Clinical Case Reports (Case Report)

Late relapse of IgM nephropathy-associated nephrotic syndrome after repeated administration of immune checkpoint inhibitor against pulmonary adenocarcinoma

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Abstract (50 words)

A man aged 60's suffered nephrotic syndrome with IgM nephropathy seven years earlier. Four years later, immune-checkpoint inhibitors (ICPIs) were administered against metastasizing pulmonary adenocarcinoma. Sixty-two weeks after 21 ICPIs injections, the cancer vanished but nephrotic syndrome relapsed. Acute pancreatitis followed and usual interstitial pneumonia exacerbated, as late-onset immune-related adverse-events.

Key words: Acute pancreatitis, IgM nephropathy, Immune checkpoint inhibitor, Immune-related adverse events, Interstitial pneumonia, Pulmonary adenocarcinoma

Key Clinical Message *(250 characters)*

ICPIs were effective for primary and metastatic foci of lung adenocarcinoma, but their repeated use provoked a late relapse of IgM nephropathy and lethal lesions in pancreas and lung. ICPIs should be carefully used in cases of immune-related disease.

Introduction

Immune checkpoint inhibitors (ICPIs) have increasingly attracted medical oncologists' attention. The target malignant diseases of ICPIs have been expanded considerably. ICPIs activate T-lymphocytes to attack tumor cells, but the activated T-lymphocytes may also injure normal cells. Immune activation by ICPIs provokes immunoglobulin production and excessive release of a variety of cytokines, including interleukin-17 [1]. This may result in immune-related adverse events (irAEs).

In most clinical trials of ICPIs, patients with immune-related disorders were excluded from study. In fact, package leaflets of ICPIs seldom describe the disadvantage for patients with pre-existing immune-related disorder. The frequency of irAEs caused by ICPIs may increase particularly in patients with poorly controlled immune-related disorder or in those who manifest organ injury [2]. Reportedly, ICPIs provoked the relapse of the primary disease in 75% of patients with immune-related disorder [3].

IgM nephropathy manifesting nephrotic syndrome was first described in 1978 [4]. Immunofluorescence study demonstrates deposition of IgM in the mesangial matrix, and ultrastructurally the deposit reveals low-electron density. The disease often affects adults, and nephrotic syndrome is commonly steroid-resistant [5]. The distinction from minimal change nephrotic syndrome or focal segmental glomerulosclerosis has long been debated [6,7]. At present, the disease entity as IgM nephropathy has not yet been established.

We report herein an autopsied Japanese adult male case presenting a late relapse of IgM nephropathy-associated nephrotic syndrome after repeated administration of ICPIs, Pembrolizumab (Keytruda®), against pulmonary adenocarcinoma with systemic metastasis. During the late clinical course, irAEs occurred in the pancreas and lung. The mechanisms of irAEs, particularly those of late-onset irAEs, are discussed from a viewpoint of pathology.

Case presentation

A chart of the complexed clinical course of the present case is displayed as in **Figure 1**. The date of hospitalization for the relapsed IgM nephropathy was regarded as day X.

A Japanese male patient aged 60's had a history of right pyothorax, lung aspergillosis and emphysema eight years earlier when he abandoned to smoke, having a smoking history for 40 years (30 cigarettes per day). One year later, he suffered from deep venous thrombosis in both legs, and warfarin was administered.

Soon, peripheral edema worsened. The diagnosis of nephrotic syndrome was made on the basis of urinary protein 12 g/day, serum protein 4.3 g/dL and serum cholesterol 330 mg/dL. Renal biopsy revealed IgM nephropathy with minimal mesangial cell growth and evident mesangial deposition of IgM. Electron microscopy demonstrated foot process effacement and mild increase of mesangial matrix with focal immune deposits with low electron density (**Figure 2**). Prednisolone therapy (50 mg/day) started. The disease was steroid-resistant, but the steroid gradually tapered to avoid exacerbation of pulmonary aspergillosis. Low-density lipoprotein adsorption treatment was done seven times, and proteinuria was improved to indicate the urinary protein-creatinine ratio at 0.2 g/gCre. Two years after the onset of nephrotic syndrome, steroid therapy was finished, reaching a delayed remission.

Four years later, transbronchial biopsy-confirmed adenocarcinoma of the lung, 21 mm in size, occurred at the peripheral part of the right upper lobe. Positron-emission tomography-computed tomography demonstrated multiple metastases in the right lung (both upper and lower lobes), hilar, mediastinal and supraclavicular lymph nodes, ribs, and pelvic and femoral bones (cT2aN3M1b). Molecular studies showed wild-type epidermal growth factor receptor gene and negative anaplastic lymphoma-kinase expression. The tumor proportion score of programmed cell

death ligand-1 was more than 95%. Pembrolizumab (Keytruda®) injection (200 mg) started at the X-63rd week, and it continued every three weeks (a total of 21 injections) until the X-2nd week. The shadow images of the primary and metastatic tumor disappeared.

At the X-1st week (62 weeks after the initiation of ICPIs), peripheral edema reappeared and at the X-2nd day, the urinary protein-creatinine ratio increased to 16 g/gCre. At the X day, the patient was hospitalized under the diagnosis of relapsed nephrotic syndrome. Pembrolizumab was discontinued, and methylprednisolone 250 mg was administered for three days, followed by prednisolone 40 mg/day. Warfarin was added to avoid thrombosis. Urinary proteinuria unchanged, so that cyclosporine 100 mg/day was challenged at the X+10th day. At the X+15th day, the patient complained of abdominal pain, and computed tomography disclosed a 9 cm-sized mesenteric hematoma: prothrombin time-international normalized ratio was 3.17 (standard value: 1.5–3.0). Prothrombin complex concentrate was administered, and warfarin and cyclosporine were discontinued. The abdominal symptoms gradually relieved. At the X+25th day, prednisolone was reduced to 30 mg/day, and cyclosporine 50 mg restarted together with administration of sulfamethoxazole/trimethoprim (ST) compound. At the X+30th day, thrombocytopenia (5.2×10^4/μL) forced to discontinue cyclosporine and ST compound. The thrombocyte count soon recovered. At the X+40th day, abdominal pain recurred, and imaging study indicated enlargement of the mesenteric hematoma, becoming cystic and 12 cm in size. At the X+58th day, the diagnosis of acute pancreatitis was made, based on elevated serum levels of amylase 538 U/L, AST 406 U/L and ALT 595 U/L and swelling of the pancreas revealed by computed tomography. Pancreatitis was controlled by diet fasting. After resumption of the diet at the X+67th day, exacerbation of pancreatitis happened at the X+74th day. The serum amylase level reached 1,600 U/L. The mesenteric cystic lesion was shrunken up to 6 cm in size.

Fever happened at the X+93rd day, and the mesenteric cyst was enlarged and the chest

shadow suggesting interstitial pneumonia appeared. Infection of the mesenteric cyst was suspected, and a drainage tube was inserted. Because of a high amylase level in the cyst fluid, the diagnosis of pancreatitis-associated pseudocyst was made. At the X+102nd day, peripheral edema, pleural effusion and hypoxemia were complicated. In spite of furosemide injection, hypoxia progressed, and the patient died of respiratory failure at the X+108th day.

Autopsy findings

Autopsy was performed one hour after death. The final autopsy diagnoses are summarized in **Table 1**.

The kidneys were mildly atrophic and weighed 125 g (left) and 85 g (right). Microscopically, there were small subcapsular clusters of sclerotic glomeruli, but the remaining glomeruli did not show mesangial cell growth or matrix increase. Mild interstitial fibrosis was noted. After prolonged protease-1 digestion of formalin-fixed, paraffin-embedded sections [8,9], mesangial deposition of IgM was demonstrated, while deposition of IgA and IgG was negative. The features were diagnostic of the relapse of IgM nephropathy (**Figure 3**).

An encapsulated, 7 cm-sized hemorrhagic mesenteric cyst, with a drainage tube inserted, was located just adjacent to the uncinate process of the pancreas head. Hemosiderin deposition was evident in the cyst wall. Encapsulated foci of fat necrosis were scattered in peripancreatic fat tissue, and interlobular pancreatic septa were mildly fibrotic. Acute hemorrhagic necrosis of the pancreatic parenchyma was not observed. The mesenteric cyst was regarded as a pancreatitis-associated lesion (pseudocyst). Pancreatic morphology is demonstrated in **Figure 4**. A hemorrhagic cystic lesion was also distributed on the rectovesical peritoneal fossa (Douglas' fossa).

A 9 mm-sized, white-colored subpleural lung nodule was noted in the anterior part of the right upper lobe. Microscopically, well-differentiated adenocarcinoma was predominant, but focally

with a component of poorly differentiated adenocarcinoma. Neither necrotic change nor lymphocytic infiltration was observed. The cancer cells were immunoreactive for thyroid transcription factor-1, napsin A and cytokeratin 7, but negative for cytokeratin 5/6 (**Figure 5**). Metastatic deposits were not confirmed in other organs and tissues.

Gross examination of the non-neoplastic lung revealed subpleural honeycombing and multifocal parenchymal infiltrative change bilaterally (**Figure 6**). The lungs weighed 280 g (left) and 465 g (right). Microscopically, the pre-existing alveolar structures were often distorted and surrounded by interstitial fibrosis. Features of diffuse alveolar damage with hyaline membrane formation were associated (**Figure 7**). The features were consistent with acute exacerbation of usual interstitial pneumonia. The right pleura exhibited severe fibrous adhesion in association with a small encapsulated caseous nodule in the collapsed right middle lobe. The pleural lesion was thus regarded as old tuberculosis (see **Figure 6**). No pulmonary aspergillosis was identified.

Discussion

The disease entity of IgM nephropathy is controversial. IgM nephropathy may be a variant of minimal change nephrotic syndrome or focal segmental glomerulosclerosis, but it commonly occurs in adults and is often steroid-resistant [5-7]. In the present case, two-years steroid administration was needed until delayed remission, and nephrotic syndrome revealed a late relapse after repeated use of ICPIs. Mesangial IgM deposition was proven by prolonged protease digestion of formalin-fixed, paraffin-embedded autopsy specimens. Antibody molecules can bind cryptic antigens after the rigorous protease digestion step, because formalin-mediated cross-linkage among protein networks in the tissue is significantly loosened, as has been reported previously [8,9].

ICPIs administration may provoke irAEs in a variety of organs and tissues. Early detection of irAEs, as well as the discontinuance of ICPIs, are requested in the clinical practice [10].

Renal irAEs are infrequent around 4%: Glomerulonephritis is especially rare, while interstitial nephritis is relatively common [11]. The period from the initiation of ICPIs to acute renal injury ranged from 21 to 245 days (median 91 days), whereas the period from the cessation of ICPIs to acute renal injury ranged from 7 to 63 days (median 21 days) [12]. In the present case, IgM nephropathy relapsed 63 weeks after the initiation of ICPIs. Such late irAEs are quite unusual.

ICPIs stimulate T-lymphocytes to struggle with cancer cells. It is reasonable to suppose that the immune activation by ICPIs provoked the relapse of IgM nephropathy, though the detailed mechanism remained unclear. In patients with immune-related disorder, 75% of the cases accompanied relapse/exacerbation of the disease after administration of ICPIs, but with little evidence for inducing novel-type irAEs [3]. In cases of malignant melanoma complicated by immune-related disorders, anti-tumor effect of ICPIs was much more beneficial than the risk of relapse/exacerbation of the immune-related disorders [13]. In non-small cell lung cancer cases complicated by immune-related disorders, 55% exhibited exacerbation of the immune-related disorders, but 74% of the irAEs were regarded as being controllable in grades 1–2 [14]. Immunosuppressants including steroid administered for controlling the immune-related disorder did not influence the anti-tumor effect of ICPIs [15].

The irAEs tended to occur when the volume of ICPIs was increased [16], and they happened within 12 weeks after the initiation of ICPIs [2]. In the present case, after the late relapse of IgM nephropathy, mesenteric hematoma (hemorrhagic pseudocyst) happened and exacerbated at the X+15th, X+40th, and X+93rd days after admission, and the diagnosis of acute pancreatitis was made at the X+58th day. Acute exacerbation of pulmonary fibrosis was complicated at the X+93rd day (two weeks prior to patient's death). Acute pancreatitis was histopathologically proven at autopsy by the presence of hemorrhagic pseudocysts in the mesentery and Douglas' fossa, multifocal fat necrosis and mild interstitial pancreatic fibrosis. In the lung, diffuse alveolar damage with

hyaline membrane formation was recognized among honeycombing pulmonary fibrosis of usual interstitial pneumonia type.

Whether or not the pancreatic and pulmonary complications in the present case were immune-related is not definitely confirmative, but the possibility of ICPIs-associated irAEs was clinically suspected strongly. Acute pancreatitis is a rare complication as ICPIs-associated irAEs. In only two cases out of 119 cases evaluated, increase of serum levels of amylase and lipase was recorded, but without associating symptomatic pancreatic lesions [17]. Acute fibrinous and organizing pneumonia and diffuse alveolar damage were listed up as ICPIs-related irAEs of the lung, and they were often lethal [18,19]. In fact, the ICPIs-related lung lesions were encountered more often in patients with non-small cell lung carcinoma than those who suffered from malignancy of other types [20,21].

Remote effects of ICPIs are debatable. The recognition or definition of irAEs may be difficult. However, the present case tells us that we should be aware of the possibility of late complications of ICPIs.

Conclusive remarks

Administration of ICPIs to cancer patients with immune-related disorders has not yet been thoroughly experienced. In the present case, ICPIs were effective enough against primary and metastatic foci of adenocarcinoma of the lung. Repeated use of ICPIs provoked a late relapse of IgM nephropathy, as well as late and intractable and lethal complications in the pancreas and lung. Accumulation of similar cases is requested to settle the appropriate use of ICPIs in patients with immune-related disorder.

Conflict of Interest Statement

The authors do not have any conflict of interest in the present report. There were no funding sources for reporting the present case.

Statement of Ethics

The patient was unmarried, so that his intimate co-worker gave the written informed consent for the publication of the case report. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Author Contributions

We declare that all the authors 1) made a substantial contribution to the concept of the case report or interpretation of data, and 2) approved the version to be submitted. 3) Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Table 1. **Final Autopsy Diagnosis** (male aged 60's)

1. LUNG CANCER (right upper lobe, well-differentiated adenocarcinoma, 9 mm in size)
    a) S/P: administration of Pembrolizumab (Keytruda®), 21 times
    b) Metastasis: not identified (but with history of lung, nodal and bone metastases)
2. IgM NEPHROPATHY (minimal change glomerulopathy with mesangial deposition of IgM)
    a) Nephrotic syndrome (kidney weight: left 125 g, right 85 g)
    b) Pleural effusion (left 1,800 mL, right 500 mL)
    c) Edema in the lower extremities
3. ACUTE PANCREATITIS
    a) Hemorrhagic cyst of the mesentery (7 cm in size)
    b) Hemorrhagic cyst on the rectovesicular fossa
    c) Fat necrosis in peripancreatic tissue
    d) Mild pancreatic fibrosis
4. USUAL INTERSTITIAL PNEUMONIA WITH ACUTE EXACERBATION
    a) Honeycomb lung (lung weight: left 280 g, right 465 g)
    b) Hyaline membrane formation (diffuse alveolar damage)
5. OLD PULMONARY TUBERCULOSIS
    a) Pleural fibrous adhesion, right
    b) Encapsulated caseous focus, right middle lobe

Figure legends

Figure 1. Schematic presentation of the clinical course of the male patient aged 60's.

Figure 2. Microscopic appearance of renal biopsy specimen (a: periodic acid-Schiff reaction, b: immunofluorescence study for IgM, c&d: electron micrographs, bars 2 μm [c] and 1 μm [d]). The glomeruli resemble minimal change glomerulopathy without increase of mesangial cells and matrix. Immunofluorescence study demonstrates mesangial IgM deposition. Fine structural study demonstrates foot process effacement and deposition of low electron density substances in the mesangial matrix along the basement membrane (arrows).

Figure 3. Microscopic features of autopsied kidney (left: hematoxylin and eosin (HE) stain, right: IgM immunostain after prolonged protease-1 digestion). Neither mesangial cell growth nor increase of mesangial matrix is noted. Immunostaining after prolonged protease-1 digestion of formalin-fixed, paraffin-embedded sections demonstrates mesangial deposition of IgM.

Figure 4. Gross appearance of mesenteric pseudocyst (a) and fat necrosis of peripancreatic tissue (b: overall appearance and c: cut surface) and microscopic features of the pancreas (d, HE stain). Old and hemorrhagic cyst of the mesentery, measuring 7 cm, is located adjacent to the uncinate part of the pancreas head. Fat necrosis is observed around the pancreas, and the cut surface displays encapsulated foci of fat necrosis. Mild interstitial fibrosis is microscopically discerned.

Figure 5. Pulmonary adenocarcinoma in fibrotic lung parenchyma (a: gross appearance of right upper lobe, b: HE stain, c: thyroid transcription factor-1 immunostain). The 9 mm white nodule is

located just beneath the pleura. The surrounding lung tissue is fibrotic and honeycombed, focally resembling emphysema. Microscopically, well-differentiated adenocarcinoma shows neither necrosis nor lymphocytic infiltration. The nuclei of the cancer cells are diffusely immunoreactive for thyroid transcription factor-1.

Figure 6. Gross appearance of usual interstitial pneumonia (pulmonary fibrosis) with acute exacerbation (a: left upper lobe, b: right upper and middle lobes). Focal subpleural honeycombing and infiltrative change in the lung parenchyma are noted. The right pleura shows diffuse fibrous adhesion, and an encapsulated caseous focus is noted beneath the pleura of collapsed middle lobe (arrow).

Figure 7. Microscopic features of usual interstitial pneumonia (pulmonary fibrosis) with acute exacerbation (HE stain, a: honeycomb lung, b: hyaline membrane formation). Interstitial fibrosis with disappearance of normal alveolar structures is observed. Hyaline membrane formation is noted at the site of acute exacerbation.