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ORIGINAL ARTICLE

CMV reactivation caused by methylprednisolone therapy for ARDS after esophagectomy

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Abstract
Background Cytomegalovirus (CMV) infection is endemic worldwide. Although CMV reactivation often becomes a serious problem in immunocompromised patients, the prevalence of CMV reactivation caused by methylprednisolone therapy for ARDS after esophagectomy has yet to be determined.
Method Among 175 consecutive patients with thoracic squamous cell esophageal cancer who underwent esophagectomy with extensive lymph node dissection at Akita University Hospital between 2007 and 2010, 11 patients (6.3 %) diagnosed with ARDS during the acute phase of esophagectomy were enrolled and treated with steroid pulse therapy, high-dose (15–20 mg/kg/day) administration and tapering in this retrospective study.
Results Seven of the 11 patients (63.6 %) were diagnosed with CMV reactivation based on CMV antigenemia assayed 19.1 days after the start of methylprednisolone administration and were treated with ganciclovir for 39.6 days. Six of the 7 patients (85.7 %) diagnosed with CMV reactivation were administered a total methylprednisolone dose of more than 4,000 mg. Though there was no significant difference between patients with and without CMV reactivation, there was a tendency that patients with CMV reactivation showed a lower minimum number of lymphocytes during the acute phase of esophagectomy ($p = 0.051$, Student's t test, average 223.3 and 298.0/μl, respectively).
Conclusion Though the number of study patients is small, the prevalence of CMV reactivation caused by high-dose methylprednisolone therapy for ARDS after esophagectomy is remarkably high. This result strikes a note of warning concerning the management of these patients and suggests the importance of screenings for CMV reactivation so as to make an accurate diagnosis and initiate treatment in a timely manner.

Keywords CMV · Esophageal cancer · ARDS · Steroid therapy · Methylprednisolone

Abbreviations
CMV Cytomegalovirus
ARDS Acute respiratory distress syndrome

Introduction

Cytomegalovirus (CMV) infections are usually established before individuals reach adolescence, and 40–100 % of the adult population, worldwide, carries the CMV antibody [1]. In most cases, CMV infection in an immunocompetent individual does not lead to symptomatic disease; these individuals are unlikely to know whether they have been infected or are shedding the virus [2, 3]. Once infected, however, the CMV virus remains in multiple organs for a person's entire life and can later be reactivated during severe dysregulation of the immune system, such as in AIDS, after chemotherapy for a malignant tumor, after

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administration of immunosuppressants for organ transplantation, or with longstanding steroid administration. In these situations, the reactivated CMV virus can lead to more serious clinical conditions, such as retinitis, enteritis, hepatitis, encephalitis and pneumonia [4].

Acute respiratory distress syndrome (ARDS) is associated with a mortality rate of up to 60 % [5]. Since the 1980s, steroid therapy has been one approach to the treatment of ARDS. In this era, a short course of high-dose steroid administration (30 mg/kg, every 6 h for 48 h) was the primary method. However, this administration method with early phase ARDS was ineffective and provided no difference in survival or in reversal of ARDS compared to placebo [6]. Moreover, prophylactic administration with high-dose administration for patients with septic shock does not reduce the incidence of ARDS and is rather harmful concerning infectious complications and mortality rate [7–10]. Even in the mid 2000s, there was no worldwide consensus about the dosage or duration of administration, or even efficacy [11, 12]. According to a recently published meta-analysis, a low-dose (1–2 mg/kg/day) administration for longer duration (average 25–32 days) with gradual tapering improved multiple outcomes, including lower lung injury scores and Multiple Organ Dysfunction Syndrome (MODS) scores, shorter durations of mechanical ventilation, shorter ICU stays, lower ICU mortality, and lower infection rates [5, 13–16].

Esophagectomy with extensive lymph node dissection for thoracic esophageal cancer is one of the most invasive of surgical procedures. After this highly invasive surgery, pulmonary edema arises easily and may form the basis of pulmonary complications such as atelectasis and pneumonia, the most common complications after esophagectomy. Moreover, ARDS appears to develop from these pulmonary complications with relative ease [17]. It is a challenge for clinicians to keep the steroid dose and period of administration as small as possible so as to avoid CMV reactivation and other opportunistic infections. However, inappropriate low-dose administration or untimely tapering can exacerbate ARDS, making it necessary to increase steroid administration. For this, methylprednisolone therapy with high-dose (15–20 mg/kg/day) administration and tapering, so-called "steroid pulse therapy," has been employed for treatment not only of autoimmune diseases [18–21], but also of ARDS empirically without credible evidence in Japan.

Given these circumstances, we conducted a retrospective study to clarify the prevalence of CMV reactivation in patients receiving methylprednisolone administration with high-dose (15–20 mg/kg/day) steroid pulse therapy for ARDS after esophagectomy. In addition, we examined the relation between the administered total methylprednisolone dose and CMV reactivation.

Patients and methods

Patients

The ethics committee of Akita University Graduate School of Medicine approved this study, and informed consent was obtained from all of the patients. Between 2007 and 2010, 175 consecutive patients with thoracic squamous cell esophageal cancer underwent esophagectomy with extensive lymph node dissection at Akita University Hospital. Among these patients, 11 (6.3 %) were diagnosed with ARDS during the acute phase of esophagectomy, treated with methylprednisolone administration and enrolled in this study. Two patients were treated with definitive CRT (cisplatin, fluorouracil and 60 Gy) and then had salvage surgery, and other nine patients were not treated with any preoperative treatments. Our standard operative procedure in these patients is right transthoracic esophagectomy with three-field lymph node dissection. This is resection of the lesser curvature with dissection of the mediastinal (involving the periesophageal region and areas around trachea and bilateral main bronchus), the abdominal (involving the perigastric region and areas around the celiac axis) and the bilateral neck lymph nodes (areas around the common carotid artery, internal jugular vein and transverse cervical artery). We avoid bilateral neck dissection in patients over the age of 75 and in those with lower thoracic esophageal cancer with no clinical evidence of upper mediastinal lymph node metastasis. Reconstruction commonly involves inserting a gastric tube via the posterior mediastinal route [22, 23]. We routinely administer 250 mg of methylprednisolone immediately before surgery and 40 mg on postoperative days (PODs) 1 and 2 as usual perioperative management based on the evidence of the usability of perioperative methylprednisolone administration [24–27]. Patients who had surgery before or during 2009 were extubated on POD1, whereas patients who had surgery in 2010 were extubated soon after surgery and managed in the ICU. Respiratory status was assessed frequently using chest X-rays and measurement of arterial blood gases. ARDS was diagnosed based on the following American-European Consensus Conference criteria for ARDS [28]: (1) acute onset; (2) PaO_2/FiO_2 ratio <200; (3) bilateral infiltrates on chest X-ray; and (4) PAWP <18 mmHg or absence of clinical evidence of left atrial hypertension. Immediately after a diagnosis of ARDS, administration of methylprednisolone was started at a dose of 15–20 mg/kg/day and then tapered in tandem with improvement of blood gas values and chest X-rays. In the event of a worsening of the disease during tapering, the dose administered was increased to the starting dose and tapered again. The usual perioperative management dose

was excluded from the total dose of methylprednisolone administered in this study.

Diagnosis and treatment of CMV reactivation

After starting methylprednisolone administration, CMV antigenemia of peripheral blood leucocytes was examined once per week at Mitsubishi Chemical Medience Co., Ltd. (Tokyo, Japan). When the number of leucocytes positive for CMV antigen (phosphorylated protein 65) was more than 1, a diagnosis of CMV reactivation was considered to be confirmed (Fig. 1), and ganciclovir administration was started at a dose of 5.0 mg/kg/twice/day. When CMV antigenemia subsequently became negative, ganciclovir administration was reduced to 5.0 mg/kg/once/day for 1 week and was then stopped.

Results

Eleven patients (1 female and 10 male, average age 64.2 years, range 57–71 years) were diagnosed with ARDS an average of 6.3 days (range 1–21 days) after esophagectomy and were immediately administered methylprednisolone (Table 1). Only one patient had been diagnosed with obstructive lung disease ($FEV_{1.0\ \%}$ <70) in the preoperative examination. The average of the minimum number of lymphocytes during the acute phase of esophagectomy was 257.3/μl (range 100–520/μl) among 11 patients. Although there was no significant difference between patients with and without CMV reactivation, there was a tendency that patients with CMV reactivation showed a lower minimum number of lymphocytes during the acute phase of esophagectomy (p = 0.051, Student's t test,

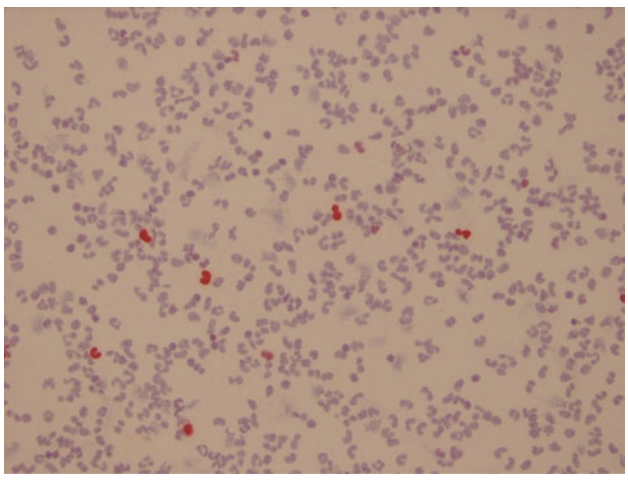

Fig. 1 CMV antigenemia pp65-positive peripheral blood leukocytes. Kindly provided by Mitsubishi Chemical Medience Co., Ltd. (Tokyo, Japan)

Table 1 Clinicopathological features of 11 patients treated with methylprednisolone for ARDS after esophagectomy

Patient no.	Age	Gender	%VC	FEV 1.0 %	Salvage surgery	Methylprednisolone administration starting date (POD)	Minimum number of lymphocytes (/μl)	Methylprednisolone starting dose (mg/kg/day)	Exacerbation and re-increase of methylprednisolone	CMV reactivation after methylprednisolone administration (days)	Methylprednisolone total dose until CMV reactivation (mg)	Methylprednisolone total dose without CMV reactivation (mg)	Duration of ganciclovir administration (days)	Cause of death in the same hospitalisation (months)
1	63	F	114.9	81.74		1	300	15	+	30	9195	–	125	ARDS (8)
2	70	M	103.6	75.61		8	140	20	+	18	6380	–	47	
3	62	M	148.3	80.76		4	520	20		–	–	4140	–	
4	52	M	97.2	82.34	+	3	170	20	+	25	7810	–	14	
5	68	M	90.8	66.34	+	21	100	20	+	15	4830	–	15	MOF (8)
6	57	M	87.1	73.82		6	230	20		–	–	1000	–	
7	71	M	98.8	77.16		5	370	15	+	–	–	1385	–	Recurrence (11)
8	63	M	99.1	74.04		10	260	15	+	–	–	500	–	
9	65	M	110.9	75.64		3	350	20		18	4770	–	33	
10	70	M	108.3	81.16		3	180	20		11	4400	–	29	
11	65	M	114.3	82.12		5	210	20		17	3740	–	14	
Average	64.2		106.7	77.3		6.3	257.3			19.1	5875	1756	39.6	

average 223.3 and 298.0/μl, respectively). The cause of ARDS was considered to be aspiration pneumonia in three patients, a mediastinal abscess caused by anastomotic leakage in three patients and was unknown in five patients. Seven of the 11 patients (63.6 %) were diagnosed with CMV reactivation based on CMV antigenemia an average of 19.1 days (range 11–30 days) after the start of methylprednisolone administration and were treated with ganciclovir for an average of 39.6 days (range 14–125 days). The average total dose of methylprednisolone before CMV reactivation for these patients was 5,875 mg (range 3,740–9,195 mg). On the other hand, the four patients who were not diagnosed with CMV reactivation were administered an average total methylprednisolone dose of 1,756 mg (range 500–4,140 mg), which was sufficient to resolve their ARDS. Among six patients who showed a worsening of their ARDS and were required to increase their methylprednisolone again to the starting dose, four (66.7 %) showed CMV reactivation. Similarly, six of the seven patients (85.7 %) who were administered more than 4,000 mg of methylprednisolone were diagnosed with CMV reactivation. Both of two patients who had salvage surgery showed CMV reactivation after methylprednisolone administration. Eventually, ten patients recovered from ARDS. However, three (27.3 %) patients died during the same hospitalization, one died of ARDS at 8 months, one died of multiple organ failure at 8 months and one died because of recurrence of esophageal cancer at 11 months. Three patients were considered to be complicated with anastomotic dehiscence related to high-dose methylprednisolone administration.

Discussion

In this study, we determined the frequency of CMV reactivation caused by high-dose methylprednisolone therapy for ARDS after esophagectomy to be 60 %. Moreover, our findings suggest a total methylprednisolone dose of 4,000 mg or more increases the likelihood of CMV reactivation.

Among all 11 patients, only one had been diagnosed with obstructive lung disease, and the other patients had normal respiratory function in the preoperative examinations. This result may suggest that preoperative respiratory function does not predict the onset of ARDS and CMV reactivation after esophagectomy.

The number of lymphocytes is an important indicator of resistivity against viral infection. In this study, all 11 patients showed an abnormally low minimum number of lymphocytes during the acute phase of esophagectomy. Although there was no significant difference between patients with and without CMV reactivation, there was a tendency that patients with CMV reactivation showed a lower minimum number of lymphocytes. This result implies that a lower minimum number of lymphocytes is an important factor for predicting the onset of CMV reactivation.

Reactivation of CMV has recently been reported in non-immunosuppressed patients, including patients with severe trauma, sepsis, shock, burns or cirrhosis, and other critically ill patients in the ICU, with the prevalence ranging from 0 to 35 % [29–32]. Patients in this study were also critically ill, had highly invasive surgery and had stayed in the ICU, which might have set up CMV reactivation even without methylprednisolone administration. However, the four patients who were administered relatively low total doses of methylprednisolone did not show CMV reactivation. Moreover, the frequency of CMV reactivation in this study was almost double that reported for non-immunosuppressed patients. Although the number of subjects in the present study is small, given the remarkably high prevalence of CMV reactivation, we now manage our patients with these findings in mind.

In this study, patient no. 1 was diagnosed with CMV reactivation 30 days after the beginning of methylprednisolone administration. The numbers of pp65 antigen-positive leucocytes were 1,378/1,353, and the patient was treated with ganciclovir. Although we did not perform a lung biopsy at the time, there was the possibility that the ARDS was complicated by CMV pneumonia (Fig. 2). With this patient, we realized the importance of CMV reactivation and now routinely check for CMV antigenemia after methylprednisolone administration. This enables us to detect CMV reactivation at an early point when pp65 antigen-positive leucocytes are in the single digits, before ARDS can be complicated by CMV pneumonia. ARDS complicated by CMV pneumonia is difficult to diagnose and presents an exceptionally dangerous situation.

Monitoring for CMV reactivation and early initiation of treatment is therefore very important, and prevention of ARDS should be considered a matter of first priority. Comprehensive management, including routine oral care, preoperative dental therapy, respiratory rehabilitation and avoiding anastomotic leakage, is the most important and efficient way to prevent ARDS. Recent efforts along these lines have reduced the incidences of both ARDS and CMV reactivation at our facility.

In this study, we administered high-dose methylprednisolone (15–20 mg/kg/day) as a starting dose and then tapered it until healing of ARDS that eventually was connected with the high volume of the total administration. As first mentioned, a recent meta-analysis recommended low-dose (1–2 mg/kg/day) administration up to 28 days for treatment of acute phase ARDS [13–15]. Although it is possible to apply this method to patients with ARDS after

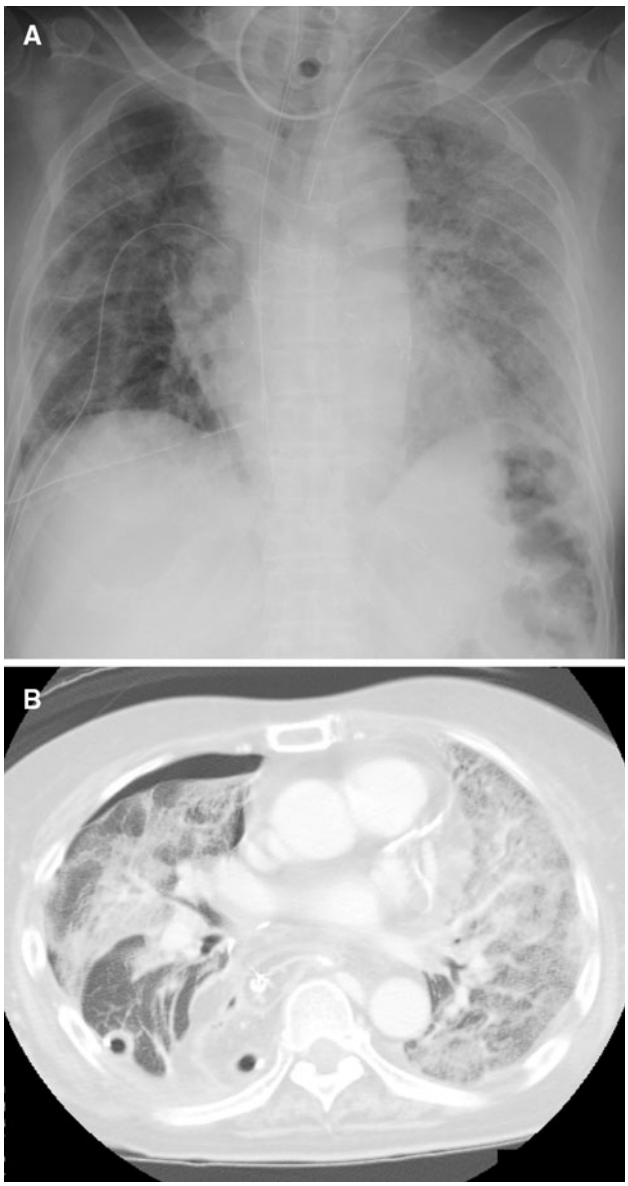

Fig. 2 Chest X-ray (**a**) and computed tomography (**b**) of patient no. 1 at diagnosis of CMV reactivation 30 days after methylprednisolone administration

esophagectomy, patient backgrounds and general conditions are different. Moreover, even starting with high-dose administration in this study, six patients (54.5 %) showed a worsening of their ARDS and required a re-increase of methylprednisolone. Therefore, the low-dose administration protocol for these patients needs further studies with a larger number of patients.

In summary, although the number of study patients was small, the prevalence of CMV reactivation caused by high-dose methylprednisolone therapy for ARDS after esophagectomy was remarkably high. This result strikes a note of warning concerning the management of these patients and suggests the importance of screenings for CMV reactivation so as to make an accurate diagnosis and initiate treatment in a timely manner.

Conflict of interest The authors declare that they have no conflict of interest.

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