A case of peripheral T-cell lymphoma presenting with acute liver failure

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Abstract

A 68-year-old woman was evaluated by her primary physician for swelling and pain in the right neck. Treatment with antibiotics failed to achieve any improvement. Two weeks later, she was hospitalized to the gastroenterology service because of liver dysfunction and pneumonia. Disseminated intravascular coagulation (DIC) was diagnosed, and protease inhibitor and steroid pulse therapy were started. She was transferred to our department for further evaluation the following day. Bone marrow examination revealed hemophagocytosis and infiltration of CD3-positive cells. Multiple masses were identified in the liver. Her prothrombin time was 35.7% of the standard value 17 days from disease onset, despite improvement of DIC. She was diagnosed with acute liver failure based on the Japanese diagnostic criteria. Her general condition worsened quickly, which prevented use of chemotherapy, and she died after a total course of 19 days. Autopsy revealed atypical lymphocytes in the liver. The diagnosis was peripheral T-cell lymphoma.

Key words: peripheral T-cell lymphoma, acute liver failure, hemophagocytic syndrome

Introduction

Acute liver failure is caused by many etiologies including malignant lymphoma. Peripheral T-cell lymphoma of unspecified type (PTCL-U) is a rare disorder that accounts for about 7% of all malignant lymphomas.[1] PTCL-U carries a poor prognosis, with a 1-year survival rate of 44%.[2] Affected organs include bone marrow in 30% of cases and liver in 12.9%.[2] We report a case of a patient with PTCL-U who presented with swollen cervical lymph nodes, followed by a rapidly declining course, including hemophagocytic syndrome (HPS) and acute liver failure.

Case

This 68-year-old woman was diagnosed with depression and hypertension at age 66 and was receiving treatment for these conditions. She noticed right cervical lymph node swelling and pain and 2 days later was evaluated by her primary physician. Treatment with cefditoren pivoxil failed to achieve any improvement. Two weeks later, computed tomography (CT) demonstrated pneumonia. Blood tests revealed severe hepatic dysfunction: aspartate aminotransferase (AST) of 5530 IU/L (normal, 10-35 IU/L), alanine aminotransferase (ALT) of 2660 IU/L (normal, 12-33 IU/L), total bilirubin (TB) of 7.8 mg/dL (normal, <1.1 mg/dL) and prothrombin time (PT) of 40.1% (normal, 70-125%). The patient was hospitalized on the gastroenterology ward.

Disseminated intravascular coagulation (DIC) was diagnosed, and protease inhibitor and steroid pulse therapy was started with addition of 8 units of fresh frozen plasma (FFP). On the following day, she was transferred to our department for further evaluation. Laboratory tests on admission to our service showed abnormalities including coagulopathy and abnormal liver function by peripheral blood and biochemical tests

(Table 1)

Chest radiograph showed bilateral infiltrates. CT revealed bilateral cervical lymphadenopathy, multiple nodules in the liver with poor contrast effect, and splenomegaly (Fig. 1). Bone marrow examination showed hemophagocytosis and infiltration of CD3-positive cells (Fig. 2A, B). Treatment with thrombomodulin, FFP and plasma exchange proved ineffective. PT was elongated to 35.2 on hospital day 3 and the patient died on hospital day 4 (Fig. 3). On autopsy, the liver showed hepatocellular necrosis and infiltration of CD3-positive malignant cells in the lobular and portal areas (Fig. 4A). The malignant cells were medium-sized lymphoid cells with round hyperchromatic nuclei and were positive for granzyme B, but negative for TIA-1 (Fig. 4B, C). Based on clinical and histological findings, the diagnosis was unspecified PTCL (PTCL-U).

Discussion

PTCL-U accounts for about 7% of malignant lymphomas and carries a poor prognosis, with a 1-year survival rate of 44%.[1-2] According to the Ann Arbor classification, stages III and IV account for 76% of cases. As in our patient, most cases are diagnosed at an advanced stage, with invasion most often to the bone marrow (30.6%), spleen (24.6%), and liver (12.9%).[2] When malignant lymphomas form tumors in liver parenchyma, the margins are well defined.[3] In primary cases, solitary tumors often form, whereas multiple tumors and diffuse infiltration are seen in secondary invasion.[4] Contrast CT usually shows homogeneous low-density areas, and based on imaging findings, secondary invasion by malignant lymphoma was also suspected in our patient.

In this patient, based on lymph node enlargement and elevated lactate dehydrogenase (LDH) and ferritin levels, malignant lymphoma was suspected at the time of hospital admission, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy was considered. However, the patient was already in poor general condition, with a rapidly declining clinical course, so this treatment could not be administered. In primary hepatic malignant lymphoma, the diagnosis is even more difficult than in our case, and taking a patient's general condition into consideration, urgent liver biopsy is important for diagnosis and treatment.[5-11] Malignant lymphoma, either hepatic primary or secondary, must be considered as a cause of acute liver failure.

Recently, the definition and diagnostic criteria for acute liver failure were established for Japanese patients.[12] Based on these criteria, patients showing prothrombin time values of 40% or less of the standard value or international normalized ratio (INR) of 1.5 or more, caused by severe liver damage, within 8 weeks of onset of symptoms are diagnosed as having acute liver failure. In addition, the causes of acute liver failure are classified into 9 categories. This patient had a PT value of 35.2% of the standard value 17 days from disease onset. As such, the patient was diagnosed with acute liver failure due to circulatory failure and hepatic infiltration of malignant lymphoma.

Our patient had DIC on admission and we cannot rule out the possibility that PT had been elongated by DIC. However, serum fibrin degradation products (FDP) were improved from 43.2 to 29.6 mg/dL, in spite of deterioration of PT and TB. According to the Child-Pugh scoring system, the patient's score changed from 9 to 13, indicating development of liver failure despite improvement of DIC. Therefore, it is reasonable to conclude that PT elongation was caused by liver failure rather than DIC.

Mechanisms of liver injury due to malignant lymphomas include: liver injury due to

the tumor cells themselves; liver injury due to ischemia, endotoxemia, or DIC associated with tumor cell invasion; and liver injury due to hemophagocytic syndrome (HPS), a complication of malignant lymphoma.[13-16] Rowbotham et al. reported a 0.45% incidence of acute liver failure associated with malignant lymphoma,[5] and onset of lymphoma in association with acute hepatitis has also been reported.[5-11]

In our patient, findings of tumor cell invasion in hepatic tissue suggested liver injury by the tumor cells, while findings of hemophagocytosis on bone marrow examination and high ferritin levels suggested that the liver injury was also related to HPS. Malignant lymphoma is a cause of HPS, and the prognosis of malignant lymphoma associated with HPS is poor. Among cases of HPS related to malignant T-cell lymphomas, 79% are associated with PTCL-U.[17-18] Hino et al. also reported a case of malignant T-cell lymphoma with HPS, which like our case also presented with liver failure. That patient died 1 week after admission.[6] Hepatosplenic gamma/delta T-cell lymphoma also has a poor prognosis, with similar symptoms and clinical course to those seen in our patient.[19] Our patient had cervical lymph node swelling. In addition, malignant cells had infiltrated mostly in the portal areas on liver examination at autopsy and were TIA-1 negative. These findings led to the diagnosis of PTCL-U.

Four prognostic factors in PTCL-U are age ≥(60 years), performance status (≥2), elevated LDH levels, and bone marrow involvement. In contrast to a 1-year survival rate of 92% in patients without any of the above factors, the 1-year survival rate is only 40% in patients with all of the above factors.[2] In cases like ours, with HPS and acute liver failure, survival is unlikely.[6,7] However, Schmitz et al. recently proposed COHP plus etoposide (CHOEP) therapy as a novel treatment strategy for T-cell lymphoma.[20] In conclusion, we should understand the differences of clinical course by subtypes of

lymphoma. Careful evaluation and early treatment are therefore important.

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Figure Legends

Figure 1

Abdominal contrast CT showed multiple masses in the liver with poor contrast effect and splenomegaly.

Figure 2

Microscopic findings of bone marrow aspiration demonstrate hemophagocytosis of red blood cells (A, magnification, ×400, Giemsa staining) and diffuse infiltration of CD3-positive malignant cells (B, magnification, ×200, Immunohistochemical staining for CD3).

Figure 3

Summary of the patient's clinical course. mPSL, methylprednisolone; CTRX, ceftriaxone; MEPM, meropenem; FFP, fresh frozen plasma.

Figure 4

Malignant cell infiltrates in the portal area and hepatic necrosis on liver biopsy specimen at autopsy (A, magnification ×100, hematoxylin and eosin staining). Infiltrated malignant cells in the portal area are positive for CD3 and granzyme B (B, magnification, ×100, immunohistochemical staining for CD3; C, magnification, ×400, immunohistochemical staining for granzyme B).

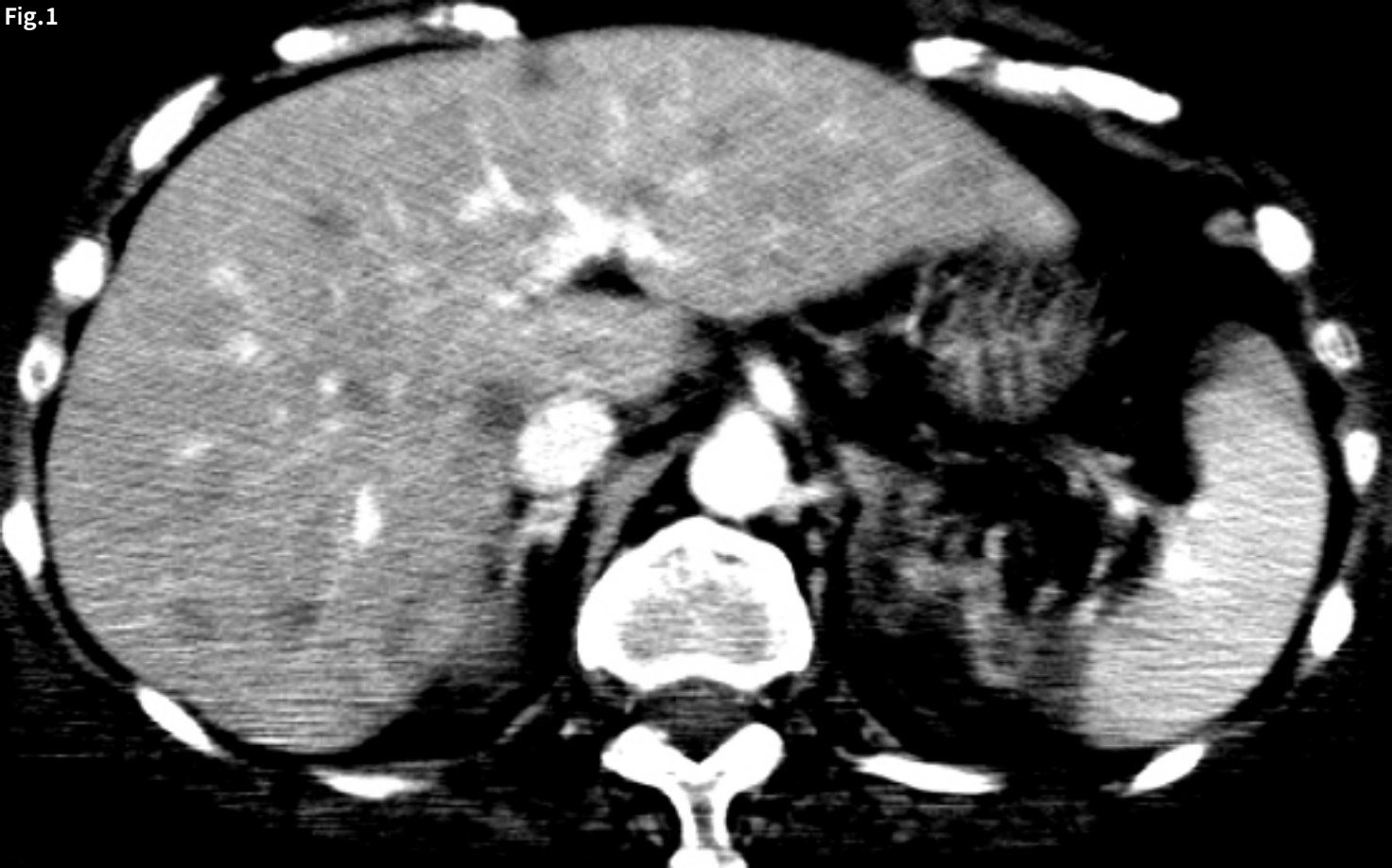
Table 1

blood count		
WBC	3700	/μL
RBC	380×10^4	/μL
Hb	11.3	g/dL
PLT	7.1×10^4	/μL
coagulation		
PT	50.7	%
APTT	48.7	sec
FDP	43.2	μg/dL

biochemistry		
Alb	2.9	g/dL
AST	4561	IU/L
ALT	2113	IU/L
LDH	2698	IU/L
ALP	592	IU/L
GTP	253	IU/L
TB	10.2	mg/dL
DB	8.4	mg/dL

BUN	41	mg/dL
Crea	2.15	mg/dL
CRP	4.81	mg/dL
NH3	68	μg/dL
ferritin	71400	ng/mL
sIL-2R	43000	U/mL
Virus marker		
HBsAg	-	
HCVAb	-	

Fig.1



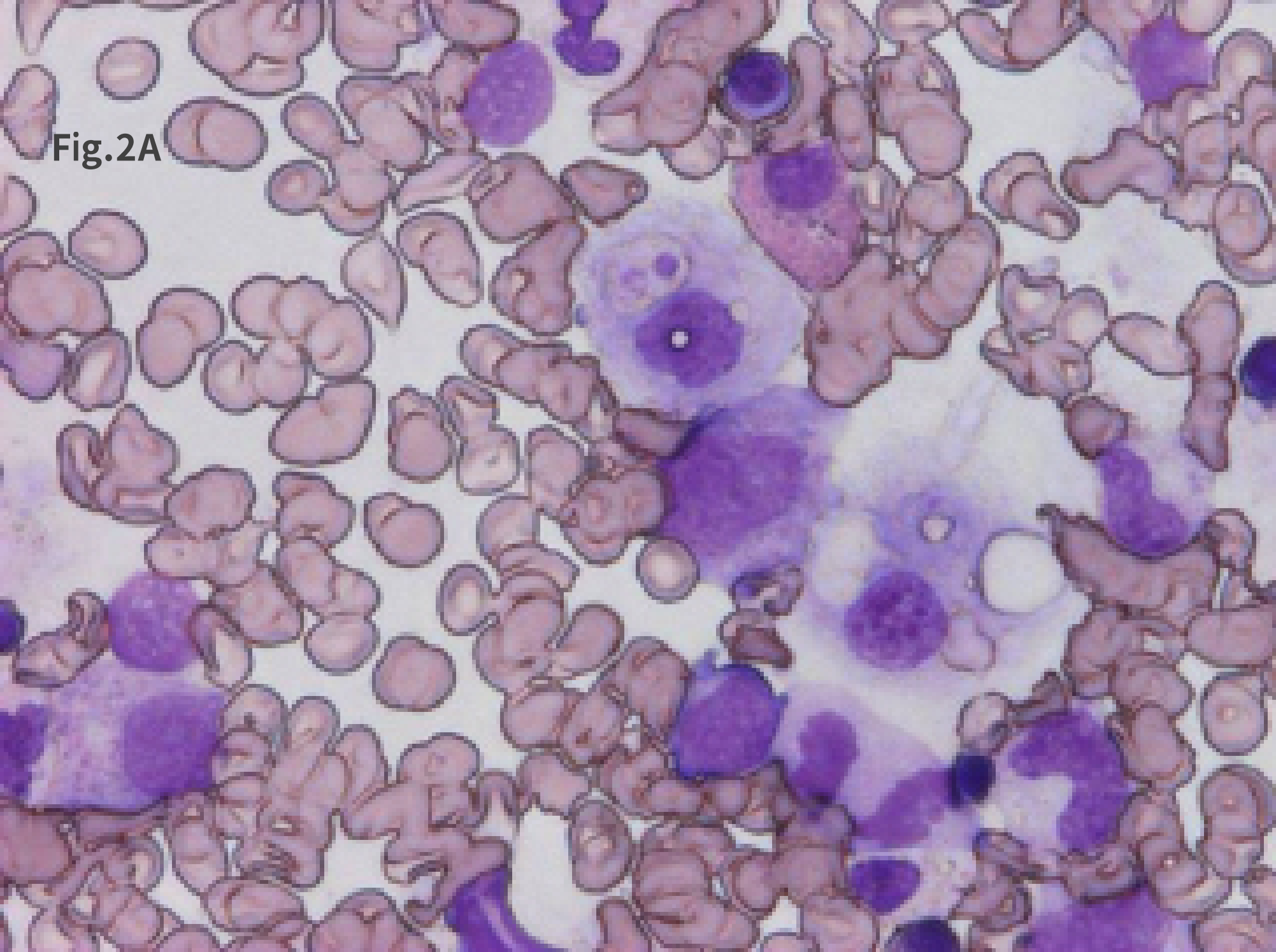


Fig.2A

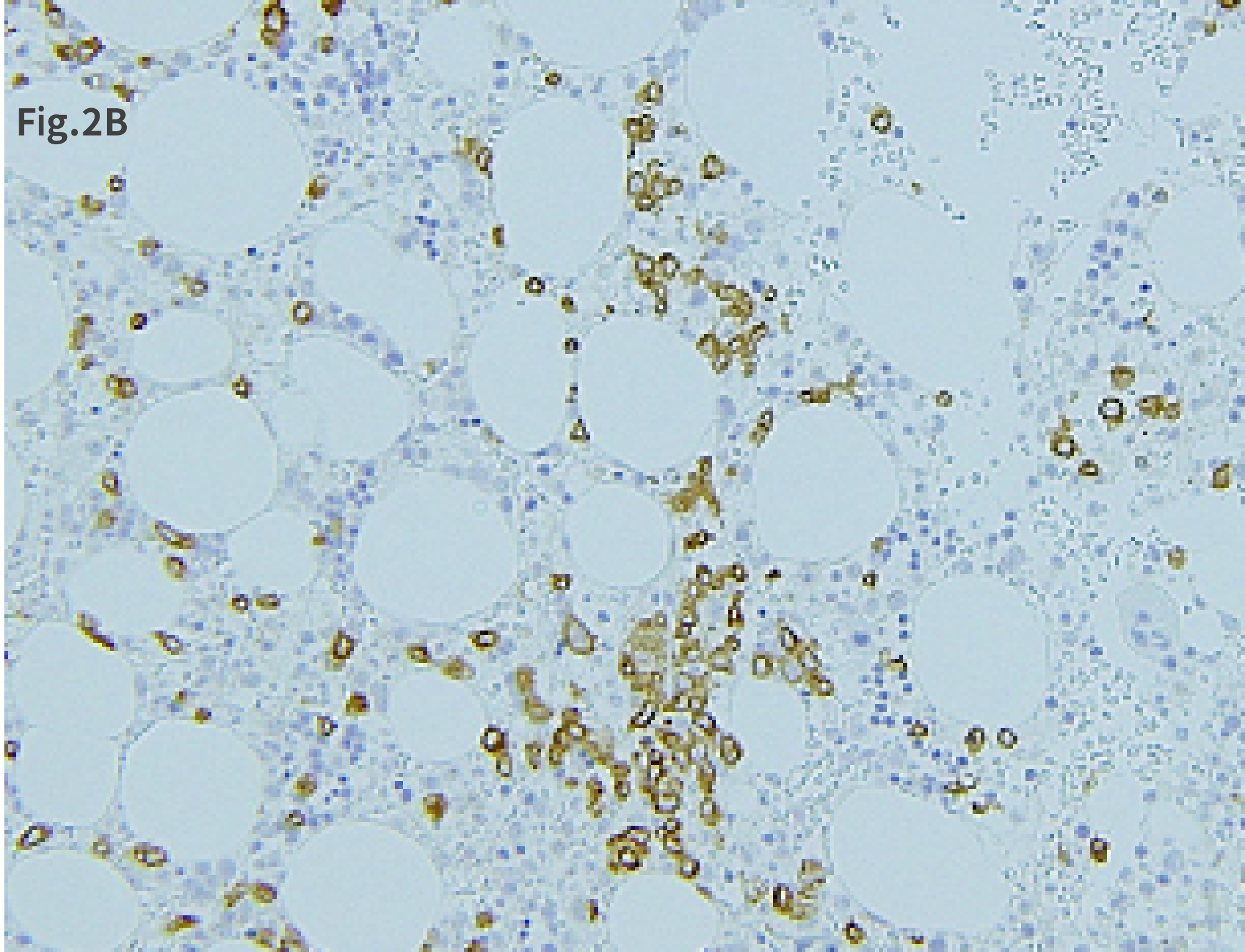


Fig.2B

Figure 3

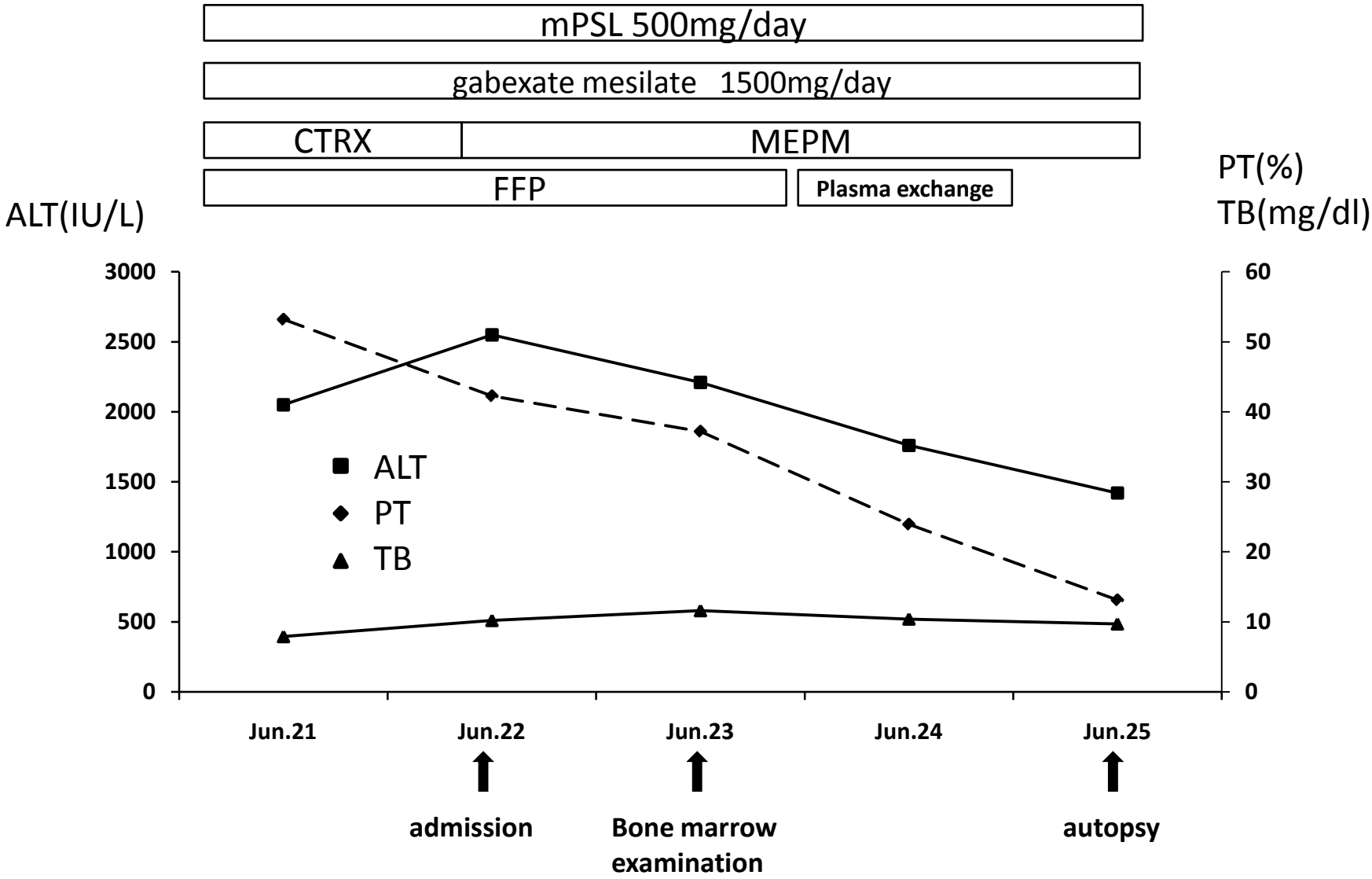

mPSL 500mg/day
gabexate mesilate 1500mg/day
CTRX
MEPM
FFP
Plasma exchange
ALT(IU/L)
PT(%)
TB(mg/dl)
3000
2500
2000
1500
1000
500
0
60
50
40
30
20
10
0
ALT
PT
TB
Jun.21
Jun.22
Jun.23
Jun.24
Jun.25
admission
Bone marrow examination
autopsy

Fig.4A

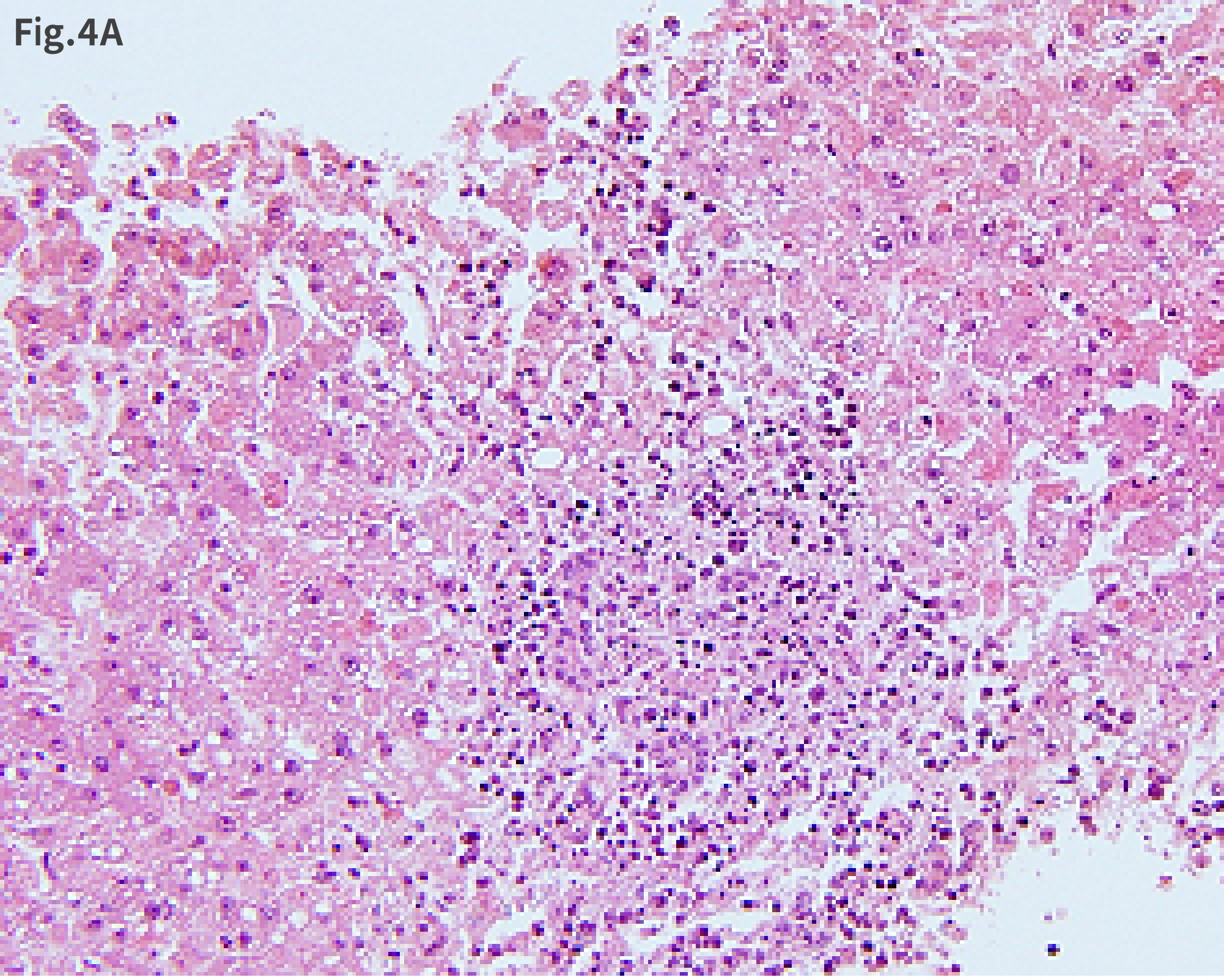


Fig.4B

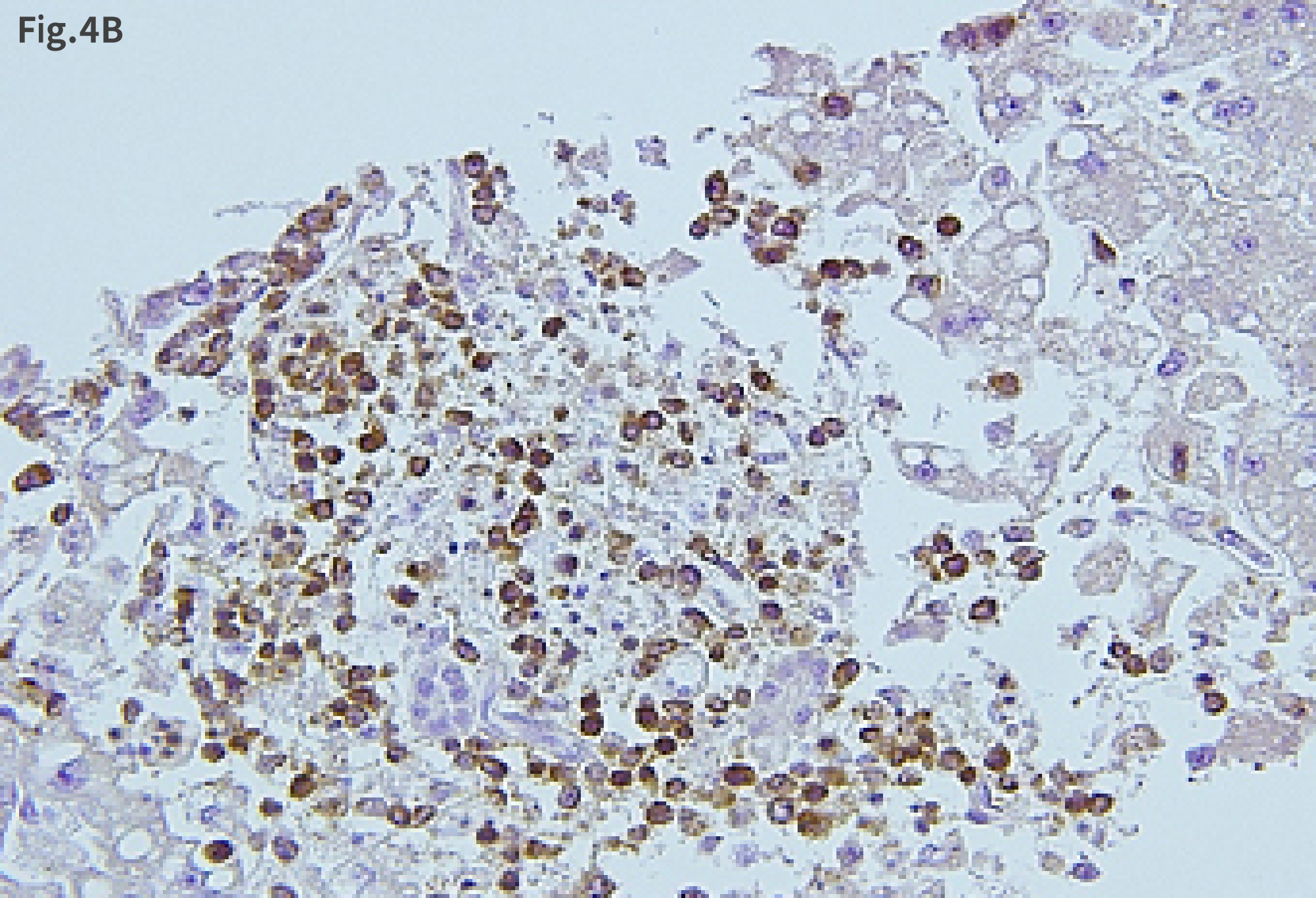


Fig.4C