Case Report

Capillary leak syndrome in a primary lung adenocarcinoma patient with thrombocytopenia from interleukin-11 treatment

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Abstract: Capillary leak syndrome (CLS) is an uncommon complication characterized by generalized edema and hypotension. We report a 62-year-old male patient with lung and liver metastasis who had undergone liver radiofrequency ablation. He was treated with interleukin (IL)-11 (3 mg per day) because of chemotherapy induced thrombocytopenia. After 9 days of therapy, the patient complained of abdominal distension and bilateral edema of all four extremities. Chest computed tomography and B ultrasound of the abdomen showed pleural effusions and ascites. IL-11 was then discontinued, fluid resuscitation was performed, fresh frozen plasma and packed red blood cells were transfused, and methylprednisolone therapy was administered. The patient had recovered after 12 days of treatment. This case report demonstrates that patients with lung cancer can develop this rare form of CLS after treatment with IL-11. The manifestation of IL-11-induced CLS indicates that it may be a severe side effect of IL-11 treatment in cancer.

Keywords: Capillary leak syndrome, lung cancer, interleukin-11

Introduction

Capillary leak syndrome (CLS) is an uncommon and severe clinical syndrome which was first reported in 1960 [1]. The incidence of CLS is unknown and the causes are varied it is probably under recognized because of its nonspecific symptoms and high mortality rate. Some diseases that result in CLS include sepsis, the idiopathic systemic capillary leak syndrome (SCLS) or Clarkson’s disease, engraftment syndrome, and other serious infection.

Drugs can also cause CLS. Several drugs have been shown to cause CLS, including some interleukins (ILs), granulocyte colony stimulating factor (G-CSF), gemcitabine, and certain monoclonal antibodies [2-5]. And we have summarized previous reports about CLS due to different causes in Table 1. Cytokine IL-2 has been reported to cause edema and dyspnea when administered for the treatment of malignancy [6]. One study has confirmed that IL-2 caused an increase in the vascular permeability to albumin in an animal model [7]. In addition, IL-11 is an agent used for the treatment of thrombocytopenia. Cytokines IL-11 has also been associated with CLS [8, 9].

To our knowledge, CLS induced by IL-11 is rare and has never been reported in patients with lung cancer. Chemotherapy-induced thrombocytopenia is common in clinical practice [10]. CLS could result in death if the blood pressure does not increase during the initial capillary leak phase. We argue that the identification of IL-11-induced CLS is therefore critical. In this report, we firstly present a case of chemotherapy-induced thrombocytopenia with IL-11 induced CLS in a patient with lung adenocarcinoma metastatic to the liver.

Case report

A 62-year-old man presented to our hospital with a one-month history of right sided chest
**Table 1. Previous reported cases of idiopathic systemic capillary leak syndrome**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/gender</th>
<th>Type of cancer</th>
<th>Causes of CLS</th>
<th>Symptom</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [3]</td>
<td>50/Male</td>
<td>Renal cell carcinoma</td>
<td>Gemcitabine</td>
<td>Pleural effusion, pericardial effusion</td>
<td>Furosemide and prednisolon</td>
<td>Recovery</td>
</tr>
<tr>
<td>3 [4]</td>
<td>37/Male</td>
<td>CML</td>
<td>G-CSF</td>
<td>Acute renal failure, oedema</td>
<td>Methyl prednisolone, fluid resuscitation</td>
<td>Died</td>
</tr>
<tr>
<td>4 [8]</td>
<td>46/Male</td>
<td>Primary hepatic carcinoma</td>
<td>IL-11</td>
<td>Pleural effusion, hypotension, ascites in the abdomen, oliguria</td>
<td>Fluid infusion, dopamine, fresh frozen plasma, hydroxyethyl starch, albumin, diuretic</td>
<td>Recovery</td>
</tr>
<tr>
<td>5 [8]</td>
<td>66/Male</td>
<td>Primary hepatic carcinoma</td>
<td>IL-11</td>
<td>Dyspnea with bilateral edema of the feet, ascites</td>
<td>Albumin, somatostatin, FFP, fluid resuscitation, furosemide</td>
<td>Recovery</td>
</tr>
<tr>
<td>6 [9]</td>
<td>61/Male</td>
<td>Primary sigmoid carcinoma</td>
<td>IL-11</td>
<td>Flushing and edema of the hands, ascites</td>
<td>Fluid infusion, furosemide, methylprednisolone albumin, FFP, abdominal drainage</td>
<td>Recovery</td>
</tr>
<tr>
<td>7 [18]</td>
<td>63/Male</td>
<td>Chronic Lymphocytic Leukemia</td>
<td>Idiopathic form</td>
<td>Hypovolemic shock</td>
<td>Catecholamine</td>
<td>Died</td>
</tr>
<tr>
<td>8 [present report]</td>
<td>62/Male</td>
<td>Non small cell lung cancer</td>
<td>IL-11</td>
<td>Pleural effusion, edema of all four limbs, ascites</td>
<td>Fluid infusion, FFP, hydroxyethyl starch, albumin, methylprednisolone, diuretic</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

G-CSF: granulocyte colony-stimulating factor; CML: chronic myeloid leukaemia; FFP: fresh frozen plasma.
pain. Computed tomography (CT) revealed a right lung mass with an associated pleural metastasis (stage IV). Hematoxylin and eosin staining showed typical morphology for adenocarcinoma; a deletion of exon 19 in the epidermal growth factor receptor (EGFR) variants was found by amplification refractory mutation system (ARMS). The patient received icotinib, after which disease progression occurred after 6 months. CT showed an increase in tumor size and a single liver lesion, which was confirmed to be a metastatic lesion by biopsy. An EGFR T790M mutation was demonstrated. He then received a third generation EGFR-tyrosine kinase inhibitor target drug, osimertinib, and underwent radiofrequency ablation of the liver metastatic lesion twice. However, the disease continued to progress after another 6 months and the patient was admitted for further treatment.

On the day of admission, his blood pressure of the patient was 136/70 mmHg, his heart rate was 79 beats per minute, and his oral body temperature was 37.5°C. Multiple small lung nodules were found on chest CT. His laboratory values were as follows: leukocytes count 9.7 × 10^9/L; hemoglobin 88 g/L; platelet count 93 × 10^9/L; albumin 39.8 g/L; aspartate aminotransferase (AST) 25 U/L; alanine aminotransferase (ALT) 24 U/L. Chemotherapy (pemetrexed 500 mg/m^2/dL; carboplatin AUC=5 mg/dL) was initiated. Two days later, his laboratory values were as follows: leukocytes count 8.9 × 10^9/L; hemoglobin 94 g/L; platelet count 56 × 10^9/L. Due to the thrombocytopenia, IL-11 was administered subcutaneously at a dose of 3 mg per day. After 4 more days, his leukocyte count was 0.4 × 10^9/L, his neutrophil count was 0.1 × 10^9/L, his hemoglobin was 83 g/L, his platelet count was 29 × 10^9/L, his albumin was 32.7 g/L, his AST was 26 U/L, and his ALT was 25 U/L. He then received G-CSF treatment and continued IL-11. Meanwhile, his granulocyte count rose but his platelet count demonstrated a continuous decline (platelet count 8 × 10^9/L). He received a platelet transfusion and continued IL-11 treatment. The patient developed a fullness of his abdomen and with edema of all four limbs (Figure 1). His temperature was 37.4°C, his blood pressure was 127/65 mmHg, and his pulse was 84 beats per minute. His laboratory values were as follows: leukocytes count 6.1 × 10^9/L; hemoglobin 83 g/L; platelet count 16 × 10^9/L; albumin 29.5 g/L; AST 20 U/L and ALT 24 U/L. His chest CT showed progressive pleural effusions (Figure 2). He had moderate ascites on B ultrasound (Figure 3). He was not hypotensive. IL-11 was then discontinued immediately. As a consequence, rapid fluid infusion was administered. Packed red blood cells (3.0 units) and fresh frozen plasma (430 ml) were transfused as well hydroxyethyl starch and albumin. Methyprednisolone was administered to improve the capillary permeability. And the patient had stabilized blood pressure for this period, we added diuretic therapy. The following day, the patient’ s abdominal distension improved and his edema was gradually alleviated. After 10 days of treatment, the patient was discharged. On the day of discharge, he had the following laboratory values: leukocytes count 10.0 × 10^9/L; hemoglobin 77 g/L; platelet count 27 × 10^9/L; albumin 34.4 g/L; AST 23 U/L and ALT 37 U/L. After one week, there is no special laboratory examination and he continued receiving anti-cancer treatment. However, because of disease progression, he died after about two months.

**Discussion**

IL-11 is a cytokine derived from stromal cells that is used extensively in thrombocytopenia...
CLS in LA from IL-11 treatment

Wang et al [8] in 2011 described two cases of CLS after IL-11 administration in primary hepatic carcinoma patients. In these patients, shock, limbs edema, and laboratory findings led to the final diagnosis. Liu et al [9] also reported a patient with sigmoid carcinoma who was hospitalized with hypotension, anasarca, and ascites after administration of IL-11. Our patient had lung adenocarcinoma with liver metastasis. We think that either primary or metastatic liver cancer influences drug metabolism, and these patients might be more susceptible to develop CLS after IL-11 treatment. Liver pathology also has a negative influence on the endothelial system [16]. However, the mechanism of IL-11 induced CLS requires further exploration in animal models.

Due to the serious consequences of CLS, expeditious diagnosis and management are important. Fluid management is the most critical element in the treatment of CLS. One report described two patients with CLS treated with 10% pentastarch, which was successful in increasing the central venous pressure and systemic blood pressure [17]. High molecular weight starches such as pentastarch are used as recovery fluids because of their size, which may exceed the endothelial defect. In addition, steroid therapy has demonstrated efficacy in CLS [2]. When the blood pressure has been stabilized for a period of time, diuretic therapy should be initiated to prevent the development of pulmonary edema. In our report, the patient received hydroxyethyl starch, albumin, methylprednisolone, and diuretics, leading to relief of edema and improved symptoms successfully. Today, since data is rare and no guidelines exist, treatment should be started immediately.
once a patient is suspected developing CLS, after excluding other diseases.

Conclusions

Further studies could be conducted to explore the mechanism of IL-11 induced CLS. Increased awareness of this adverse effect will lead to increased identification of cases in different cancers. Patients with lung cancer and liver primary or metastatic disease might be more susceptible to CLS. Better insight into the pathogenesis and treatment of CLS is required.

Disclosure of conflict of interest

None.

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