Preceptorship Programme
1st June 2023

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Unexplained Transaminitis with significant weight loss

- 50-year-old Myanmar gentleman
- C/O – **Significant Unexplained weight loss** with **Unexplained Transaminitis**
  - reported unexplained weight loss of approximately 20% of his previous body weight within the past 5-6 months
  - Elevated liver enzymes for 5-6 months without knowing the definite diagnosis
- He had been previously healthy and had not experienced any significant illnesses or hospitalizations
- No prior history of liver disease, non-alcoholism, or non-smoking

Initial Presentation

- Hepatitis screen showed **HBsAg and Anti-HCV Ab negative**, ruling out viral hepatitis as a cause of transaminitis
- **Initial Lab: Tests (December 2022);**
  - CBC – Hb% = 16.3 (HCT = 49%), WBC = 5.48, **Platelets = 283**
  - Total Bilirubin = 20 (μ mol/L), Albumin = 4 (N = 3.5), PT / INR = 11.1 / 0.93 **(Normal Liver Functions)**
  - Total Cholesterol = **343** ↑, Triglycerides = **173** ↑, HDL = 88, LDL = **235** ↑, VLDL = 35
  - Creatinine = 68

Initial Presentation (Contd.) – November & December 2022

- AST = **97** (UNL = 40)
- ALT = **97** (UNL = 41)
- AST/ALT ratio = 1
- GGT = **764** (UNL = 71)

- AFP = **8.86**

- **Ceruloplasmin = 0.262** (N = 0.2 - 0.6)

- ANA = Positive

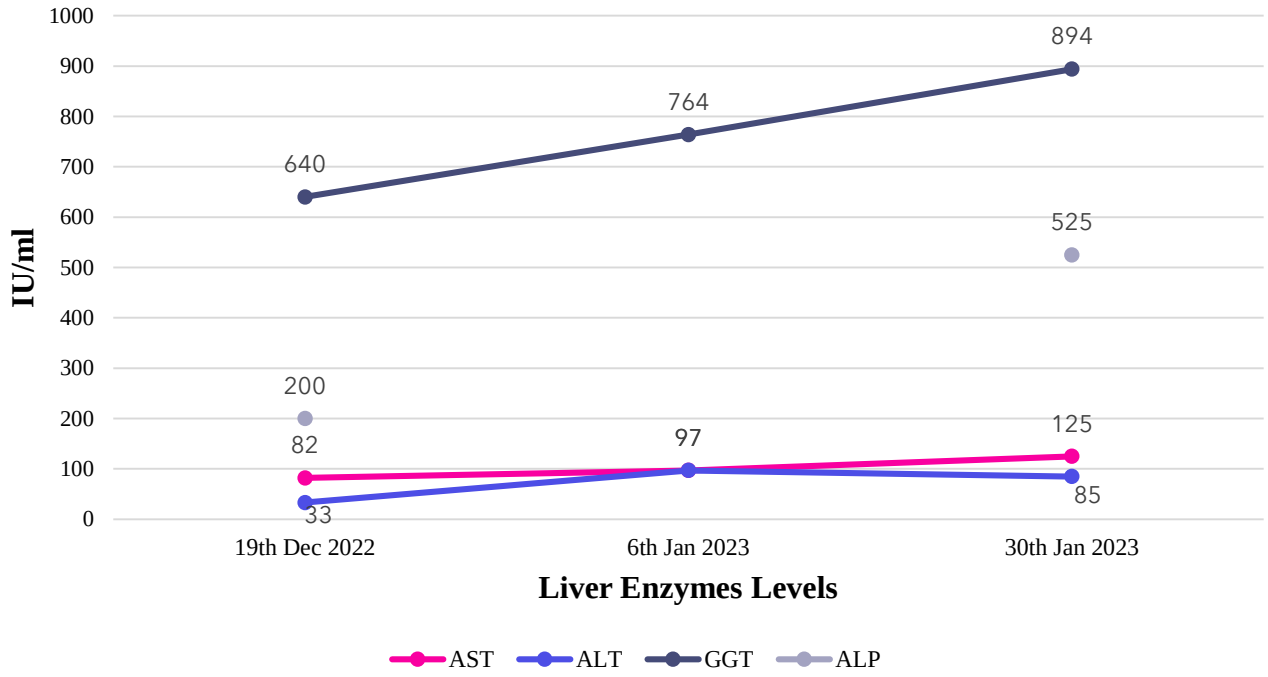
- **USG (Abd + Pelvis) (16th Nov 2022)**
  - Reduced and Coarse Hepatic and Splenic Echogenicity ~ Chronic Parenchymal Disease (Metabolic Causes should be considered)
  - ? Bilateral Mild Nephropathy

- **FibroScan (21st Dec 2022)**
  - CAP = 204 S_0 / LSM = 75 F_4

- **AMA (Anti-Mitochrondrial Ab) = Negative**

Follow-up Visits – January 2023

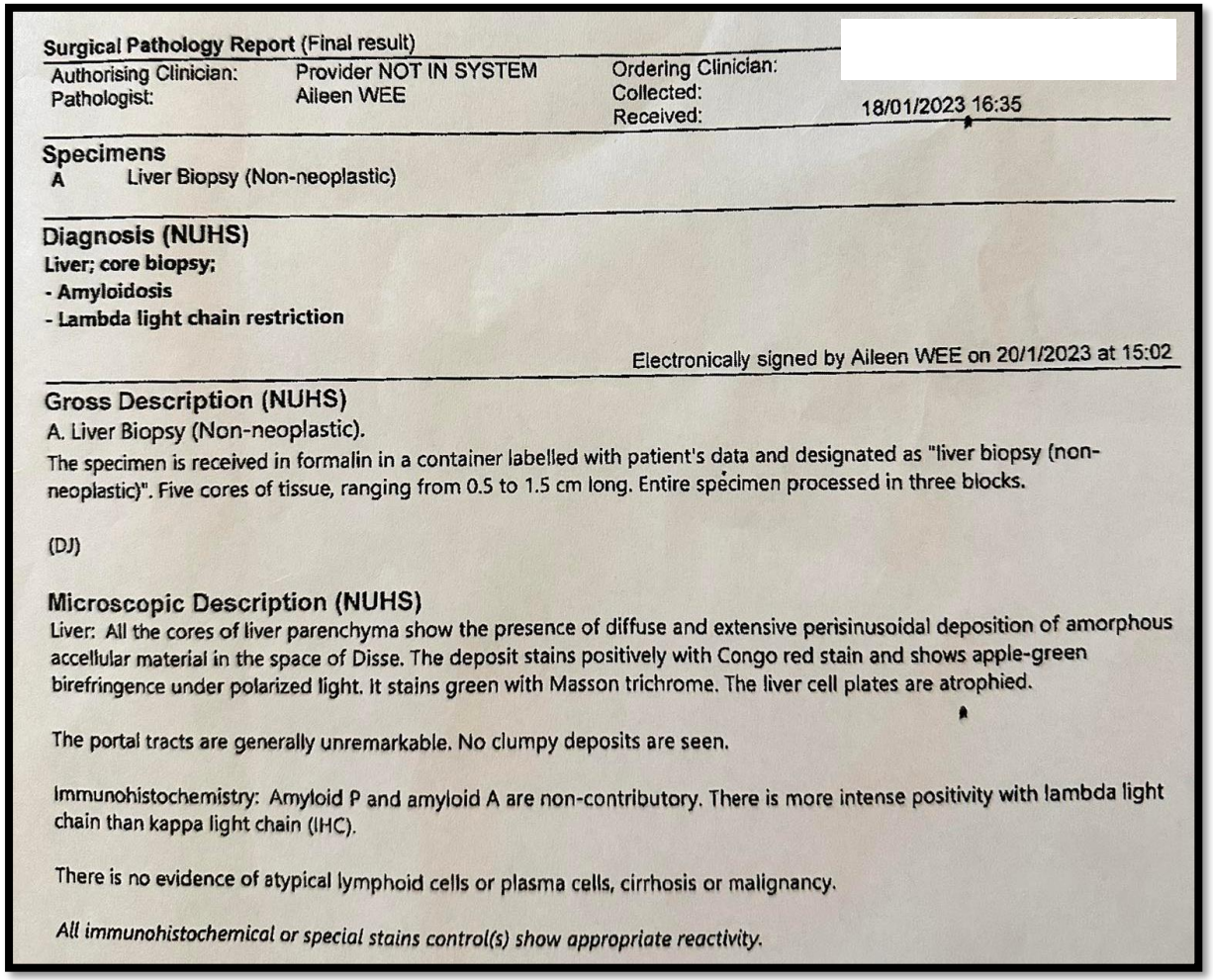
- Liver Enzymes – progressively elevated
- Total Bilirubin = 0.7, Direct Bilirubin = 0.4, Albumin = **2.56** (N = 3.5), PT / INR = 11.9 / 1.05
- **CTP Score = B (7 points)**
- CBC – Hb% = 16.5 (HCT = 45.3%), WBC = 4.8, **Platelets = 235**
- FBS = 76, HBA_{1c} = 4.8%
- Total Cholesterol = **394.4** ↑, Triglycerides = **156.1** ↑, HDL = 87.4, LDL = **251** ↑
- Creatinine = 0.74 (eGFR = 107)
- **MELD Score = 8 points**



Confirmation of Liver Fibrosis

- **Ultrasound again in** January 2023
  - Coarse Parenchyma with Hepatonegaly
  - Normal Spleen size and No SOL
  - **Dx ~ Chronic Parenchymal Liver Disease**
- **MRE (Magnetic Resonance Elastography)** was done in January 2023
  - The MRE findings are consistent with **cirrhosis (F4)** with widespread increased stiffness throughout the liver. Further clinical correlation are recommended.

Liver Biopsy was done in Singapore



Surgical Pathology Report (Final result)

Authorising Clinician:	Provider NOT IN SYSTEM	Ordering Clinician:	
Pathologist:	Aileen WEE	Collected:	
		Received:	18/01/2023 16:35

Specimens

A Liver Biopsy (Non-neoplastic)

Diagnosis (NUHS)

Liver; core biopsy;
- Amyloidosis
- Lambda light chain restriction

Electronically signed by Aileen WEE on 20/1/2023 at 15:02

Gross Description (NUHS)

A. Liver Biopsy (Non-neoplastic).
The specimen is received in formalin in a container labelled with patient's data and designated as "liver biopsy (non-neoplastic)". Five cores of tissue, ranging from 0.5 to 1.5 cm long. Entire specimen processed in three blocks.

(DJ)

Microscopic Description (NUHS)

Liver: All the cores of liver parenchyma show the presence of diffuse and extensive perisinusoidal deposition of amorphous accellular material in the space of Disse. The deposit stains positively with Congo red stain and shows apple-green birefringence under polarized light. It stains green with Masson trichrome. The liver cell plates are atrophied.

The portal tracts are generally unremarkable. No clumpy deposits are seen.

Immunohistochemistry: Amyloid P and amyloid A are non-contributory. There is more intense positivity with lambda light chain than kappa light chain (IHC).

There is no evidence of atypical lymphoid cells or plasma cells, cirrhosis or malignancy.

All immunohistochemical or special stains control(s) show appropriate reactivity.

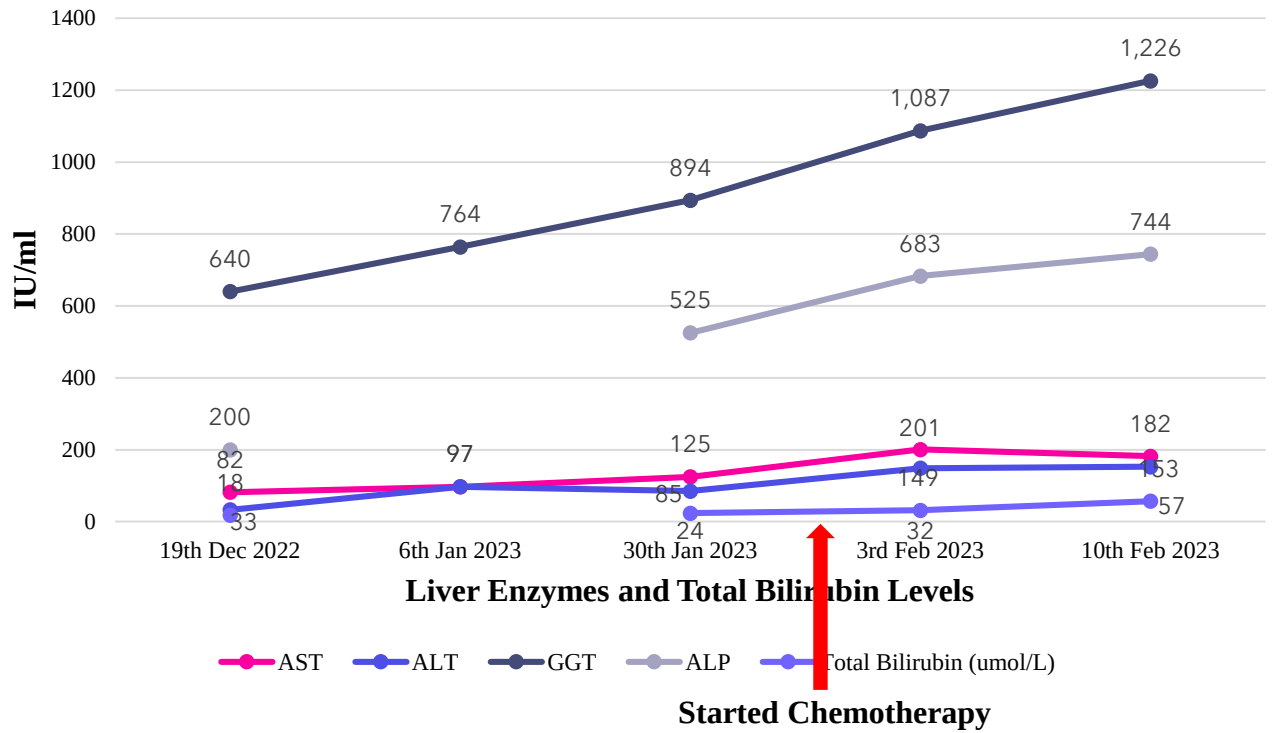
- **Definite Diagnosis**
  - Lambda Light-chain Hepatic Amyloidosis
  - No evidence of Cirrhosis or malignancy

Investigations for Systematic Involvement

- **Echocardiography**
  - Increased left ventricular wall thickness with a high E/A ratio on Doppler echocardiography
  - No valvular involvement
  - Normal LVEF and diastolic function
- **Urine Albumin-Creatinine Ratio**
  - Nephrotic-range proteinuria without haematuria
- **Bone Marrow Biopsy**
  - Amorphous eosinophilic material in the interstitial spaces ~ presence of amyloid deposits
  - Associated increase in the number of plasma cells in the bone marrow ~ underlying plasma cell dyscrasia
  - 8% plasma cells which are clonal with translocation [11:14]
- **Serum Protein Immunofixation**
  - Monoclonal band with anti-lambda light chain
  - **Serum light chain assay for lambda light chain 1258 mg/L**

Treatment given by Haemato-Oncologist in February 2023

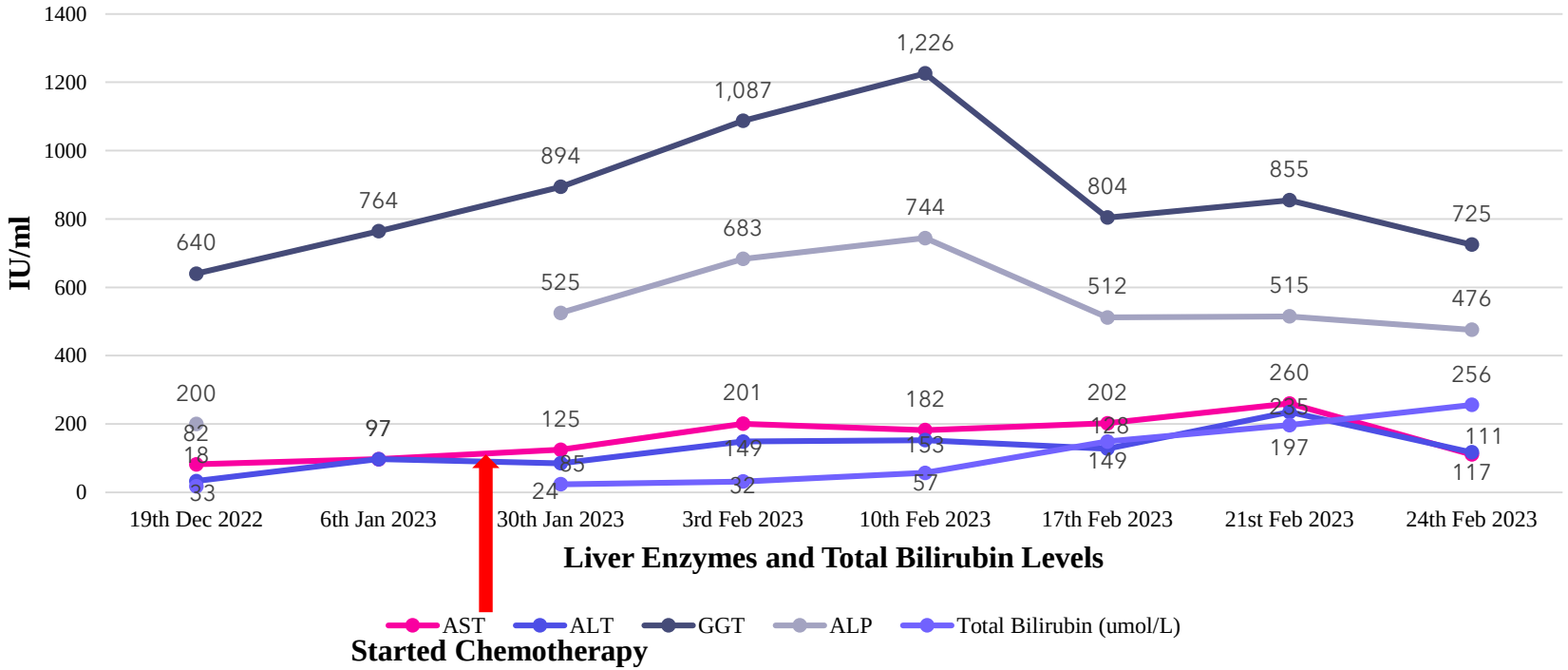
- Chemotherapy regimen containing **Daratumumab 1800 mg**, **Cyclophosphamide**, and **Dexamethasone** weekly



	30th Jan 2023	3rd Feb 2023	10th Feb 2023
Creatinine	60	65	68
eGFR	112	108	106
Uric Acid	264	262	226
Urea	5	6.4	8.6↑
Sodium	136	130↓	122↓
Potassium	4.9	5.5↑	4.3
Chloride	104	98	90↓
Bicarbonate	27	23	24
Total Bilirubin	24	32↑	57↑
Direct Bilirubin			
Total Protein	29↓	42↓	38↓
Albumin	20↓	23↓	20↓
Globulin	19	19	12↓
A:G	1.1	1.2	1.1
PT			11.8
INR			1.06
AST	125↑	201↑	182↑
ALT	85↑	149↑	153↑
GGT	894↑	1087↑	1226↑
ALP	525↑	683↑	744↑
LDH	476↑		
Troponin T	15.8		
RBS	5.1	4.5	5.2
Lactate			
β2 Microglobulin	1666		
Hb%	17.6	17.5	17.8
HCT	51.7	53	52.7
WBC	4.71	3.8	2.64
TNC	2.41	1.22	1.32
Platelets	260	244	225

Treatment (Contd.)

- After 2nd dose of Chemotherapy, the total bilirubin level started to increase and thus, the Oncologist stopped Cyclophosphamide and changed to a regimen containing **Bortezomib with Daratumumab 1800 mg and Dexamethasone**.

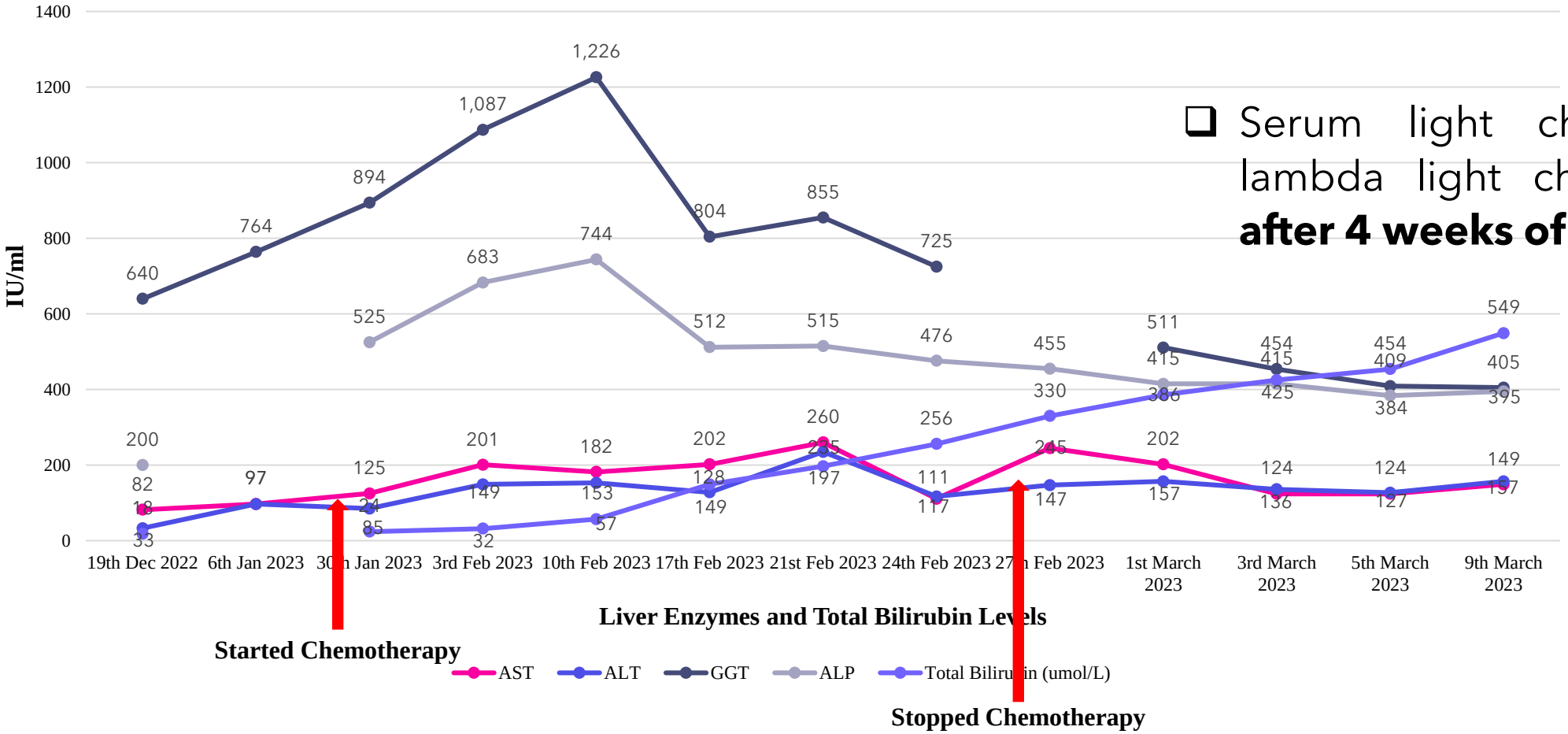


Stopped Chemotherapy

	30th Jan 2023	3rd Feb 2023	10th Feb 2023	17th Feb 2023	21st Feb 2023	24th Feb 2023	27th Feb 2023	1st Mar 2023	2nd Mar 2023	3rd Mar 2023	4th Mar 2023
Creatinine	60	65	68	83	78	69	107	95		127	103
eGFR	112	108	106	94	100	105	69.5	73		52	72
Uric Acid	264	262	226	261	311	257					
Urea	5	6.4	8.6↑	7.2	10↑	7	10.8↑	12.17↑	16↑	15.9↑	15.7↑
Sodium	136	130↓	122↓	132↓	134↓	134↓	128↓	127.1↓	126.5↓	127.4↓	128↓
Potassium	4.9	5.5↑	4.3	5	4.3	4	4.4	3.94	4.42	4.22	
Chloride	104	98	90↓	100	98	100	93↓	99.7		101.7	
Bicarbonate	27	23	24	23	26	24	19↓	21↓		23	
							6.94↑			3.45	
Total Bilirubin	24	32↑	57↑	149↑	197↑	256↑	330.4↑	386↑	399↑	425↑	404↑
Direct Bilirubin					143↑						
Total Protein	29↓	42↓	38↓	44↓	43↓	41↓					
Albumin	20↓	23↓	20↓	29↓	28↓	27↓	2.9↓				
Globulin	19	19	12↓	15↓	15↓	14↓					
A:G	1.1	1.2	1.1	1.9	1.9	1.9					
PT			11.8		12.1	13.2					
INR			1.06		1.09	1.19	12.1			12.3	
AST	125↑	201↑	182↑	202↑	260↑	111↑	1.02			1.27	
ALT	85↑	149↑	153↑	128↑	235↑	117↑	245↑	202↑		124↑	
GGT	894↑	1087↑	1226↑	804↑	855↑	725↑	147↑	157↑		136↑	
ALP	525↑	683↑	744↑	512↑	515↑	476↑		511↑		454↑	
							455↑	415↑		415↑	
LDH	476↑						135↑				
Troponin T	15.8						14.2	13.2		13.8	
RBS	5.1	4.5	5.2	5.1	4	5.2	36.3	36.1		39.2	
							8.68	10.47		11.44	
Lactate						0.94	3.82	6.5		8.62	
β2 Microglobulin	1666						137	162		217	
							2.33				
Hb%	17.6	17.5	17.8	14.6	14.9	14.3	1.1				
HCT	51.7	53	52.7	43.6	44.6	43.1				2.5	
WBC	4.71	3.8	2.64	3.36	4.21	3.79					
TNC	2.41	1.22	1.32	1.75	1.73	2.2					
Platelets	260	244	225	203	187	219					

	4th Mar 2023	5th Mar 2023	6th Mar 2023	9th Mar 2023
Creatinine	103		84	59
eGFR	72		84	126
Uric Acid				
Urea	15.7↑	14↑	15.3↑	12.8↑
Sodium	128↓	133.4↓	129.8↓	131.6↓
Potassium		4.05		3.77
Chloride				105.2
Bicarbonate				30
CRP				
Total Bilirubin	404↑	454↑	505↑	549↑
Total Protein				
Albumin			26↓	
Globulin				
A:G				
PT			11.6	11.3
INR			1.2	1.17
AST		124↑		149↑
ALT		127↑		157↑
GGT		409↑		405↑
ALP		384↑		395↑
Amylase				
Hb%			13.7	14.7
HCT			37.5	38.3
WBC			8.18	7.19
TNC			6.1	5.31
Platelets			235	204

Progressively increasing Bilirubin Level with normal INR



Liver Enzymes and Total Bilirubin Levels

- Serum light chain assay for lambda light chain **130 mg/L after 4 weeks of Chemo**

- **2nd March 2023**
  - Anti-HBc Ab (Total) = Positive
  - Anti-HCV Ab = Negative

  - HBV DNA (Quantitative Viral Load) = Not Detected

AARC – ACLF Score was 6 (Grade I) on 24th Feb 2023 and became Score 8 with Grade II on 3rd March 2023.

AARC Score and ACLF Grade

AARC Score and ACLF Grade	
Component	Value to be Selected
Total Bilirubin (mg/dl)	< 15
HE Grade	I - II
PT-INR	<1.8
Lactate (mmol/lit)	<1.5
Creatinine (mg/dl)	<0.7

Submit Clear

Score:	6
AARC ACLF Grade	Grade I

Survival Rate (Percentage)

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
100	96	94	87	87	79	79	79	79	79	79	79

AARC Score and ACLF Grade

AARC Score and ACLF Grade	
Component	Value to be Selected
Total Bilirubin (mg/dl)	< 15
HE Grade	I - II
PT-INR	<1.8
Lactate (mmol/lit)	>2.5
Creatinine (mg/dl)	<0.7

Submit Clear

Score:	8
AARC ACLF Grade	Grade II

Survival Rate (Percentage)

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
96	92	87	81	77	74	74	74	74	73	70	70

Acute on Chronic Liver Failure

Singapore Hepatology Conference

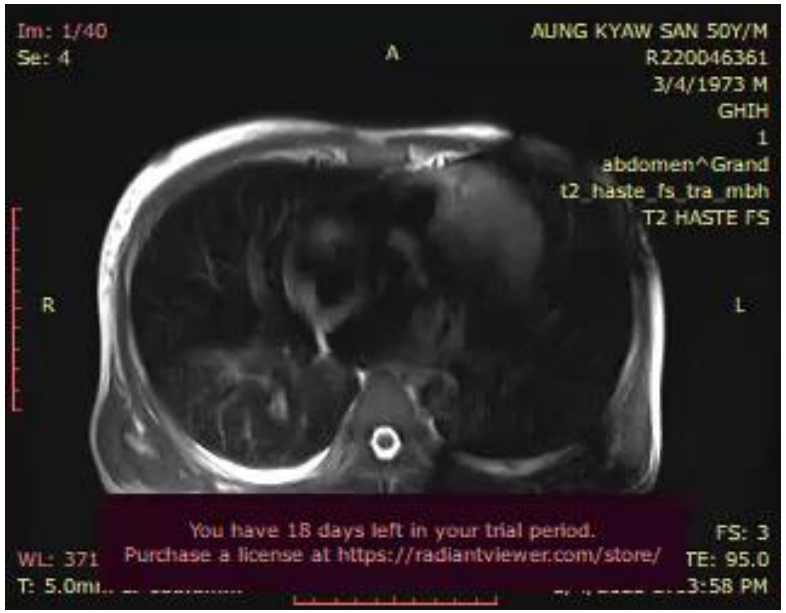
MRI done in March 7, 2023

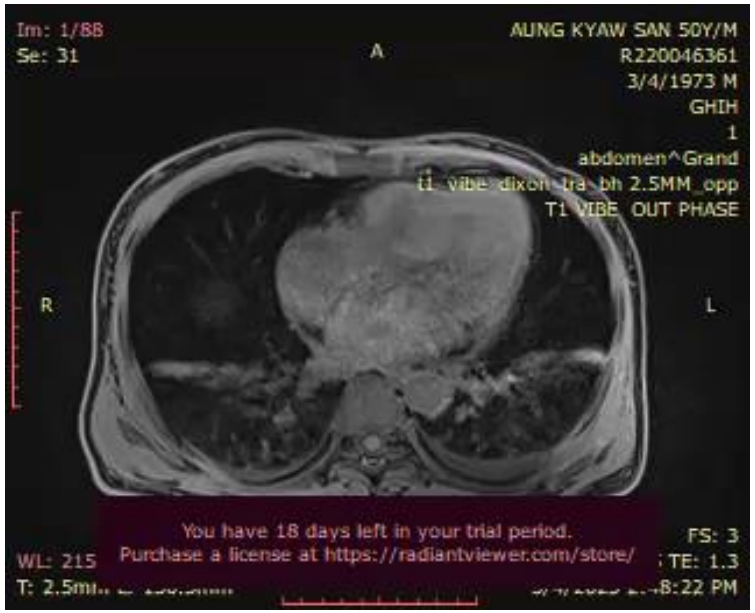
Impression: Status known primary hepatic amyloidosis.

1. Findings are in keeping with active hepatitis. No evidence of biliary obstruction.

2. Portosystemic collaterals and ascites-in keeping with portal hypertension.

Overall findings suggest persisting active hepatitis with intrahepatic cholestasis and liver failure leading to portal hypertension.





Final Diagnosis

Acute on Chronic Liver Failure after Chemotherapy for ? Primary Hepatic Lambda Light Chain Amyloidosis with Systemic Involvement

Listed for Liver Transplantation

- Plasma Exchange were done before Liver Transplantation (to reduce the bilirubin level and to prevent the progress of Hepatic Encephalopathy)
- Liver Transplantation was planned
- Unfortunately, the patient expired while waiting for liver transplantation
- Cause of death – **Massive Spontaneous ICH with Multi-organ Failure**

Questions to Panel of Experts

1. Was the chemotherapy regimen appropriate for the patient's condition? Were there any known risk factors for liver toxicity associated with the drugs used?

2. Was the timing of the onset of liver failure consistent with drug-induced toxicity? Were there any other potential contributing factors?

3. Were there any other potential causes of acute on chronic liver failure?

4. Could this case have been prevented or managed differently to avoid the development of acute on chronic liver failure?

5. Should this patient be transplanted first before Chemotherapy?

6. Any experiences of performing timely Liver Transplantation in such case?