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Case Report

Sorafenib-Induced Capillary Leak Syndrome

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Abstract
Capillary leak syndrome is a rare life-threatening disorder of acute endothelial hyperpermeability. It consists of initial fluid extravasation resulting in hypotension, hypoalbuminemia, and hemoconcentration, followed by noncardiogenic pulmonary edema from rapid fluid remobilization into intravascular compartment. Drug-induced etiology is an important diagnostic consideration in cancer patients, particularly with use of antimetabolites, immunostimulants, and monoclonal antibodies. Sorafenib-mediated capillary leak syndrome has never been reported. Here, we present the case of a 29-year-old female patient with a desmoid tumor of the thigh, who was admitted for acute hypoxic respiratory failure after recent initiation of sorafenib. She was found to have extensive pulmonary edema, bilateral pleural effusions, and hemoconcentration, all of which stabilized on supportive care with noninvasive mechanical ventilation and intravenous diuresis. Her infectious and cardiac work-up were negative. Given the temporal relationship between sorafenib use and symptom onset as well as a lack of an alternative etiology of her findings, patient was deemed to have sorafenib-induced acute capillary leak syndrome. Importantly, she did not become hypotensive prior to or during this hospitalization. To our knowledge, we reported for the first time an atypical presentation of acute capillary leak syndrome due to sorafenib use without hemodynamic instability.

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Introduction

Capillary leak syndrome can be a fatal condition with hemodynamic collapse from fluid extravasation due to increased vascular permeability, followed by flash pulmonary edema from fluid remobilization into intravascular space [1, 2]. It is often idiopathic (also known as Clarkson's disease), but it can be secondary to various infectious and inflammatory insults that compromise the vascular endothelial barrier. In oncology, a drug-induced etiology is a critical diagnostic consideration due to the effects of various immunotherapeutic and chemotherapeutic agents on endothelial cell behavior and direct cytotoxicity. Here, we present the first reported case of sorafenib-induced capillary leak syndrome with predominantly respiratory complications. Purpose of this case report is to raise awareness of an atypical presentation of capillary leak syndrome as a rare side effect of sorafenib, clinical suspicion for which is critical to its early diagnosis and improved outcome.

Case Report

A 29-year-old female with a desmoid tumor of the thigh and no other significant medical history presented to the hospital with acute hypoxic respiratory failure 10 days after initiation of sorafenib. She was recently diagnosed with desmoid fibromatosis (smooth muscle actin and beta-catenin positive) of the proximal right thigh. Surgical resection was considered high risk given the close proximity of the poorly marginated mass to femoral neurovascular bundle and abutting femur. Next-generation sequencing (NGS) testing was notable for a hotspot beta-catenin (*CTNNB1*) mutation (p.S45F, c134C>T) and a heterozygous-level receptor tyrosine-protein kinase erbB-2 (*ERBB2*) mutation (p.N857S, c.2570A>G). She was started on 200 mg sorafenib daily with 200 mg celecoxib twice daily [3, 4] 1 week prior to presentation and remained on this therapy up until the day of admission. During this time, she experienced worsening headaches and dyspnea with increasing diastolic blood pressure readings at home with the highest measurement of 147/108. Additionally, she had chest pressure as well as nausea and an episode of emesis. She denied fever, chills, congestion, rhinorrhea, coughs, orthopnea, and lower extremity swelling.

Upon arrival in the emergency department, she was afebrile, tachycardic but hemodynamically stable. Her oxygen saturation was 86% on room air with an improvement to 92% on 5 L of oxygen through nasal canula. Physical exam findings were notable for an acutely distressed appearance, tachycardia, diminished bilateral breath sounds with crackles, as well as 1+ pitting edema in bilateral lower extremities. Initial chest radiograph showed diffuse hazy and interstitial opacities including Kerley B lines (Fig. 1, left). Complete blood count was significant for total white blood cell (WBC) of 3,710 cells/μL (reference range: 3,990–11,190/μL), hemoglobin 18.3 g/dL (11.4–15.2 g/dL), hematocrit of 52% (34.9–44.3%), and platelet count 128,000/μL (150,000–393,000/μL). Comprehensive metabolic panel and liver function tests including albumin were unremarkable. Urine analysis was unremarkable and without proteinuria. Additional laboratory findings included elevated high-sensitivity D-dimer 3.11 μg/mL (<0.50 μg/mL), but normal qualitative beta-human chorionic gonadotropin, high-sensitivity troponin <3 ng/L (≤34 ng/L), B-type natriuretic peptide 4 pg/mL (≤100 pg/mL), and thyroid stimulating hormone 1.816 uIU/mL (0.550–4.780 μIU/mL). Chest computed tomography with contrast showed extensive pulmonary edema with bilateral effusions (Fig. 2). Electrocardiogram demonstrated sinus tachycardia without other abnormalities. Trans-thoracic echocardiogram showed reduced left ventricular size suggestive of reduced filling, but otherwise global systolic function and regional wall motion were normal with an

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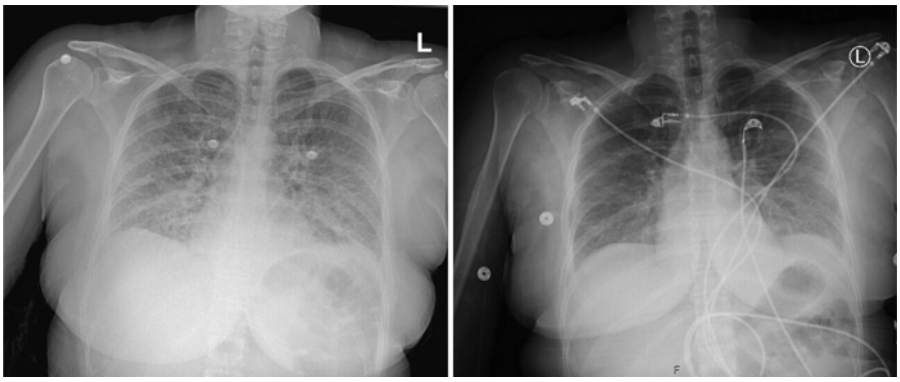

Fig. 1. Chest radiographs from days 0 (left) and 1 (right), demonstrating rapid improvement of diffuse bilateral pulmonary edema.

ejection fraction of 63%. Right ventricle as well as right and left atria were normal in size and function with intact valves. Respiratory infectious work-up including COVID-19 and influenza A/B was negative.

Given the lack of an alternative etiology for acute hypoxic respiratory failure, non-cardiogenic pulmonary edema, bilateral pleural effusions, and hemoconcentration, patient was deemed to have an acute capillary leak syndrome due to sorafenib use. She was briefly on continuous positive airway pressure for ventilatory support, but otherwise remained hemodynamically stable throughout her hospital course. She received 40 mg intravenous furosemide on day 0, but the dose was increased to 80 mg on days 1–3 to optimize her urine output to achieve net negative 500 cc fluid balance. Her respiratory status and pulmonary edema improved (Fig. 1, right) with continuous positive airway pressure and intravenous furosemide, and she was weaned to nasal cannula by day 2. By day 4, she no longer required supplemental oxygen. By day 5, she was discharged on oral furosemide with outpatient follow-up. Her symptoms did not recur after discontinuation of sorafenib. She has started methotrexate and vinblastine with the goal of pain relief and cytoreduction. Patient continues to have stable tumor burden on imaging.

Discussion

We describe a 29-year-old female who presented with acute hypoxic respiratory failure within 10 days after initiating sorafenib for her desmoid tumor of the thigh. Her extensive pulmonary edema and hemoconcentration were consistent with an acute capillary leak syndrome with rapid resolution following discontinuation of sorafenib, as evidenced by stabilization of her respiratory status on supportive care with noninvasive mechanical ventilation and intravenous diuresis. Her diagnostic studies, including an electrocardiogram and echocardiogram, did not suggest acute myocardial ischemia, myocarditis, valve dysfunction, arrhythmia, drug-induced cardiomyopathy, or other derangements concerning for cardiogenic etiology. Patient's infectious work-up was also negative. A timeline of her hospital course is shown in Figure 3. Patient and her family were highly anxious of her rapidly progressing respiratory distress, but grateful for her recovery without the need for invasive measures, including intubation.

Capillary leak syndrome is a rare disorder characterized by systemic fluid extravasation into interstitial compartments [1, 2, 5]. It consists of three phases: (i) prodromal phase with nonspecific symptoms, (ii) fluid extravasation (leak) phase with a triad of severe hypotension,

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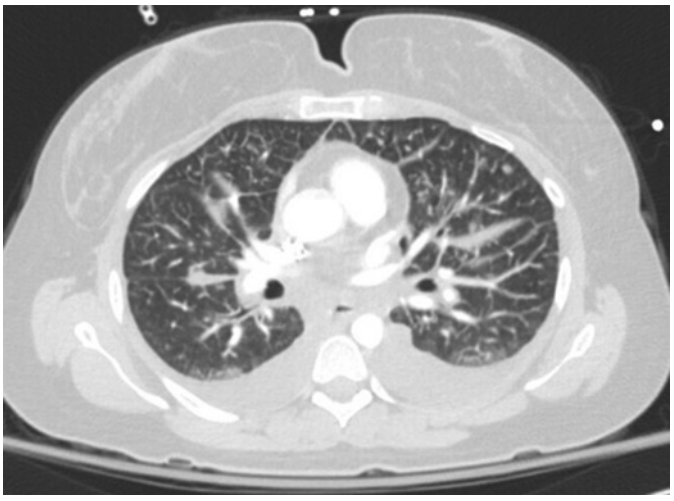

Fig. 2. Chest computed tomography on day 0 demonstrating extensive pulmonary edema with bilateral effusions.

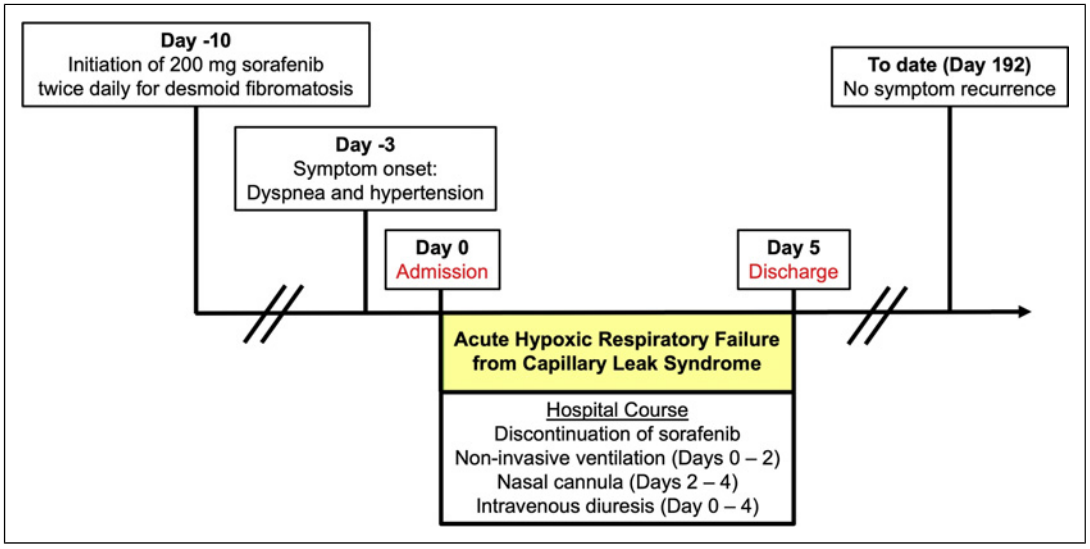

Fig. 3. A timeline of the patient's hospital course. Patient was hospitalized for acute hypoxic respiratory failure from capillary leak syndrome related to sorafenib use. In addition to drug discontinuation, noninvasive positive pressure ventilation (later weaned to nasal cannula) and intravenous diuresis were administered for her life-threatening pulmonary edema. Immunosuppression was not needed inpatient given symptom resolution with more conservative therapies. Patient was discharged home without supplemental oxygen requirement. She has not shown evidence of symptom recurrence to date, most recently on day 192 at the time of case report preparation.

hypoalbuminemia in the absence of albuminuria, and hemoconcentration, and (iii) fluid recruitment (post-leak) phase with fluid remobilization into vascular space [5]. It is often an idiopathic disease, though it can be observed in sepsis, autoimmunity, differentiation syndrome on induction therapy with all-trans retinoic acid (ATRA) for acute promyelocytic

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leukemia, ovarian hyperstimulation syndrome, hemophagocytic lymphohistiocytosis, viral hemorrhagic fever, and other inflammatory conditions [2]. Drug-induced etiologies are an important diagnostic consideration, particularly with chemotherapeutic agents like gemcitabine and clofarabine, as well as immune-modulators including IL-2, OKT3, anti-CD28, and rituximab [2, 6, 7]. While the details of each underlying mechanism are unclear, they collectively involve increased vascular permeability via endothelial cell dysfunction or direct cytotoxicity [2]. Rapid fluid shifts in capillary leak syndrome can be fatal from a variety of mechanisms including hypovolemic shock with intravascular depletion and acute hypoxic respiratory failure from flash pulmonary edema, necessitating a high level of clinical suspicion for prompt diagnosis, drug removal, and supportive care. This patient's acute hypoxic respiratory failure in the setting of extensive bilateral pulmonary edema is most consistent with the post-leak phase of capillary leak syndrome. Of note, patient did not develop hypotension or signs of organ failure from hypoperfusion before or during this hospital course. Hypotension is one of the most frequently observed signs of capillary leak syndrome which can be seen in nearly 80% of the cases [8]. This observation raises the intriguing possibility that capillary leak associated with sorafenib could manifest in an atypical manner without hemodynamic instability. Severe hemodynamic compromise is frequently associated with pericardial effusion or cardiac tamponade that necessitates drainage with pressor support and rarely extracorporeal membrane oxygenation [9–12], but neither was observed with our patient. Current candidate therapies for capillary leak syndrome, including intravenous immunoglobulins, steroids, terbutaline, theophylline, and biologics [13], were not needed inpatient given her rapid improvement on conservative measures.

Sorafenib is an oral multi-targeted tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, platelet-derived growth factor (PDGFR)-β, c-Kit, and rearranged during transfection (RET), as well as their downstream rapidly accelerated fibrosarcoma (Raf) kinase [14]. Sorafenib-mediated inhibition of multiple signal transduction kinases may preferentially regulate the balance between vasoconstrictors and vasodilators within the pulmonary vasculature. To this end, vascular endothelial growth factor (VEGF), angiopoietin-2, and C-X-C motif chemokine ligand 10 have previously been implicated in systemic capillary leak syndrome [15]. In particular, several case reports have demonstrated elevated VEGF levels during acute episodes of systemic capillary leak syndrome [16, 17], although our patient had a normal VEGF level of 21.0 pg/mL (<96.2 pg/mL). In light of the previous report illustrating rapid improvement of systemic capillary leak syndrome on a 5 day course of 5 mg/kg/day dosing of bevacizumab (a humanized anti-VEGF monoclonal antibody) [18], the mechanism behind capillary leak syndrome due to sorafenib, which also blocks VEGFR, remains to be determined. Our case argues that the pathophysiologic mechanisms underlying sorafenib-induced capillary leak syndrome may be distinct from that of previously known capillary leak syndromes.

Importantly, sorafenib is approved by the US Food and Drug Administration (FDA) for broad use in the treatment of solid malignancies, including advanced renal cell carcinoma [19], hepatocellular carcinoma [20–22], and radioactive iodine-resistant advanced thyroid carcinoma [23]. Despite the growing appreciation for immunotherapy as an effective treatment modality for various malignancies such as hepatocellular carcinoma [24–26], sorafenib and other tyrosine kinase inhibitors remain widely used with currently over 50 medications with FDA approval. Our case highlights a rare adverse event with sorafenib that clinicians must closely monitor in addition to its more frequent constitutional, gastrointestinal, and dermatologic dose-limiting toxicities as it can be potentially fatal if left undiagnosed [27]. Of note, while sorafenib has also been implicated with cardiotoxicity [28] and acute interstitial pneumonia [29], neither condition was observed in our patient. Since the discontinuation of sorafenib, patient has not redemonstrated symptoms or signs of capillary

leak syndrome on outpatient follow-ups. Given that patient continued to take celecoxib and the tumor burden remains stable, they appear as less likely etiologies at this time. Also, it is worth noting that patient's symptoms and signs developed only a week after initiation of sorafenib. While the prevalence of sorafenib-related adverse events increases over time, they have been shown to occur as early as within the first 2 weeks of treatment as previously observed with hand-foot skin reaction, hypertension, and diarrhea in nearly 30% of patients in a retrospective single-institutional analysis [30]. The mean half-life of sorafenib can range from approximately 25–48 h, but it has significant interpatient variability owing to hepatic CYP3A4-mediated oxidative metabolism and UGT1A9-dependent glucuronidation, as well as enterohepatic circulation [31]. Given that no apparent relationship has been observed between onset or severity of toxicity and plasma concentration of sorafenib [32, 33], it is currently unclear if the capillary leak syndrome is driven by its direct endothelial cytotoxicity or indirect cytokine-mediated effects.

While this is the first case report of sorafenib-induced capillary leak syndrome to the best of our knowledge, four reports exist on suspected capillary leak syndrome out of 31,541 reports (0.01%) on all adverse reactions to sorafenib from the review of VigiBase (http://www.vigiaccess.org/), which is the World Health Organization's individual case safety report database. Given the rarity and nonspecific symptoms as well as the atypical presentation of sorafenib-induced capillary leak syndrome, this frequency may be underestimated and necessitates further investigation. Also, future research is needed to determine optimal treatment strategies in the event of suspected capillary leak syndrome with dose reduction versus temporary interruption of sorafenib therapy. In the absence of a therapeutic algorithm due to limited data on capillary leak syndrome, permanent cessation of sorafenib should be considered based on individual patient characteristics, risk of recurrence, and alternative treatment options. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533957).

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Ethics

Authors declare no competing interests in the publication of this work.

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Author Contributions

H.K. wrote the manuscript and reviewed the pertinent literature. J.O., M.H., and D.A.L. provided helpful discussion, critical reading, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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