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Teaching Case

Effectiveness of Single-Fraction, Low-Dose, Bilateral Whole Lung Radiation Therapy for Diffuse Alveolar Hemorrhage Secondary to Extramedullary Hematopoiesis: A Case Report and Review of the Literature

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Introduction

Extramedullary hematopoiesis (EMH) is an uncommon phenomenon that arises following inadequate blood cell production from the bone marrow. Bone marrow dysfunction can be caused by several etiologies including various hereditary genetic hematologic abnormalities (eg, thalassemia), hemolytic anemias, certain infectious diseases, autoimmune disorders (eg, immune thrombocytopenic purpura), primary myelofibrosis, and myeloproliferative neoplasms (eg, polycythemia vera, essential thrombocytopenia, chronic myeloid leukemia, and primary myelofibrosis). All of these etiologies typically trigger either overproduction or proliferation of one of more blood cell lines, hypercellular or fibrotic bone marrow, frequent characteristic cytogenetic abnormalities, and hemostasis disorders (ie, thrombosis or hemorrhage). They can even trigger transformation into malignant neoplasms.

Most commonly, EMH arises in the liver and spleen, but it can occur in other tissues as well, including the lungs or spine. EMH can form at a single site or multiple sites and cause diffuse nodularity in one or more organs. These lesions are prone to bleeding, and when diffusely present within the lungs, diffuse alveolar hemorrhage (DAH) can occur. When this arises, it creates a complex, potentially life-threatening complication that is often difficult to treat.

Prior reports have described the causes and treatment options for EMH, which include medications, surgery (most commonly splenectomy in the setting of splenic EMH), and involved field radiation.[1] Specifically, a small number of case reports have described instances where myelofibrosis and EMH were effectively treated with low-dose radiation.[2-4] In one letter to the editor, a patient, who was also a physician himself, described his own experience having myelofibrosis that suddenly progressed and was complicated by EMH, which caused DAH and acute respiratory distress syndrome (ARDS) requiring

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intubation and mechanical ventilation. He was treated with a single 100 cGy dose of radiation to his lungs, and 4 days later, he was able to be extubated and was discharged shortly thereafter.[4] The standard of care at Mayo Clinic is to treat patients with pulmonary EMH with low-dose (100 cGy), single-fraction, whole-lung irradiation.

Herein, we describe a patient with life-threatening DAH that progressed to ARDS and acute respiratory failure requiring intubation. Treatment with concurrent intravenous cytarabine and a single fraction of low-dose, bilateral, whole-lung radiation resulted in a rapid clinical improvement.

Case Presentation

A 64-year-old male patient presented to our emergency department with acute onset chronic fatigue, pallor, and shortness of breath.

History of Present Illness

His past medical history was significant for JAK2-mutated polycythemia vera, diagnosed approximately 5 years prior. Since his diagnosis of polycythemia vera, he required intermittent therapeutic phlebotomy and was treated with hydroxyurea for approximately 4 years. Over 1 year before presentation, he was transitioned to ruxolitinib. Baseline blood counts included a hemoglobin of 14 g/dL and white blood cell count of 30,000 to 40,000/uL.

Before his presentation to the emergency department, he had spent the prior 10 days admitted at an outside hospital for similar symptoms. He was noted to have bilateral lung infiltrates on chest computed tomography (CT) and was started on broad-spectrum antibiotics, antifungals, and steroids for presumed infectious pneumonia of unclear etiology. Ultimately, his infectious workup was negative; however, he continued to be hypoxic and required high-flow nasal cannula during his admission. There was concern for possible development of acute myeloid leukemia (AML), and he underwent a bone marrow biopsy. His hospitalization was also complicated by acute kidney injury. After 10 days in the hospital, his respiratory symptoms stabilized, but he continued to require supplemental oxygen, and he was discharged on 2 to 3 L via nasal cannula.

On Presentation

The patient's ongoing symptoms prompted him to present to our emergency department. He reported having significant fatigue and shortness of breath. His family had noticed increasing pallor and somnolence at home before presentation. He denied having cough, chest pain, palpitations, or abdominal pain.

On presentation, he was somnolent but arousable to voice. He was afebrile, borderline tachycardic with heart rate in the 90s, and hypertensive, with a blood pressure of 150/90. His oxygen saturation was in the mid-90s despite him being on 10 L of supplemental oxygen via nonrebreather mask. Laboratory studies were significant for white blood cells of 100.25×10^3 (normal: 4.16-9.95×10^3/uL); hemoglobin, 10.8 (normal: 13.5-17.1 g/dL); platelets, 241×10^3 (normal: 143-398×10^3/uL); lactate dehydrogenase, 2425 (normal: 125-256 U/L); D-dimer, 2.35 (normal < 0.60 ug/mL); lactate, 23 (normal 5-25 mg/dL); and procalcitonin, 0.78 (normal < 0.1 ug/L). A chest CT angiogram was ordered to rule out pulmonary embolism, which demonstrated diffuse interlobar septal thickening with coalescent ground-glass attenuation of the upper lung and dependent consolidative densities in both lungs concerning for severe pulmonary edema, trace bilateral pleural effusions, and subsegmental atelectasis of bilateral lower lobes. No evidence of pulmonary embolism was identified. CT of the abdomen and pelvis demonstrated marked hepatosplenomegaly of unclear etiology. He was started on broad-spectrum antibiotics with vancomycin, cefepime, and azithromycin.

With concern for possible infectious etiology, Infectious Disease was consulted, and a comprehensive infectious workup was initiated, particularly to rule out alternative atypical infections, which included MRSA nares screening, respiratory pathogen panel polymerase chain reaction (nasopharyngeal and included COVID-19), hepatitis B antigen and antibodies, hepatitis C virus antibodies, HIV 1/2 antigen and antibodies, Cryptococcal antigen, Legionella antigen, Aspergillus antigen, Histoplasma antigen, Strongyloides antibodies,[1,3]-Beta-D-Glucan (Fungitell) assay, and bacterial blood culture. Notably, his Coccidioides IgM was positive at 0.477 (normal: <0.150), and Cocci TP Ab was indeterminate; however, all other Coccidioides testing was negative, including Coccidioides IgG and Coccidioides antibody (complement fixation). Coccidioides IgM has a high false positive rate; therefore, confirmatory testing was pursued. He was started on fluconazole (400 mg every other day) for empirical treatment while confirmatory tests were pending, given his immunocompromised status and high likelihood of prior exposure. He was also continued on cefepime, vancomycin, trimethoprim/sulfamethoxazole, and azithromycin, as well as acyclovir for possible bacterial, viral, or fungal pneumonia.

On Hospital Day 2, vancomycin and trimethoprim/sulfamethoxazole were discontinued. He underwent bone marrow biopsy. He also started to require blood transfusions (Hgb of 7.8 with protocol to transfuse if Hgb <8) and received a unit of packed red blood cells (pRBC).

On Hospital Day 3, chest x-ray revealed unchanged patchy and confluent ground-glass and air space

attenuation involving the left greater than right lung, consistent with capillary leak edema, pulmonary hemorrhage, and/or multifocal pneumonia. He received an additional unit of pRBC.

Over the next several days, he developed worsening hypoxic respiratory failure and acute kidney injury thought to be secondary to auto-tumor lysis syndrome and volume overload. He was started on methylprednisone for worsening respiratory status. A bronchoscopy showed DAH. He was started on inhaled tranexamic acid and aminocaproic acid. He continued to require a unit of pRBC daily, and on Hospital Day 6, a unit of platelets was also transfused, as his platelets had dropped to 67 $\times$ 10^3/uL, and he had ongoing active bleeding.

Given his new diagnosis of DAH, a broad differential diagnosis was considered and included possible autoimmune causes (although no obvious systemic symptoms), infectious causes (although patient was afebrile and with infectious workup largely negative), or exogenous exposures from drug/medication-related side effects (the patient recently started on ruxolitinib, with no history of cocaine use). A complete evaluation was initiated with rheumatology, infectious disease, and hematology/oncology teams consulted to assist in identifying the etiology of his DAH. The infectious disease workup initiated on his admission was expanded with additional bronchoalveolar lavage (BAL) studies, including a Gram stain that demonstrated no bacteria, few white blood cells, and many red blood cells. The remaining BAL infectious workup was negative and included acid fast stain, respiratory pathogen panel polymerase chain reaction, bacterial culture, fungal stain and culture, Legionella culture, pneumocystis direct detection assay (sputum and BAL), and Nocardia culture. Urine analysis and bacterial culture were also negative, as well as repeat blood fungal and bacterial cultures and cytomegalovirus DNA polymerase chain reaction.

Inflammatory markers were elevated, including erythrocyte sedimentation rate at 15 (normal, ≤12 mm/h), C-reactive protein at 9.6 (normal, <0.8 mg/dL), and ferritin at 2,564 (normal, 8-350 ng/mL). However, the remaining rheumatologic workup was negative, including C-ANCA, *P*-ANCA, proteinase-3 antibody, myeloperoxidase antibody, ANA, anti-GBM IgG, cryoglobulins, rheumatoid factor, cardiolipin antibody, total CK, cyclic citrulline peptide antibody/IgG, C3, C4, dsDNA antibody, SSA/SSB antibody, Sm/RNP antibody, histone antibody, Beta-2-glycoprotein antibodies, aldolase, centromere antibody, Jo-1 antibody, Scl-70 antibody, MI-2 autoantibody, myositis panel (HMGCR antibody), and direct antiglobulin test. Urine drug screening was also negative.

On Hospital Day 7, in the late afternoon, he had worsening hypoxia and ultimately required intubation.

On Hospital Day 8, peripheral blood smear showed a leukocytosis, including numerous left-shifted myeloid cells with abnormal granulation. Macrocytic anemia and thrombocytopenia were also noted. Bone marrow biopsy demonstrated markedly hypercellular marrow (95% cellularity) with increased blasts with a myeloid predominance. Moderate bone marrow fibrosis was noted (MF score, 2 out of 3) with reduced erythroid and megakaryocytic hematopoiesis. Flow cytometry studies revealed no excess level of blasts but did note the presence of myeloblasts (3% of total) with left-shifted granulopoiesis. Further cytogenetic testing revealed inversion of chromosome 16 (inv(16)). Molecular testing revealed mutations in ASXL1, DNMT3A, JAK2, TET2, and NOTCH1 (VUS). Taken together, these studies were suggestive of AML with inv (16), which can present with a low blast count. He required 4 units of pRBC and 1 unit of platelets.

Given his acute status in the setting of a newly confirmed diagnosis of AML and known JAK2-mutated polycythemia vera, the etiology of his DAH was determined to be EMH in the lungs secondary to AML. He was started on cytarabine (Hospital Day 8, Chemo Day 1) and continued on his home ruxolitinib (reduced dose given concurrent use of fluconazole). Radiation oncology was consulted to explore the potential for concurrent, low-dose radiation therapy (RT). The multidisciplinary consensus was to treat with a single fraction of 100 cGy delivered AP/PA to the bilateral lungs using a clinical setup (Fig. 1). He was also continued on intravenous aminocaproic acid and inhaled tranexamic acid.

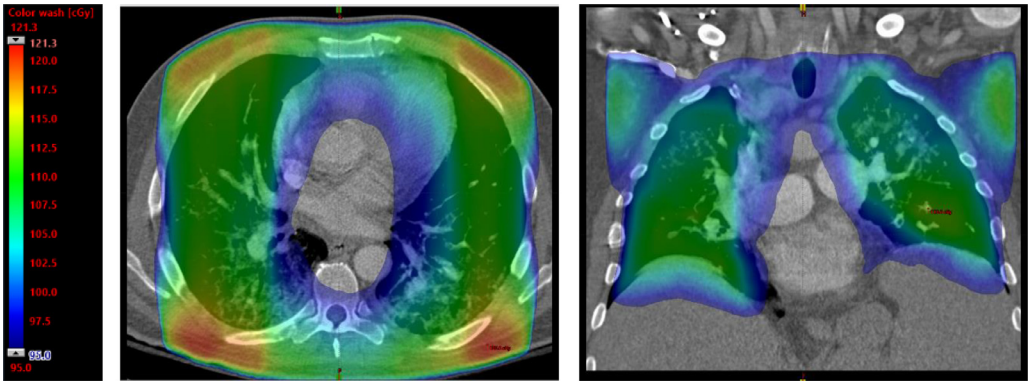

Figure 1 Reconstructed clinical setup fields delivering 100 cGy to bilateral, whole lungs.

He completed a 5-day course of daily IV 500 mg cytarabine. The initial plan was to complete low-dose RT on day 2 of this course, but unfortunately, he was not stable enough for transport to the radiation oncology department, as he required 3U pRBC and 2U platelets and was found to be acidotic, prompting initiation of continuous renal replacement therapy. He stabilized over the next 2 days and was able to undergo RT as planned on Hospital Day 11 (Chemo Day 4).

The day after receiving RT, he underwent repeat bronchoscopy with no signs of active bleeding and was able to be extubated. Tranexamic acid and aminocaproic acid were discontinued. For the next several days, he was continued on continuous renal replacement therapy, antibiotics, and an extended prednisone taper with intermittent requirement for pRBC and platelet transfusions.

Antibiotics and antifungals were discontinued 2 days later (Hospital Day 14) because of elevated liver function testing, and the next day, confirmatory tests for Coccidioides were negative.

Six days after completion of RT (Hospital Day 17), he was stable and was discharged from the ICU. He was continued on ruxolitinib and extended prednisone taper. Over his 17-day hospitalization, he required 14 total units of pRBC and 12 total units of platelets (10U pRBC and 6U platelets before RT and 4U pRBC and 6U platelets after RT).

One month after hospital discharge, he underwent a repeat bone marrow biopsy with 2% myeloblasts and 2% signal of inv(16) with persistence of the genetic mutations noted above. The diagnosis of AML was confirmed, and treatment was initiated with plans for future bone marrow transplantation.

Discussion

The use of low-dose, single-fraction whole-lung radiation to treat pulmonary EMH has been used at Mayo Clinic for many years with good safety and efficacy profiles, with 50% to 70% of patients experiencing symptomatic improvement and a significant increase in overall survival being observed.[2,5-7] If the initial course of RT is not efficacious, additional courses of RT (potentially with higher doses) can be administered. In patients who responded to the initial course of RT, their response was often sustained and without long-term toxicity or complications. Herein, we describe an emergent case where a patient experienced acute respiratory failure due to DAH secondary to EMH with rapid clinical improvement following a 5-day course of cytarabine with a concurrent, single fraction of 100 cGy radiation to the bilateral lungs. This case corroborates the promising results described by Mayo Clinic, which have shown that low-dose RT is an effective treatment for EMH and improves patient overall survival in this setting, while expanding upon their experience by demonstrating the safety and efficacy of this regimen when given with concurrent chemotherapy.

Whole-lung irradiation is rarely used in the setting of adult malignancies; however, it is regularly used in several pediatric malignancies, including Ewing sarcoma, rhabdomyosarcoma, and Wilms tumors, and is often prescribed at much higher radiation doses (1200-1500 cGy) than described in this case. Low-dose bilateral whole-lung irradiation has also been explored as a possible treatment for viral and bacterial pneumonias (most recently in clinical trials examining its efficacy against COVID-19 infections) with mixed results in regard to efficacy, but with little to no toxicity consistently observed.

Radiation is well established as a highly efficacious treatment option for EMH, particularly when it occurs in the spleen; however, radiation of the spleen can cause pancytopenia. This has limited the use of splenic irradiation, and additional systemic therapies have been developed. In contrast, hematologic cytopenias have not been reported following low-dose bilateral whole-lung RT. This may be because of earlier detection of EMH within the lungs and with decreased reliance on EMH in the lung for blood production, or the particularly low doses of RT used for treatment in this setting (often as low as a single 100 cGy fraction versus splenic irradiation regimens typically treating between 400-1000 cGy over the course of 1-2 weeks). However, there have only been a limited number of cases using low-dose bilateral whole-lung RT in the literature, so it is also possible that cytopenias could be noted as a possible treatment-related complication in the future.

Overall, this case highlights the importance of early identification and rapid treatment of pulmonary EMH and redemonstrates the efficacy and safety of low-dose, whole-lung RT for pulmonary EMH, uniquely in the context of concurrent intravenous cytarabine.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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