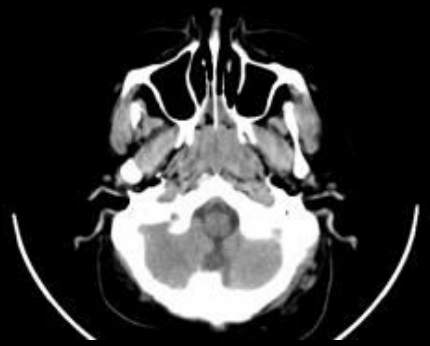
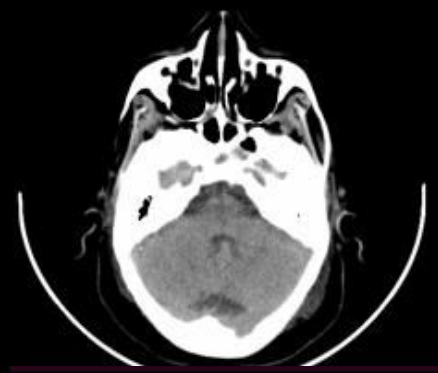
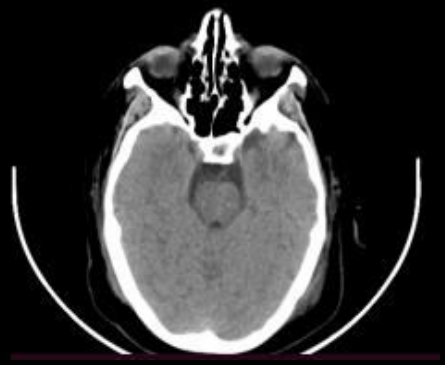
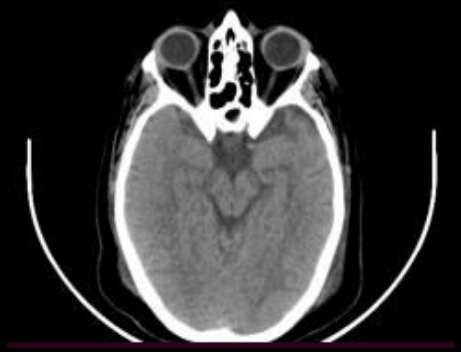
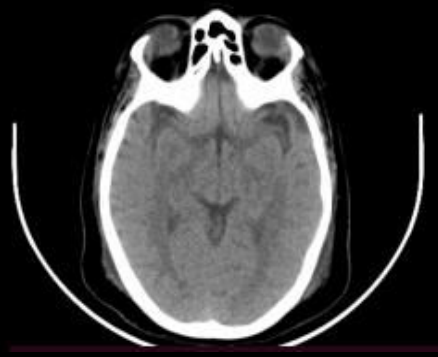
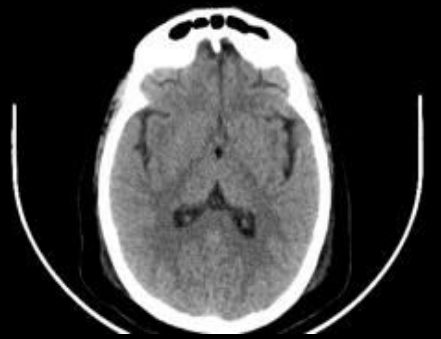
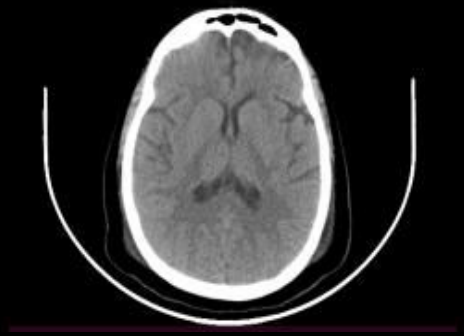
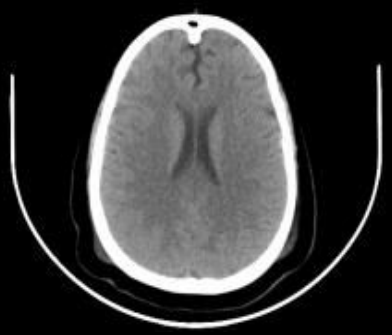
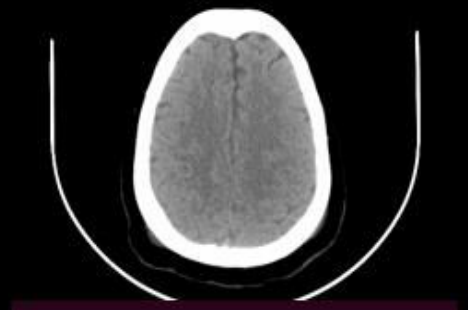
CECT Abdomen (15/6/22)
Hepatosplenomegaly mesenteric and retroperitoneal lymphadenopathy Mural thickening with the differential enhancement of large bowel loops – infective
Moderate ascites

FNAC Lymph Node (15/06/2022) - left posterior cervical LN - reactive lymphoid hyperplasia

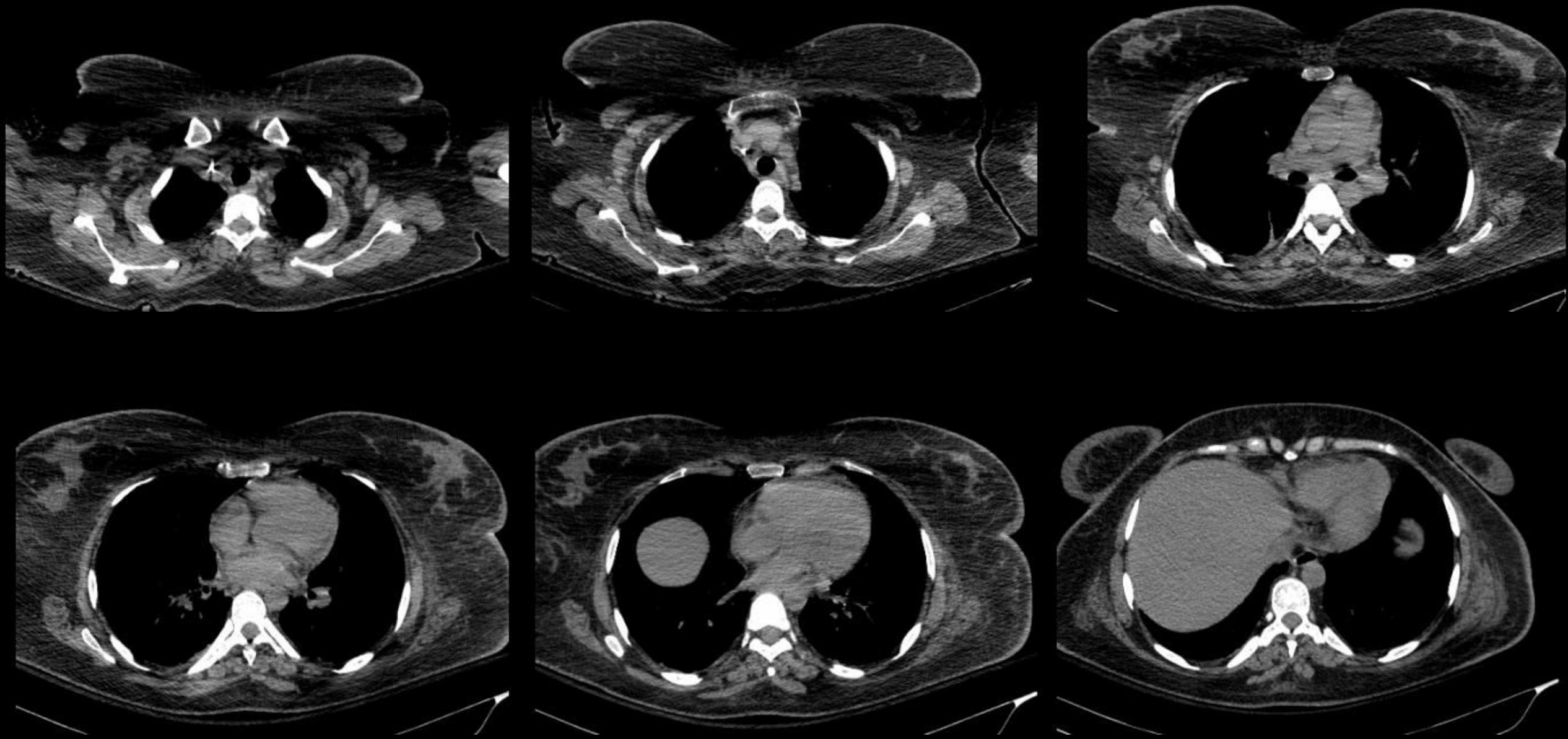
Bone marrow examination (16/6/22): Hypercellular bone marrow show infection/sepsis-associated changes and evidence of increased Hemophagocytic activity

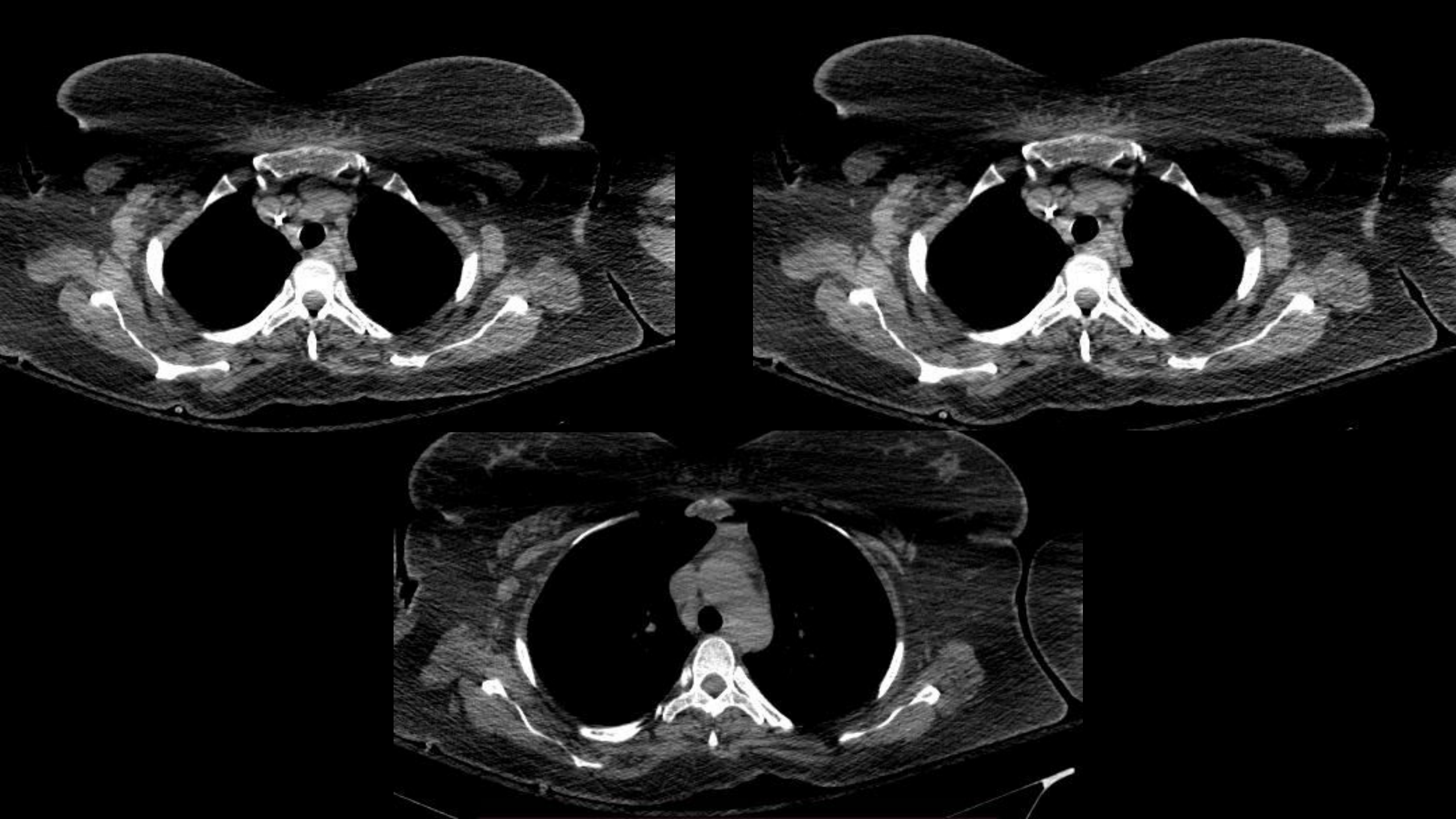
NCCT Head

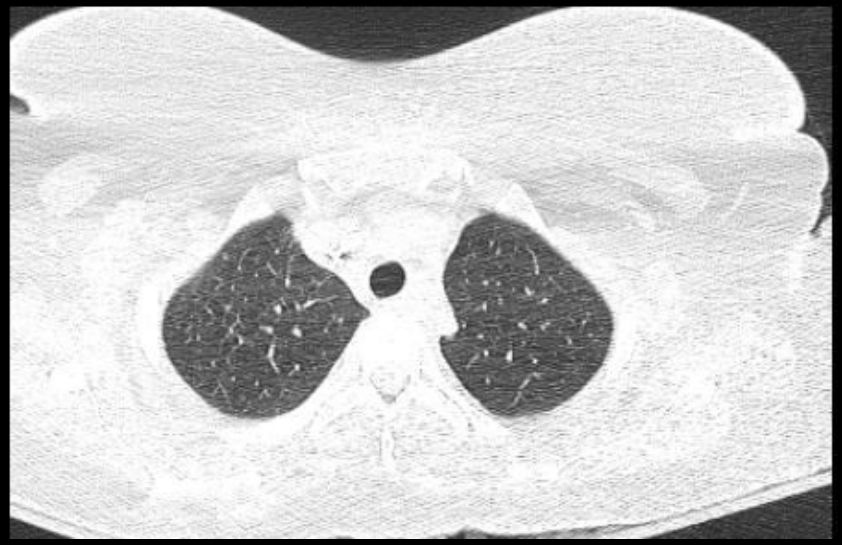
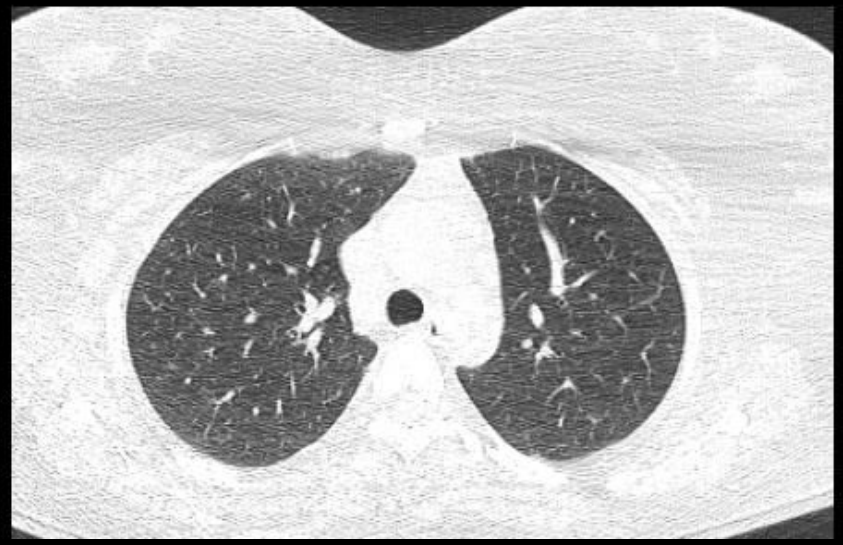
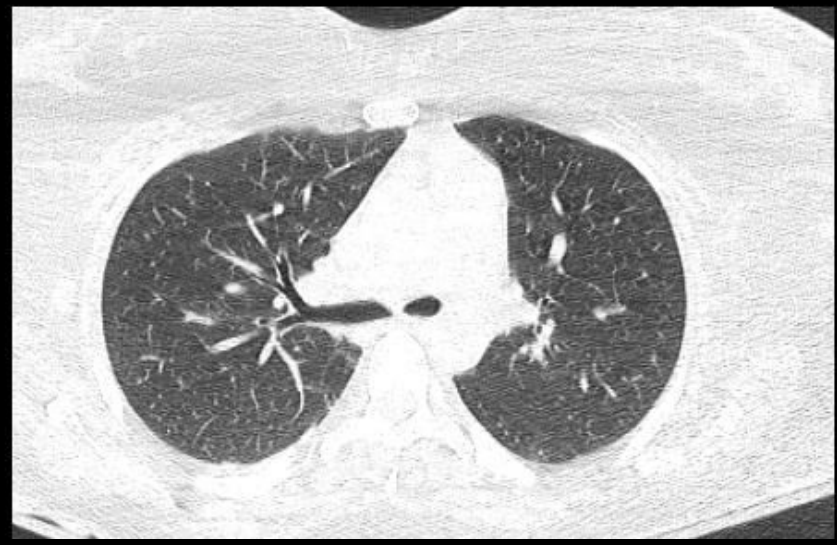
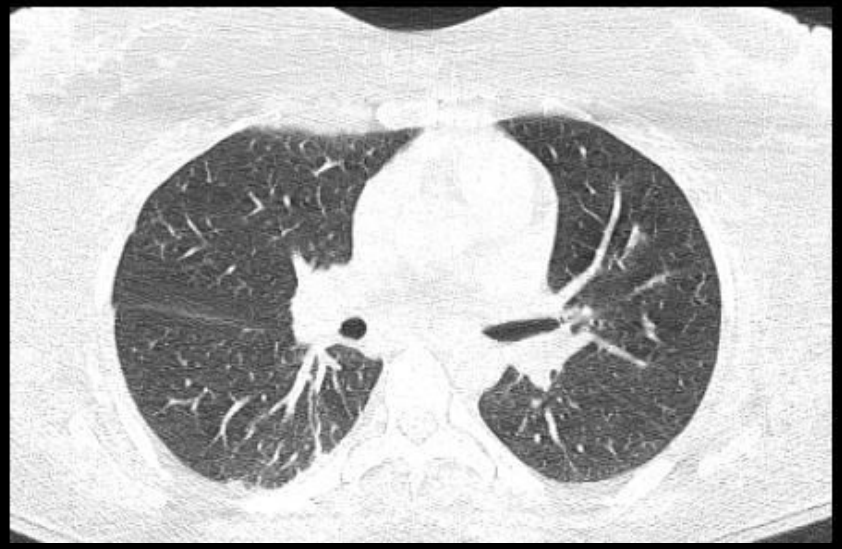
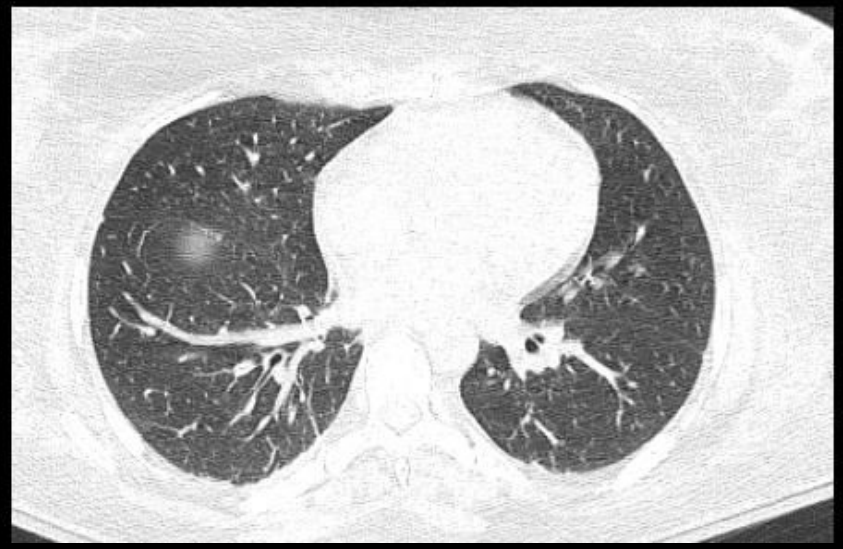
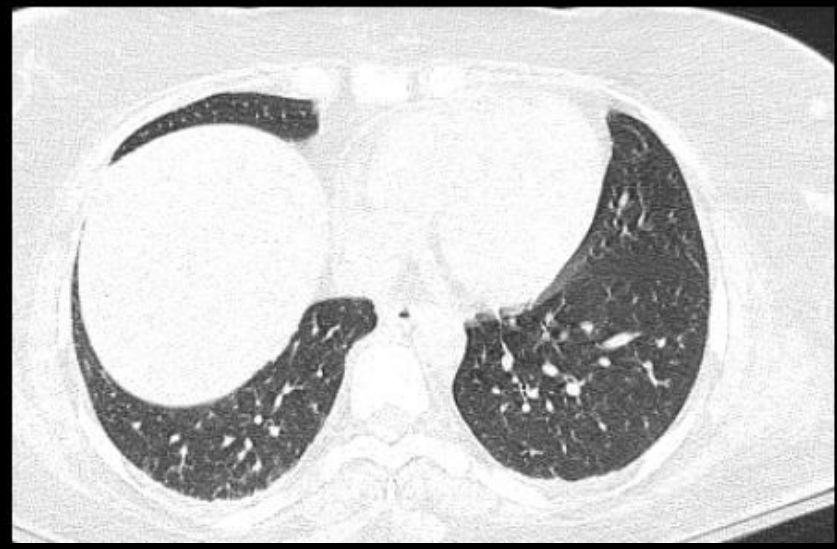
8/6/22

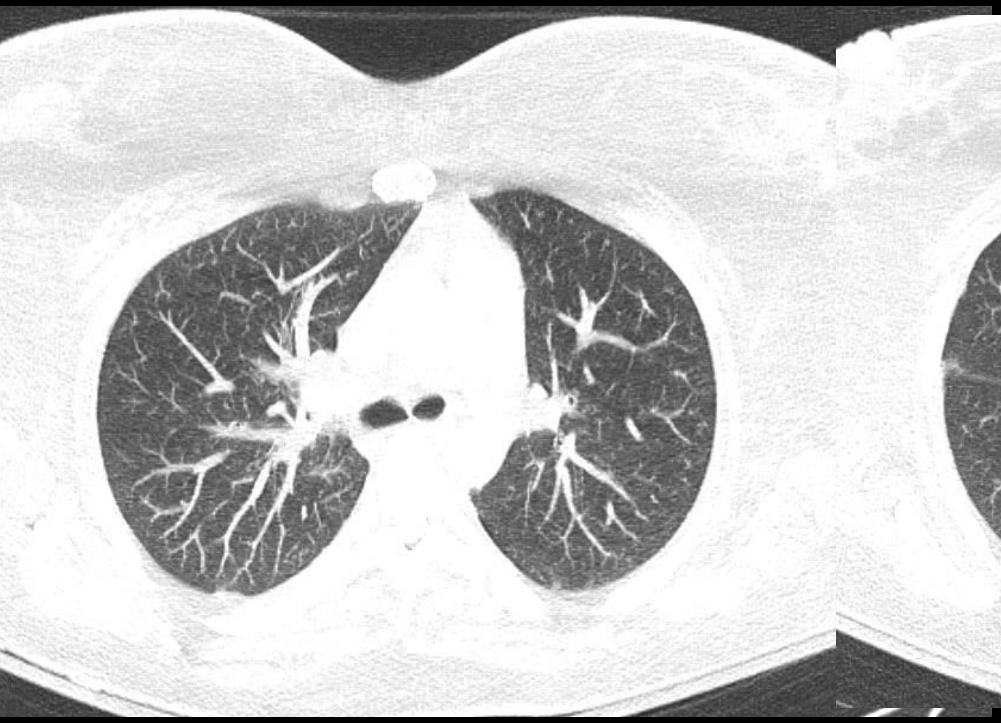
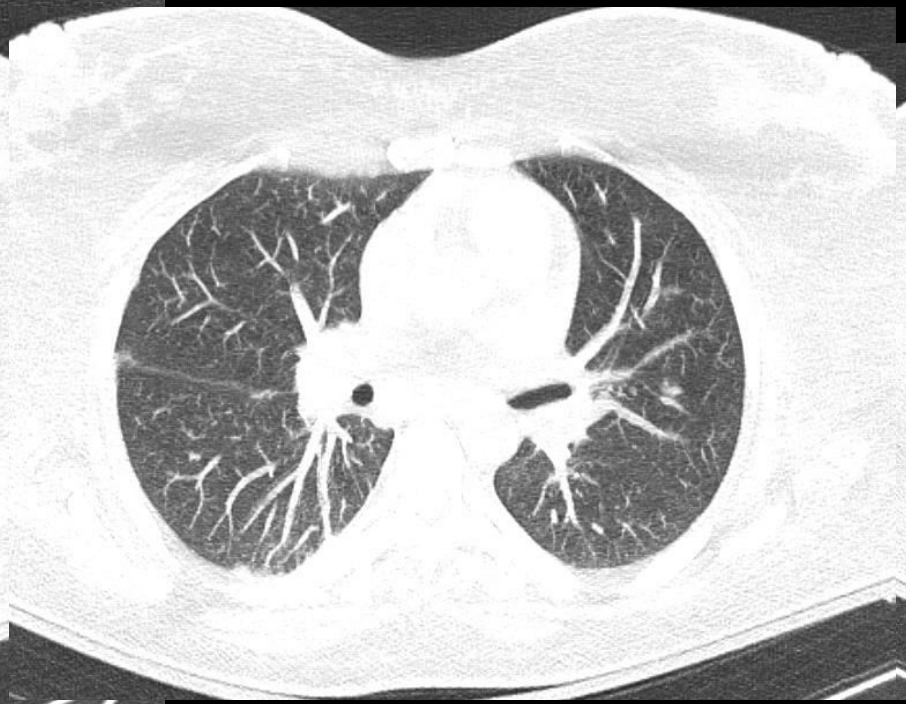
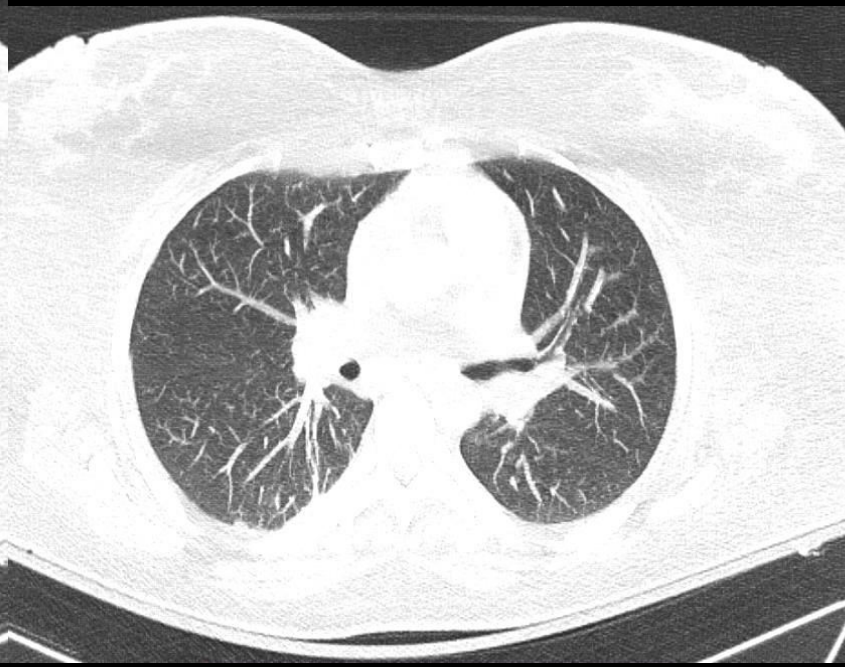
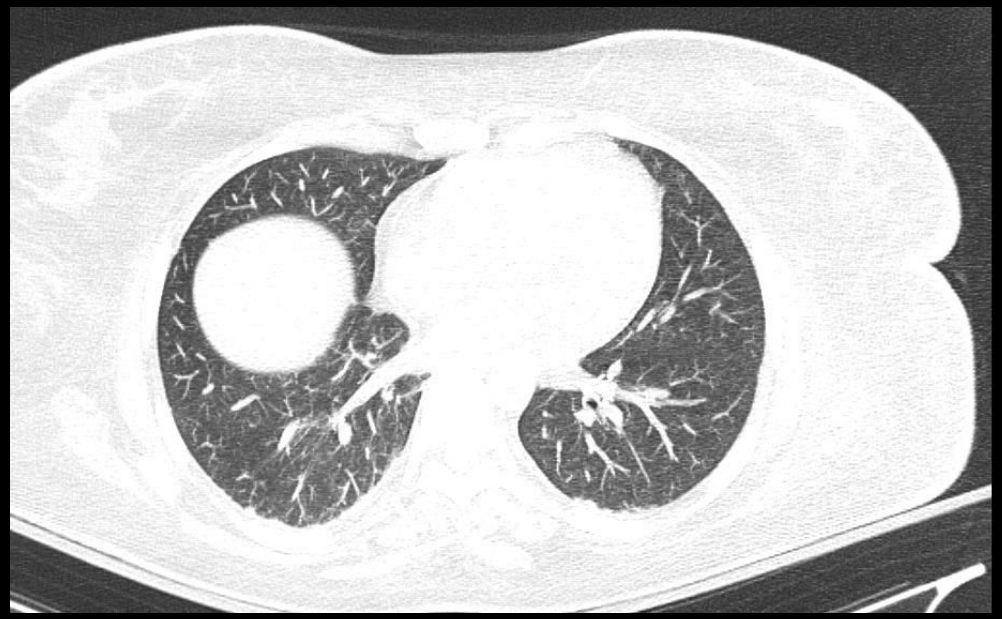
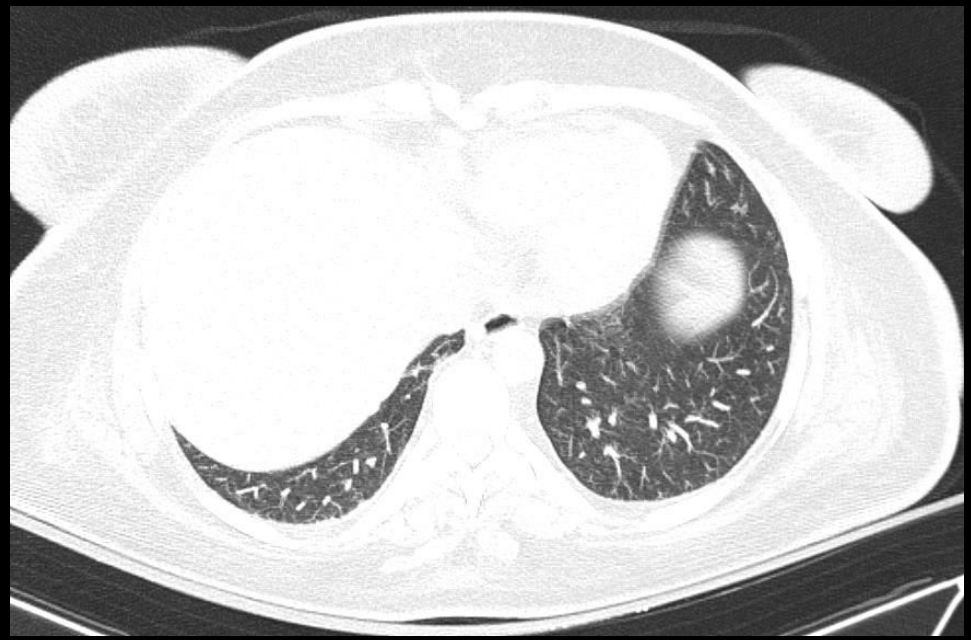










HRCT Thorax
8/6/22

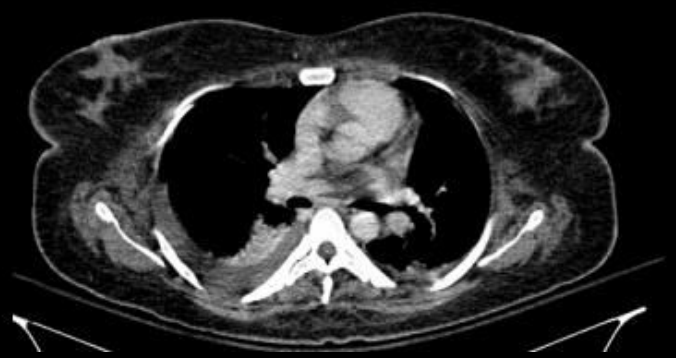
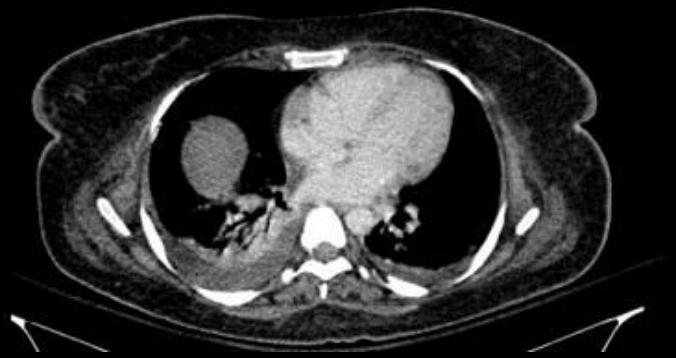
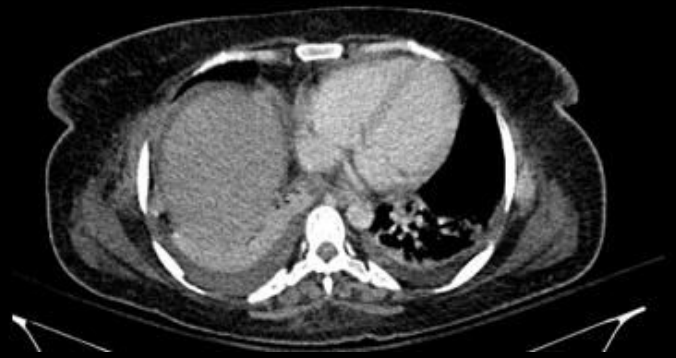
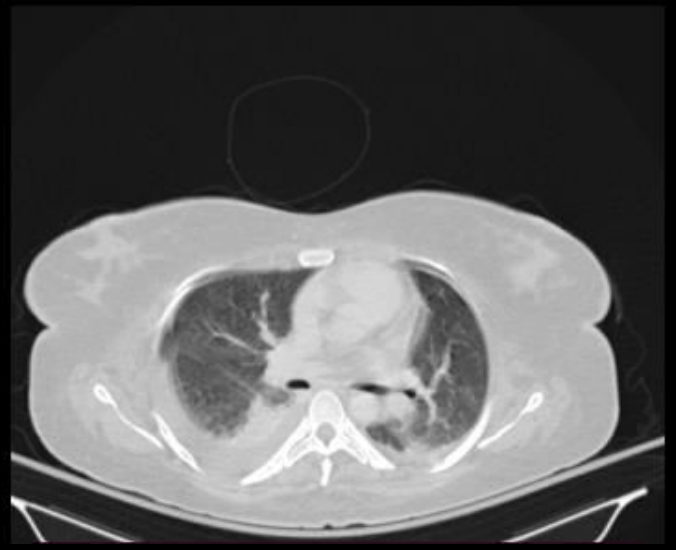
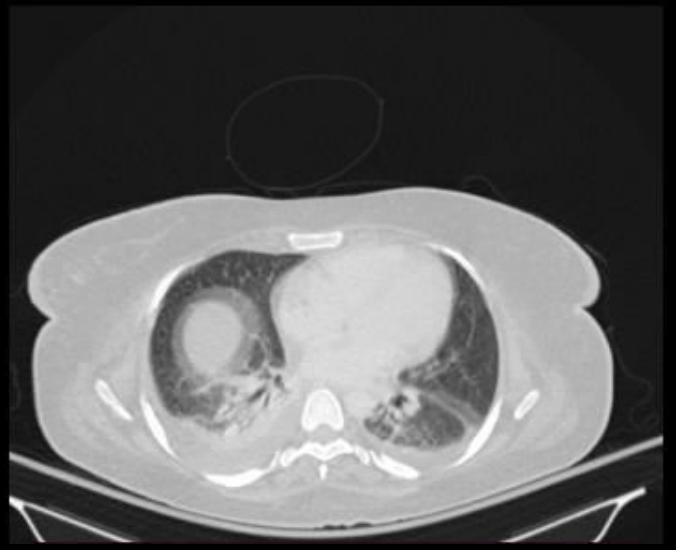
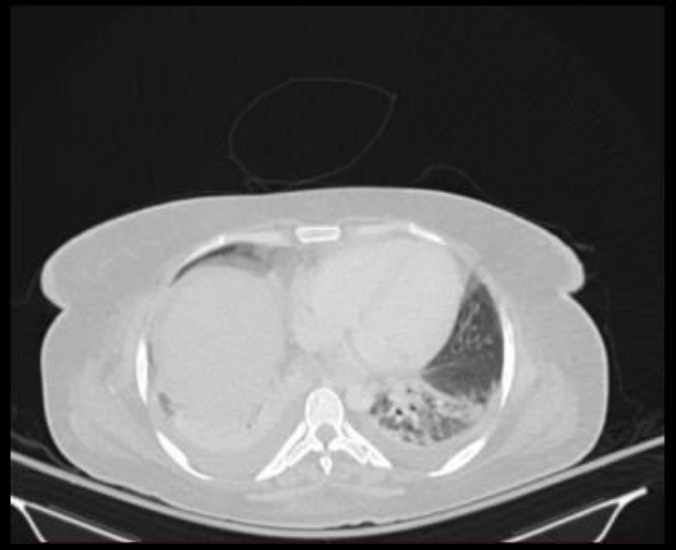


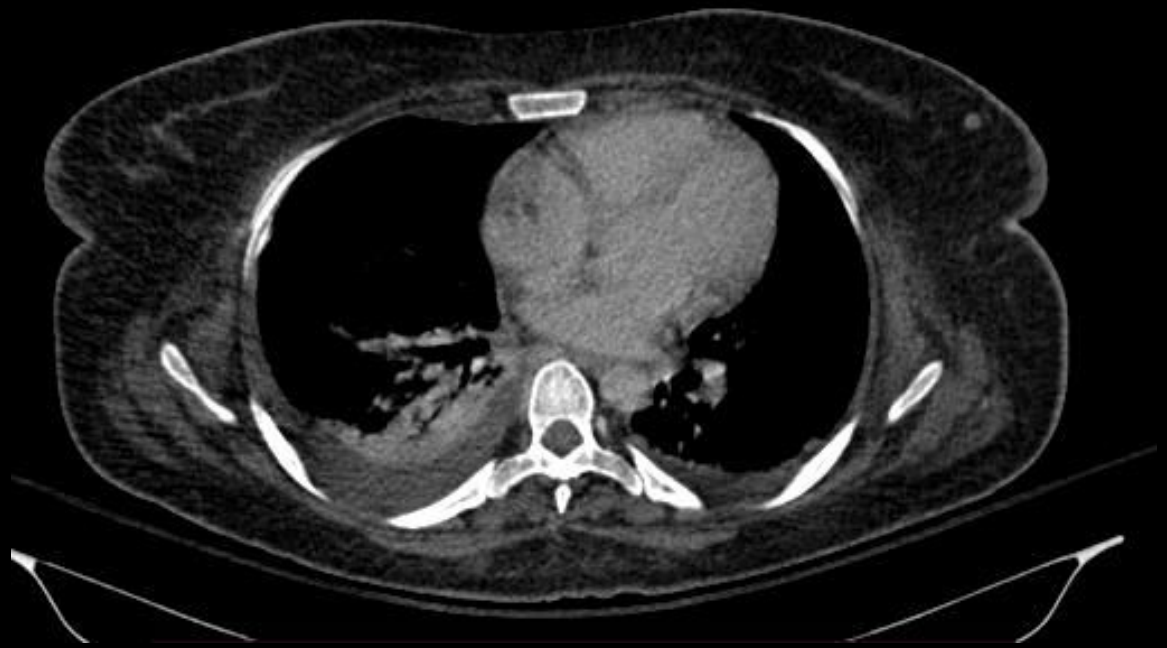


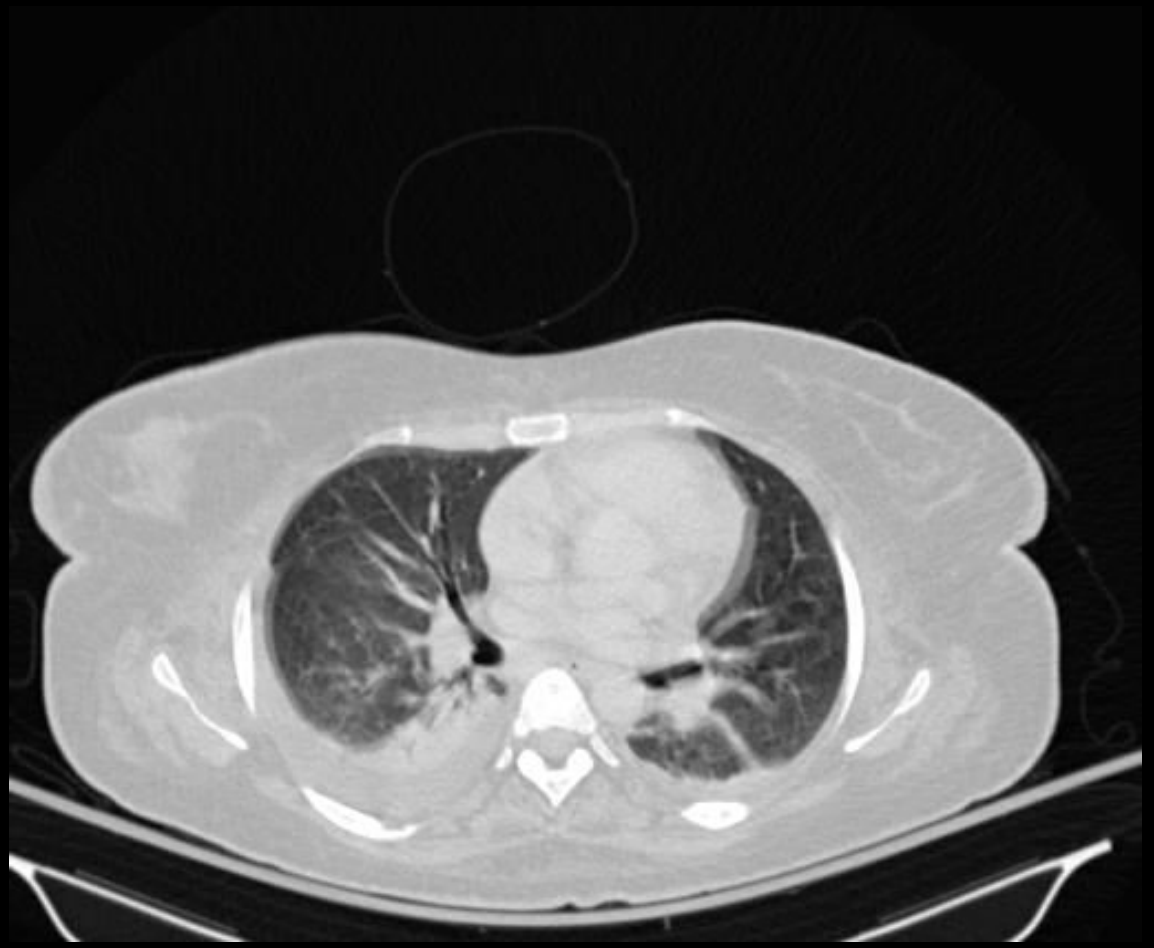







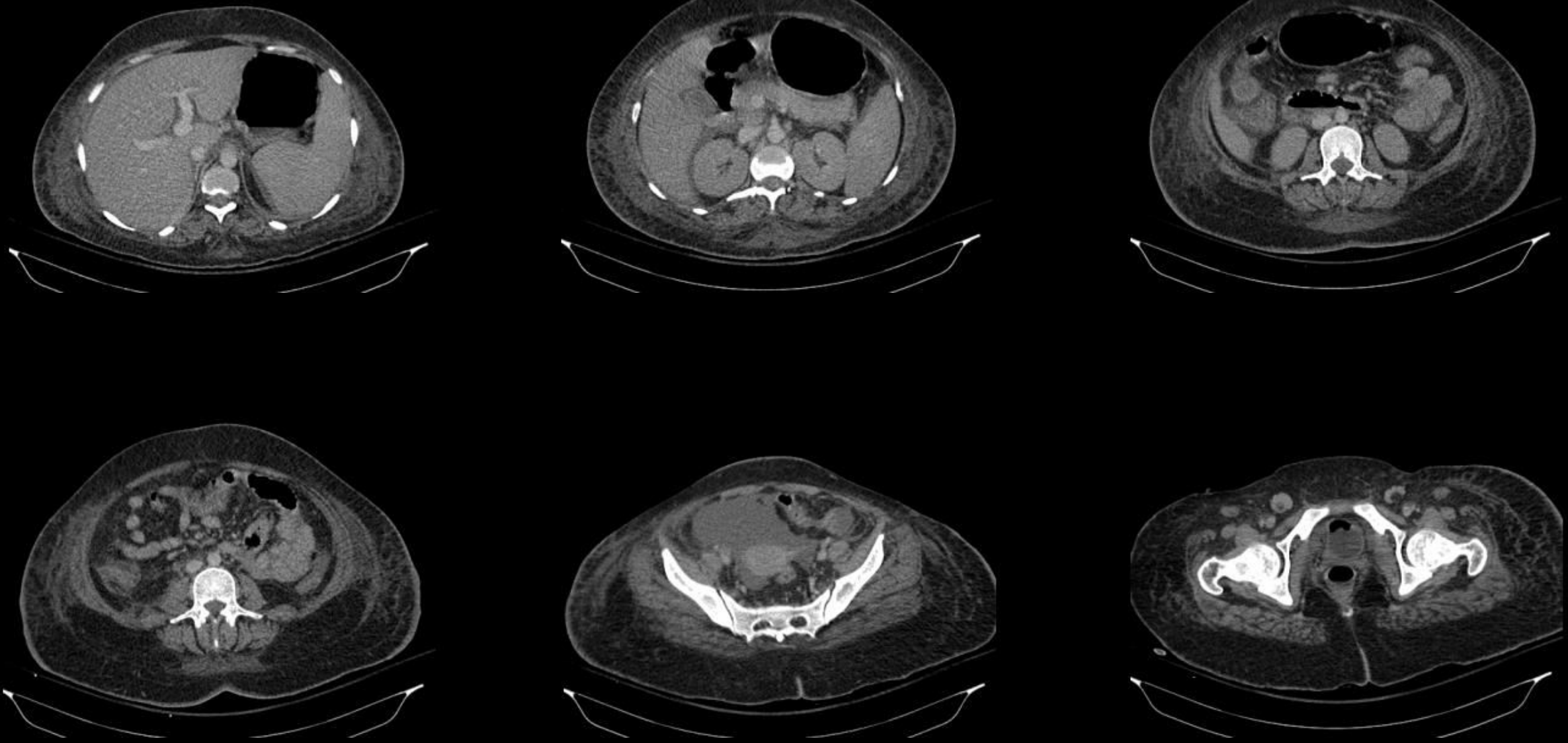






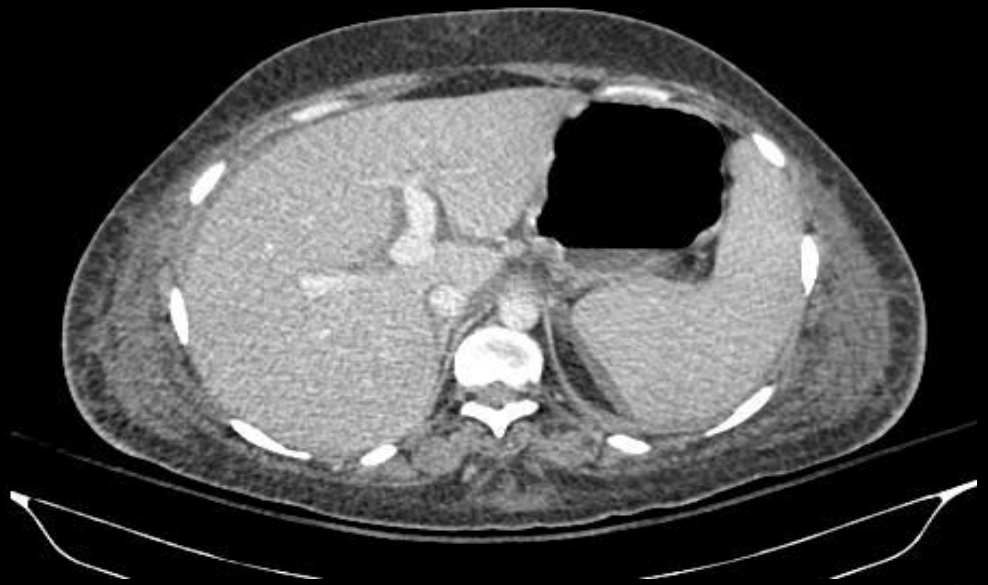
CECT Abdomen
16/6/22

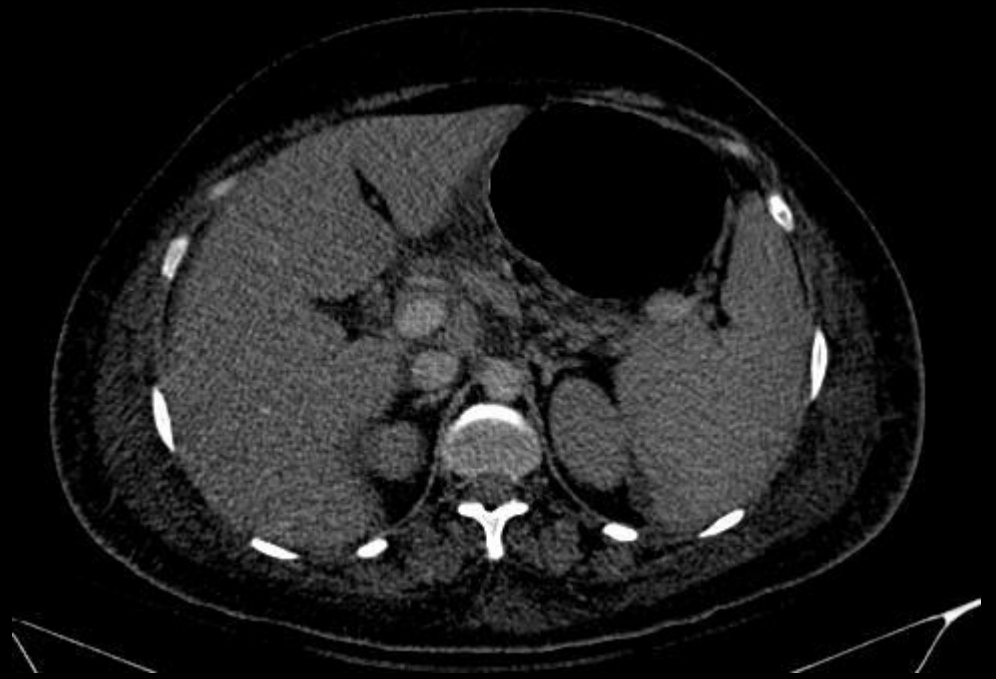







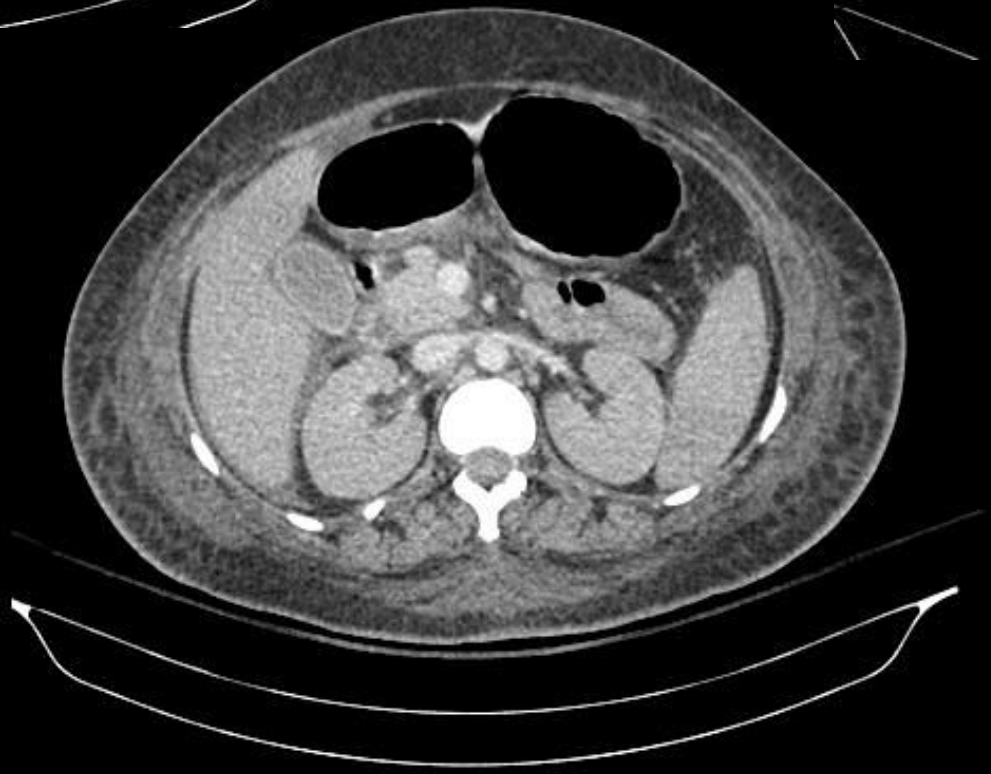


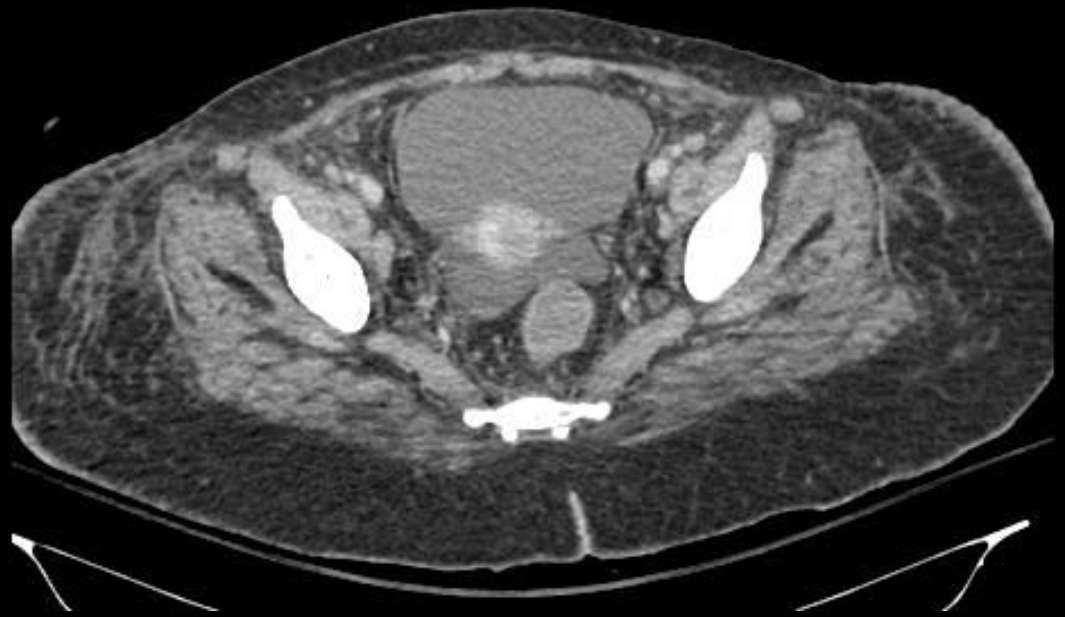


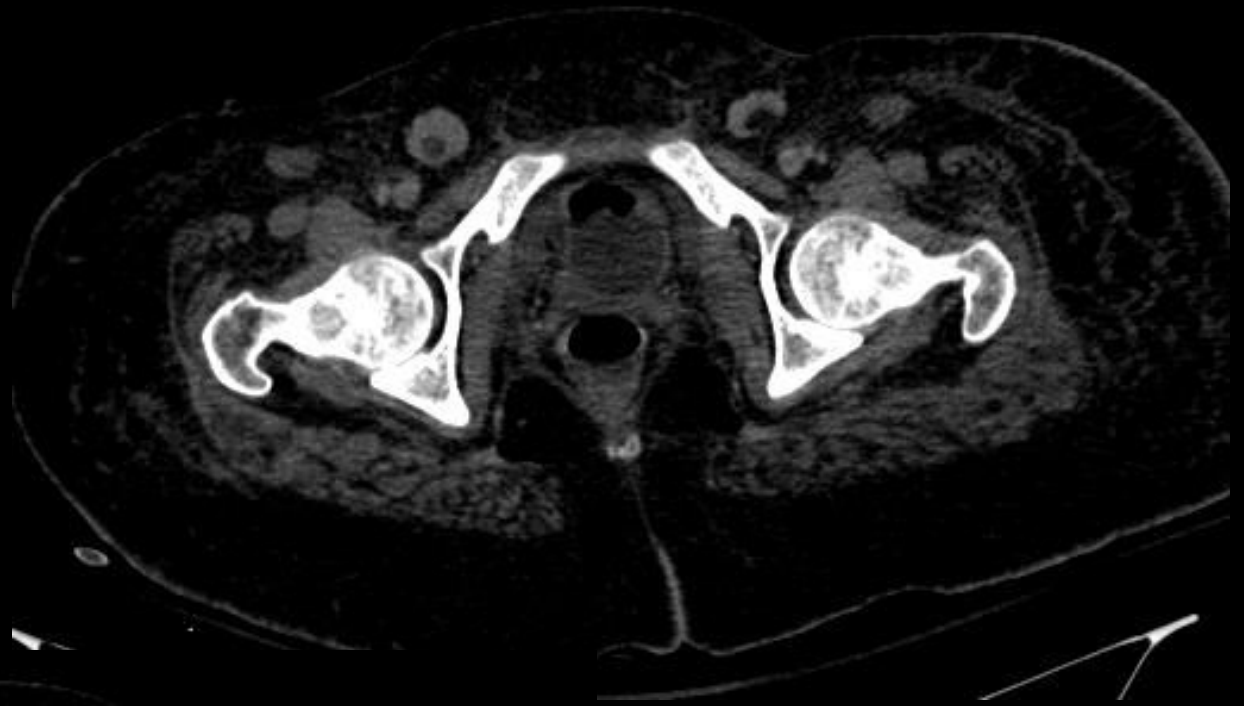


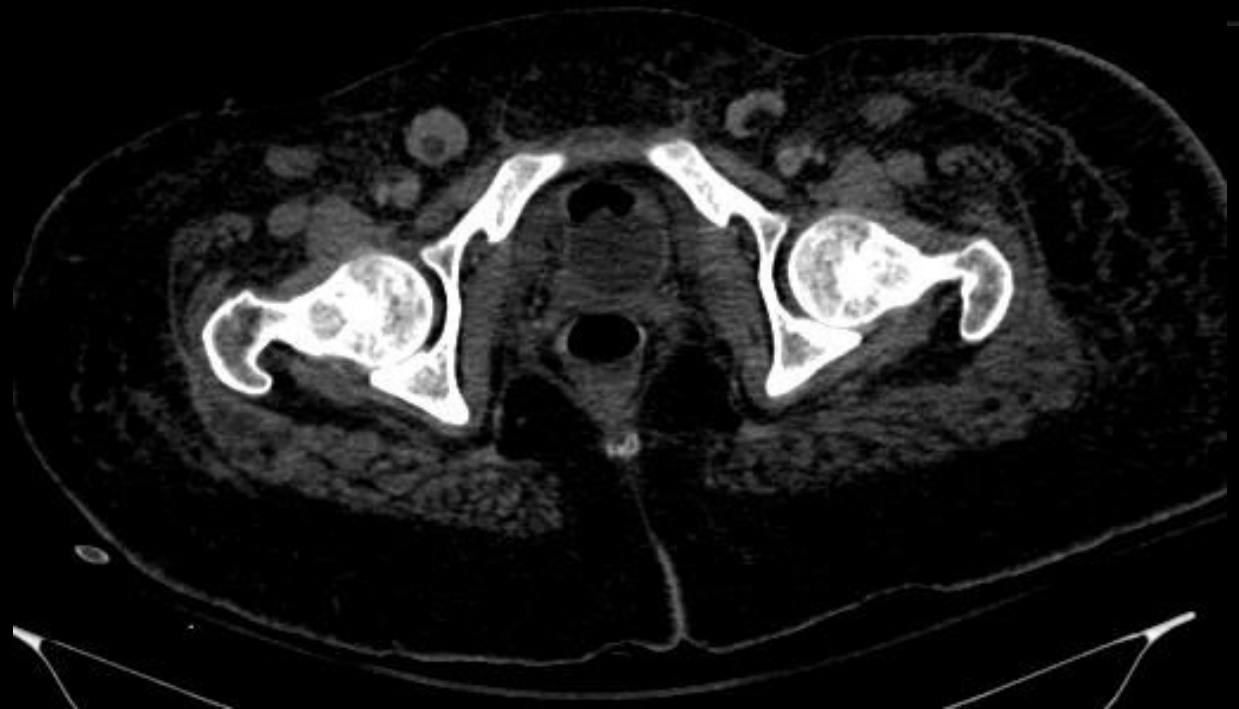


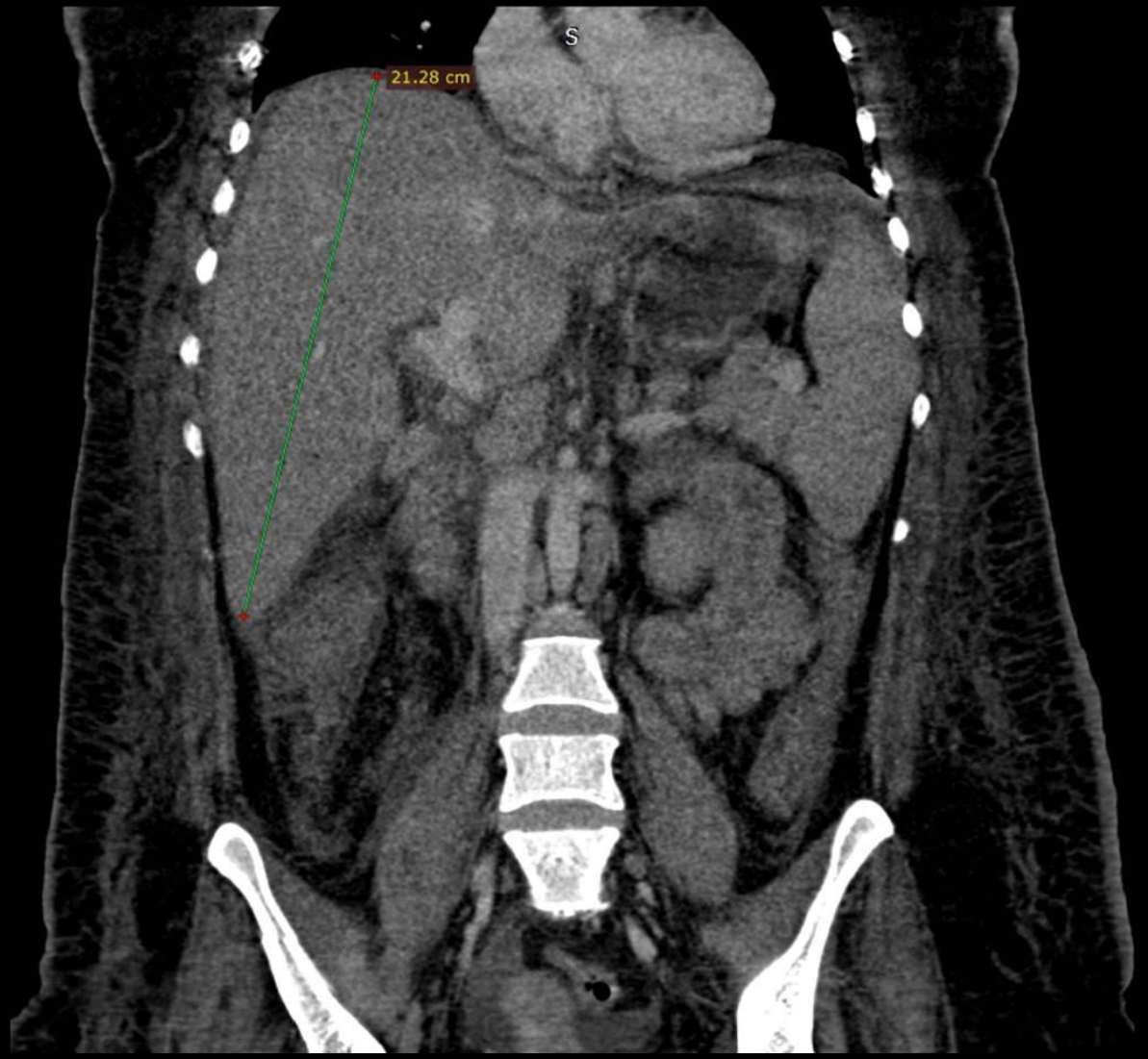








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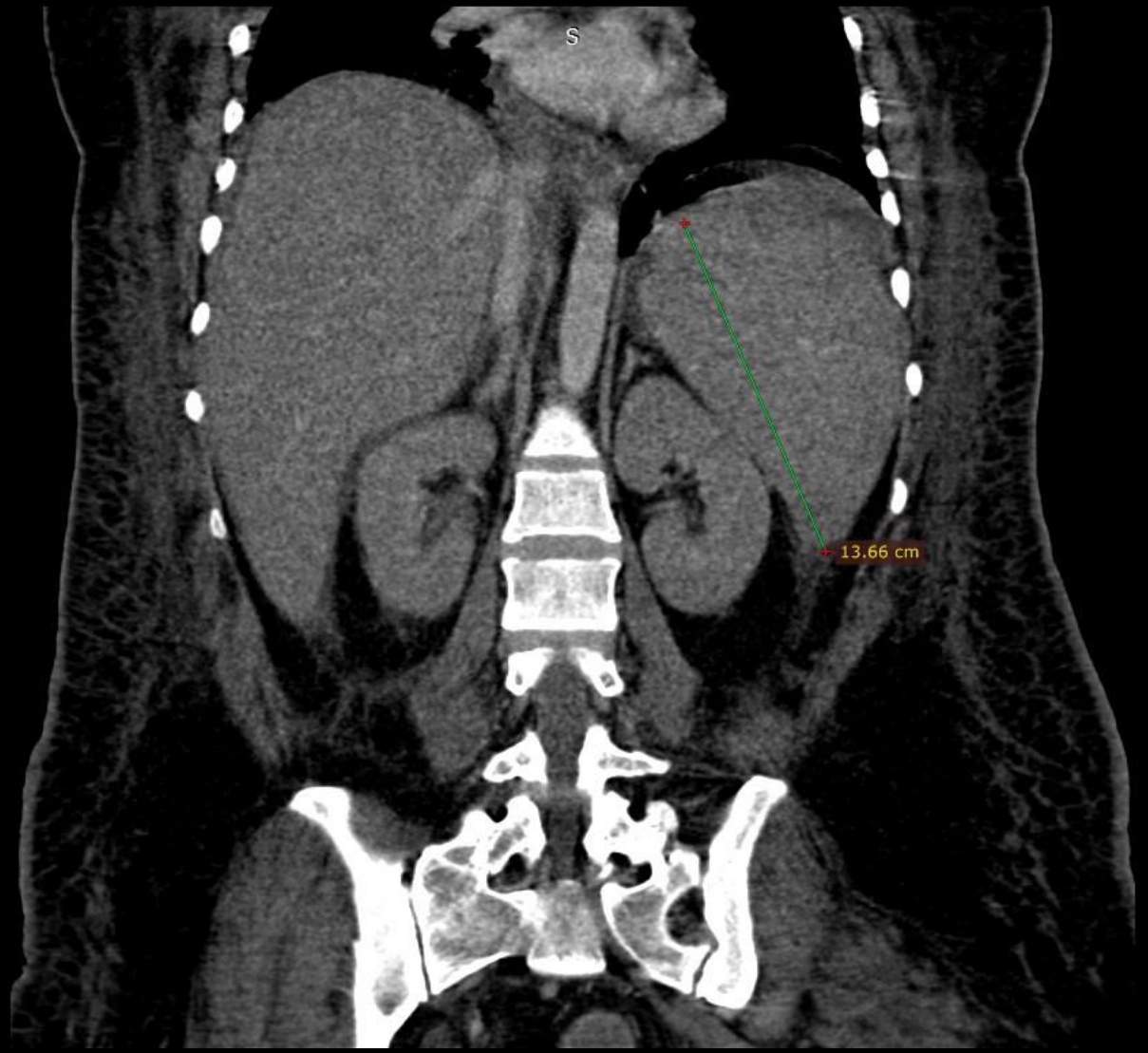
21.28 cm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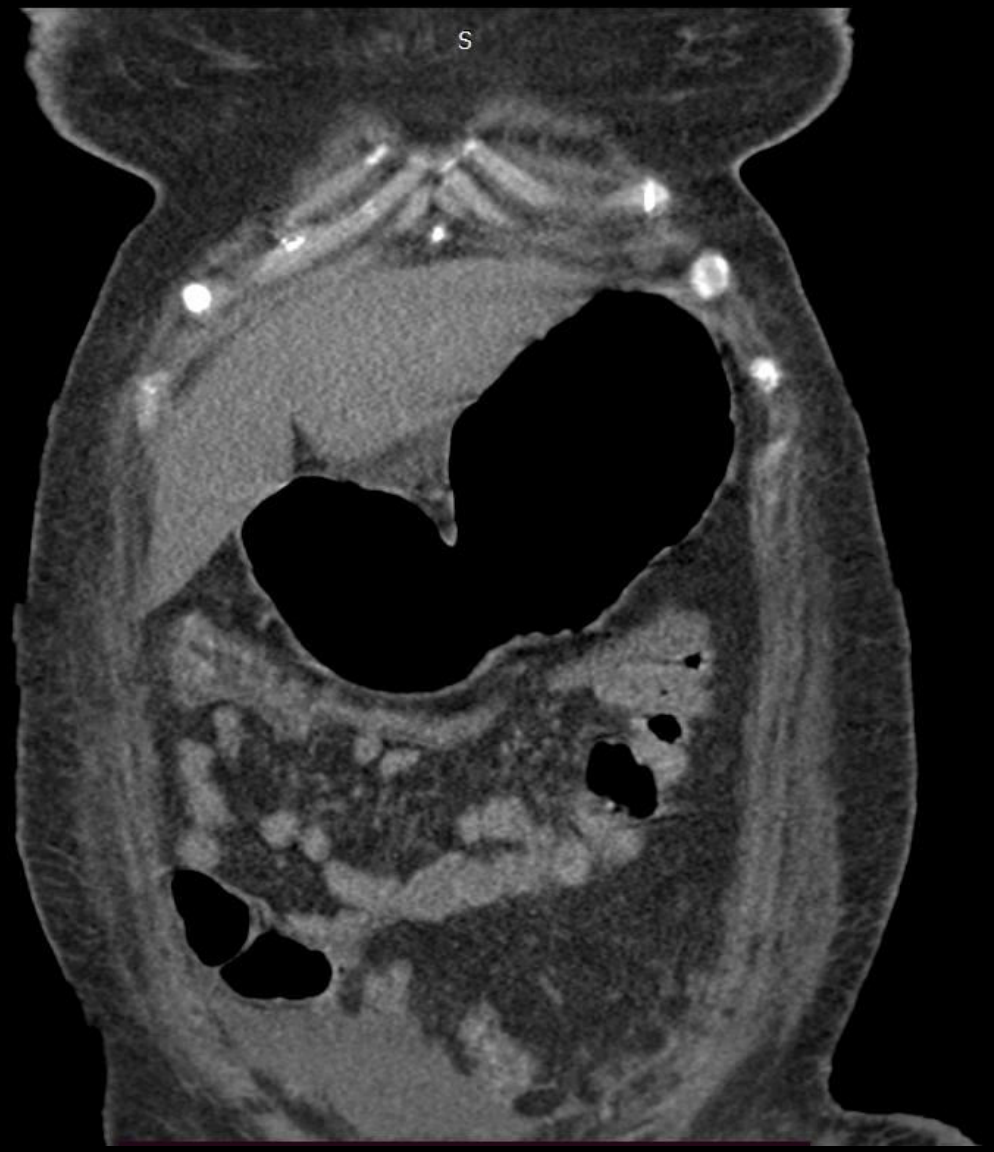
13.66 cm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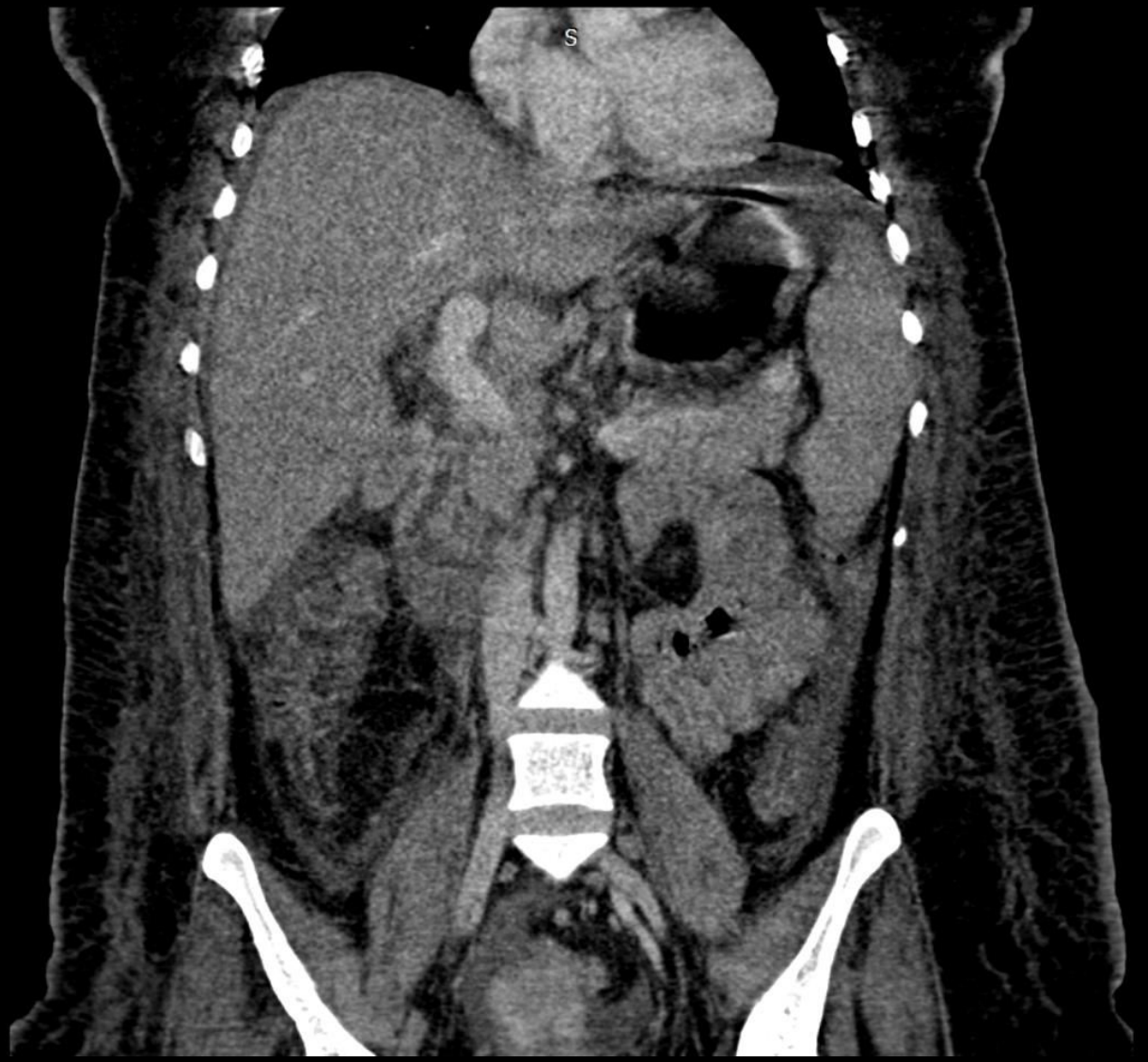
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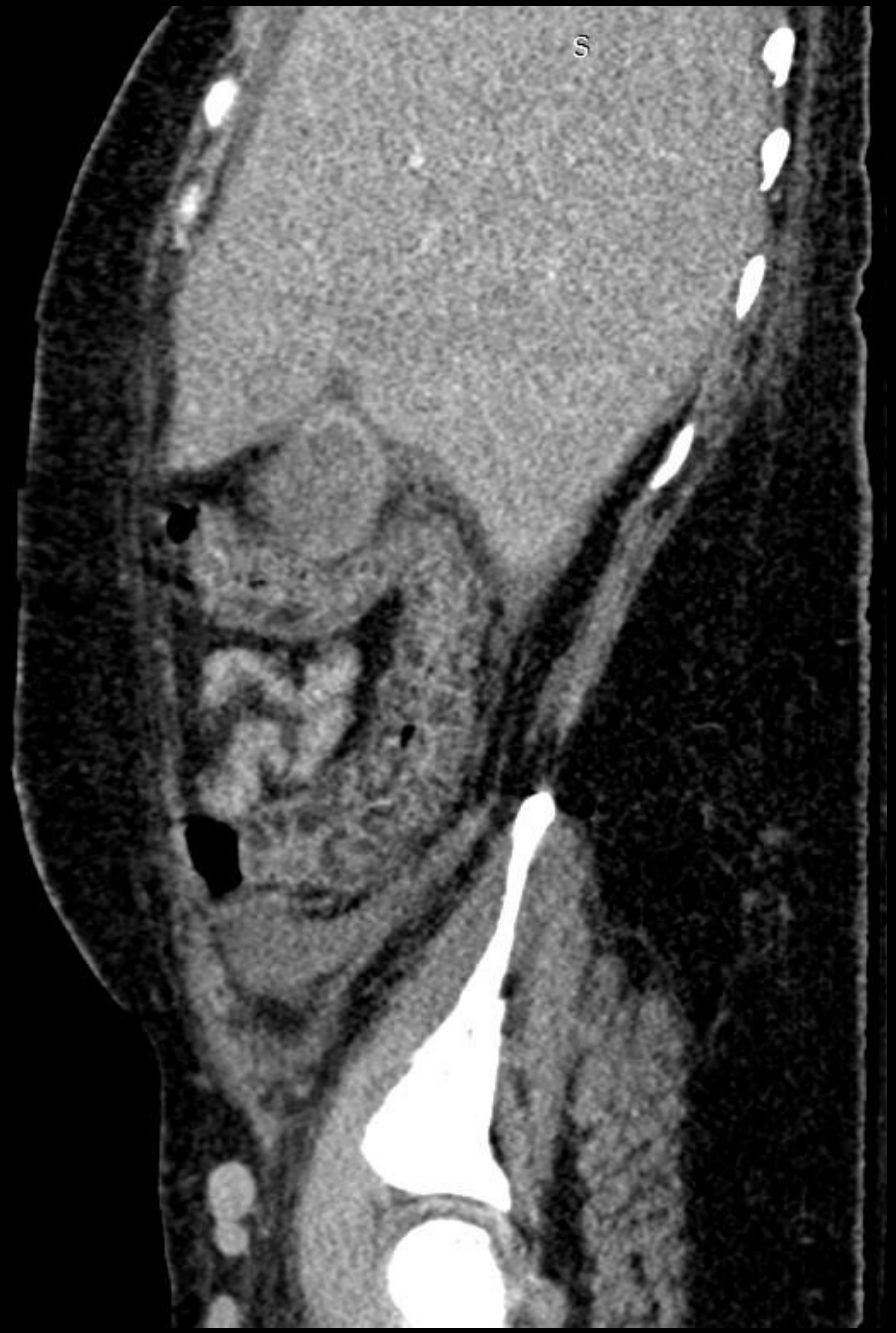
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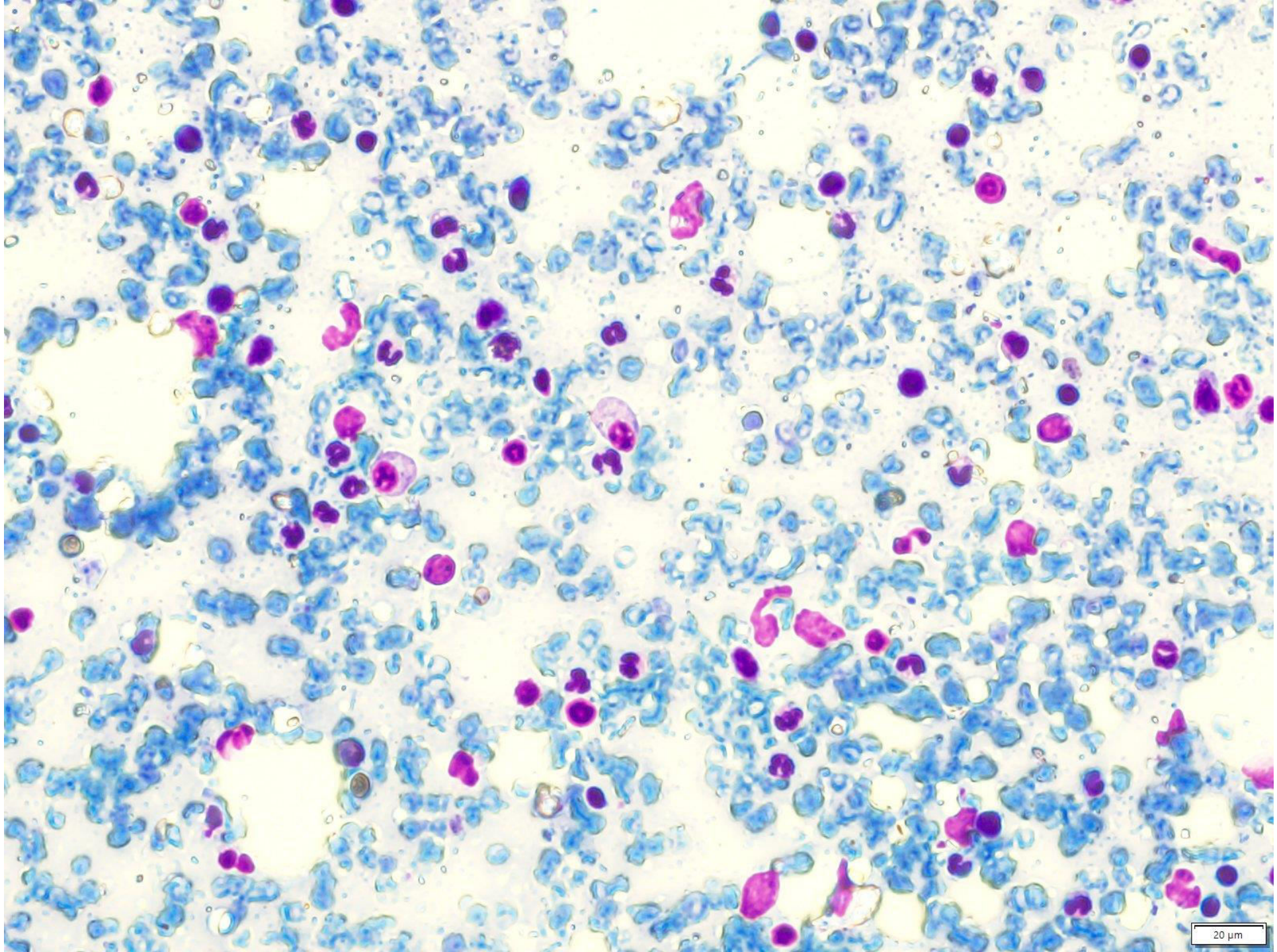
Radiological Impression

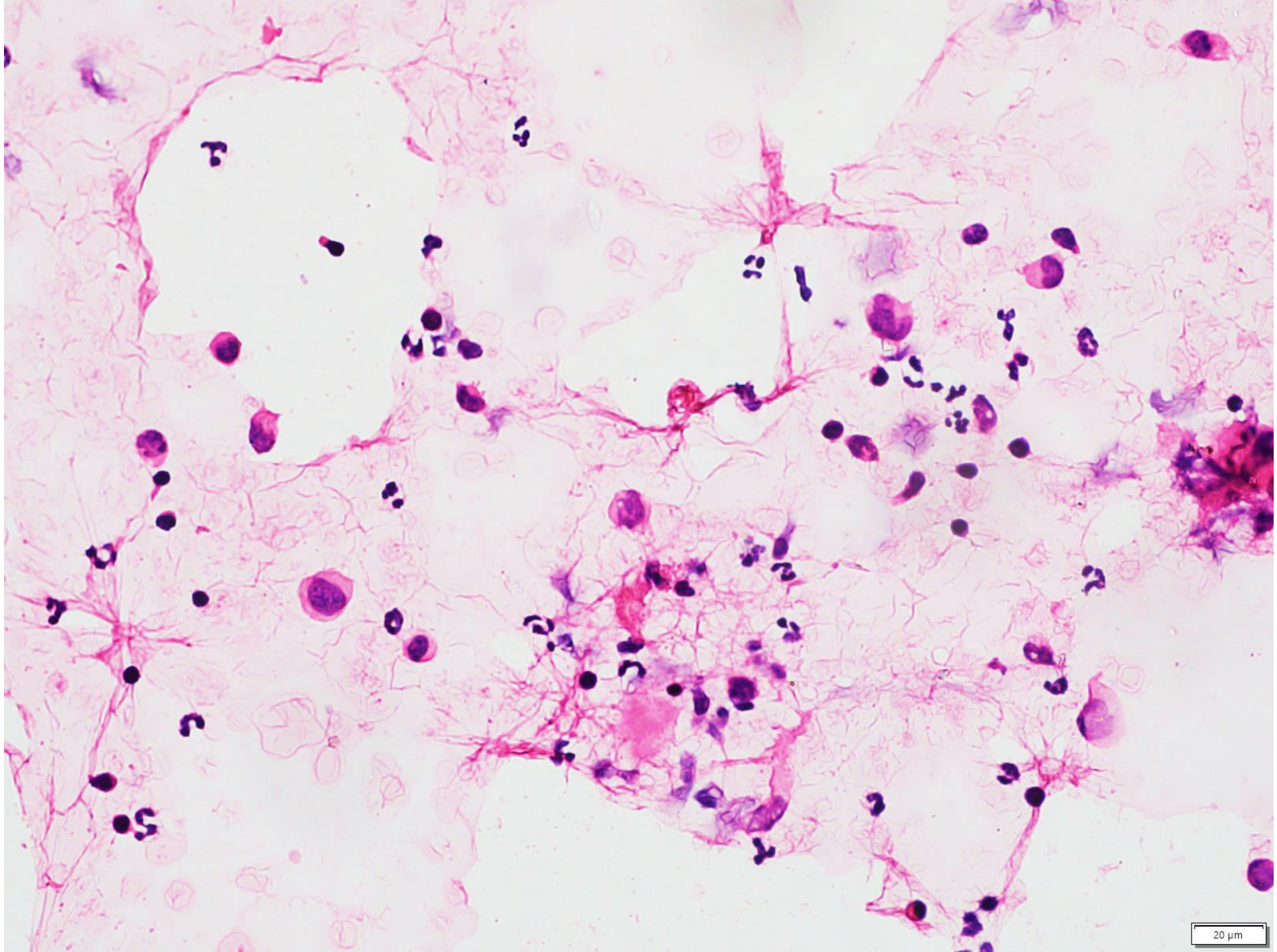
- Hepatosplenomegaly
- Enlarged portal and axillary lymph nodes with predominantly sub centimetric mesenteric, retroperitoneal and inguinal lymph nodes.
- Mild ascites, bilateral pleural effusion and diffuse subcutaneous oedema.
- Diffuse long segment bowel wall thickening with submucosal fat proliferation involving ascending, transverse and descending colon, with mild pericolonic fat stranding – Likely Infective colitis.

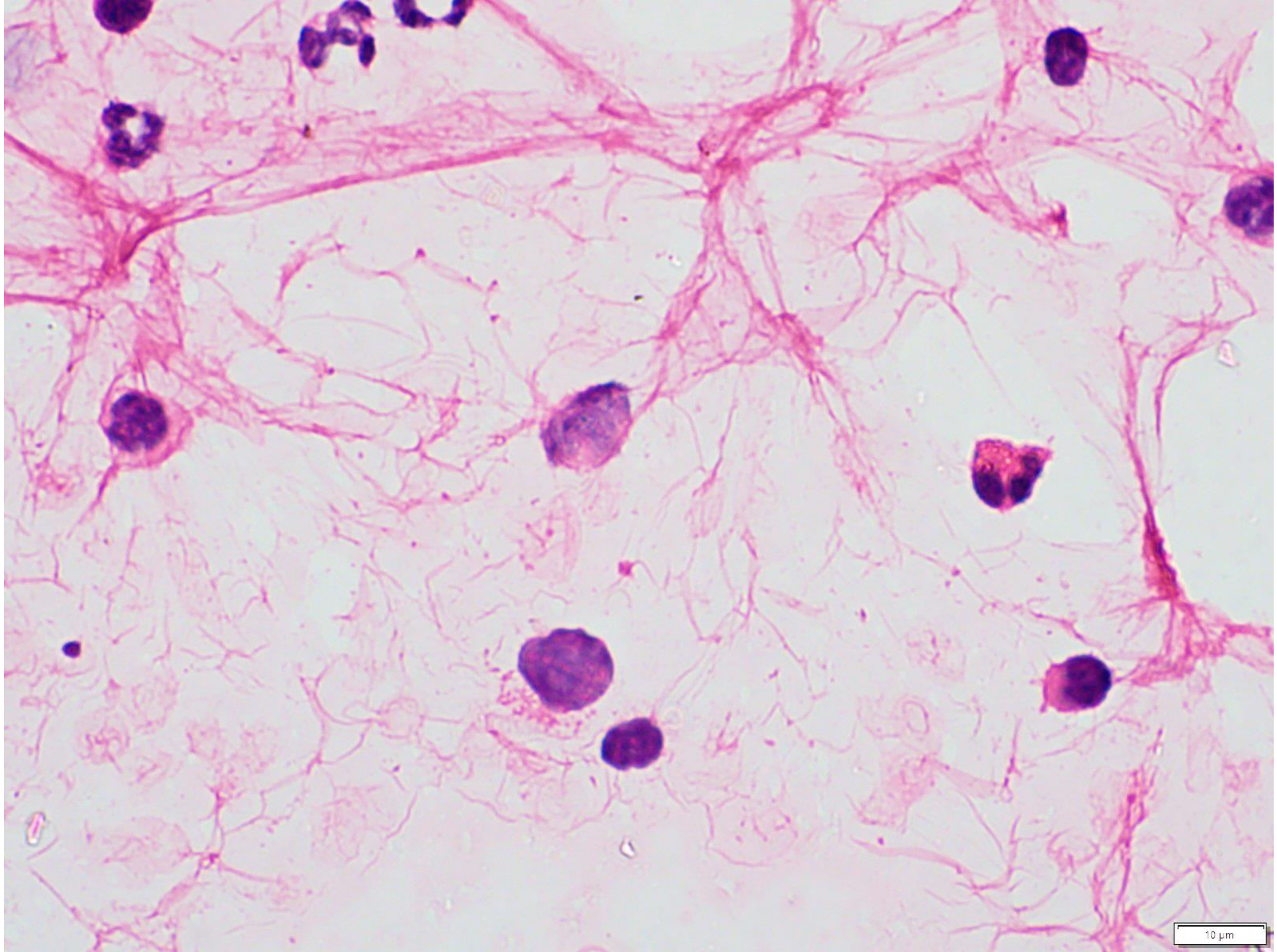
? Clostridium difficile colitis ?? CMV colitis

FNAC

A- 3213/2022


20 µm


20 µm


10 µm

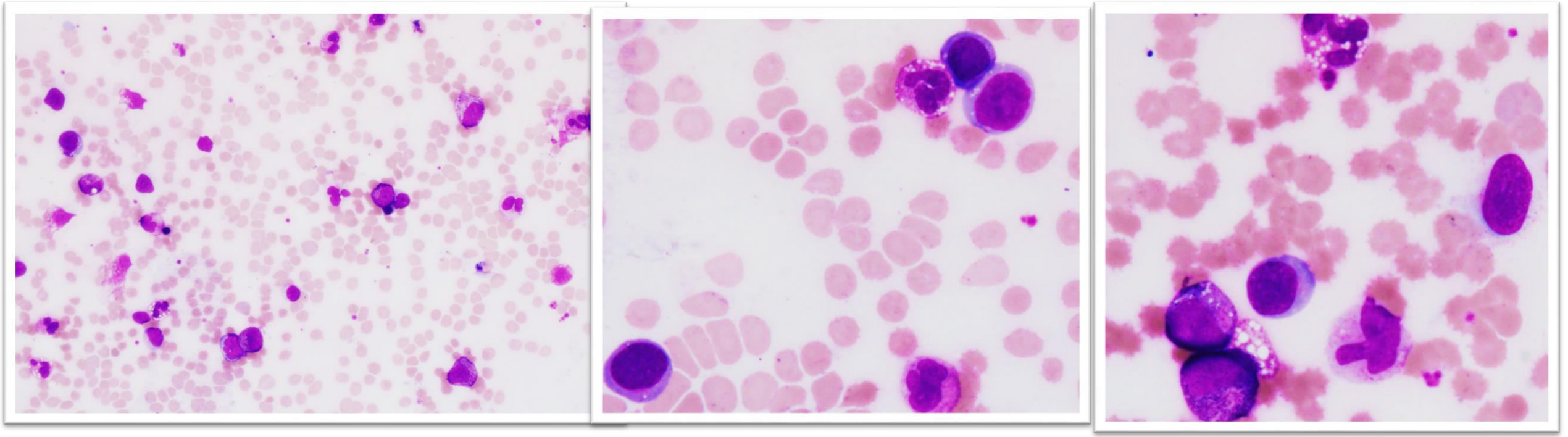
A- 3213/2022:
Reactive Lymphoid hyperplasia

Bone Marrow Aspiration

A-1338/22
CR No: 202202828050
Date of BM- 16/06/2022

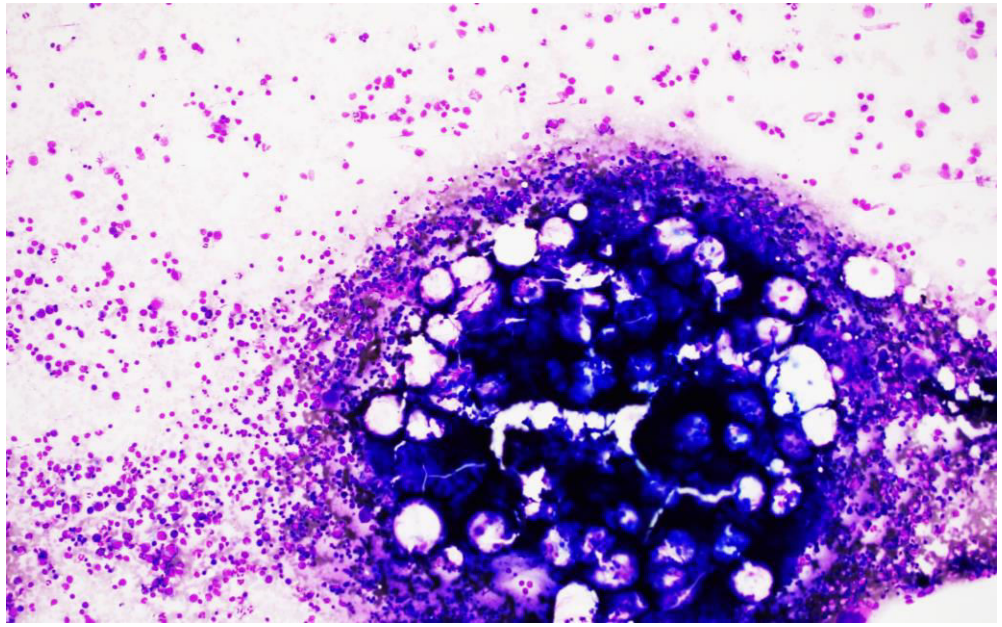
Hb. (g/dl)	Retic (%)	Plt (× 10^9/L)	TLC (× 10^9/L)
7.1	1.38(c)	**163**	**81.0**

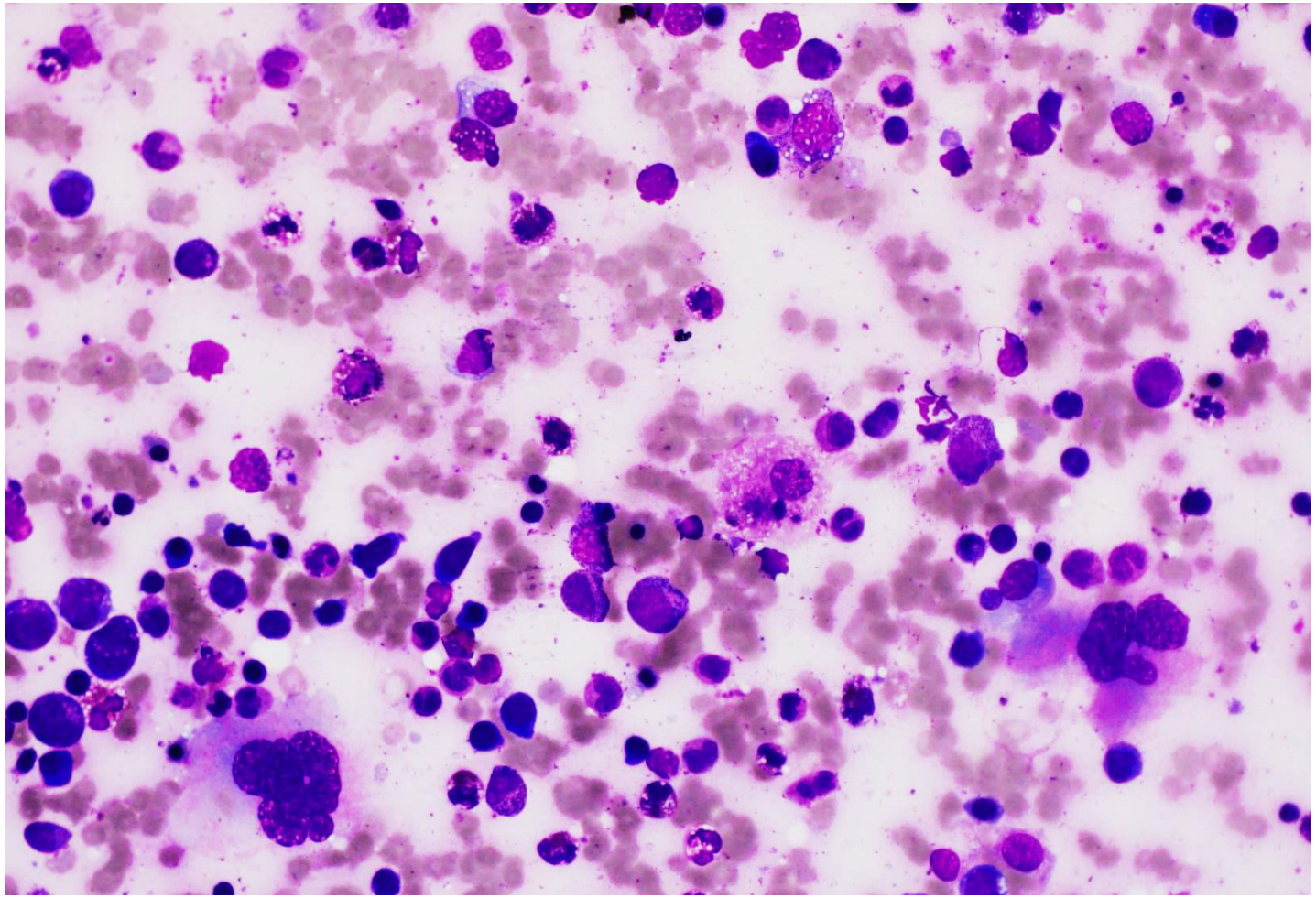
P	L	M	E	05	Blast	Myelo	MM	nRBC
42	25	05	03	Ba	02	12	06	20



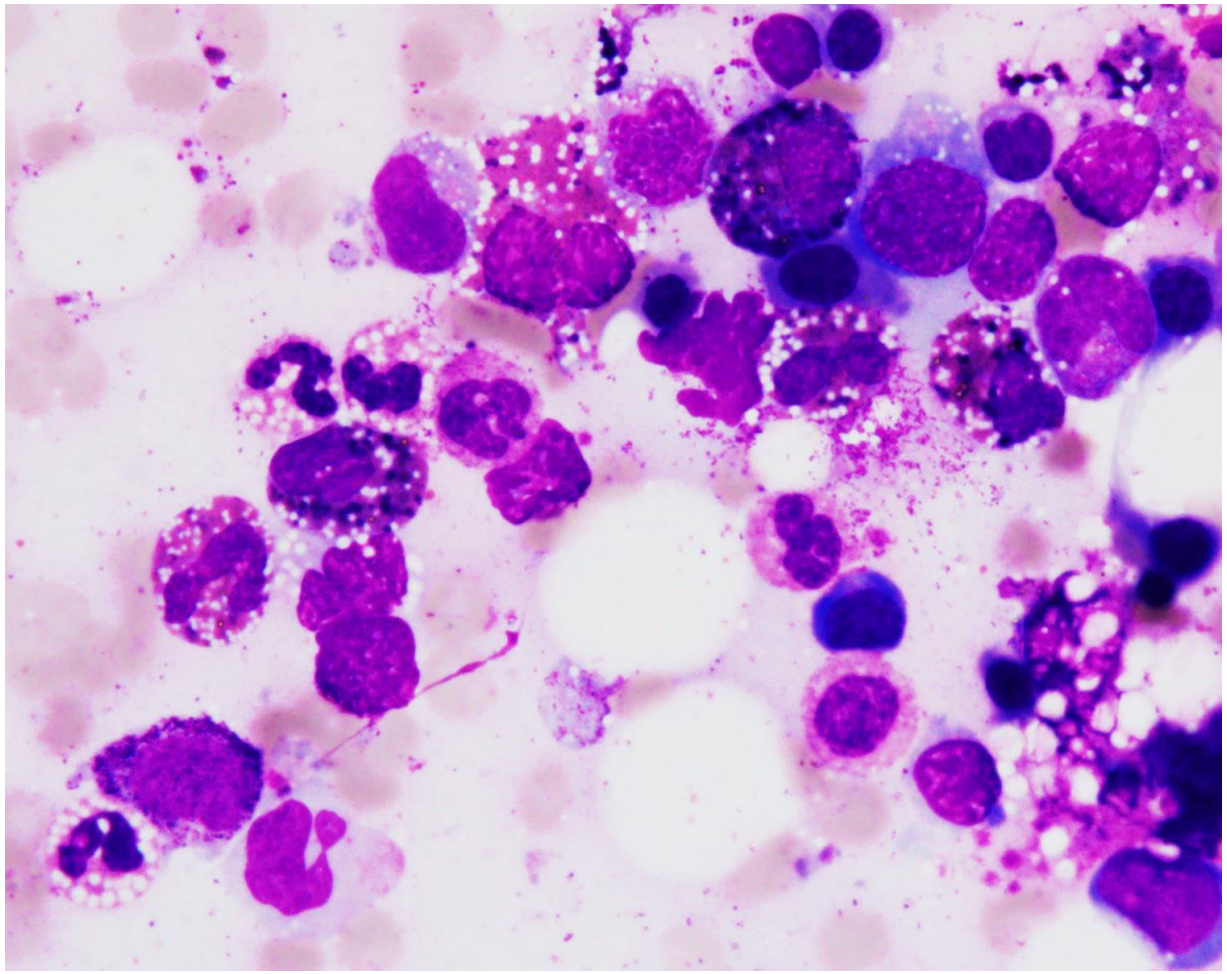
PBF-Normocytic normochromic RBCs with macrocytes, spherocytes and elliptocytes. Prominent vacuolations seen in granulocytic lineage and lymphoid cells. Platelets were adequate.

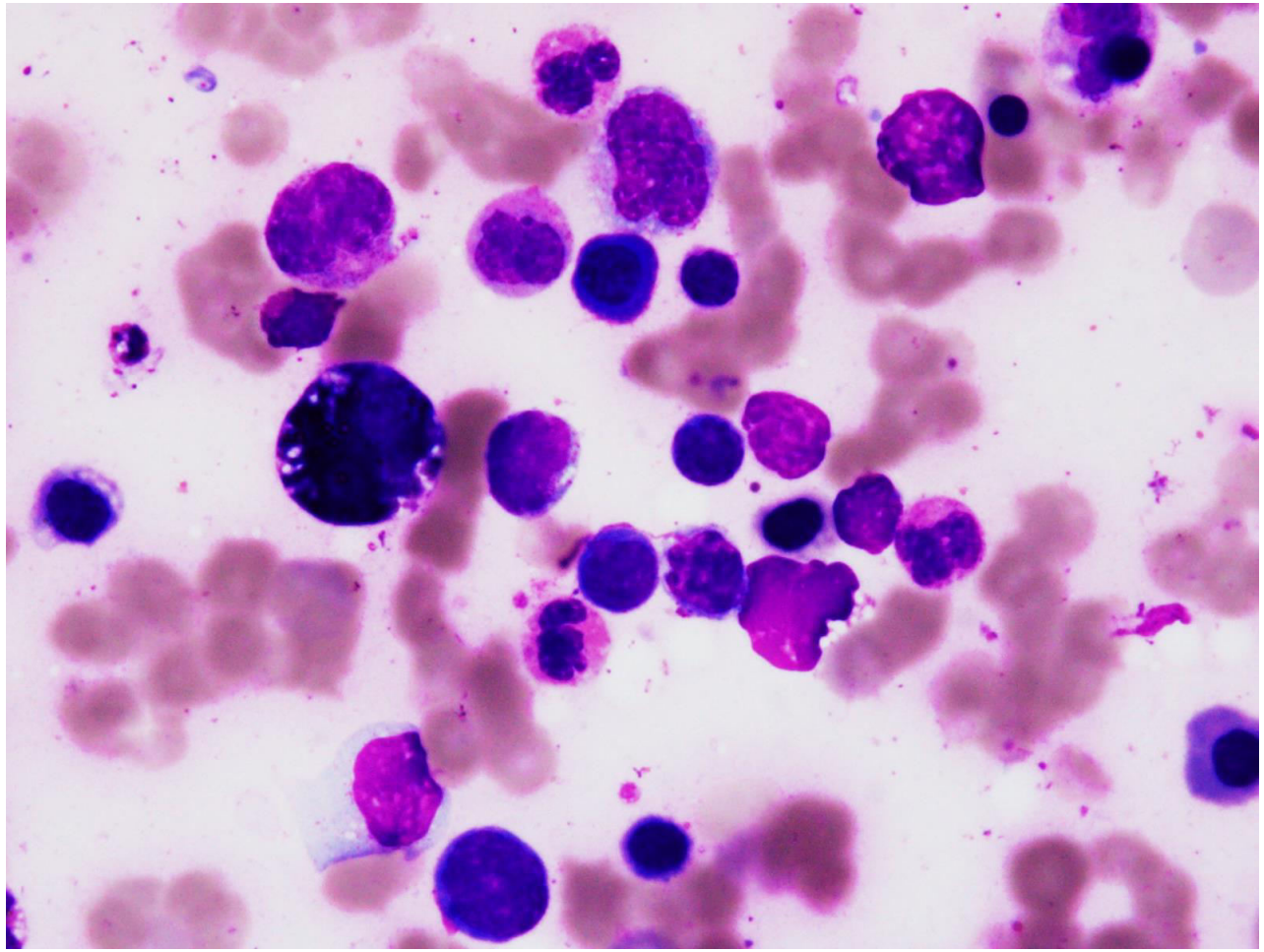
BMA





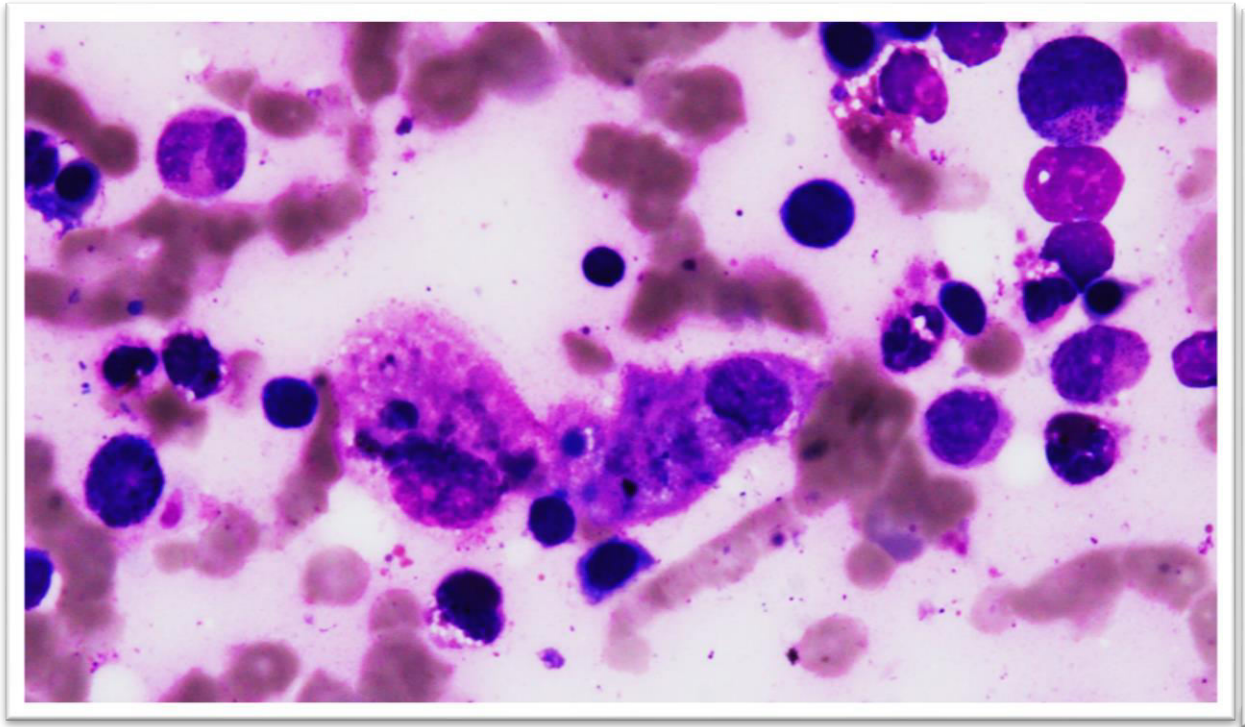
- Particulate, Hypercellular for age
- Thrombopoiesis: Adequate, normal morphology

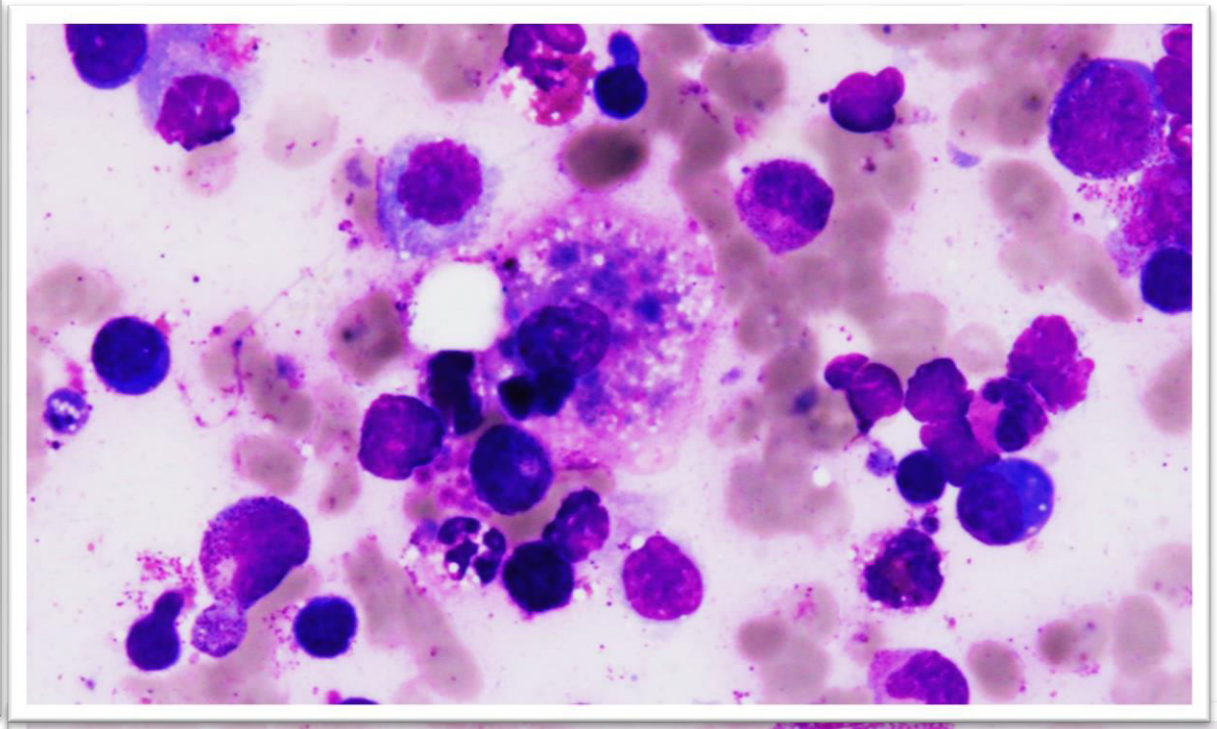


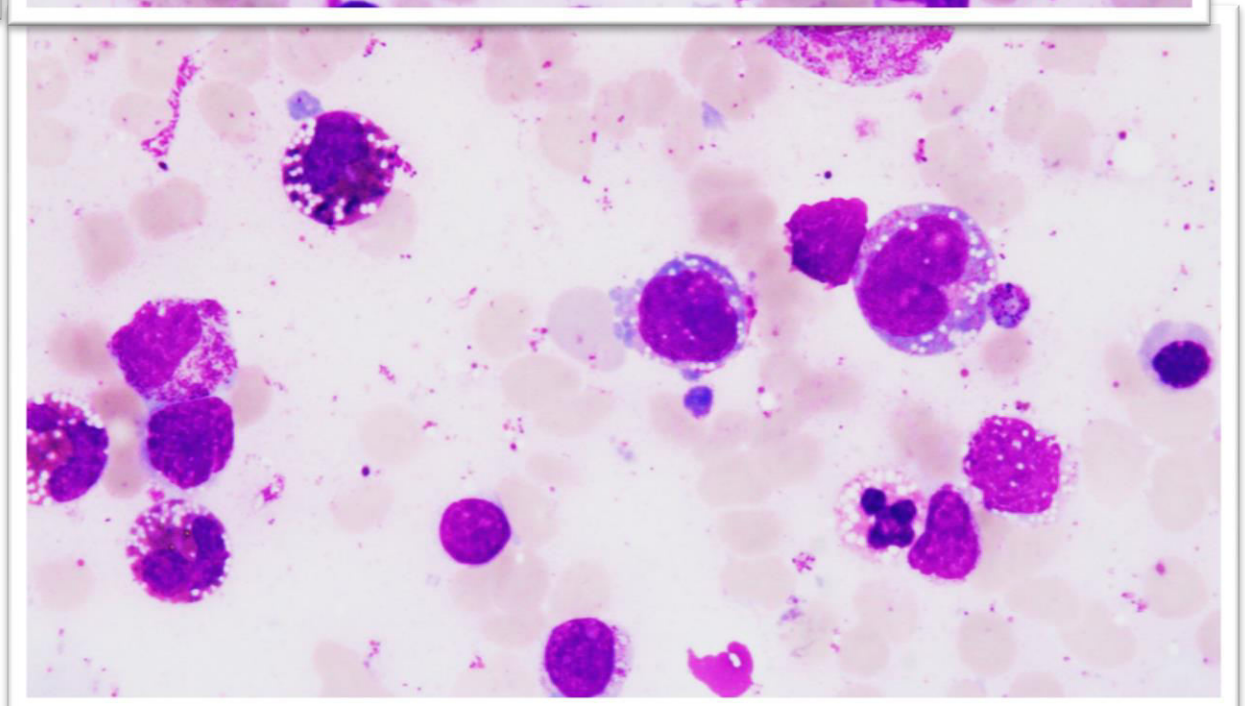


- **M:E- 2.5:1**
- **Erythropoiesis: Mild to moderate megaloblastic maturation**

Bl	Pmy	My	MM	P	L	Baso	Mono	Eobaso	Plasma cells	Ery Prec
03	04	25	03	18	10	-	-	04	03	30

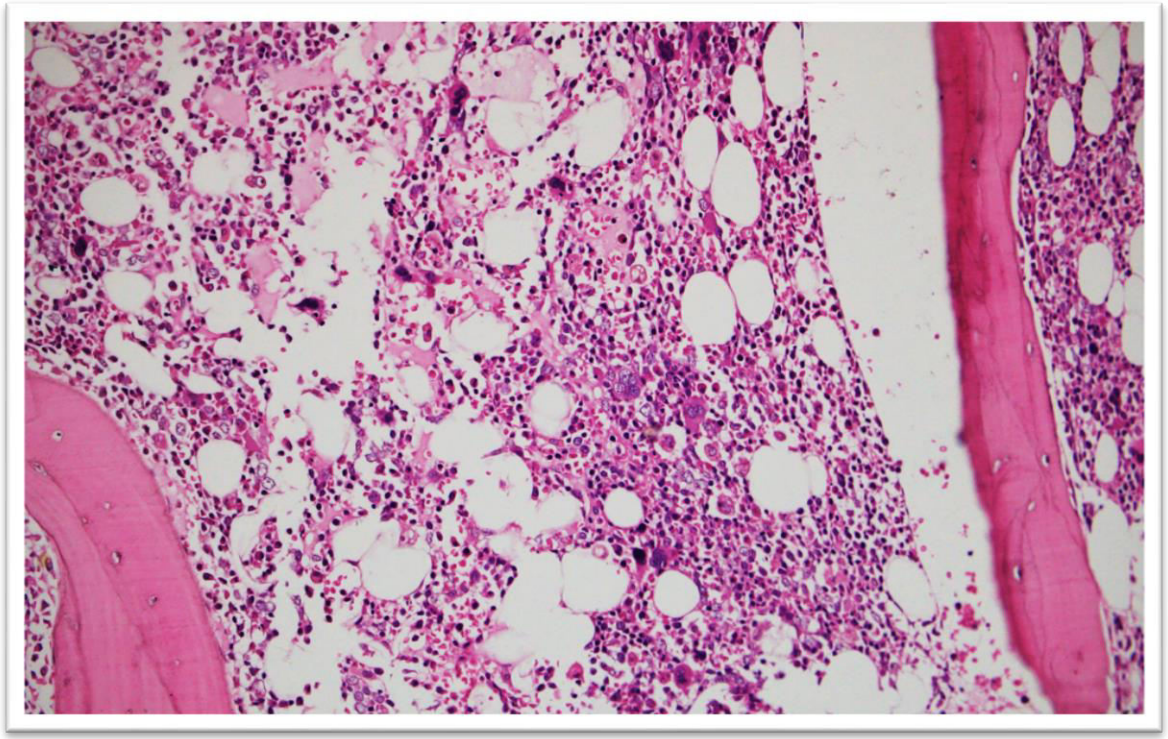


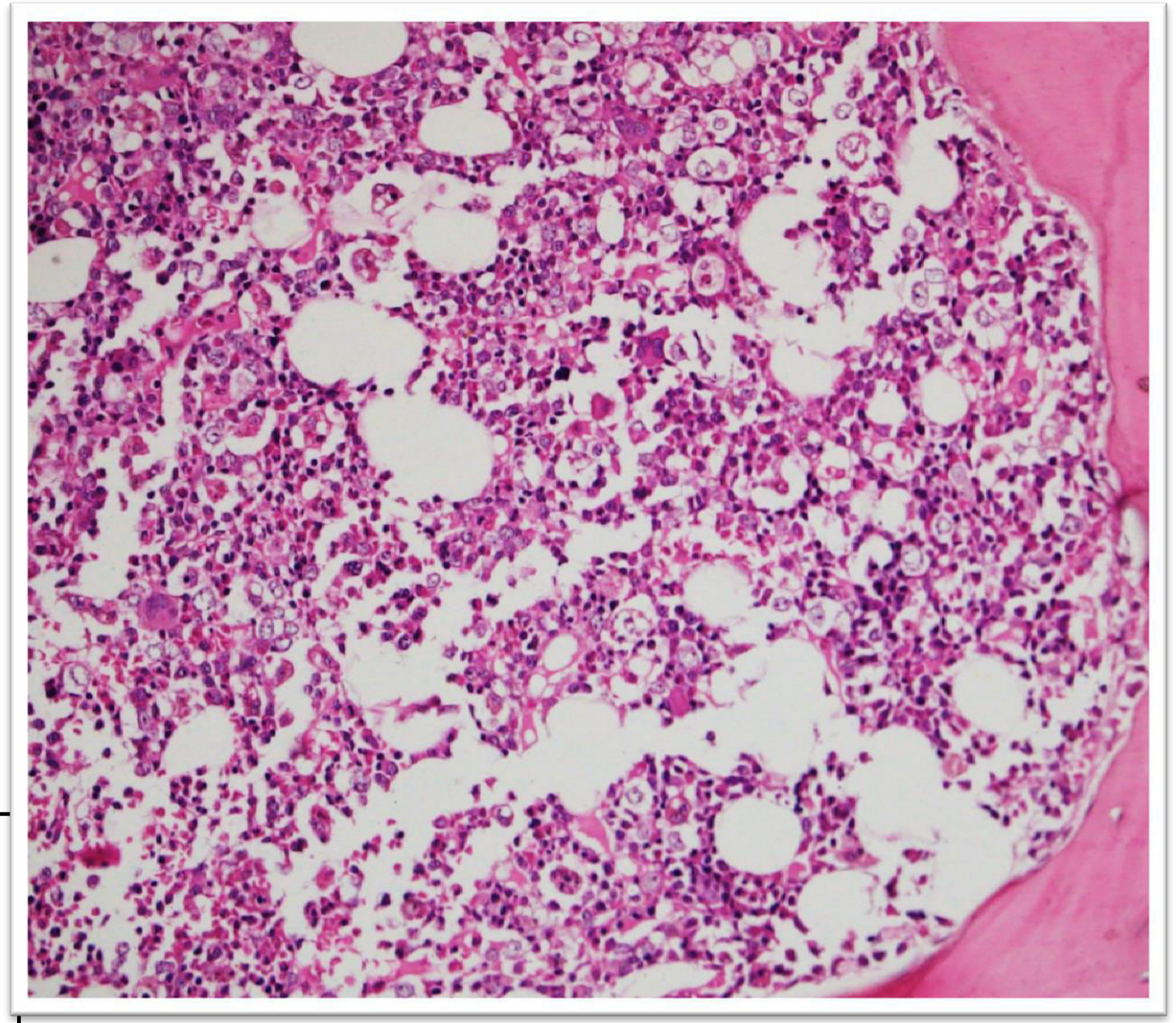




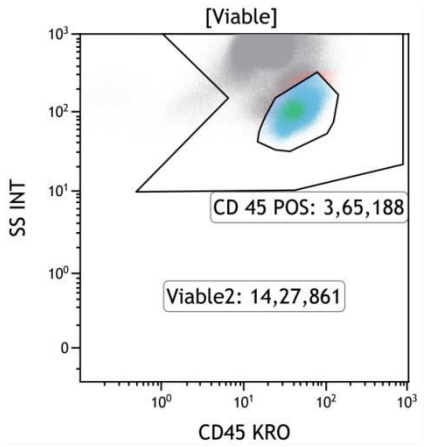
- Histiocytes –increased,a few of them show hemophagocytosis

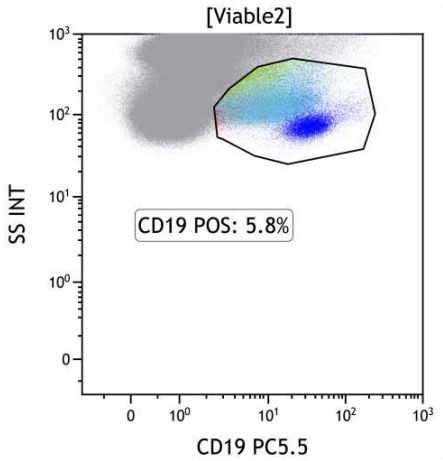
BMBx

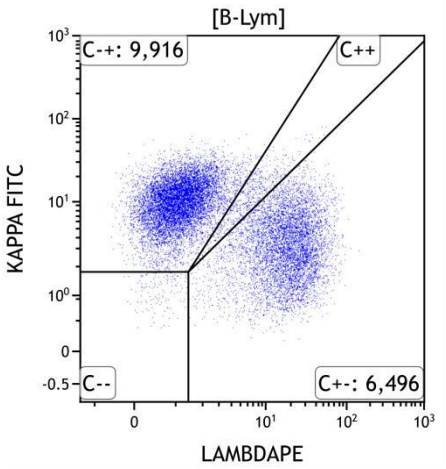


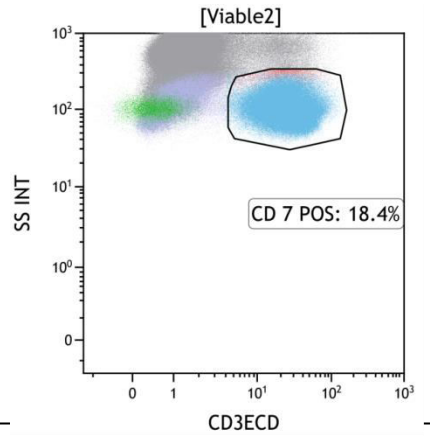


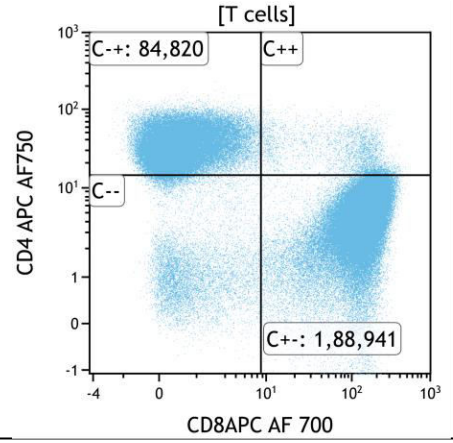
- Mildly Hypercellular with background mild edema.
- Interstitial excess of histiocytes with few showing hemophagocytosis.
- Granulocytic series-mildly increased.
- Megakaryocytic and erythroid lineage-proportionately represented.

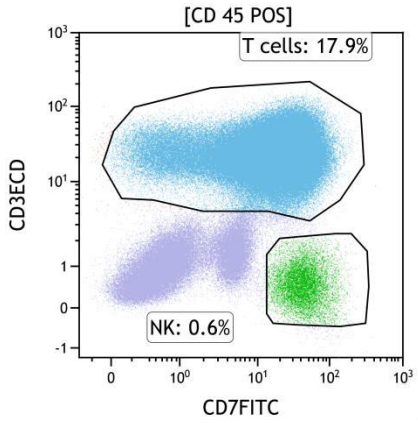












Flowcytometry

- **Gated low SSC vs CD19 positive events(5.8% of all viable events) reveal B-cells(1.1 % of all viable cells and 17.9% all CD19 positive events) with Kappa lambda ratio of 2.5:1.**
- **Low SSC vs CD7 revealed T-cells (18.9% of all viable cells) with CD8:CD4 ratio of 2.2:1.**
- **NK cells constitute 0.6% of all viable cells.**
- **No abnormal immunophenotype was seen.**

Final Interpretation

- Hypercellular Bone marrow –infectious/sepsis associated changes
- Evidence of increased hemophagocytic activity.

COURSE AND MANAGEMENT:

A 30-year-old female with no previous comorbidities presented with fever and large bowel type of diarrhoea for ten days. She was treated in another hospital with intravenous fluids and antibiotics, after which she developed oral ulcers and generalized erythema. CBC done there showed 10.9 /47,700/2.2 lakh with 28% blasts; hence she was referred to PGI. At PGIMER, on examination, she was found to have a generalized erythematous rash, palmoplantar hyperaemia, oral ulcers, generalized lymphadenopathy, and hepatosplenomegaly. Investigations: peripheral blood smear was suggestive of a leucoerythroblastic picture and deranged liver functions. With the working diagnosis of tropical illness-related liver dysfunction, started on Ceftazidime and Azithromycin. The possibility of EBV-related viral exanthematous reaction was also considered. Coagulopathy and diarrhoea episodes persisted despite antibiotic treatment, while the evaluation for tropical illness, hepatotropic virus and blood culture were all negative.

On 13/6/2022, liver function worsened further; the possibility of sepsis/ drug induced/ HLH was considered. On 15/06/2022, she was started on Dexamethasone (H SCORE - 214); the patient also developed anuria with VBG suggestive of severe metabolic acidosis and did not respond to intravenous fluids and diuretics hence underwent haemodialysis. CECT done before haemodialysis revealed hepatosplenomegaly with some mural thickening of bowel loops. Post dialysis patient developed shock, and inotropic support was started. With suspicion of sepsis, antibiotics were hiked up to Meropenem and Vancomycin. On 16/03.2022, she underwent bone marrow biopsy s/o reactive marrow with secondary HLH. The hypotension continued to worsen, she also required intubation, and she succumbed to her illness on the same day.

Database

- 30-year-old female - Fever and Diarrhea
- Oral Ulcers, generalized Lymphadenopathy, hepatosplenomegaly
- Anemia, Lymphocytosis
- Deranged Liver Function
  - Elevated Transaminases >10ULN
  - Elevated alkaline phosphatase >5ULN
  - Conjugated hyperbilirubinemia
  - Coagulopathy
- Hep A, Hep B, Hep C, Hep E - negative
- CMV IgM – Positive
- CMV PCR – Negative
- ANA – Negative
- Infective colitis on cross-sectional Imaging
- FNAC – Reactive Lymphadenopathy
- Bone Marrow Study – Hypercellular marrow with increased Hemophagocytic activity
- Pre terminally Acute Kidney Injury, raised Lactate, Shock, raised Procalcitonin

Points of discussion

- Basic Disease
- Terminal event

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Viral	CMV, EBV, HIV
Bacterial	Brucellosis, Tuberculosis
Fungal	Histoplasmosis
Parasitic	Leishmaniasis
Rickettsial	Scrub typhus

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Systemic Lupus Erythematosus

Mixed Connective Disease

IgG4 related disease

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Hematological Malignancy

Leukemia

Lymphoma

Metastatic Malignancy

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Lipid Storage Disorders

Gaucher’s disease

Niemann Pick’s disease

Tangier’s disease

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Castleman’s disease

Sarcoidosis

Kikuchi s Disease

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy + Lymphocytosis

- Infectious Disease
- Immunological disease
- Malignant disease
- Storage disorders
- Other Disorders

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy + Lymphocytosis

- **Infectious Disease**
- Immunological disease
- **Malignant disease**
- Storage disorders
- Other Disorders

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy + Lymphocytosis

- **Infectious Disease**
  - Viral — **CMV, EBV, HIV**
  - Bacterial — **Brucellosis, Tuberculosis**
  - Fungal — Histoplasmosis
  - Parasitic — Leishmaniasis
  - Rickettsial — **Scrub typhus**
- Immunological disease
- **Malignant disease**
  - Haematological Malignancy **Leukemia**, **Lymphoma**
  - Metastatic Malignancy
- Storage disorders
- Other Disorders

Basic disease

Fever + Hepatosplenomegaly + Lymphadenopathy + Lymphocytosis

- **Infectious Disease**
  - Viral — **CMV, EBV**, HIV
  - Bacterial — **Brucellosis, Tuberculosis**
  - Fungal — Histoplasmosis
  - Parasitic — Leishmaniasis
  - Rickettsial — **Scrub typhus**
- Immunological disease
- **Malignant disease**
  - Haematological Malignancy Leukemia, **Lymphoma**
  - Metastatic Malignancy
- Storage disorders
- Other Disorders

Basic disease – Infectious Mononucleosis like syndrom

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Diarrhea
- CMV IgM – Positive

Against

- CMV PCR - Negative
- Immunocompetent
- EBV PCR – Not available

Basic disease – Infectious Mononucleosis like syndrom

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Diarrhea
- CMV IgM – Positive

Against

- CMV PCR - Negative
- Immunocompetent
- EBV PCR – Not available

Likely

› Hepatogastroenterology. 2012 Oct;59(119):2137-41. doi: 10.5754/hge10825.

Cytomegalovirus colitis in immunocompetent patients: a clinical and endoscopic study

Tae Ho Seo [1], Jeong Hwan Kim, Soon Young Ko, Sung Noh Hong, Sun-Young Lee, In-Kyung Sung, Hyung Seok Park, Chan Sub Shim, Hye Seung Han

Affiliations + expand

PMID: 23435132 DOI: 10.5754/hge10825

Conclusions: CMV colitis in immunocompetent patients presented in **older patients** and in those with **other comorbidities.** Gastrointestinal bleeding was the most common initial presentation. Despite aggressive clinical manifestations, the prognosis of CMV colitis is good if diagnosed and treated early.

Basic disease - Lymphoma

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Cholestatic pattern of Liver functions

Against

- Short duration of illness
- Reactive Lymphocytosis on PBF
- Lymph node FNAC – Reactive
- No Lymph node Biopsy available
- Bone Marrow study – not suggestive

Basic disease - Lymphoma

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Cholestatic pattern of Liver functions

Against

- Short duration of illness
- Reactive Lymphocytosis on PBF
- Lymph node FNAC – Reactive
- No Lymph node Biopsy available
- Bone Marrow study – not suggestive

Less Likely

Basic disease - Disseminated Tuberculosis

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Deranged Liver Functions

Against

- Short duration of illness
- Imaging – not suggestive
- Lymph node FNAC – Reactive
- Bone Marrow study – not suggestive

Basic disease - Disseminated Tuberculosis

For

- Fever
- Lymphadenopathy
- Hepatosplenomegaly
- Deranged Liver Functions

Against

- Short duration of illness
- Imaging – not suggestive
- Lymph node FNAC – Reactive
- Bone Marrow study – not suggestive

Unlikely

Pre terminal

- Hemophagocytic lymphohistiocytosis

HLH-2004 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 (hemoglobin <100 g/L in infants <4 wk)
     - Platelets $<100 \times 10^9$/L
     - Neutrophils $<1.0 \times 10^9$/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

H-Score

(probability of HLH)

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopeniast†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (μg/L)	0 (<2000), 35 (2000-6000), or 50 (>6000)
Triglyceride (mmol/L)	0 (<1.5), 44 (1.5-4), or 64 (>4)
Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)
Aspartate aminotransferase (U/L)	0 (<30) or 19 (≥30)
Hemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)

HLH-2004 Criteria

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1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
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Low or no NK cell activity (according to local laboratory reference)
✓ Ferritin ≥500 μg/L
sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

5 | 8

H-Score 265

(>99% probability of HLH)

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
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Aspartate aminotransferase (U/L)	0 (<30) or 19 (≥30)
Hemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)

Things I missed

- Erythematous Rash
- Diarrhea

Erythematous Rash

- Drug-induced – temporal correlation
- CMV mononucleosis associated – one third can have dermatological manifestations

Diarrhea

- CMV colitis – IgM positivity
- Clostridium difficile associated colitis – radiology

Terminal event

- Worsening of renal and liver functions with sepsis – probably precipitated by a hospital-acquired infection

- Refractory septic shock and PTE as a contributing factor

Final diagnosis

CMV/EBV -associated Mononucleosis

Secondary Hemophagocytic lymphohistiocytosis

Cause of Death: Refractory Septic Shock, Acute Pulmonary Thromboembolism


POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH CHANDIGARH

Thank You