An autopsy case of severe acute pancreatitis induced by administration of pazopanib following nivolumab

Tanaka, Takeshi ; Sakai, Arata ; Shiomi, Hideyuki ; Masuda, Atsuhiro ; Kobayashi, Takashi ; Tanaka, Shunta ; Nakano, Ryota ; Shigeoka, Manabu…

(Citation)
Pancreatology,21(1):21-24

(Issue Date)
2021-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

An autopsy case of severe acute pancreatitis induced by administration of pazopanib following nivolumab

Takeshi Tanaka, MD[1], Arata Sakai, MD, PhD[1], Hideyuki Shiomi, MD, PhD[1], Atsuhiro Masuda, MD, PhD[1], Takashi Kobayashi, MD, PhD[1], Shunta Tanaka, MD[1], Ryota Nakano, MD[1], Manabu Shigeoka DDS, PhD[2], Yu-ichiro Koma, MD, PhD[2], and Yuzo Kodama, MD, PhD[1]

[1] Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine

[2] Division of Pathology, Department of Pathology, Kobe University Graduate School of Medicine

Affiliation:

Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine

7-5-1 Kusunoki-cho, Chuo-ku, Kobe,650-0017, Japan

Corresponding author: Arata Sakai

Tel.: +81-78-382-6305

Fax: +81-78-382-6309

E-mail: asakai@med.kobe-u.ac.jp

Key words:

acute pancreatitis

immune-related adverse events

autopsy

Acknowledgement:

This work was supported by JSPS KAKENHI Grant Number JP19K07938.

Disclosure statement:

The authors have no conflicts of interest to disclose concerning this article.

ABSTRACT

Drug-induced pancreatitis is often mild to moderate in severity, but severe and even fatal cases can occur. Here, we report a 74-year-old woman undergoing chemotherapy for recurrent renal cell carcinoma, who presented with abdominal pain after administration of pazopanib following nivolumab and was diagnosed with severe acute pancreatitis. Administration of methylprednisolone and conservative treatment were initiated, but clinical findings and laboratory tests rapidly worsened. When she died, an autopsy was performed. The autopsy findings suggested the possibility of pancreatitis and hepatitis as immune-related adverse events. To the best of our knowledge, no fatal cases of acute pancreatitis due to nivolumab or pazopanib have been reported. We considered that the effects of nivolumab were sustained in the pancreas, and pazopanib administration might have worsened the toxicity.

Introduction

Drug-induced pancreatitis is similar to acute pancreatitis (AP) and is often mild and has a good prognosis, but can be severe and fatal in some cases [1]. The use of multi-targeted tyrosine kinase inhibitors (TKIs) in patients with advanced renal cell carcinoma (RCC) improves their prognosis. However, several adverse events, including AP, have been reported [2]. Immune checkpoint inhibitors (ICIs) have become a new standard in cancer treatment, but have often been reported to induce adverse events, called immune-related adverse events (irAEs) [3]. Although ICIs can potentially induce irAEs in any organ system, AP as an irAE remains a rare complication. There are few reports of severe AP induced by TKIs or ICIs; in addition, no fatal cases have been reported. Herein, we present an autopsy case of severe AP that resulted in death due to administration of pazopanib following nivolumab.

Case report

A 74-year-old woman undergoing chemotherapy for recurrent RCC was admitted to our hospital with abdominal pain. She had undergone a right nephrectomy for RCC eighteen years prior. Twelve years after the surgery, multiple lung metastases were detected, and systemic chemotherapy was initiated. However, five years later, she developed liver metastases, and nivolumab was administered as third-line treatment. One year after nivolumab initiation, she received fourth-line treatment with pazopanib because of disease progression. Two months after pazopanib initiation (three months after discontinuation of nivolumab), she

was admitted to our hospital with abdominal pain. Laboratory tests revealed increased levels of aspartate transaminase (339 U/L [13–30 U/L]), alanine transaminase (609 U/L [7–23 U/L]), pancreatic amylase (4050 U/L [16–52 U/L]), and lipase (8788 IU/L [16–60 IU/L]). Contrast-enhanced computed tomography (CE-CT) showed diffuse pancreatic swelling without evidence of either necrotic lesions or peripheral exudative effusions (Figure 1a). As there was no evidence of cholelithiasis and no history of alcohol consumption, she was diagnosed with severe AP induced by nivolumab or pazopanib. In addition to conservative treatment, methylprednisolone 40 mg (1 mg/kg) was administered for presumed irAEs. Even though conservative treatment had been undertaken, her condition rapidly worsened with electrolyte abnormalities and respiratory failure on day 3 of admission. The blood gas analysis showed PaO2 121mmHg and PaCO2 23.9 mmHg under oxygen mask with a FiO2 0.4. Afterwards, hypoxemia rapidly worsened and SPO2 showed 90 % under oxygen mask with a FiO2 0.9. Chest X-ray showed multiple pulmonary metastases, bilateral pleural effusion and pulmonary edema (Figure 1b). Thus, she required intensive treatment, including mechanical ventilation and continuous hemodialysis and ultrafiltration. However, she refused to undergo intensive treatment because of her poor RCC prognosis. She died on the same day, and an autopsy was performed 16 hours after death. Macroscopically, the pancreas showed parenchymal and fat necrosis with bleeding, which weighed 345g. Inflammation had spread to the retroperitoneum, abdominal cavity, transverse colon, and left adrenal gland (Figure 2a and b). Microscopically, the fat necrosis was observed around the parenchymal necrosis (Figure 2c and d). Infiltration of myeloperoxidase-

positive neutrophils and CD68-positive macrophages were observed in necrotic lesions of the pancreatic parenchyma, suggested severe necrotizing acute pancreatitis (Figure 2e-g). In addition, markedly more CD8+ T cells were detected than CD4+ T cells in the remaining pancreatic parenchyma (Figure 2h and i). On the other hand, bilateral, red and clear pleural effusions (left 300 ml, right 300 ml) were found in the pleural cavity. The gross specimen showed that the multiple lung metastases were observed, and some of them were exposed to the bronchial lumen. (Figure 3a and b). Microscopically, other than pulmonary congestion in alveolar cavities, there were no other specific findings leading to respiratory failure (Figure 3c), and lung tumors were consistent with metastasis of renal cell carcinoma (Figure 3d).

Discussion

AP from nivolumab [4] or pazopanib [5] has been reported, but to the best of our knowledge, no fatal cases have been reported. We present an autopsy case of severe AP that resulted in death due to administration of pazopanib following nivolumab. The autopsy findings revealed infiltration of neutrophils, bleeding and fat necrosis and suggested typical AP. However, infiltration of CD8 + T cell-dominant lymphocytes was observed, suggested the possibility of AP as irAEs. In cases with autoimmune diabetes and autoimmune pancreatitis, some studies reported CD8 + T cells infiltrated in the pancreatic islets and the pancreatic parenchyma [6-8]. But in this case, laboratory tests revealed normal range of serum HbA1c (6.0% [4.9–6.0 %]), serum fasting blood sugar (95 mg/dl [73-109 mg/dl]) and

serum IgG4 (28 mg/dl [5-117]) at the time of admission to our hospital. As she had no background disease process in the pancreas such as chronic pancreatitis, autoimmune pancreatitis and autoimmune diabetes, we considered that irAEs may be involved in CD8+ T cells infiltration.

A previous study reported that some AP patients with respiratory failure did not have any respiratory complications and the respiratory failure may reflect acute lung injury probably due to systemic inflammation [9]. In our case, as the autopsy revealed no diffuse lung disorders other than pulmonary congestion and pleural effusions, we considered that respiratory failure involved a systemic inflammation response due to sever AP.

Since there have been no reports of severe pancreatitis as an irAE thus far, it is unlikely that irAEs due to nivolumab alone resulted in severe AP. The CheckMate 016 study showed that the combination of pazopanib and nivolumab results in a high incidence of high-grade toxicities [10].Therefore, in this case, we considered that the effects of nivolumab were sustained in the pancreas, and pazopanib administration worsened the toxicity; severe AP then occurred. Although the frequency of severe AP is rare with ICI or TKI monotherapy, this may increase with combination therapy.

References

[1] Jones MR, Hall OM, Kaye AM, Kaye AM. Drug-Induced Acute Pancreatitis: A Review. Ochsner J 2015; 15: 45–51.

[2] Baraibar I, Quílez A, Salas D, Román M, Rolfo C, Pérez-Gracia JL, et al. Pazopanib-induced asymptomatic radiological acute pancreatitis: A case report. Mol Clin Oncol 2017; 6: 651-4.

[3] Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60: 190-209.

[4] Ikeuchi K, Okuma Y, Tabata T. Immune-related pancreatitis secondary to nivolumab in a patient with recurrent lung adenocarcinoma: A case report. Lung Cancer. 2016; 99:148-50.

[5] Kawakubo K, Hata H, Kawakami H, Kuwatania M, Kawahataa S, Kuboa S,et al. Pazopanib-Induced Severe Acute Pancreatitis. Case Rep Oncol 2015; 8: 356-8.

[6] Jörns A, Wedekind D, Jähne J, Lenzen S. Pancreas Pathology of Latent Autoimmune Diabetes in Adults (LADA) in Patients and in a LADA Rat Model Compared With Type 1 Diabetes. Diabetes. 2020 Apr;69(4):624-633.

[7] Pinkse Gabrielle G M, Tysma Odette HM, Bergen Cees AM, Kester Michel GD, Ossendorp F, van Veelen P A, et al. Autoreactive CD8 T cells associated with beta cell destruction in type 1 diabetes.

Proc Natl Acad Sci U S A. 2005 Dec 20;102(51):18425-30.

[8] Li SY, Huang XY, Chen YT, Liu Y, Zhao S. Autoimmune pancreatitis characterized by predominant CD8+ T lymphocyte infiltration. World J Gastroenterol. 2011 Nov 7;17(41):4635-9.

[9] Dombernowsky T, Kristensen MØ, Rysgaard S, Gluud LL, Novovic S. Risk factors for and impact of respiratory failure on mortality in the early phase of acute pancreatitis. Pancreatology. Sep-Oct 2016;16(5):756-60.

[10] Amin A, Plimack ER, Ernstoff MS, Lewis LD, Bauer TM, McDermott DF, et al. Safety and efficacy of nivolumab in combination with sunitinib or pazopanib in advanced or metastatic renal cell carcinoma: The CheckMate 016 study. J Immunother Cancer 2018; 6: 109-121.

Figure legends

Figure 1

(a) CE-CT shows diffuse pancreatic swelling without evidence of either necrotic lesions or peripheral exudative effusions. (b) Chest x-ray showed multiple pulmonary metastases, bilateral pleural effusion and pulmonary edema.

Figure 2

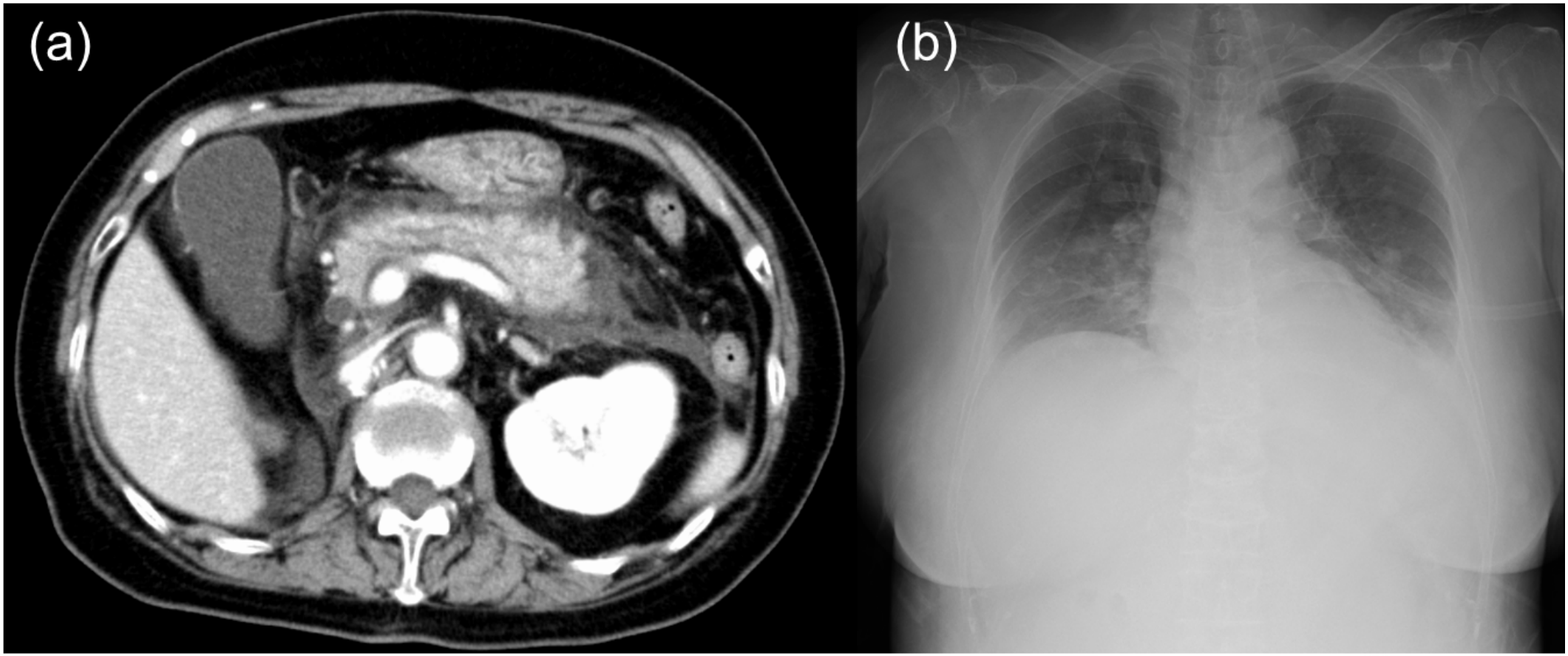
Gross and pathological findings of the pancreas on autopsy. (a) Gross examination: The pancreas was

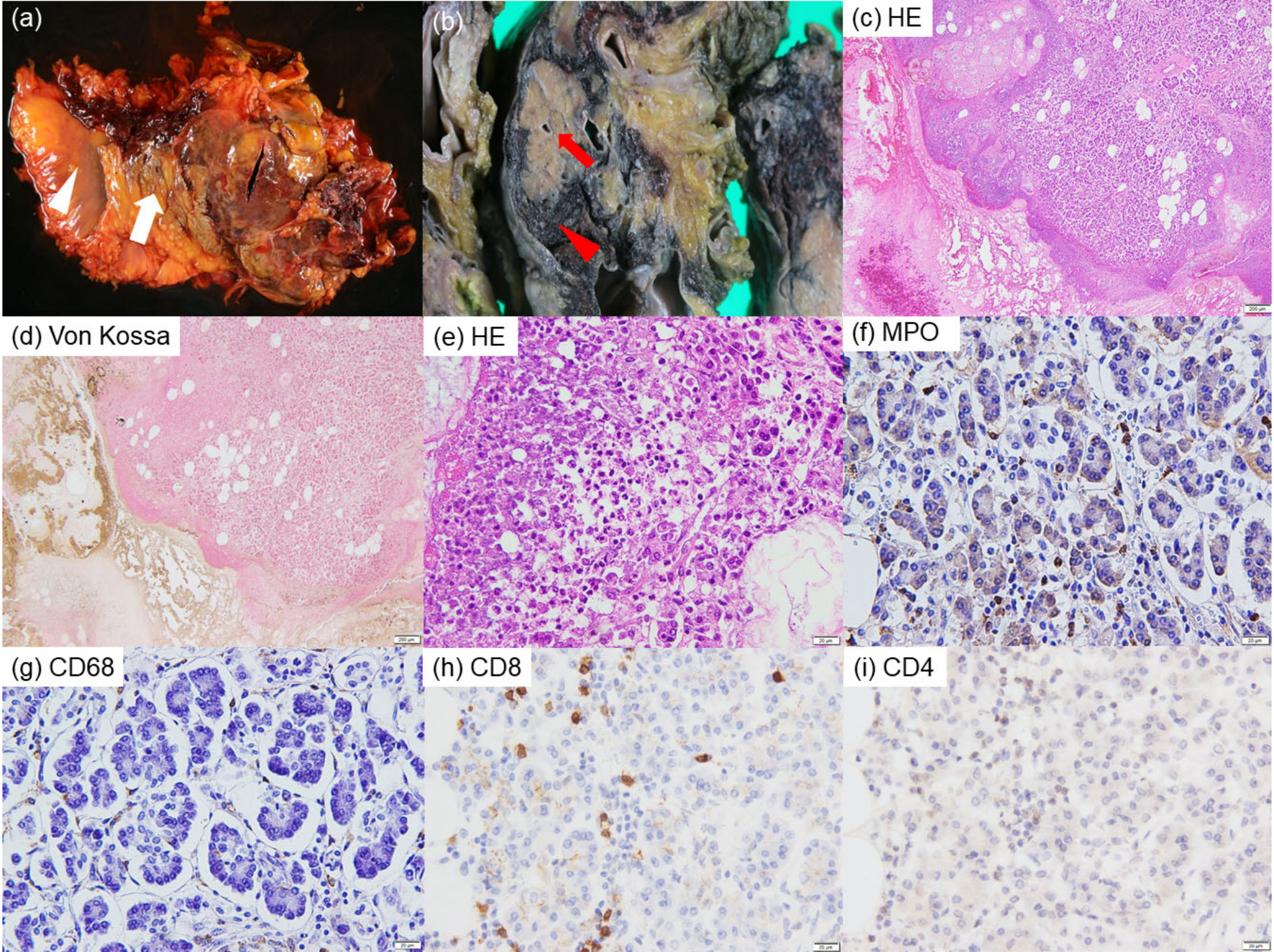
extracted, including the duodenum (white arrowhead) because of severe necrosis and adhesions. The pancreas showed necrotic changes (white arrow); thus, normal pancreatic tissue was difficult to identify macroscopically. (b) Gross examination: The cut surface of the pancreas showed necrotic and hemorrhagic changes (red arrowhead) around the remaining pancreatic parenchyma (red arrow). (c) Hematoxylin–eosin staining (×40): Histologically, necrosis and bleeding were observed, and the acinar cells were destroyed, which was consistent with AP. (d) Von Kossa staining (×40): Fat necrosis with calcification was observed around the pancreatic parenchyma. (e) Hematoxylin–eosin staining (×400): Inflammatory cell infiltration centering on neutrophils was observed in necrotic lesions of the pancreatic parenchyma. (f and g) Myeloperoxidase staining and CD68 staining (×400): Myeloperoxidase-positive neutrophils (f) and CD68-positive macrophages (g) were observed in necrotic lesions of the pancreatic parenchyma. (h and i) CD4 and CD8 staining (×400): In the remaining pancreatic parenchyma, T cell infiltration was conspicuous, particularly infiltration of CD8-positive T cells (h), but few CD4-positive T cells were observed (i). HE; Hematoxylin–eosin, MPO; Myeloperoxidase.

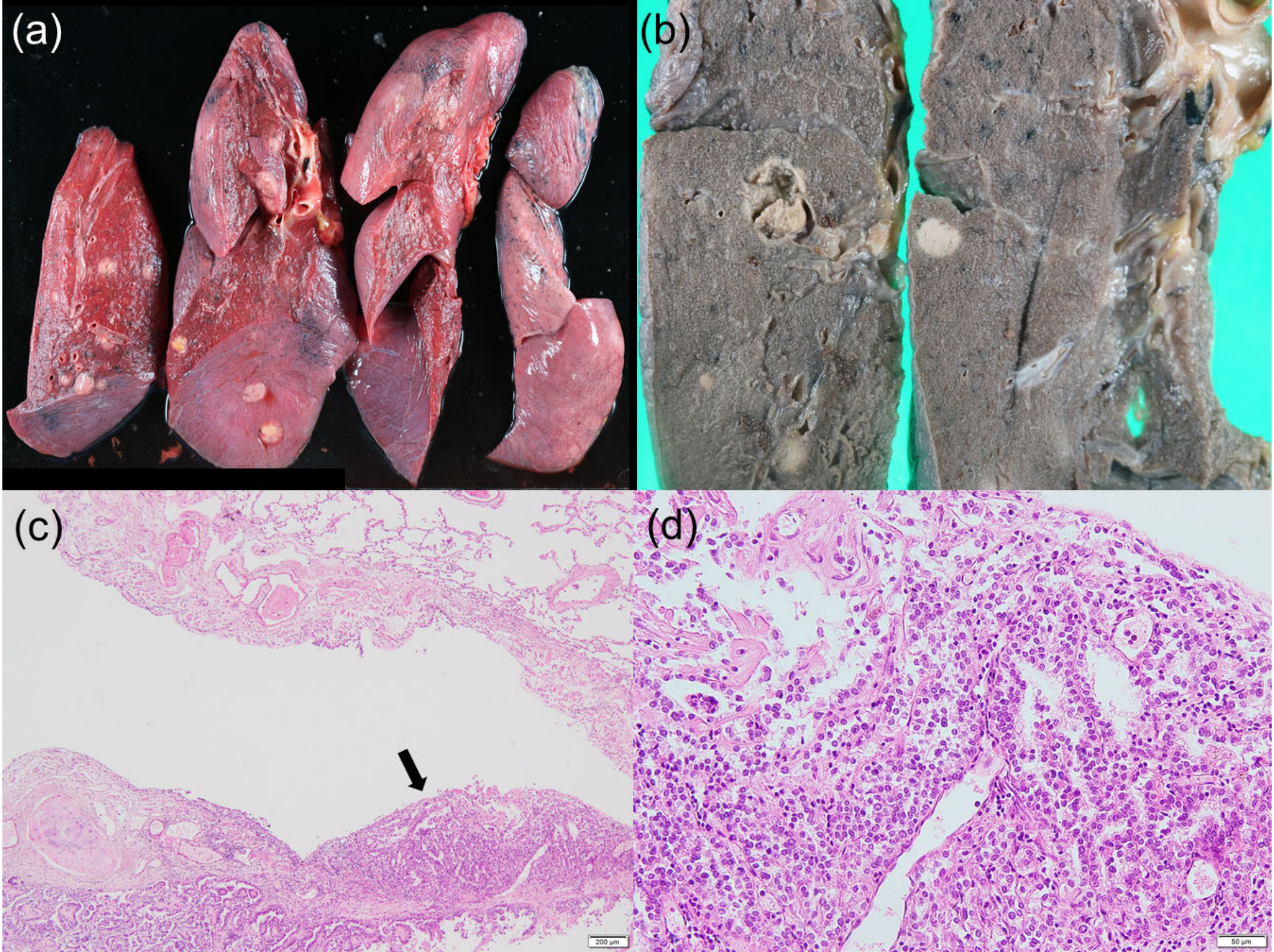
Figure 3

Gross and pathological findings of the lungs on autopsy. Gross examination, (a) cut surface before fixation and (b) cut surface after fixation: The multiple lung metastases were observed, and some of them were exposed to the bronchial lumen. (c) Hematoxylin–eosin staining (×40): Microscopically, lung metastases

were exposed to the bronchial lumen (black arrow). The pulmonary congestion was observed in alveolar cavities, but there was no detected obvious lung injury. (d) Hematoxylin–eosin staining (×400): The lung tumors were consistent with metastasis of renal cell carcinoma.


(a)
(b)


(a)
(b)
(c) HE
(d) Von Kossa
(e) HE
(f) MPO
(g) CD68
(h) CD8
(i) CD4


(a)
(b)
(c)
(d)
200 µm
50 µm