Pathol. Oncol. Res. (2014) 20:435–437
DOI 10.1007/s12253-013-9713-2

RESEARCH

Trastuzumab-Induced Systemic Capillary Leak Syndrome in a Breast Cancer Patient

Fan Zhang · Junlan Yang · Zijian Li

Received: 16 July 2013 / Accepted: 14 October 2013 / Published online: 27 October 2013

Abstract Systemic capillary leak syndrome (SCLS) is a rare health condition. It is characterized by recurrent episodes of generalized edema and severe hypotension along with hypoproteinemia. The condition is under recognized because of its nonspecific signs and symptoms, and high mortality rate. SCLS triggered by trastuzumab, a target drug for Her2-positive breast cancer patients, has not been previously reported. A 59-year-old Chinese woman, diagnosed with breast cancer with accompanying liver and bone metastasis, was treated with 3 cycles of docetaxel with capecitabine and a regimen of 12 cycles of capecitabine with trastuzumab. The patient developed systemic capillary leak syndrome during the 16th cycle of chemotherapy. Post-diagnosis treatment regimen is also presented in the current case report. SCLS has been previously observed in breast cancer patients. However, SCLS incidence post-chemotherapeutic treatment with trastuzumab has not been reported elsewhere. Hence, our report highlights the need for rigorous investigation of the side effects of trastuzumab usage and the increasing need of insightful diagnosis to manage any incidence of SCLS. The case provides valuable experience for treating the uncommon adverse effects of trastuzumab in Her2-positive breast cancer patients.

Keywords SCLS · Trastuzumab · Chemotherapy · Breast cancer

F. Zhang
Key Laboratory, Tumor Center, PLA General Hospital, Beijing, China

Z. Li
Oncology Department, PLA No.161 Hospital, Wuhan, China

J. Yang (✉)
Oncology Department, Tumor Center, PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China
e-mail: yangjunlan1123@126.com

Introduction

Systemic capillary leak syndrome (SCLS) is a rare disease of reversible plasma extravasation and vascular collapse accompanied by hemoconcentration and hypoalbuminemia [1]. The condition is probably under recognized because of its nonspecific signs and symptoms, and high mortality rate. This syndrome has been associated with snakebites, sepsis, rhabdomyolysis, acute renal failure, post-administration of recombinant interleukin (IL)-2, docetaxel, and gemcitabine [2–6]. In recent years, trastuzumab has been generally used in Her2-positive breast cancer patients. The main adverse events of trastuzumab include cardiovascular events and fever [7]. However, SCLS has not been previously reported as a contraindication of trastuzumab usage. In the current study, a case of SCLS induced by trastuzumab administration was observed in an adult Chinese patient with metastatic breast cancer.

Materials and Methods

Breast lump biopsy guided by B-ultrasound revealed invasive carcinoma in the breast (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor 2-positive) in a 59-year-old Chinese woman on July 6, 2009, with concomitant bone and liver metastasis. Fluorescent in situ hybridization (FISH) revealed gene amplification in the patient. The patient was administered a standard dose regimen of 3 cycles of docetaxel (75 mg/m^2) and capecitabine (950 mg/m^2) and 12 cycles of capecitabine and trastuzumab (6 mg/kg), repeated every 3 weeks between July, 2009 and July, 2010. This amounted to 5.28 g of trastuzumab in the aforementioned duration. The patient received the 16th cycle of chemotherapy (regimen of capecitabine and trastuzumab) on July 8, 2010. The patient complained of dyspnea,

palpitation, breathlessness, and abdominal distention 10 days following the 16th cycle of chemotherapy, but refused any treatment for the symptoms. Heart ultrasound, performed when the symptoms became severe, on July 20, 2010 revealed slight pericardial effusion (2 cm×2 cm) and compromised hepatic function (serum alanine aminotransferase (ALT): 173 U/L; aspartate aminotransferase (AST): 148 U/L). Administration of liver protection treatment for 4 days did not alleviate the symptoms, instead the serum ALT and AST levels were significantly high (>400 U/L). She was admitted to the General Hospital of the People's Liberation Army on July 27, 2009. The current study was approved by the Institutional Scientific and Ethics Committees of People's Liberation Army (PLA) General Hospital. The study was performed after obtaining signed patient consent.

Results

On admission, her body temperature was 36.7 °C, pulse rate was 110/min, respiratory rate was 22/min, blood pressure was 120/75 mmHg. Respiratory sounds in both lungs were weak, and her face and four limbs were edematous. The complete blood count, blood biochemistry, and arterial blood gas analysis on Day 1 is shown in Table 1. Imaging studies indicated pleural effusion on both lungs and pericardial effusion. On the basis of her history of unexplained shock, symptoms, and prolonged trastuzumab treatment, systemic capillary leak syndrome (SCLS) was diagnosed.

The patient was resuscitated with fluid infusion under intensive care and appropriate diuretic to relieve the edema and underwent continuous thoracocentesis and pericardiocentesis to decrease effusion. Prophylactic therapy with macromolecule hetastarch was done to improve colloid osmotic pressure. Radiosone was administered to improve the capillary permeability, relieve the capillary leak, and to ensure the perfusion of major organs. She was also administered hepatoprotectants and additional nutrition support to improve her condition. Her condition improved and her laboratory investigation results returned to normal levels by 10 days (Table 1). As of September 2011, the patient was still alive.

Discussion

SCLS was first reported in 1960 [1] and fewer than 150 cases have been reported since then [4]. SCLS has a high mortality rate and is characterized by rapidly developing edema, weight gain, hypotension, hemoconcentration, and hypoproteinemia [4]. The disease has been previously indicated in only one case of solid lobular carcinoma of the breast, where it was idiopathic [8]. SCLS has been described after the administration of recombinant interleukin-2, docetaxel, and gemcitabine [2]. In recent years, trastuzumab has been generally used in Her2-positive breast cancer patients. The main adverse events of trastuzumab include cardiovascular events and fever [7].

With the increasingly wide application of biotherapy, SCLS may be more common in clinical treatment as patients might suffer from whole body edema after using bio therapeutic agents. However, successfully treating such a severe SCLS patient is uncommon. A patient who had suffered from severe SCLS after infusion of recombinant IL-11 died of multiple organ failure in our hospital several years before [9], which increased our awareness regarding SCLS. Even though we did not see any direct evidence to connect trastuzumab with SCLS, the case history and presentation was used to make the circumstantial inference that trastuzumab usage was responsible for the SCLS case. Of note, the patient did not develop SCLS until the 16th round of chemotherapy

Table 1 Results of laboratory tests in the patient diagnosed with SCLS

Analyte	Unit	Day 1	Day 3	Day 5
Hb	g/L	104	–	–
WBC	$\times 10^9$/L	8.17	–	–
PLT	$\times 10^9$/L	63	–	–
ALT	U/L	4890	526.3	357
AST	U/L	3940	168.9	90.1
BUN	mmol/L	15.33	9.69	6.44
Albumin	g/L	40.9	32.7	34
Total bilirubin	μmol/L	36.3	42.5	39.8
Direct bilirubin	μmol/L	17.1	18.7	16.9
LDH	U/L	6570	283.1	265.2
Oxygen pressure from arterial blood		64.6	72.2	Normal
Oxygen saturation from arterial blood		90.1 %	87 %	Normal

WBC white blood cell, *PLT* platelet count, *ALT* alanine amino transferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *LDH* lactate dehydrogenase, "–" no obvious change

suggesting that it can be an accumulation or drug metabolism related occurrence, in turn necessitating further stimulated studies in animal models. It is thus recommended that physicians pay extra attention to the rare adverse events during chemotherapy to avoid the occurrence of severe SCLS.

Acknowledgments This work was supported by Roche's Scientific Corporation Program (03YH606), Project of PLA Eleventh-Five Year Research Program of China (06G106), and Research Fund of Ministry of Public Health (WKJ2006-3-007).

Conflict of Interest We declare no conflicts of interest.

References

1. Clarkson B, Thompson D, Horwith M et al (1960) Cyclical edema and shock due to increased capillary permeability. Am J Med 29:193–216
2. Dhir V, Arya V, Malav IC et al (2007) Idiopathic systemic capillary leak syndrome (SCLS): case report and systematic review of cases reported in the last 16 years. Intern Med 46:899–904
3. de Martino M, Sasso L, Pirozzi F et al (2009) Systemic capillary leak syndrome or Clarkson's disease: a case report. Intern Emerg Med 4: 357–358
4. Druey KM, Greipp PR (2010) Narrative review: the systemic capillary leak syndrome. Ann Intern Med 153:90–98
5. Hollenberg J, Frykman J, Lundberg LG et al (2010) A case report of systemic capillary leak syndrome (Clarkson's disease). Acta Anaesthesiol Scand 54:649–652
6. Guillaume M, Tolsma V, Colombe B et al (2011) Idiopathic systemic capillary leak syndrome: a case report with cardiac involvement. Rev Med Interne 32:e69–e71
7. Hudis CA (2007) Trastuzumab–mechanism of action and use in clinical practice. N Engl J Med 357:39–51
8. Bencsath KP, Reu F, Dietz J et al (2011) Idiopathic systemic capillary leak syndrome preceding diagnosis of infiltrating lobular carcinoma of the breast with quiescence during neoadjuvant chemotherapy. Mayo Clin Proc 86:260–261
9. Kai-Feng W, Hong-Ming P, Hai-Zhou L et al (2011) Interleukin-11-induced capillary leak syndrome in primary hepatic carcinoma patients with thrombocytopenia. BMC Cancer 11:204