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CLINICAL VIGNETTE

A Fine Balance: Managing End of Life Symptoms in a Patient with Metastatic Cancer and Sickle Cell Disease

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Case Description

A 27-year-old woman with Sickle Cell Disease (SCD) had been diagnosed four years previously, with squamous cell cancer (SCCA) of the larynx. Despite multiple cycles of disease-directed treatment, her metastatic disease progressed to involve the liver. In the six months prior to her final admission to hospital, the patient's clinical status had progressively deteriorated and she experienced increased pain, both related to the SCD and to the metastatic cancer, ascites, pleural effusions and other stigmata of end stage liver disease. She was also treated for infections and sepsis.

Additionally, the patient was profoundly fatigued and emotionally distressed as she realized that she was dying. She was followed regularly for pain and symptom management by outpatient palliative care. Her pain was relatively well controlled with transdermal fentanyl 50 mcg/hr. q 72 hours, methadone 5 mg QID, PO hydromorphone 8 mg to 16 mg Q 3 hours PRN, and pregabalin 75 mg BID. During outpatient palliative care visits, the patient repeatedly declined to engage in goals of care discussion saying, "I don't want to talk about anything that will make me sad".

Two weeks prior to her final admission, the patient was hospitalized with increased abdominal pain, fever and ascites and treated empirically for spontaneous bacterial peritonitis with ceftriaxone and metronidazole. After discharge, she and her mother visited her treating oncologist who, in light of the patient's ongoing deterioration and tumor progression during chemotherapy, initiated a goals of care discussion. The oncologist recommended DNR/DNI status. In response, the patient replied that she had been considering it, but did not want "to give up". Despite the oncologist's explanation that electing DNR/DNI status in the setting of advanced, terminal illness was not "giving up", the patient requested all possible treatment for life extension and reiterated that she desired further disease-directed treatment.

Her back and abdominal pain worsened significantly, despite increases in pain medications and she presented to the ER for evaluation.

Upon arrival at the ER, she was alert, oriented and conversant. Her vital signs were T 36.6, HR 109, BP 110/71, SpO2 99% on RA. Notable laboratory values were albumin 2.7, total protein 5.5, total bilirubin 8.8, conjugate bilirubin 6.3, alkaline phosphatase 450, aspartate amino transferase 234. WBCs were 43.77 with 81.2% neutrophils, hemoglobin was 9.2 and platelets were 133. INR was 1.7. CT of the abdomen done during the previous admission showed at least moderate ascites, pleural effusions, anasarca of the abdominal wall and hepatomegaly due to confluent areas metastatic disease. The bile ducts appeared markedly dilated, likely due to compression from metastases.

The patient was admitted to hospital and pain management was initiated via IV hydromorphone PCA. IV fluids were started in efforts to prevent a sickle cell crisis. The patient's transaminitis worsened while her leukocytosis remained stable in the range of 30k. The patient's pain came under better control, but her mental status began to deteriorate. Goals of care discussion took placed on hospital day 3 with the hospitalist attending. Again, the patient reiterated her strong desire to receive all available treatments to prolong life even if they increased her pain and symptom burden.

On hospital day 4, MRCP demonstrated bile duct obstruction due to worsening compression from metastatic disease. However, the ducts were judged by GI to be too narrow for stenting.

By hospital day 5, the patient's mental status had deteriorated to the point that she was unable to participate in both goals of care discussion and in medical decision-making. Her mother, therefore, acted as her healthcare proxy. Goals of care discussion took place between the patient's mother, the hospitalist team and the palliative care team. The patient's mother decided to make her DNR/DNI and to initiate comfort measures. She was placed on an IV methadone infusion with bolus doses of IV hydromorphone, and IV lorazepam. The patient's fluid balance was carefully monitored, clinically. She died peacefully in her mother's arms on the morning of the eighth hospital day while being examined by the palliative care team.

Discussion

Sickle Cell Disease (SCD) refers to a group of genetic disorders caused by a point mutation in the genes coding for the polypeptide chains in the metalloprotein hemoglobin, the tetrameric oxygen transport macromolecule found in the red blood cells of most vertebrates. These illnesses, transmitted from one generation to the next via an autosomal recessive pattern of inheri-

tance, result from changes in hemoglobin's physico-chemical characteristics causing red blood cells to change shape, becoming crescent like "sickle cells", particularly under oxygen stress. These stiff, eccentrically shaped red blood cells occlude small arteries and arterioles resulting in ischemia, endothelial dysfunction and their sequelae. In addition to agonizing "pain crises" that increase in duration, frequency and intensity with the patient's age, vaso-occlusion by sickled red blood cells leads to hemolysis, chronic anemia and, not infrequently, iron deposition disorders from repeated RBC transfusions. Each of these processes contributes to the end organ damage and reduced life expectancy associated with SCD, particularly the SS variant.[1]

While there are treatments for SCD and its sequelae - most notably, hydroxyurea and deferoxamine - that increase both quality and years of life, many patients, as they "age out" of the pediatric SCD treatment programs, discontinue them and are lost to regular follow up by a hematologist. The only definitive cure for SCD presently available is bone marrow transplantation, a therapeutic option open to a tiny fraction of affected patients.

This case highlights a number of clinical issues important in end of life care. 1. Nuanced management of competing illnesses, end stage liver disease (ESLD) due to metastatic cancer, and SCD. 2. Pain management in a patient who was opioid tolerant requiring high doses of opioid pain medications. 3. Compassionately, yet realistically, addressing end of life care in a young patient who had not yet come to terms with her impending death.

This patient carried the stigmata of ESLD due to overwhelming hepatic tumor burden and possibly due to iron deposition. She had large volume ascites and pleural effusions, anasarca, and increased INR with abdominal distension, pain and dyspnea. End of life symptom management typically involves fluid restriction, often gentle diuresis, in an effort to reduce the volume of the effusions. However, this patient's relative dehydration, due to both lack of PO intake and intravascular volume depletion resulting from hypoalbuminemia, placed her at increased risk of developing a painful sickle cell crisis while actively dying. As such, intermittent boluses of IV fluid (500 cc NS) were administered to prevent this distressing complication, with frequent clinical monitoring of volume status.

In end of life symptom control, a state of relative dehydration often produces the greatest comfort, particularly facilitating free and unlabored breathing. As such, management of this patient's end of life symptoms involved a maintaining a balance between relative dehydration, to treat the abdominal wall edema, ascites and pleural effusions contributing to her dyspnea and abdominal pain, and hydration, to reduce to risk of a painful sickle cell crisis.

Interestingly, the role of hydration in the prevention and treatment of sickle cell crises has not been confirmed by evidence based studies, which may suggest new clinical strategies for the management of patients such as this one.[2]

The patient had experienced pain related to SCD and its sequelae since early childhood and was tolerant to opiod and centrally sensitized. Her central nervous system had up regulated the pain processing network. Prior to admission, the patient's pain was managed with a combination of transdermal fentanyl 75 mcg/hr. patch q 72 hours, PO methadone 5 mg QID and PO hydromorphone 8 mg – 16 mg q 3 hours PRN. In hospital, her pain management continued with an IV hydromorphone PCA, but as her mental status deteriorated and she became incapable of using a PCA machine, the patient was rotated to an equal analgesic IV methadone infusion. IV methadone was the agent of choice because it is the longest acting IV opioid available and, it was hoped, this would provide the most constant pain relief. It was also felt that methadone's action at the N-methyl-d-aspartate (NMDA) receptor might make it a more effective therapeutic option in the setting of both pain from SCD and from metastatic cancer, where significant neuropathic injury underlies the pain. Finally, the back-up plan in the event of an SCD pain flair during the actively dying process was to have available a potent and long acting opioid to manage the pain while initiating sedation regime to maintain comfort.

The patient's youth, her determination "not to give up" and her reluctance to discuss "anything that makes me sad" caused goals of care discussions to be both challenging and protracted. When the subjects of resuscitation status, ICU transfer or hospice care were raised, the patient immediately changed the subject, ended the conversation or referred the discussion to her mother. Our strategy for goals of care discussion was to engage with the patient in her own comfort zone and to attempt to maintain a trusting and cordial relationship reminding the patient that if she did not feel able to engage in discussion of goals and prognosis she could appoint her mother to act as her healthcare proxy, which she eventually did as her mental status deteriorated further.

Despite the reduced life expectancy of patients with SCD, the heavy pain and symptom burden it confers, and the increased incidence of solid tumors among those with the disease, SCD has often fallen outside of the purview of palliative care.[3] As SCD treatments continue to be refined and life expectancy more closely approaches that the general population, skill at managing SCD pain and symptoms in the setting terminal illness and end of life care will become an important competence for providers of all specialties and backgrounds.

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