Case report

Pathologic complete response after chemotherapy with atezolizumab plus bevacizumab for hepatocellular carcinoma with tumor thrombus in the main portal trunk

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Abstract

We report a case of pathologic complete response after successful treatment for advanced hepatocellular carcinoma (HCC) complicated with portal venous tumor thrombus by atezolizumab and bevacizumab followed by radical resection. The patient was a male in his 60s. During follow-up for chronic hepatitis B, abdominal ultrasonography revealed a huge tumor located in the right lobe of the liver with the portal vein thrombosed by the tumor. The tumor thrombus extended to the proximal side of the left branch of the portal vein. The patient's tumor marker levels were elevated (AFP, 14,696 ng/ml; PIVKA-II, 2,141 mAU/ml). Liver biopsy revealed poorly differentiated hepatocellular carcinoma. The lesion was categorized as advanced stage according to the BCLC staging system. As systemic therapy, atezolizumab plus bevacizumab was administered. Imaging showed marked shrinkage of the tumor and portal venous thrombus with a remarkable decrease of tumor marker levels after 2 courses of

chemotherapy. After 3 additional courses of chemotherapy, radical resection was considered possible. The patient underwent right hemihepatectomy and portal venous thrombectomy. A pathological examination revealed a complete response. In conclusion, we experienced a successful curative treatment for advanced HCC with atezolizumab plus bevacizumab as an option of systemic therapy with a view to conversion surgery.

Introduction

Advances in molecular targeted agents have improved the outcome of hepatocellular carcinoma (HCC), and the advent of immune checkpoint inhibitor (ICI) therapy has led to the further development of combination therapies. The results of IM brave 150, which showed the efficacy of atezolizumab plus bevacizumab over sorafenib, are likely to change the treatment strategy for HCC (1). Although atezolizumab plus bevacizumab is indicated for the treatment of unresectable HCC, subsequent resection (i.e., conversion surgery) may be curative in patients with a smaller tumor size or improved vascular invasion as a result of treatment.

We herein report a case of highly advanced HCC in the right lobe of the liver with a portal vein tumor thrombus extending to the left branch of the portal vein. This patient was treated with atezolizumab plus bevacizumab followed by successful radical resection.

Case report

The patient was a man in his 60s (height, 160 cm; body weight, 57 kg). During follow-up for chronic hepatitis B, alpha-phetoprotein (AFP) elevation and contrast CT showed a multinodular tumor in the anterior segment of the right lobe of the liver and a tumor thrombus in part of the right to left branch of the extrahepatic portal vein

(Fig 1, 2). Liver biopsy revealed poorly differentiated HCC. The patient's tumor marker levels were markedly elevated (AFP, 14,696 ng/ml; PIVKA-II, 2,141 mAU/ml). The lesion was categorized as advanced stage according to the BCLC staging system (2). As systemic therapy, atezolizumab plus bevacizumab was administered. Imaging showed marked shrinkage of the tumor and portal venous thrombus with a remarkable decrease in the tumor marker levels after 2 courses of chemotherapy (Fig. 3, 4) After 3 additional courses of chemotherapy, radical resection was considered possible. Considering the adverse effect of bevacizumab on wound healing and hemorrhage, only atezolizumab was administered at the 5^{th} course. Preoperatively, the Child-Pugh score was 6 (class A). The tumor marker levels measured before surgery were as follows: AFP, 2.8 ng/ml; PIKA-II, 75 mAU/ml. The liver functional reserve was also evaluated by the indocyanine green retention rate at 15 minutes (ICGR15) and asialo-scintigraphy. The ICGR15 was 20.6% and the LHL15 in asialo-scintigraphy was 0.907. Before the introduction of atezolizumab plus bevacizumab, the ICGR15 was 29.8% and the LHL15 was 0.937. According to our criteria regarding the liver functional reserve (3), right hemihepatectomy was considered feasible.

The patient underwent right hemihepatectomy and portal venous thrombectomy 25 days after the last administration of atezolizumab. The operation time was 523 minutes

and the estimated blood loss was 1,620 g. On POD1, a portal vein thrombus was found, and percutaneous trans-splenic thrombus removal was performed as interventional radiology. Follow-up portal angiography showed a tendency for the thrombus to shrink, and anticoagulant therapy was started with heparin. After confirming that the portal vein thrombus had almost disappeared, the patient was changed to an oral anticoagulant. On the 29th day after the operation, he was transferred to another hospital for rehabilitation.

Microscopic examination detected focal lesions in the resected liver specimens, which show fibrous granulation tissue with lymphoplasmacytic and ceroid/pigment-laden macrophage infiltration, and deposition of fine reticular or hyalinized large collagen bundles, but no residual carcinoma. Immunohistochemical staining demonstrated that the infiltrating lymphocytes composed of CD3+CD4+ and CD3+CD8+ T cells (Fig. 5).

We investigated the expression of PDL1, PD1 and CD4 +, CD8+ T cells in a biopsy sample of the tumor taken before the introduction of atezolizumab and bevacizumab. In pre-treatment samples, a significant number of PD1+CD4+ T cells and CD8+ T cells were recognized. In addition, PDL1+ mononuclear cells but not tumor cells were detected (Fig. 6).

In addition, an organized thrombus was also detected in a portal vein. The thrombus composed of coagulation necrosis of AE1/AE3-positive cohesive nests and inflamed

granulation tissue infiltrated by abundant lymphocytes and plasma cells (Fig. 7). The response after the systemic chemotherapy was determined classified as a pathological complete response after extensive pathological examination through all the resected samples. At the time of writing this report (16 months after surgery), the patient is being followed up without signs of recurrence.

Discussion

This is the first report showing that a pathological complete response was obtained not only for the main tumor but also for the portal vein tumor thrombus after hepatic resection following systemic therapy with atezolizumab + bevacizumab for a patient with HCC with portal vein tumor thrombus in the main portal trunk and contralateral to primarily involved lobe. Although thrombus formation around the portal vein tumor thrombus is well known (4), the fact that necrosis of tumor cells surrounded by thrombus was obtained, as shown in the histopathological examination, may be due to the characteristics of immune checkpoint inhibitors.

A significant number of CD4+ and CD8+ T cells were detected in both pre-treatment and post-treatment samples, and the CD8+ T cell infiltration relatively increased in post-treatment resected specimen. The favorable outcomes in HCC patients with high

114 expression of CD8+ T cells in tumorous lesion have been reported (5, 6); this
115 phenomenon was also reported in patients with advanced HCC undergoing atezolizumab
116 and bevacizumab (7). In this case, PDL1 expression was detected in the mononuclear
117 cells but not abundant. PD-L1 expression in both tumor cells and mononuclear cells have
118 been shown to be associated with clinical benefits of immune checkpoint inhibitors in
119 several cancer types (7-10). Combined immunotherapy including anti-VEGF for
120 enhancing T cell trafficking and infiltration into the tumor has been investigated and
121 established to benefit patients who were less likely to benefit from PD-L1 inhibition alone,
122 because their tumors were PD-L1 negative (11). Recent literature showed a nonsignificant
123 trend of high PD-L1 expression with improved clinical outcomes from atezolizumab and
124 bevacizumab in patients with unresectable HCC (7). Although the PD-L1 expression was
125 evaluated with the biopsy specimens, but not with entire HCC specimens, the fact that
126 pathological CR was obtained in this case, in which PDL1 expression was originally low,
127 is a good example of the remarkable effect of combined immunotherapy.

128 According to the algorithm included in “Guidelines for HCC treatment in Japan”
129 by The Japan Society of Hepatology, patients with major vascular invasion are candidates
130 for hepatic resection (12). The proven efficacy of atezolizumab plus bevacizumab in the
131 treatment of unresectable HCC is changing the treatment strategy for HCC (13, 14).

Unresectable HCC includes a variety of conditions, some of which cannot be completely eliminated by hepatic resection alone, such as extrahepatic metastasis, and some of which are anatomically resectable depending on the degree of vascular invasion. Although the patient in this report had a tumor thrombus in the main trunk of portal vein, IMBrave 150 included many advanced BCLC stage patients with macrovascular invasion (1), which would be considered a resectable lesion in Japan (15-17). When these patients are determined to be unresectable and chemotherapy is started, there is an issue regarding how far to continue the regimen. In the present case, the patient's tumor marker levels decreased quickly, and the tumor size gradually decreased as chemotherapy continued. In this case report, we were able to perform hepatic resection after treatment with atezolizumab plus bevacizumab, but the liver functional reserve mildly decreased on asialo-scintigraphy. A pathological examination showed mild lobular inflammation with inflammatory infiltrate consisting of lymphocytes. These findings were compatible with previously reported ICI-related hepatic injury (18). Large regenerative nodules are detected in the background liver. Portal lymphocytic inflammation and lobular inflammation associated with focal necrosis of hepatocyte were observed. Although orcein stain-positive "ground-grass" hepatocytes were detected and differentiation anti-PD-1-induced hepatic injury from natural chronic hepatitis B is difficult, it is plausible

that administration of anti-PD-1 antibody enhanced the chronic hepatitis B.

Although no significant decrease in the liver functional reserve was observed in evaluations based on the general liver function or ALBI grade in previous reports (19), the accumulation of knowledge on the changes in the liver functional reserve (e.g., ICGR15, asialo-scintigraphy, etc.) before and after administration is considered important when considering atezolizumab plus bevacizumab therapy for conversion therapy or neoadjuvant therapy. This insight will also lead to the establishment of the optimal period for the preoperative administration of atezolizumab plus bevacizumab and the optimal interval between the end of administration and resection.

Recently, we reported that the hepatobiliary phase of EOB-MRI was useful for predicting the therapeutic effect of atezolizumab plus bevacizumab on unresectable HCC. Patients with HCC showing a heterogeneous pattern had significantly shorter progression-free survival in comparison to patients with HCC showing a homogenous pattern, and patients with hyperintense tumors had significantly shorter progression-free survival in comparison to patients with hypointense tumors (20). The appropriate selection of patients who will respond to atezolizumab plus bevacizumab will help establish criteria for its introduction for advanced HCC with consideration of possible future conversion therapy.

In conclusion, for advanced HCC with portal venous tumor thrombus, atezolizumab plus bevacizumab was considered effective and was safely administered without influencing the perioperative course when conversion therapy was conducted. Furthermore, this regimen may be a treatment option as a part of multidisciplinary treatment strategy for advanced-stage HCC with a view to conversion surgery.

Ethical Statement: Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethical Committee of the Nagasaki University Hospital (decision number 19102143), and informed consent was taken from the patient.

Conflict of interest statement:

Akihiko Soyama and other co-authors have no conflict of interest.

Funding sources:

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Author contributions statement:

(I) Conception and design: Kurisaki, Soyama, Eguchi

(II) Administrative support: Hara, Matsushima, Imamura, Tanaka

(III) Provision of study materials or patients: Kurisaki, Soyama, Hara, Matsuhima, Hidaka

(IV) Collection and assembly of data: Kurisaki, Soyama, Hidaka, Hara, Matsushima

(V) Data analysis and interpretation: Kurisaki, Soyama, Hara, Matsushima, Okano, Hidaka, Ito, Kanekata, Eguchi

(VI) Manuscript writing: Kurisaki, Soyama, Eguchi

(VII) Final approval of manuscript: Soyama, Eguchi

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. Contrast-enhanced CT shows a hypo-attenuated mass with an indistinct border in the anterior sector. Portal venous tumor thrombus (PVTT) is observed in the posterior branch and the left branch of the portal vein. Arrowhead shows PVTT.

Figure 2. EOB-MRI. The hepatobiliary phase shows multiple nodules with a portal tumor thrombus.

Figure 3. CE-CT shows shrinkage of the portal venous tumor thrombus.

a) PVTT was present in P6, P7 and LPV. b) After 2 courses of chemotherapy

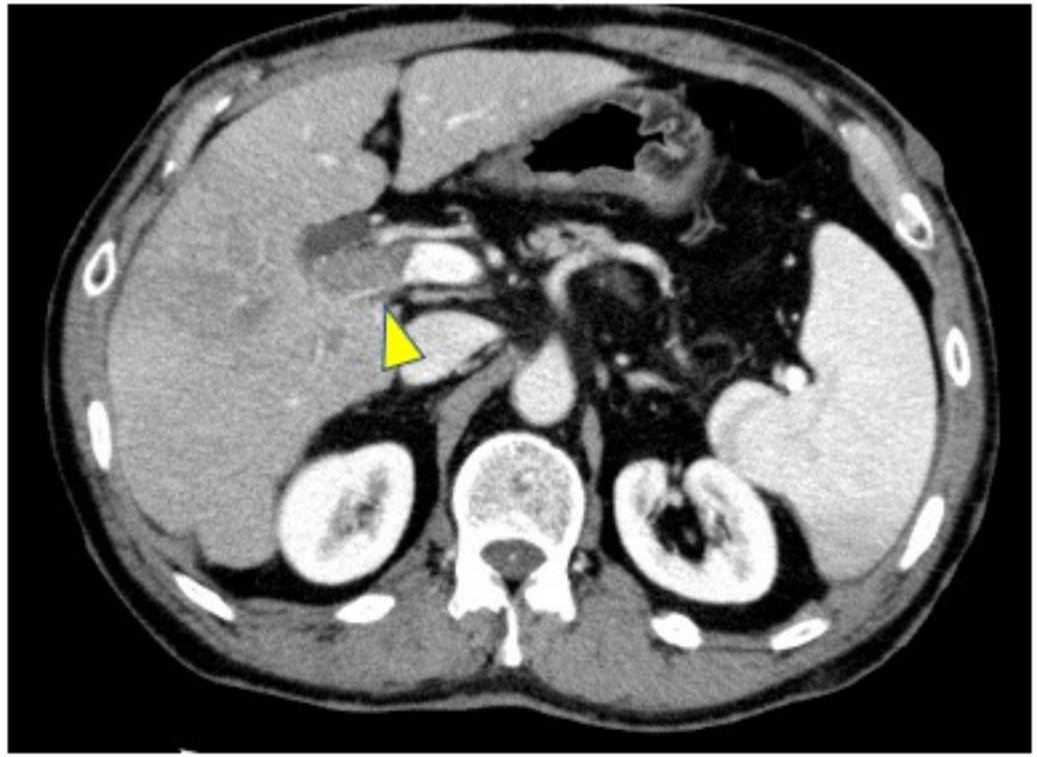
c) Before the operation

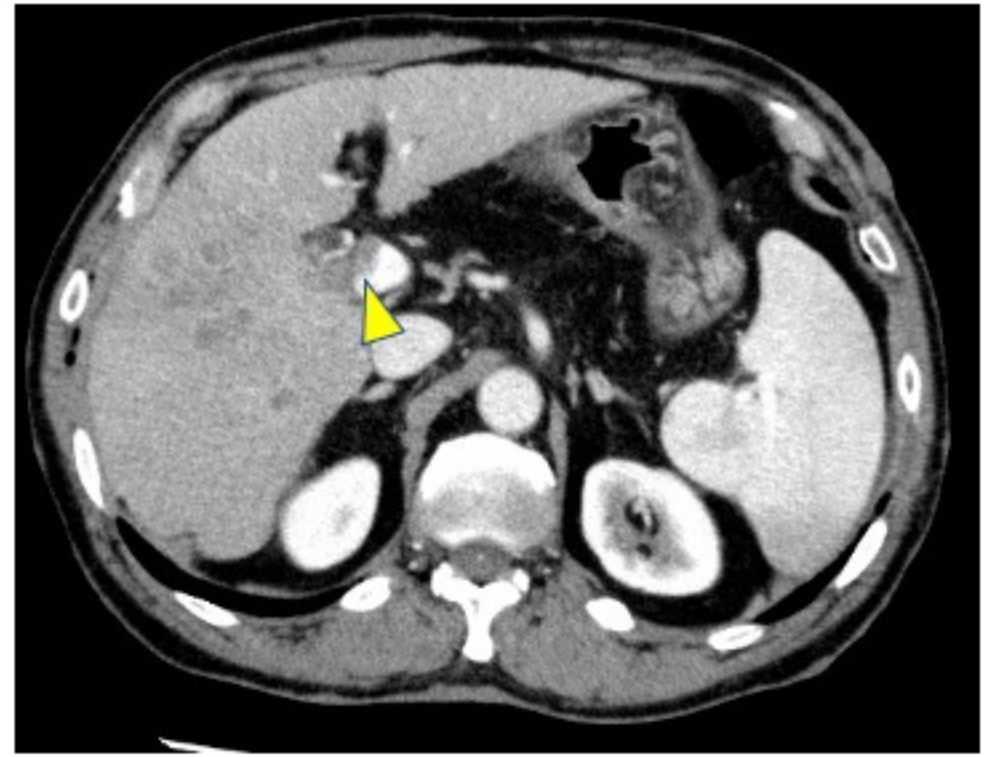
Figure 4. Chronological change in the tumor marker levels

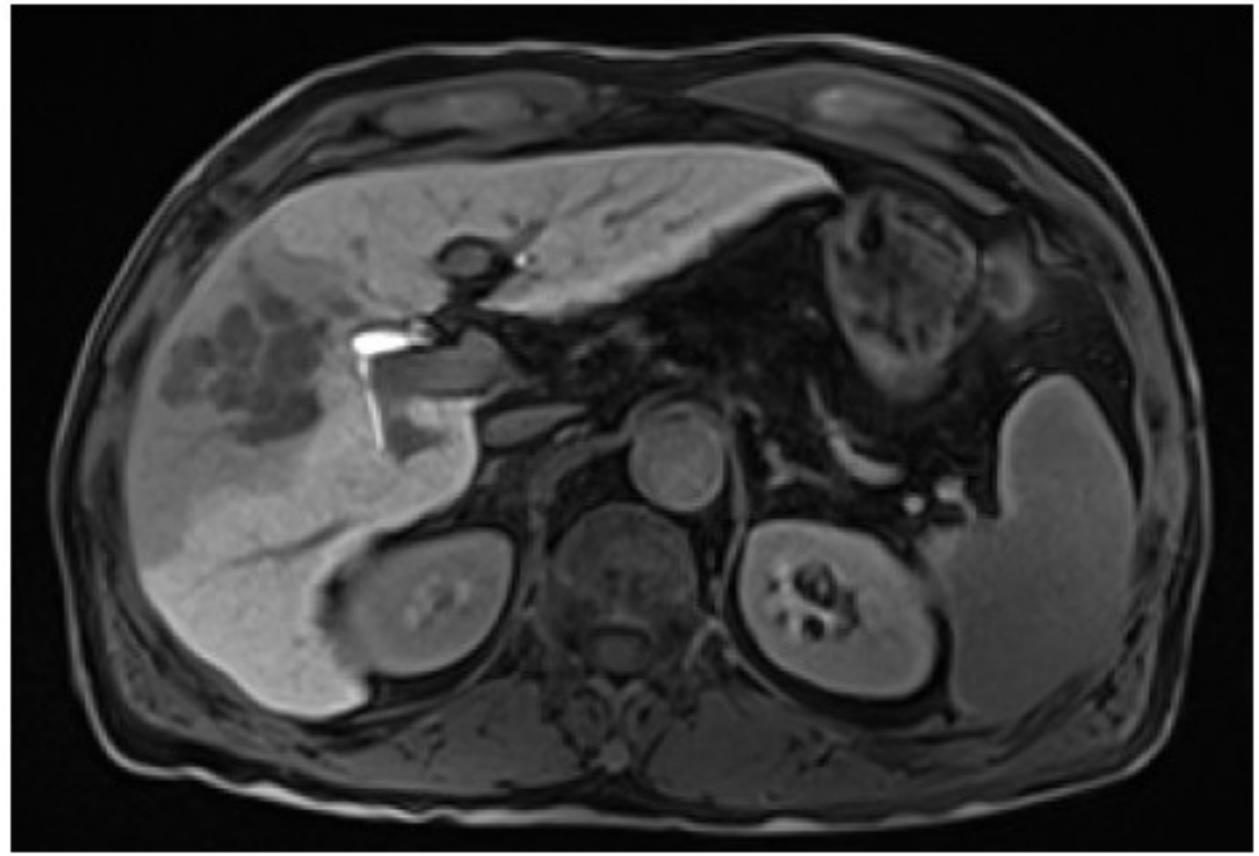
Figure 5. Immunohistochemical staining of lymphocytes. T-lymphocyte infiltration was detected by positive staining of CD3, CD4, and CD8 in the resected specimen.

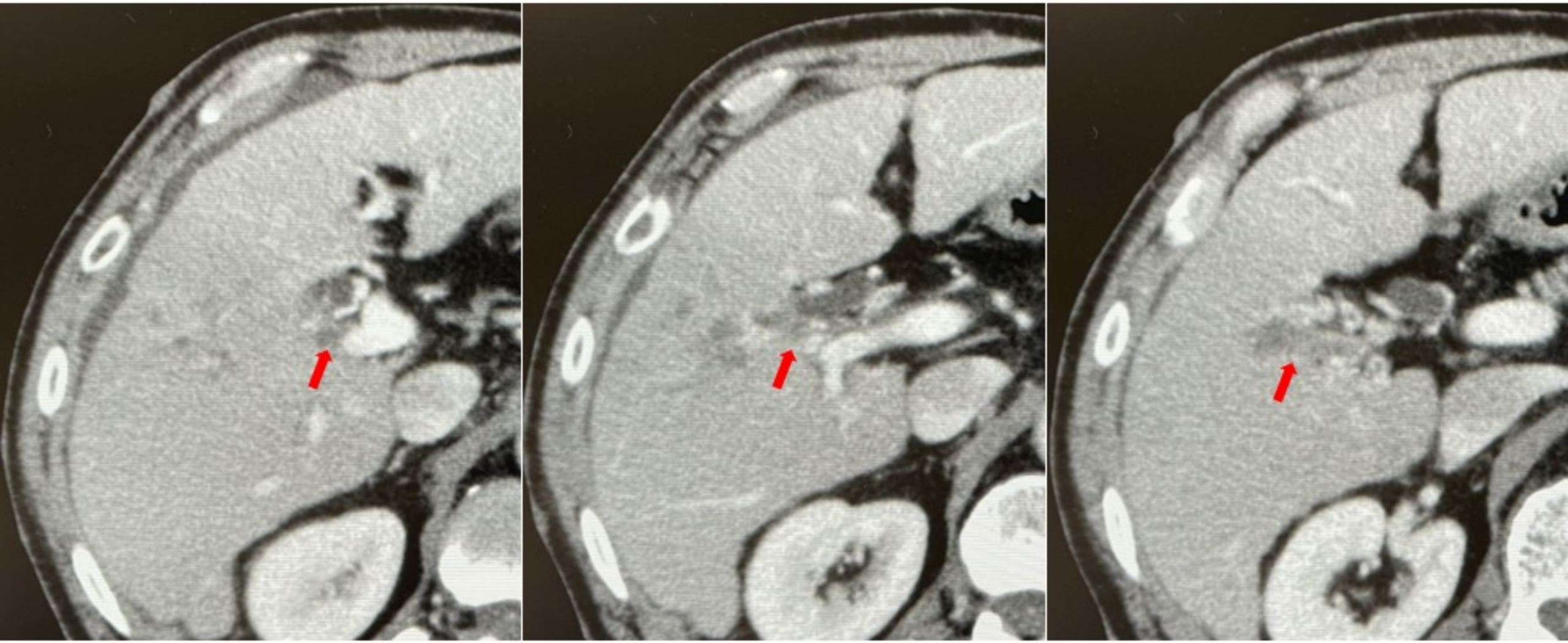
Figure 6. Immunohistochemical staining of PDL1, PD1, CD4+ T-cells, and CD8+ T-cells in the pre-treatment biopsy sample.

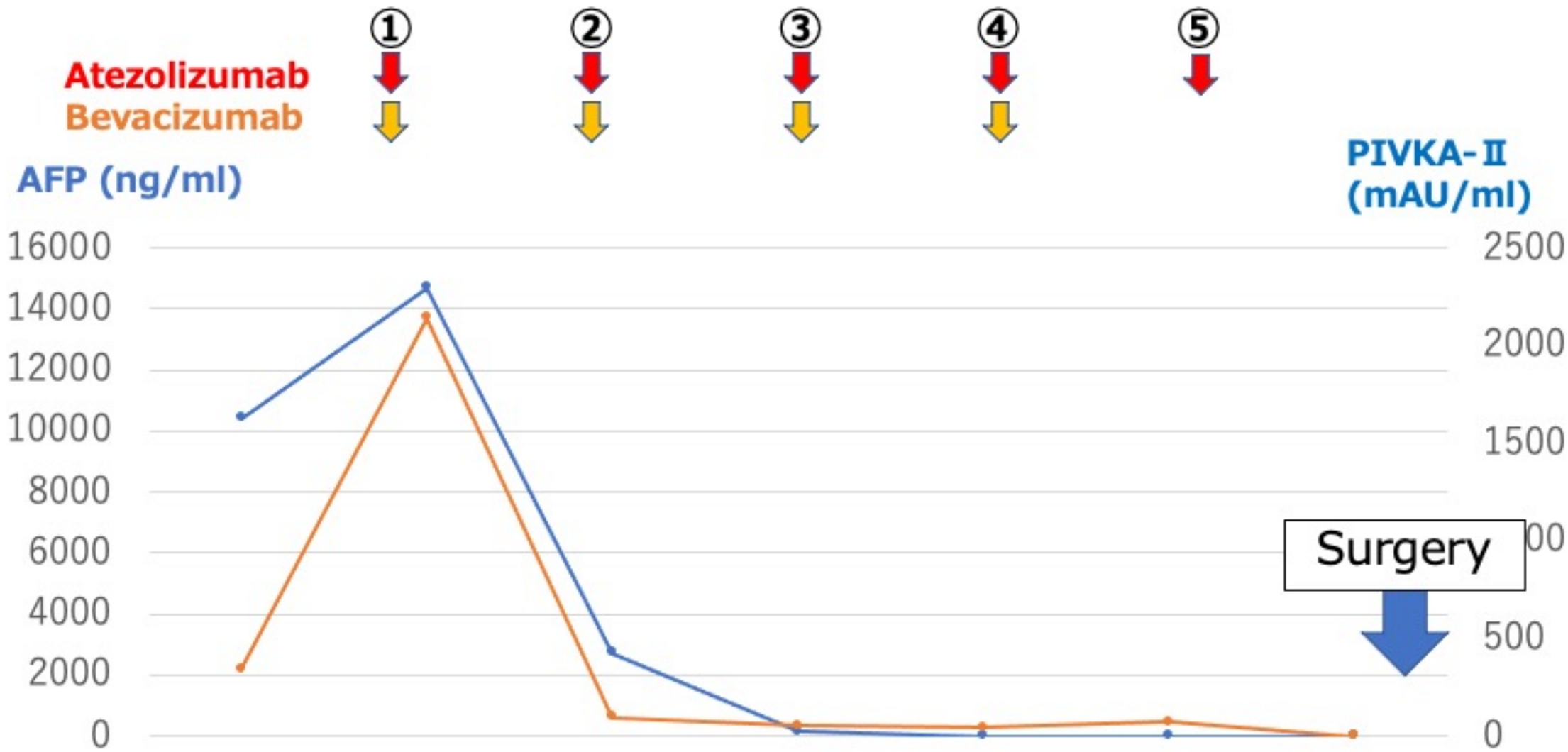
Figure 7. Pathological findings (a: H&E staining 20×, b : AE1/AE3 20×, c : H&E staining 200×, d: AE1/AE3 200×). a) Portal venous thrombus. b) Tumor cells in the portal venous thrombus. c) Completely necrotic tumor cells.

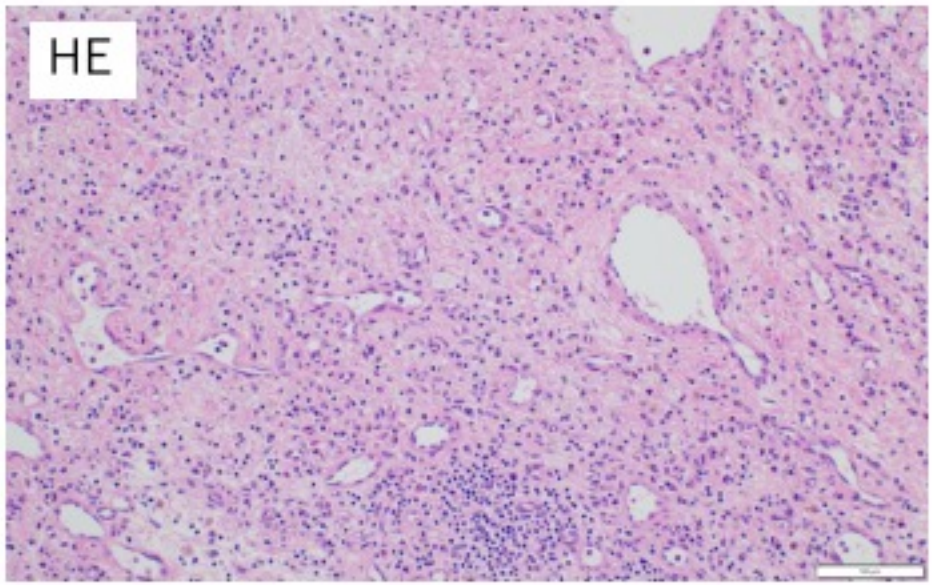









①
②
③
④
⑤
Atezolizumab
Bevacizumab
AFP (ng/ml)
PIVKA-Ⅱ (mAU/ml)
16000
14000
12000
10000
8000
6000
4000
2000
0
2500
2000
1500
500
0
Surgery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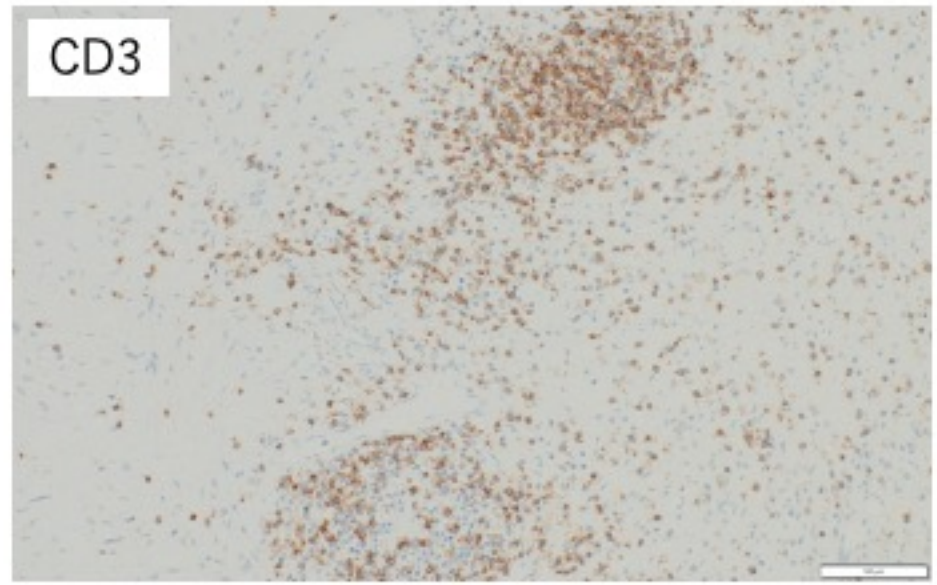
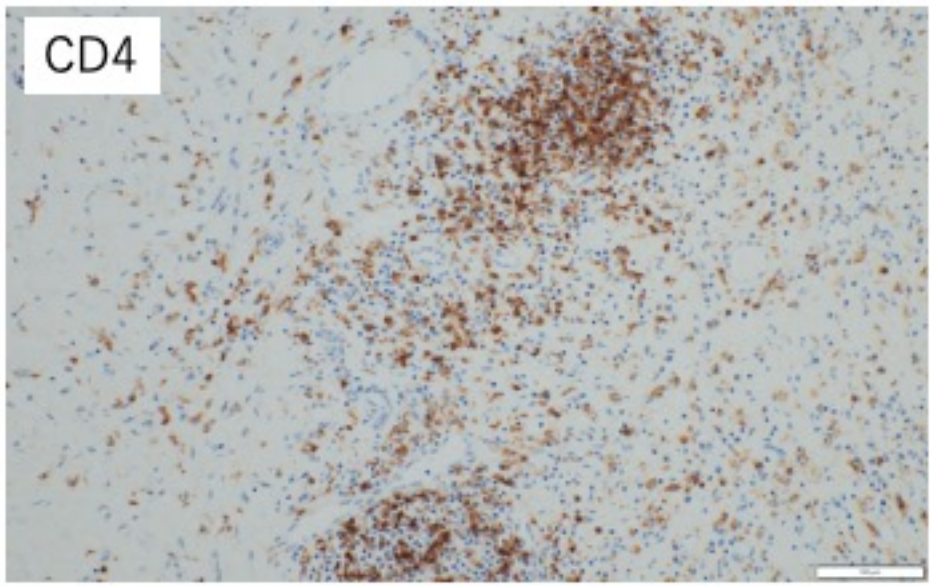

CD3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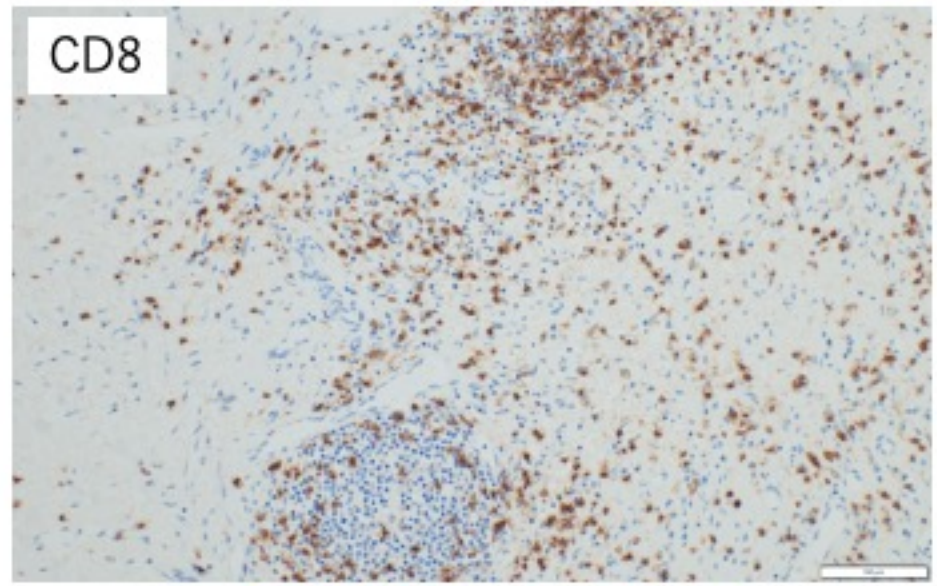
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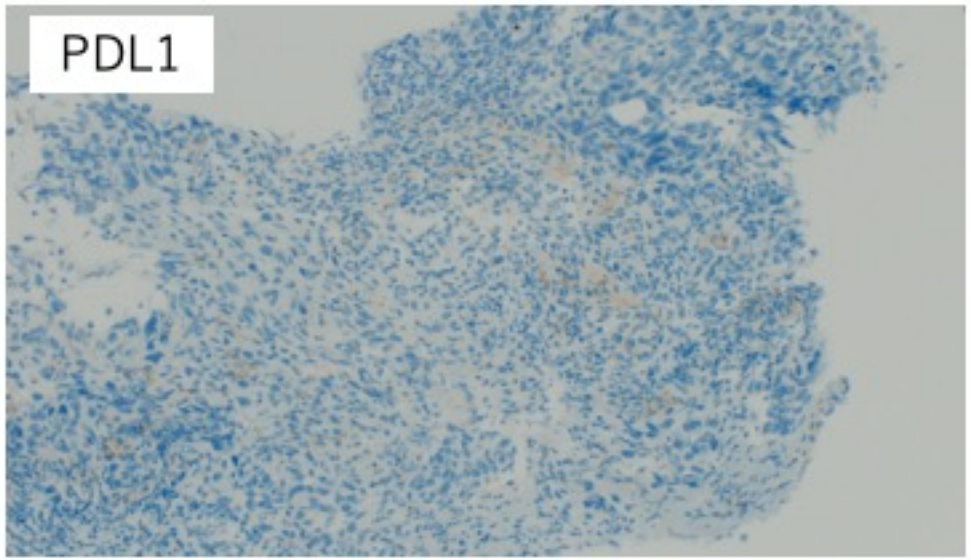
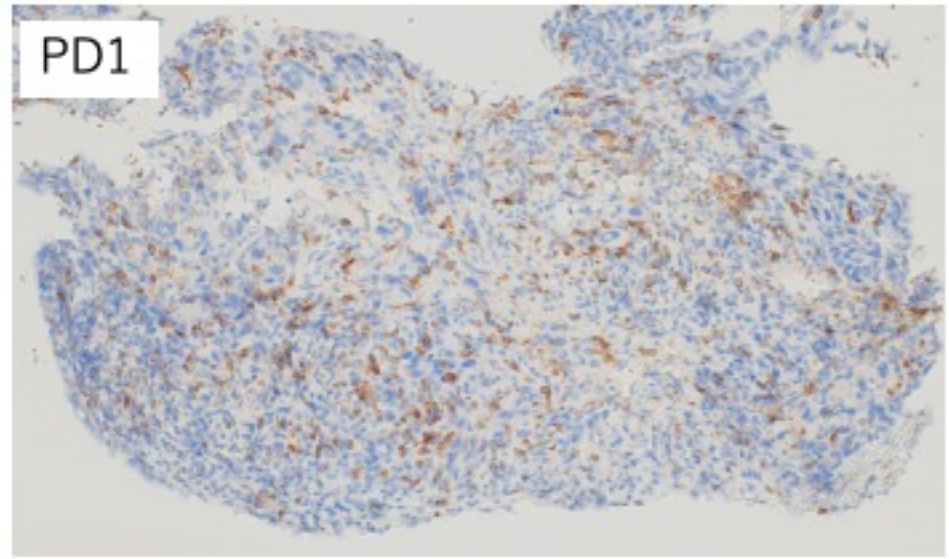
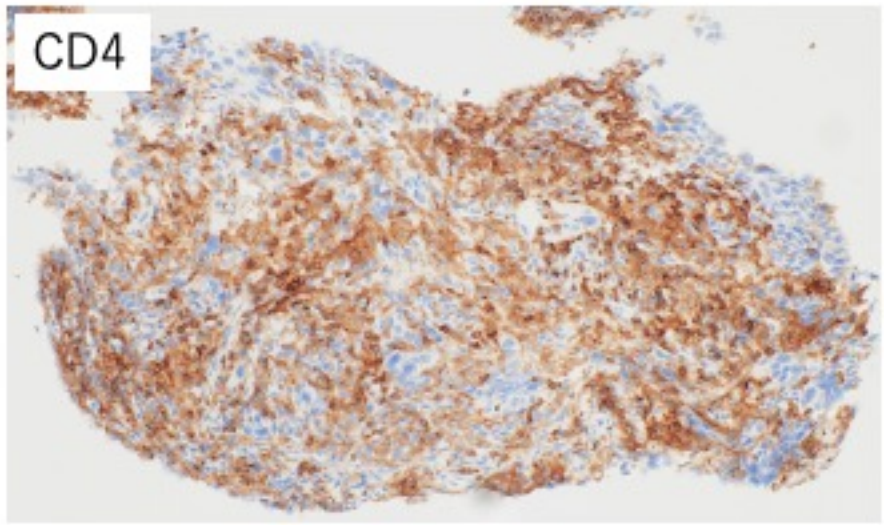

PDL1


PD1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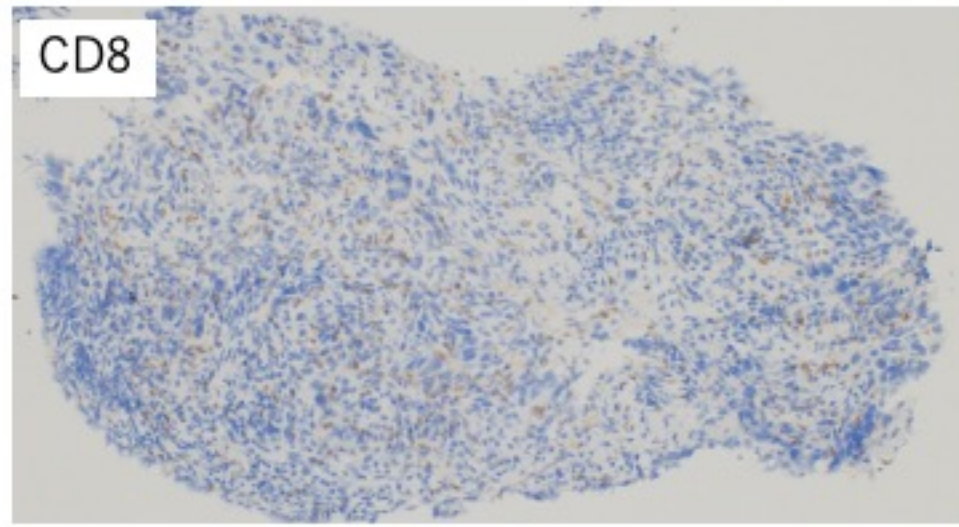
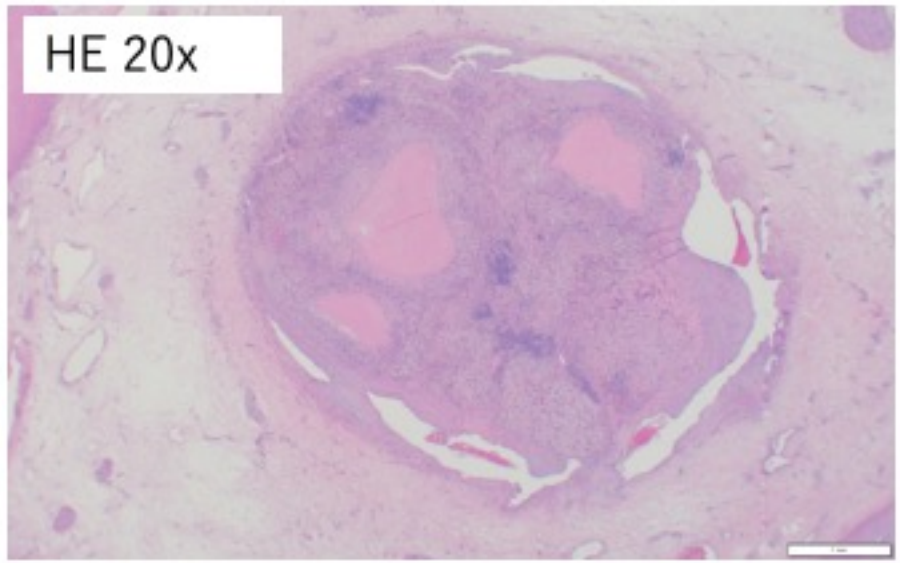
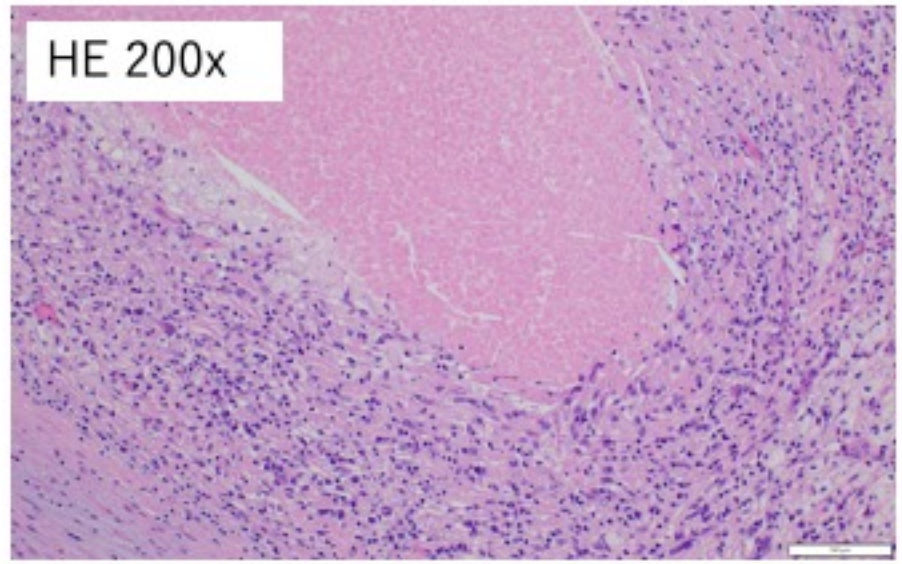

CD8

a)



b)



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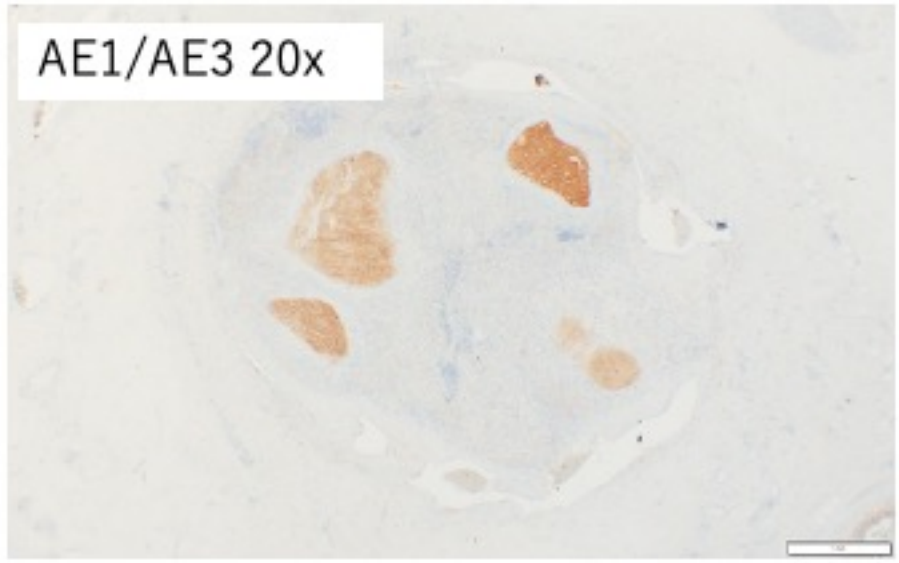

d)