Diagnostic Snapshot

What Is Happening to This Patient With a Rare Leukemia?

AMANDINE NDJE, MS, MBA, APRN, FNP-C, and JACQUELINE B. BROADWAY-DUREN, PhD, DNP, APRN, FNP-BC

From The University of Texas MD Anderson Cancer Center, Houston, Texas

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Amandine Ndje, MS, MBA, APRN, FNP-C, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX. E-mail: apndje@mdanderson.org

https://doi.org/10.6004/jadpro.2022.13.8.9

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare cancer with primary sites in the skin and bone marrow and secondary sites in the lymph nodes, spleen, and central nervous system. First described in the 1990s, these cells express a CD123 antigen hinting at a plasmacytoid dendritic cell origin. A CD123-directed cytotoxin called SL-401 was approved by the US Food and Drug Administration and the European Medicines Agency. During BPDCN treatment, a life-threatening syndrome can occur, but early awareness leads to positive patient outcomes.

HISTORY

Mr. Jones is a 68-year-old male with a rare leukemia called blastic plasmacytoid dendritic cell neoplasm (BPDCN) who was recently treated with a CD123-directed cytotoxin, tagraxofusp (Elzonris; SL-401). He presents to the emergency center with fever (38.4°C), headaches, a transient nosebleed, excessive fatigue and malaise, shortness of breath, nausea, abdominal edema and pain, and a substantial weight gain in 24 hours. He also reports edema of the lower extremities and low blood pressure (88/58 mmHg) using a home blood pressure monitor. He has had a runny nose, dyspnea, and cough for 24 hours.

A review of systems shows that he has been positive for fever for 24 hours, has facial edema, abdominal edema, pedal edema, nonproductive cough, runny nose, shortness of breath, palpitations, nausea, and vomited once. Mr. Jones denies diarrhea, hematuria, musculoskeletal complaints, or syncopal episodes. An initial evaluation shows vital signs are blood pressure 82/54 mmHg, temperature 38.7°C, heart rate 110 beats per minute (bpm), respirations 26 per minute, oxygen saturation 89% on room air, and weight increased by 7.7 lbs in 1 day. On physical examination, Mr. Jones is an ill-appearing male, alert and oriented × 3 who responds appropriately to verbal commands but needs the assistance of a wheelchair to ambulate due to severe painful pedal edema. He is notably short of breath with increased respiratory effort and a runny nose.

PHYSICAL EXAMINATION

A head, eyes, ears, nose, and throat examination reveals periorbital and facial edema. Pupils are equal, round, and reactive to light and accommodation. The oral mucosa is intact, and nasal mucus

is clear. The neck is supple without nuchal rigidity. Four previously present BPDCN lesions on his back are red and painful with skin breakdown. There are small ecchymoses on his arms. His lungs have fine crackles in lower lobes bilaterally. Decreased inspiratory effort is noted. His heart has a regular rhythm but at a fast rate. His abdomen is distended with tenderness on palpation. Hypoactive bowel sounds are present. There is no palpable organomegaly. The ankles are more swollen than the knees. He has peripheral edema 3+ to the bilateral lower extremities. There is generalized weakness and an altered gait, and no acute tremors noted. He ambulates with the assistance of a wheelchair due to pedal pain and not because of focal deficits. There is no notable lymphadenopathy, and he has appropriate mood and affect.

FURTHER ASSESSMENTS

A complete blood count shows white blood count 2.2 K/µL, absolute neutrophil count 1.0 K/µL, hemoglobin 10.2 g/dL, hematocrit 47.5%, and platelets 80 K/µL. A complete metabolic panel shows albumin 2.0 g/dL, total protein 5.8 g/dL, creatinine 2.2 mg/dL/blood urea nitrogen 35 mg/dL, and liver function tests are normal. A chest x-ray reveals mild pleural effusion but no pulmonary infiltrates or opacities bilaterally. The superior vena cava is not obstructed. A CT of the chest without contrast confirms the chest x-ray findings and does not show other abnormalities. An electrocardiogram shows a sinus rhythm with tachycardia (112 bpm). A CT of the head without contrast shows no intracranial abnormalities. A CT of the abdomen shows that the inferior vena cava is not obstructed. He has mild ascites but no tumors or infection. In a urinalysis, the urine is hazy in appearance but has otherwise normal findings. An echocardiogram shows left ventricular ejection fraction of 55% and no pericardial effusion. Vascular endothelial growth factor plasma levels are elevated. Brain natriuretic peptide is mildly elevated. Thyroid function tests are normal. Lactic acidosis is mildly elevated. Procalcitonin is normal. A coagulation panel is normal. A COVID-19 test is negative. The respiratory viral panel is positive for rhinovirus. C-reactive protein and urea are elevated.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MR. JONES?

A ☐ Sepsis

B ☐ COVID-19

C ☐ Pneumonia

D ☐ Superior vena cava syndrome

E ☐ Capillary leak syndrome

SEE BACK FOR ANSWER ▶

WHAT IS THE CORRECT DIAGNOSIS FOR MR. JONES?

A Sepsis

B COVID-19

C Pneumonia

D Superior vena cava syndrome

E Capillary leak syndrome (correct answer)

A **Sepsis.** Fever and mild neutropenia are worrisome given potential bacterial entry sites at Mr. Jones' BPDCN skin lesions, but the most objective data do not support sepsis. His lactic acid is only mildly elevated, while his procalcitonin is normal. His low blood pressure is likely not from sepsis, but to be prudent, broad-spectrum IV antibiotics are given within 1 hour of arrival in the emergency center while further assessments are completed (CDC, 2021).

B **COVID-19.** The COVID-19 test is negative by polymerase chain reaction (Johns Hopkins University of Medicine, 2022).

C **Pneumonia.** Despite dyspnea, cough, and adventitious sounds on auscultation, his chest x-ray shows no pulmonary infiltrates or opacities (CDC, 2020).

D **Superior vena cava syndrome.** Despite his upper body edema, his superior vena cava is not obstructed in chest imaging (Cancer.Net, 2020).

E **Capillary leak syndrome (correct answer).** Mr. Jones was recently treated with tagraxofusperzs (SL-401), a CD123-directed cytotoxin, for his BPDCN. So far, it is the only US Food and Drug Administration–approved front-line and relapsed/refractory treatment for BPDCN. A side effect of this medication (which occurs in 21% of patients and resolves in a median of 5 days) is capillary leak syndrome (CLS), which is life-threatening but has good outcomes when diagnosed and treated promptly (Pemmaraju et al., 2019, 2021; Stemline Therapeutics, Inc., 2021).

Capillary leak syndrome (or systemic capillary leak syndrome) is characterized by capillary hyperpermeability leading to edema or anasarca, hypotension, hypoalbuminemia, hemoconcentration, and occasionally can lead to hypovolemic shock with multiorgan failure (Siddall et al., 2017). Because signs and symptoms are nonspecific, CLS is often underdiagnosed or diagnosis is often delayed (NORD, 2020; Siddall et al., 2017). Capillary leak syndrome is not to be confused with cytokine release syndrome, which has some similar signs and symptoms.

Capillary leak syndrome can be idiopathic (also called Clarkson's disease) or secondary to certain autoimmune diseases, infections (sepsis), snakebites, cancers, and drugs (Aneja, 2021; Fuentes Fernandez et al., 2017; Jeong et al., 2019; Massafra et al., 2021; Qin et al., 2021; Siddall et al., 2017). The following has been observed in cases of CLS: increased levels of monoclonal proteins, anti-inflammatory mediators, interleukin-2, and vascular endothelial growth factor, as well as endothelial cell apoptosis (Aneja, 2021). Idiopathic CLS has low prevalence (< 1/1,000,000), with approximately 260 cases reported worldwide (Aneja, 2021; NORD, 2020).

For secondary CLS, approximately 50% of cases in patients with cancer are related to anticancer drugs, but the underlying mechanisms are not well known. Furthermore, 45 antineoplastic and immunomodulatory drugs have been associated with CLS, with episodes occurring at a median of 8 days after drug administration. Most drug-induced CLS occurrences are serious adverse events (86%), with a 27% mortality rate (related or unrelated to CLS; Mertz et al., 2019; Percik et al., 2021; Polishchuk et al., 2021; Shin et al., 2018).

Since there are no standard recommendations for diagnosis and treatment of drug-induced CLS, some providers use their institutional guidelines or follow guidelines from the prescribing information. Given the complexity of the types of CLS

and based on our practice as leukemia advanced practitioners who treat this patient population, we have summarized the data in an algorithm we created titled "Algorithmic Approach to Diagnosis and Management of Capillary Leak Syndrome" (Figure 1). The aim of this algorithm is to outline initial assessments and treatment for CLS, because early intervention and appropriate management help to reduce drug-induced CLS mortality.

TREATMENT

Based on information gathered during SL-401 clinical trials, in the prescribing information, from our clinical practice, in a literature review, and summarized in the algorithm, the treatment includes (1) intravenous albumin to correct low albumin level that is causing the generalized edema and weight gain; (2) fluid resuscitation to resolve acute kidney failure, hemoconcentration, and hypotension; (3) diuretics to resolve fluid overload, and (4) glucocorticoids.

Mr. Jones and any patient experiencing this type of CLS must be monitored closely with frequent labs and vital signs until they are stable for discharge. They should also have close outpatient monitoring after discharge.

Disclosures

The authors have no conflict of interest to disclose.

References

Aneja, R. (2021). Idiopathic systemic capillary leak syndrome. https://www.uptodate.com/contents/idiopathic-systemic-capillary-leak-syndrome

Cancer.Net. (2020). Superior vena cava syndrome. https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/superior-vena-cava-syndrome

Centers for Disease Control and Prevention. (2020). Pneumonia. https://www.cdc.gov/pneumonia/index.html

Centers for Disease Control and Prevention. (2021). What is sepsis? https://www.cdc.gov/sepsis/what-is-sepsis.html

Fuentes Fernandez, I., Hernandez-Clares, R., Carreón Guarnizo, E., & Meca Lallana, J. E. (2017). Capillary leak syndrome in neuromyelitis optica treated with rituximab. *Multiple Sclerosis and Related Disorders*, *16*, 22–23. https://doi.org/10.1016/j.msard.2017.06.001

Jeong, G. H., Lee, K. H., Lee, I. R., Oh, J. H., Kim, D. W., Shin, J. W.,...Shin, J. I. (2019). Incidence of capillary leak syndrome as an adverse effect of drugs in cancer patients: A systematic review and meta-analysis. *Journal of Clinical Medicine, 8*(2), 143. https://doi.org/10.3390/jcm8020143

Johns Hopkins University of Medicine. (2022). Testing FAQ: How is COVID-19 diagnosed? https://coronavirus.jhu.edu/testing/testing-faq/overview#how-is-covid-19-diagnosed

Massafra, M., Passalacqua, M. I., Lupo, G., Altavilla, G., & Santarpia, M. (2021). Capillary leak syndrome induced by neoadjuvant cisplatin and gemcitabine in a patient with bladder cancer. *Urology Case Reports*, *34*, 101461. https://doi.org/10.1016/j.eucr.2020.101461

Mertz, P., Lebrun-Vignes, B., Salem, J. E., & Arnaud, L. (2019). Characterizing drug-induced capillary leak syndromes using the World Health Organization VigiBase. *Journal of Allergy and Clinical Immunology, 143*(1), 433–436. https://doi.org/10.1016/j.jaci.2018.09.001

National Organization for Rare Disorders. (2020). Rare Disease Database: Systemic capillary leak syndrome. https://rarediseases.org/rare-diseases/systemic-capillary-leak-syndrome/

Pemmaraju, N., Lane, A., Sweet, K., Stein, A., Vasu, S., Rizzieri, D.,...Konopleva, M. (2021). Tagraxofusp in patients with blastic plasmacytoid dendritic cell neoplasm: Long-term follow-up and additional clinical experience. [Poster presentation]. European Hematology Association (EHA) 2021 Virtual Congress.

Pemmaraju, N., Lane, A. A., Sweet, K. L., Stein, A. S., Vasu, S., Blum, W.,...Konopleva, M. (2019). Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *New England Journal of Medicine, 380*(17), 1628–1637. https://doi.org/10.1056/NEJMoa1815105

Percik, R., Nethanel, A., & Liel, Y. (2021). Capillary-leak syndrome: An unrecognized early immune adverse effect of checkpoint-inhibitors treatment. *Immunotherapy, 13*(8), 653–659. https://doi.org/10.2217/imt-2020-0332

Polishchuk, I., Yakobson, A., Zemel, M., Sharb, A., Shalata, W., Rosenberg, E.,...Kian, W. (2021). Nivolumab-induced systemic capillary leak syndrome as an ultra rare life-threatening phenomenon of late toxicity and intravenous immunoglobulin efficacy. *Immunotherapy, 13*(10), 807–811. https://doi.org/10.2217/imt-2020-0335

Qin, H., Vlaminck, B., Owoyemi, I., Herrmann, S. M., Leung, N., & Markovic, S. N. (2021). Successful treatment of pembrolizumab-induced severe capillary leak syndrome and lymphatic capillary dysfunction. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 5*(3), 670–674. https://doi.org/10.1016/j.mayocpiqo.2021.01.004

Shin, J., Lee, K., Lee, I., Oh, J., Kim, D., Shin, J.,...van der Vliet, H. (2018). Systemic capillary leak syndrome (Clarkson syndrome) in cancer patients: A systematic review. *Journal of Clinical Medicine*, *7*(11), 418. https://doi.org/10.3390/jcm7110418

Siddall, E., Khatri, M., & Radhakrishnan, J. (2017). Capillary leak syndrome: Etiologies, pathophysiology, and management. *Kidney International, 92*(1), 37–46. https://doi.org/10.1016/j.kint.2016.11.029

Stemline Therapeutics, Inc. (2021). Elzonris (tagraxofusperzs) package insert. https://www.elzonris.com/hcp/Content/documents/ELZONRIS_US_Full_Prescribing_Information.pdf

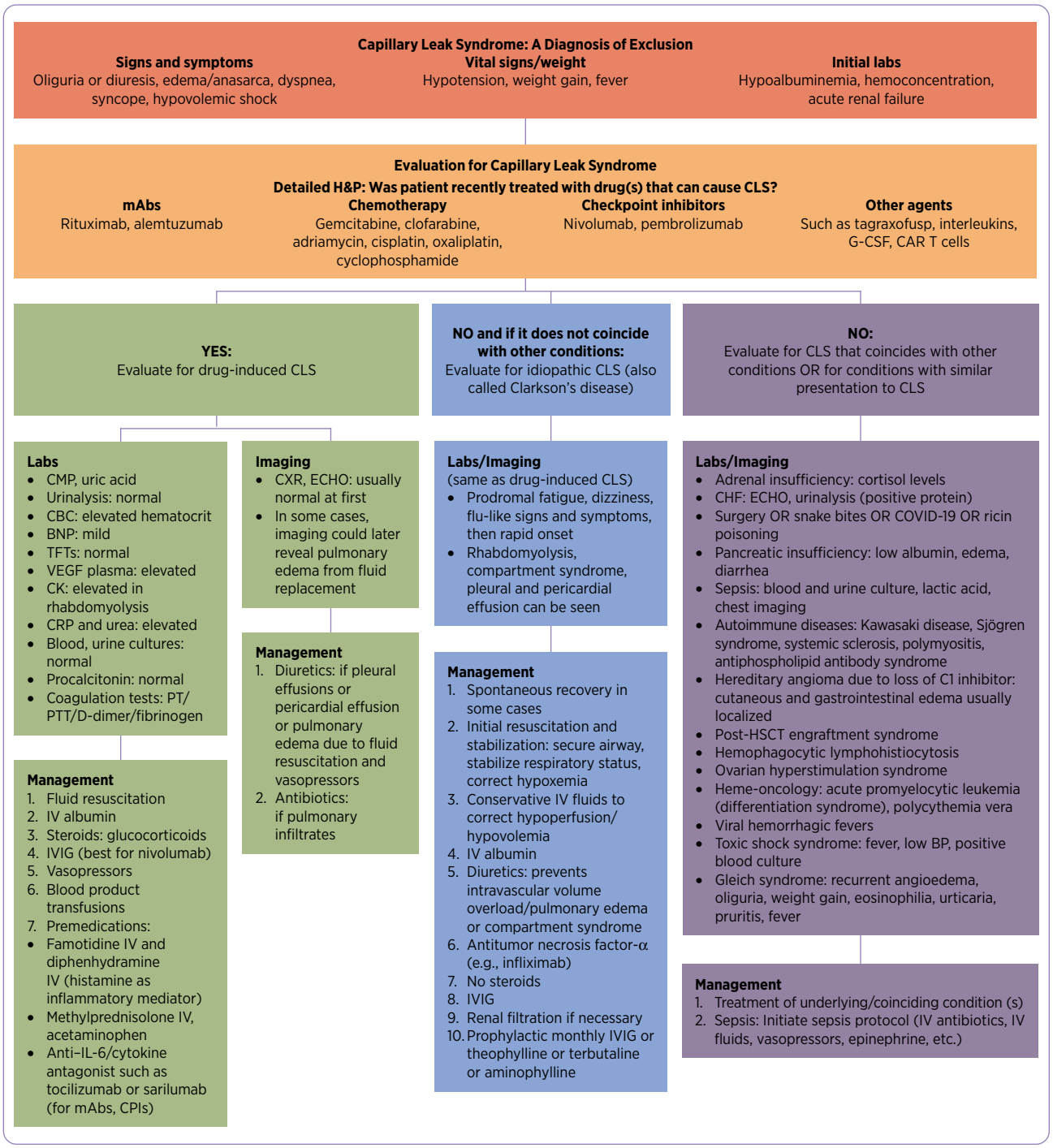

Figure. Algorithmic approach to diagnosis and management of capillary leak syndrome. BNP = brain natriuretic peptide; BP = blood pressure; CAR = chimeric antigen receptor; CBC = complete blood count; CHF = congestive heart failure; CK = creatine kinase; CLS = capillary leak syndrome; CMP = comprehensive metabolic panel; CPI = checkpoint inhibitor; CRP = C-reactive protein; CXR = chest radiography; ECHO = echocardiography; G-CSF = granulocyte colony-stimulating factor; H&P = history and physical; HCT = hematocrit; HSCT = hematopoietic stem cell transplant; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; labs = laboratory assessments; mAbs = monoclonal antibodies; premed = premedication; PT = prothrombin time; PTT = partial thromboplastin time; s/e = side effect; TFT = thyroid function tests; VEGF = vascular endothelial growth factor.