JPPT | Case Report

Capillary Leak syndrome within an hour of G-CSF

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Capillary leak syndrome (CLS) is a well-known phenomenon that has been reported commonly in association with septic shock, polytrauma, and pancreatitis in intensive care settings. In the hematologic literature, it has been reported following granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, tumor necrosis factor, interleukin 2, and interleukin 4 infusions; and autologous and allogenic bone marrow transplantations in both pediatric as well as adult populations. Only a few cases of CLS have been reported in the pediatric population following G-CSF. We report here a case of a 9-year-old female who developed CLS within 60 minutes of receiving the first dose of G-CSF that was successfully treated with immediate symptomatic management.

ABBREVIATIONS CLS, capillary leak syndrome; G-CSF, granulocyte colony-stimulating factor

KEYWORDS capillary leak syndrome; G-CSF; pediatric; systemic capillary leak syndrome

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Introduction

Granulocyte colony-stimulating factor (G-CSF) is a recombinant human methionyl granulocyte-colony stimulating factor that was approved in 1991. It stimulates the proliferation and maturation of neutrophil progenitors, functional end cell activation, and facilitates their release into the bloodstream.[1] By the above mechanisms, G-CSF helps in decreasing the incidence of febrile neutropenia and severe neutropenia, shortening the hospital stay, decreasing the incidence of infections, and improving the tolerance to cytotoxic chemotherapy.[2] It can be administered subcutaneously or intravenously. The common side effects of G-CSF include arthralgia, bone pain, back pain, chest pain, fever, cough, rash, and fatigue. Capillary leak syndrome (CLS) is a rare side effect of G-CSF, reported primarily in adults receiving chemotherapy or after bone marrow transplantation.[3,4] Capillary leak syndrome is a rare disease of reversible plasma extravasation and vascular collapse that was first described in 1960 and is believed to cause transient endothelial dysfunction.[4] We present a case of a 9-year-old female with cervical osteosarcoma who developed CLS within an hour of the first dose of intravenous G-CSF.

Case Description

A 9-year-old female with cervical osteosarcoma underwent total resection of her tumor and hardware placement for stabilization of C5 to C7 spinal vertebral bodies. After resection she was started on chemotherapy per Children's Oncology Group AOST0331 protocol. She received cisplatin, doxorubicin, and dexrazoxane on days 1 to 2 of the cycle, which were uneventful. On day 4 of the cycle, she was given a dose of G-CSF intravenously at 5 mcg/kg over 30 minutes. Within 60 minutes of administration of the intravenous G-CSF, she experienced generalized abdominal pain and dyspnea. She developed hypoxia, with her SpO2 dropping to the low 80s, tachycardia with a heart rate between 110 and 120 bpm, and hypotension, with blood pressure of 72/46 mm Hg. She was very uncomfortable and agitated on examination and had decreased breath sounds in bilateral lung bases. She was given supplemental oxygen and a 20 mL/kg normal saline bolus during 60 minutes. Laboratory and diagnostic studies were done after the event, which are outlined in Tables 1 through 3 below. Blood culture was collected, and she was given a dose of cefepime at 50 mg/kg to empirically cover for presumed septic shock. Her blood pressure, mental status, abdominal pain, and dyspnea all improved after these interventions. She was weaned to room air within a few hours and remained stable and afebrile during the next several days. The antibiotics were discontinued after 48 hours of negative blood culture results.

Given the onset of symptoms acutely after administration of the intravenous filgrastim, her clinical presentation, and laboratory results (hypoalbuminemia, hemoconcentration, and hypotension, as evident in the laboratory results below), and her response to the symptomatic treatment, CLS due to filgrastim was presumed to be the cause (Naranjo score of 4). To prevent similar complication, she was given subsequent doses of G-CSF subcutaneously, preceded by dexamethasone, which she tolerated without any complications or recurrent symptoms. In the subsequent courses of chemotherapy, she tolerated subcutaneous G-CSF without premedication with steroids.

Discussion

Shin et al[5] performed a systematic review on CLS in cancer patients in 2018 where they reviewed 62 case reports on CLS associated with cancer or anticancer agents, of which 21% were pediatric cases. Among anticancer agents, G-CSF was the most frequent potentially causative drug (14.6%), followed by interleukin 2.[5] Literature review on CLS secondary to G-CSF revealed only 2 case reports. These were a report by Heitger et al,[6] who reported on a 15-year-old male with mediastinal granulocytic sarcoma presenting with CLS 36 hours after G-CSF administration in 1998, and a report by Dagdemir et al,[7] who reported on a 14-year-old female with acute lymphoblastic leukemia who developed CLS on the fourth day of G-CSF therapy during her third course of chemotherapy. The timing of CLS following drug administration has not been well studied. There are few case reports of CLS following the first dose of G-CSF, and some after a few doses or even a few courses of G-CSF therapy. Our patient developed CLS within 60 minutes of the first intravenous dose of G-CSF.

Capillary leak syndrome can be idiopathic (also known as Clarkson disease), which typically presents in the fifth and sixth decades of life with recurrent acute attacks, or it can be secondary to pathologies, like viral infection, sepsis, autoimmunity, snake envenomation, stem cell transplantation, malignancies, and certain drugs (chemotherapy and leukocyte growth factors).[1,8–14]

Capillary leak syndrome is a rare syndrome characterized by triad of hypotension, hemoconcentration, and paradoxic hypoalbuminemia caused by capillary hyperpermeability leading to extravasation of fluid and proteins from intravascular to extravascular space.[8] The common clinical presentation includes peripheral edema, hypotension, pleural effusion, dyspnea, ascites, oliguria, weight gain, fever, and pulmonary edema.[2,4,8–14] Severe cases can present with cardiovascular collapse, shock, and death.[9] Other rare manifestations include rhabdomyolysis and sometimes compartment syndrome of the extremities.[9–12] Our patient presented with hypotension, hemoconcentration, and hypoalbuminemia within an hour of administration of the drug.

There are 2 different theories of pathogenesis proposed for the causation of CLS following G-CSF administration: the role of cytokine surge from G-CSF administration which leads to endothelial injury on a cellular level, and increased capillary permeability,[9,11] and the direct effect of G-CSF on endothelium that is already damaged by high-dose chemotherapy that the patient often receives prior to getting G-CSF.[6]

Fluid management is the most critical element in the treatment of CLS. Hemodynamically, the patients with capillary leak can have stable blood pressure with intact perfusion or signs of fluid overload progressing to fulminant hypovolemic shock. In those with mild hypotension, blood pressure often responds to intravenous fluids in the form of crystalloids. Albumin or plasma infusion has been reported to have a use in those who fail to respond to crystalloids. These patients are at high risk for noncardiogenic pulmonary edema during fluid

Table 1. Laboratory and Diagnostic Studies Drawn After the Event Compared With Previous Day Laboratory Studies

Blood	Previous Day	At the Time of the Event	Reference Laboratory Range
White blood cell count, cells/mm^3	6100	3100	4000–110,000
Hemoglobin/hematocrit, g/dL (%)	8.9 (26.4)	9.7 (29.7)	12–15.4 (35–45)
Absolute neutrophil count, cells/mm^3	5200	1300	1600–8500
Albumin, g/dL	3.4	2.9	3.8–5.4

Table 2. Other Laboratory Tests Performed at the Time of Event

Blood	At the Time of Event	Reference Laboratory Range
pH on capillary blood gas	7.306	7.35–7.45
$PaCO_2$ on capillary blood gas, mm Hg	44.1	35–40
Bicarbonate on capillary blood gas, mEq/L	22	23–29
Prothrombin time, sec/international normalized ratio	14.4/1.1	11.6–15/0.9–1.1
Activated plasma thromboplastin time, sec	21.9	23–40
D-dimer, FEU mcg/mL	1.31	<0.5 FEU

Table 3. Results of Diagnostic Studies Ordered at the Time of Event

Diagnostic Studies	At the Time of Event
Chest X-ray	Lungs were clear with mild cardiomegaly slightly worse
Electrocardiogram	Normal sinus rhythm and normal intervals
Computed tomography angiogram chest	No pulmonary embolus, mild dependent atelectasis in left > right lower lobes

resuscitation, which often develops after the blood pressure has stabilized due to the return of interstitial fluid to the intravascular space.[12] For these reasons, a fluid-restrictive strategy is advocated during volume resuscitation. Once the blood pressure has stabilized following fluid resuscitation, diuretic therapy may be needed to prevent the development of pulmonary edema.[12] In addition to fluid therapy, steroid therapy has demonstrated efficacy in drug-induced CLS. Capillary leak syndrome is generally believed to be a cytokine-mediated disease, and the benefit of steroids presumably relates to their ability to reduce the expression of multiple cytokines. Dexamethasone has been reported to be effective in blocking CLS in patients who received interleukin 2 as cancer treatment.[13] Methylprednisone has been reported to be effective in other case reports.[11] However, steroids have been reportedly ineffective in some cases of CLS caused by endothelium-damaging substances.[12] As in Clarkson disease, many agents have been tried sporadically in secondary CLS, with varying degrees of effectiveness, including corticosteroids, β2-agonists (aminophylline, theophylline, or terbutaline), thalidomide, antihistamines, plasmapheresis, and intravenous immunoglobulin.[9,10,13,14] Our patient improved with immediate symptomatic management and did well with minimal interventions. She did not have recurrences after subsequent doses given subcutaneously.

With respect to the prognosis of systemic calillary leak syndrome in cancer patients, hematologic malignancies have been reportedly associated with an increased risk for mortality.[5] Prognosis is uncertain, but patients who survive an initial severe SCLS episode are estimated to have a 10-year survival rate greater than 70%.[4] It is hard to prognosticate based on limited data, but our patient did not have recurrence of CLS in subsequent courses of chemotherapy.

Conclusion

Capillary leak syndrome is a rare but life-threatening complication of G-CSF administration. Awareness of this complication is essential given the widespread use of G-CSF in the pediatric hematology and oncology community. Rapid identification and symptomatic management can prevent severe acute complications, and preventative strategies can prevent future episodes. Our patient provides an example of the successful management and further prevention of CLS.

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