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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 underwent 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 with bilateral edema of all four extemities. 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

Patient No.	Age/ gender	Type of cancer	*Causes of CLS*	Symptom	Treatment	Prognosis
1 [3]	50/Male	Renal cell carcinoma	Gemcitabine	Pleural effusion, pericardial effusion	Furosemide and prednisolon	Recovery
2 [4]	57/Male	Myeloma	G-CSF	Respiratory distress, hypotension, oliguria	Noradrenaline, enteral Nutrition, methyl prednisolone	Recovery
3 [4]	37/Male	CML	G-CSF	Acute renal failure, oedema	Methyl prednisolone, fluid resuscitation	Died
4 [8]	46/Male	Primary hepatic carcinoma	IL-11	Pleural effusion, hypotension, ascites in the abdomen, oliguria	Fluid infusion, dopamine, fresh frozen plasma, hydroxyethyl starch, albumin, diuretic	Recovery
5 [8]	66/Male	Primary hepatic carcinoma	IL-11	Dyspnea with bilateral edema of the feet, ascites	Albumin, somatostatin, FFP, fluid resuscitation, furosemide	Recovery
6 [9]	61/Male	Primary sigmoid carcinoma	IL-11	Flushing and edema of the hands, ascites	Fluid infusion, furosemide, methylprednisolone albumin, FFP, abdominal drainage	Recovery
7 [18]	63/Male	Chronic Lymphocytic Leukemia	Idiopathic form	Hypovolemic shock	Catecholamine	Died
8 [present report]	62/Male	Non small cell lung cancer	IL-11	Pleural effusion, edema of all four limbs, ascites	Fluid infusion, FFP, hydroxyethyl starch, albumin, methylprednisolone, diuretic	Recovery

G-CSF: granulocyte colony-stimulating factor; CML: chronic myeloid leukaemia; FFP: fresh frozen plasma.

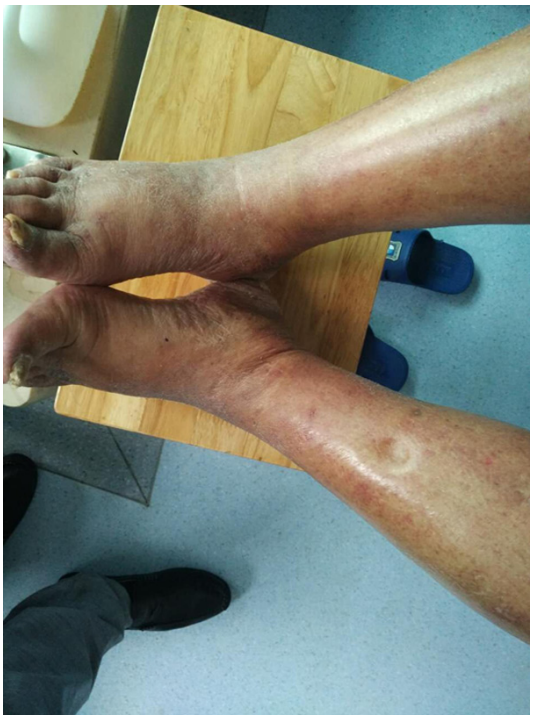

Figure 1. Edema of the limbs.

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, his respiratory rate was 18 breaths 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; AST20 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. Methylprednisolone 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

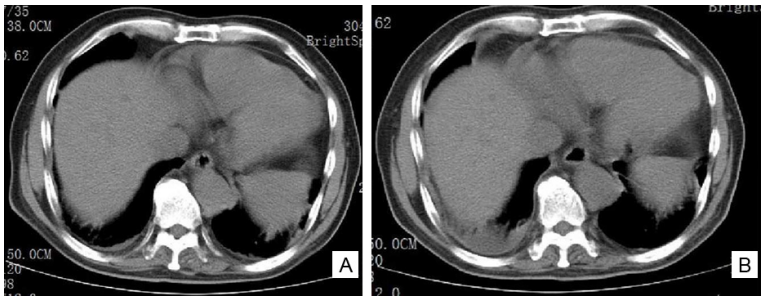

Figure 2. A. Chest CT demonstrates pleural effusion; B. Increased effusions on subsequent chest CT 8 days later.

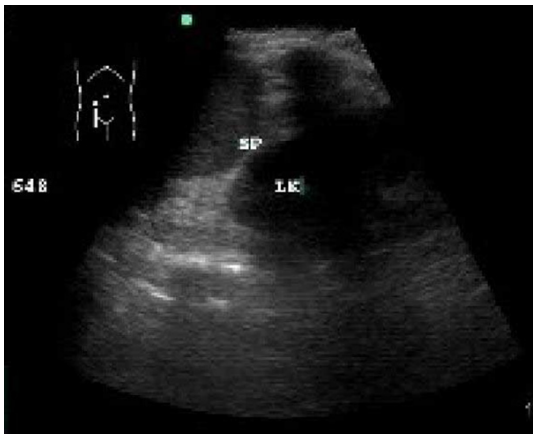

Figure 3. Moderate ascites on B ultrasound after treatment with IL-11.

induced by chemotherapy. The most common side effects of IL-11 include muscular pain, fatigue, nausea, edema of the face and limbs, fever, and headache. Cardiovascular side effects such as tachycardia and hypotension are regarded as the most severe and while rare, can lead to death [11]. The treatment of IL-11 induced CLS has ever been reported previously in two cases [8, 9], however, it has never been reported in lung cancer patients. Herein, we describe one patient with lung cancer metastatic to the liver, who developed limb dropsy, pleural effusion, and ascites after IL-11 treatment.

CLS is clinically diagnosed after exclusion of other diseases in clinical. Although the cause of CLS is still uncertain, all of the diseases causing CLS due to the similar underlying pathophysiologic abnormality which is an increase in capillary permeability to proteins [12]. Hyper-cytokinemia is considered to be the underlying cause of capillary leak. Inflammatory stimuli induce endothelial cell separation, resulting in gaps between endothelial cells and in significant increases in permeability [13]. Individual cytokines have been shown to increase vascular permeability via disruption of the adherens junctions [14]. It has been suggested that IL-2 leads to endothelial damage, which can alter the permeability of the endothelial cells, as confirmed in an animal models [7, 15]. However, the mechanism of CLS induced by IL-11 induced CLS is unknown.

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 that 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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