中文題目：食道癌 Nivolumab 免疫治療所致心包膜填塞：首例病例報告

英文題目：Immune-mediated cardiac tamponade during nivolumab therapy for esophageal cancer: a case report

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Introduction:

Immune checkpoint inhibitors get increasing use for the treatment of advanced cancer. The patterns of immune-related adverse effects (IrAE) are different from the conventional cancer therapy. We described an immune-mediated cardiac tamponade in a patient with esophageal cancer who was treated with nivolumab.

Case presentation:

A 62-year-old man with advanced esophageal cancer under Nivolumab therapy came to our emergency department because of progressive dyspnea for 2 weeks.

Upper third esophageal squamous carcinoma, cT3N2M0, stage IIIB was diagnosed in May 2017, with initial presentation of dysphagia and weight loss for weeks. He had alcohol drinking and heavy smoking (10 cigarettes per day for 10 years). The patient was treated with neoadjuvant chemoradiotherapy with cisplatin and 5-flurouracial (5-FU) with concurrent radiation to a dose of 5040GY till June 2017. Salvage operation was failed due to dense adhesion of esophagus and trachea in August 2017. Another chemoradiotherapy with radiation boost dose of 2000GY was completed. CT image revealed partial metabolic response. He then received adjuvant chemotherapy with paclitaxel for four cycles since October 2017. The recurrence disease was confirmed by upper gastrointestinal endoscopic biopsy in February 2018. He underwent cetuximab infusion combined with cisplatin plus 5-FU. Nivolumab were administered with a fixed dose of 100 mg every two weeks due to disease progression.

Seven days after two cycles of Nivolumab, he presented with chest tightness, exertional dyspnea, and orthopnea. Electrocardiogram during admission showed atrial flutter and bisoprolol was used. But the dyspnea persisted after he discharge. Two weeks later, he came to emergency department with one-day history of fever, productive cough, and progressive dyspnea. Physical exam showed fever up to 38’C, tachycardia (124bpm, regular), tachypnea (38bpm), and decreased pulse pressure (127/116mmHg). Intubation was done with mechanical ventilator support for the acute respiratory failure. Chest X ray showed alveolar pattern over right upper lobe

and left lower lobe, cardiomegaly, and bilateral pleural effusion (Fig 1a). Electrocardiogram revealed sinus tachycardia with premature atrial contracts. Lab data showed elevated neutrophil count (white blood cell 7700/ul, neutrophil 86%) and c-reactive protein (17.8). He was admitted to intensive care unit with impressions of severe pneumonia with acute respiratory failure. Meropenem was used.

After admission, tachycardia (130 bpm), hypotension (101/73 mmHg under norepinephrine 10ug/min), tachypnea (30 bpm), and hypoxemia (SpO_2 90%, PaO_2: 50mmHg under ventilator pressure 28mmHg, PEEP 8mmHg, FiO_2 80%) were noted. Bedside sonography showed massive pericardial effusion (2.27cm around the heart) with tamponade, distended inferior vena cava, and bilateral pleural effusion (Fig 2). Pericardiocentesis was done with 550ml of orange colored exudative effusion drainage (LDH: 678 u/l, WBC: 550/ul, neutrophil: 59%, ADA: 21). After the drainage of the pericardial effusion, the dyspnea, tachycardia, and hypotension got improving. We stopped norepinephrine and tapered down FiO_2 to 30%. The sputum culture showed Actinobactor baumannii and Bacteroides pyogenes. Blood culture were negative. Fever subsided after the 3-days treatment of meropenem.

The daily drainage amount the pericardial effusion was around 300ml. Cytology and culture of pericardial effusion are negative of malignant cells nor pathogens. According to the history of nivolumab injection recently and no evidence of cancer involvement, infective pericarditis, or autoimmune pericarditis, immune-related adverse effect of Nivolumab was suspected. Methylprednisolone 0.6mg/Kg/day was infused since day 5. The drainage amount of the pericardial effusion was decrease and the drain was removed on the day 7. No pericardial effusion was noted by sonography then. He tolerated with weaning and extubation was done on day 14. He discharged on day 23.

Discussion:

Nivolumab is a check point inhibitor which targets the programmed cell death protein 1 (PD 1). The toxicities of anti-PD 1 are less than anti-cytotoxic T-lymphocyte–associated antigen 4. Gastrointestinal tract, endocrine glands, skin, and liver are the common involving sites. The possible pathogenesis of immune-related adverse events includes increased T-cell activity against healthy tissue, increased level of preexisting autoantibody, increased level of cytokine, and enhancing complement-mediated inflammation. Cardiac adverse effects are less common, and the incidence of pericardial effusion caused by anti-PD 1 is less than 1%. To our best search, this is the first case of immune-related cardiac tamponade successfully treated with steroid in patient with advanced esophageal cancer under

Nivolumab therapy.

Figure 1 a. CXR on admission day. b. CXR on day-20 after admission

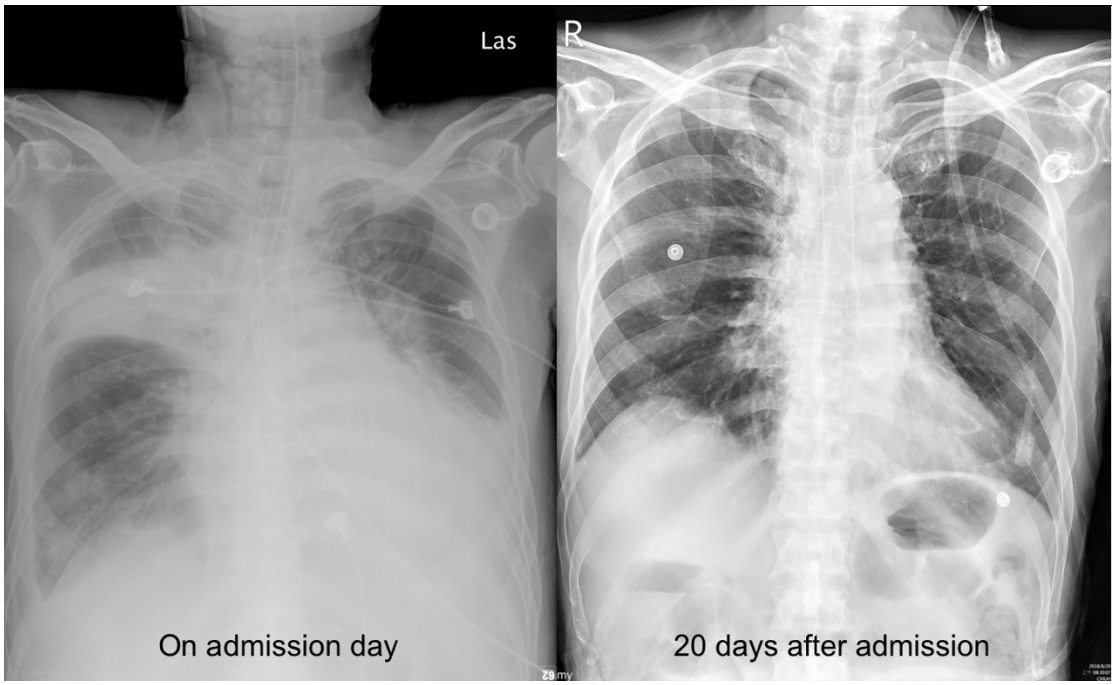

Figure 2 Echocardiogram at admission showed pericardial effusion (2.27cm around the heart)