Unraveling the Link: Angioedema in a 60-Year-Old Woman With AML Who Underwent a Stem Cell Transplant

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Case in point

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Introduction: Angiotensin-converting enzyme inhibitors (ACEi) are a common class of medication used to treat hypertension as a first-line therapy. Common side effects of ACEi include dry cough, hyperkalemia, and renal impairment. One of its most serious side effects, though rare, is angioedema, which generally manifests in the head and neck, potentially compromising the airway.[1] Patients will present with sudden swelling around the face, eyes, and lips. This occurs because ACEi prevents the breakdown of bradykinin, which then accumulates in cells. Bradykinin, a peptide that promotes cellular inflammation, then binds to bradykinin type 2 receptors leading to increased vascular permeability, which promotes a buildup of fluid in the submucosal space,[2] leading to swelling of structures, such as the neck subcutaneous and submucosal regions around the airway causing emergent obstruction. This rare, but potentially fatal, complication of ACEi, occurs in about 0.1% to 0.5% of patients, predominantly affecting Black patients.[1,3] The timeline of presenting symptoms after medication exposure varies. Some reports have estimated a 6-month median time from initial exposure to ACEi, though patients can experience these side effects at any point during therapy.[3]

Acute myeloid leukemia (AML) is a hematologic cancer characterized by rapid growth of immature white blood cells.[4] This results in hemopoietic insufficiency and can lead to pancytopenia, which can severely compromise the immune system.[4] To achieve remission, patients receive induction chemotherapy generally with an anthracycline and cytarabine. Long-term remission requires consolidation therapy with either chemotherapy, or more commonly, allogeneic stem cell transplantation (SCT) in those who are physically eligible.[4] In allogeneic SCT, patients receive stem cells from a donor. An HLA-matched donor sibling is often preferred, though most do not have a matched sibling available.[5] Even if a matched unrelated donor is not available, most patients have a feasible donor, given advances in

immune suppression and supportive care, allowing transplant across HLA-mismatch, such as with haploidentical (half-matched), mismatched unrelated, and umbilical cord blood donor sources.

To facilitate both disease control and successful engraftment, a combination of chemotherapeutic agents and radiation are given prior to stem cell infusion. Following stem cell infusion, ongoing immunosuppressive therapy (IST) is administered to prevent graft rejection and graft-versus-host disease (GVHD). mTOR inhibitors are frequently utilized IST. These medications (including sirolimus) are serine/threonine kinases that regulate cell growth and metabolism.[6] Several case reports in the last decade have linked concurrent sirolimus and ACEi use in patients who underwent SCT to the development of angioedema.[6,7]

Tacrolimus is also a frequently utilized IST after SCT. Although thought to have different mechanisms of action, recent studies have shown a link between tacrolimus and inhibition of the mTOR pathway.[8]

Here, we present the case of a 60-year-old woman with AML (on lisinopril for hypertension) who received a haploidentical-SCT. She was diagnosed with angioedema and ultimately died due to her complicated hospital course. Based on the complications associated with her case, we explore the potential link between tacrolimus therapy and ACEi-induced angioedema.

Case description. A 60-year-old woman with a past medical history of hypertension (on lisinopril 40 mg), hypothyroidism, anxiety, hyperlipidemia, and AML in first remission after high-dose chemotherapy induction and consolidation, presented to our institution for haploidentical stem cell transplant (from her brother). Upon presentation, her home medications were continued (table 1), including her ACEi (lisinopril). Seven days before her SCT, she started myeloablative conditioning chemotherapy with thiotepa, busulfan, and fludarabine. She received her SCT with no complications.

Table 1. Active medications before admission

Active Medications Prior to Admission	Dosage/Route
Acyclovir	400 Mg BID PO
Allopurinol	300 Mg Daily PO
Desvenlafaxine Succinate	100 Mg ER Daily PO
Isavuconazonium Sulfate	2 x 186 Mg Daily PO
Levofloxacin	500 Mg Daily PO
Levothyroxine	25 Mcg Daily PO
Lisinopril	40 Mg Daily PO
Midostaurin	2 x 50 Mg BID on Days 8 to 21 of each 28-day cycle PO
Mirabegron ER	25 Mg Daily PO
Ondanestron	8 Mg every 8 hours as needed PO
Simvastatin	40 Mg Daily PO
Tranexamic acid	2 x 650 Mg TID PO

Levofloxacin and acyclovir were started on day +2 for antimicrobial prophylaxis; these were medications she was on prior to the transplant while receiving chemotherapy. Post-transplant cyclophosphamide for GVHD prophylaxis was given as per usual on days 3 and 4. Tacrolimus and mycophenolate mofetil, as additional IST, were started on day +5.

On the morning of day 5, the patient was febrile up to 100.9 °F. She was empirically started on meropenem. Infectious work-up including blood cultures did not reveal the source of infection. After day +5, her fevers subsided, though she remained on meropenem for febrile neutropenia management. On day +5, filgrastim injections were also started. She intermittently required packed-red blood cells and platelets for her anemia and thrombocytopenia during the next 2 days, which occurred without issues. She remained hemodynamically stable.

On day +9, she endorsed some soreness in her throat and started diphenhydramine/aluminum/magnesium/lidocaine ("magic mouthwash") for presumed mucositis. That same night, the patient's throat symptoms worsened. She developed sudden onset tongue swelling. On the morning of day +10, submandibular fullness was noted on examination. Angioedema was considered, and her lisinopril was stopped and IV diphenhydramine and famotidine were started (table 2).

We consulted with ENT specialists, who recommended emergent intubation or possible tracheostomy. The patient was intubated, which was complicated by massive hemoptysis and clotting, requiring emergent tracheostomy. A CT of the patient’s neck was completed, which showed no concern for abscess formation, but glossal and soft palate edema with concern for airway compromise.

Table 2. Active Medications as of Day 9 post-SCT

Active Medications on Day 9	Dosage/Route
Acyclovir	400 Mg BID PO
Aminocaproic Acid	4000 Mg in dextrose 5% 250 ml every 6 hours IV
Desvenlafaxine Succinate	100 Mg ER Daily PO
Folic Acid	1 Mg in dextrose 5% 50 ml IVPB daily
Famotidine	20 Mg Daily PO
Insulin Lispro	1-21 U SSI TID IM
Isavuconazonium Sulfate	2 x 186 Mg Daily PO
Levothyroxine	25 Mcg Daily PO
Loratadine	10 Mg Daily PO
Lisinopril	40 Mg Daily PO
"Magic Mouth Wash"	10 ML PRN PO
Melatonin	6 Mg Nightly PO
Meropenem	1 g in NaCl 0.9% 100 ml IVPB Daily
Mirabegron ER	25 Mg Daily PO
Mycophenolate	1000 mcg in dextrose 5% 167 ml IVPB Daily
Ondanestron	8 Mg every 8 hours as needed PO
Pantoprazole	40 Mg IV Daily
Polyethylene Glycol	17 g packet Daily as needed PO
Prochlorperazine	10 mg IM every 6 hours as needed
Simvastatin	40 Mg Daily PO
Tacrolimus	2.5 Mg in NaCl 0.9% 250 ml IVPB Daily
Tramadol	50 Mg every 6 hours as needed PO

Her course was subsequently complicated by persistent altered mental status and acute encephalopathy of unknown origin. Initially, it was thought to be due to prolonged sedation, given her obesity, though it persisted for the next 2 weeks. Neurology, infectious disease, and psychiatry were all consulted, with unrevealing work-up. Her clinical course grew increasingly complicated with recurrent tracheal bleeding, mucus plugging, small bowel obstruction, and the eventual development of acute respiratory distress syndrome (ARDS). She required paralysis and prone ventilation and developed pneumothorax requiring multiple pigtail chest tubes. She remained unstable and poorly ventilated, and the family elected for comfort care. The patient was transitioned to comfort care status, extubated, and died shortly after (39 days after tracheostomy).

Discussion. This case illustrates a patient who experienced fatal angioedema in the setting of concurrent administration of ACEi with tacrolimus for IST shortly after SCT. Severe angioedema started 4 days after starting tacrolimus, requiring emergent tracheostomy, but she died shortly thereafter.

Tacrolimus is an immunosuppressive agent commonly used in patients after SCT generally for 60 days to 180 days to prevent GVHD. Similarly, sirolimus is an immunosuppressive agent commonly used in solid organ transplants and sometimes after SCT instead of tarcolimus. Both medications act on different pathways, though they share a common link at their starting target: a protein called FK506-binding protein 12 (FKBP12). FKBP12 is a protein that is expressed in almost all human tissues. Its functions include regulating transforming growth factor beta (TGF-beta) type 1 receptor (TGF-beta R1),[8] affecting endoplasmic reticulum calcium channel ryanodine receptor 2 (RyR2),[8] and interaction with the mTOR pathway. Both tacrolimus and rapamycin drugs bind to this protein.[9] Tacrolimus binds to FKBP12 which then forms a complex that inhibits a protein called “calcineurin-calmodulin”. By inhibiting this complex, tacrolimus inhibits IL-2 gene transcription, cell degranulation and apoptosis, making it an effective immune-suppressing medication for patients who undergo SCT.[10] In a similar way, sirolimus binds to FKBP12, though this causes direct inhibition of mTORc1, which inhibits cell growth and similarly leads to immunosuppression.

Additionally, recent studies have proposed that tacrolimus may act indirectly on the mTOR pathway. Some have attributed this to tacrolimus having similar structure to sirolimus, and thus potentially targeting some of the same receptors.[11] Although the mechanism of action remains unclear between sirolimus, ACEi, and angioedema, studies in rabbit endothelial cells have shown that exposure to sirolimus increases the amount of prostacyclin released. Prostacyclin, a form of prostaglandin, induces vasodilation through vascular smooth muscle leading to angioedema.[7]

Given that tacrolimus and sirolimus may share downstream effects, it is reasonable to question whether a similar mechanism can occur in patients who undergo SCT while on tacrolimus and lisinopril. This is especially important, as studies have shown that the rates of ACEi angioedema are potentially increased in patients undergoing various transplants when compared with nontransplant controls.[12] The authors of one study argued that immunosuppressants can increase angioedema by decreasing CD26, another peptide that functions to activate T lymphocytes, though the amount to which they can decrease CD26 activity differs between the type of immunosuppressant used.[12] Future research should investigate the similarities between tacrolimus and sirolimus in causing beta cell toxicity in patients who undergo renal transplant on sirolimus IST. Similar effects of these two drug classes might also be seen in patients who undergo SCT, and how their mechanisms of immune suppression impact ACEi-related angioedema still needs to be clarified as well. This knowledge would be instrumental in guiding future medication management in patients undergoing transplant.

Patients who receive a SCT are more likely to incur acute kidney injury during transplantation.[13] Because of this, diuretics and ACEi are often held at admission. In our patient, ACEi was not held at presentation. Patients who present for SCT need astute medication management throughout their treatment course, and unless medications are clearly indicated, some might be withheld until patients are engrafted after transplant.

Many other medications can also lead to angioedema. Some studies have seen links between DPP-4 inhibitors (for type 2 diabetes), neprilysin inhibitors (for heart failure), and medications that contain estrogen.[14] Our patient was on more than 20 medications when she developed angioedema. However, none of the medications, other than lisinopril, had been previously implicated in angioedema. Given this fact, it is difficult to identify a direct link between tacrolimus and ACEi in angioedema; however, it is something all clinicians should consider given this patient's history of immunosuppression. Clinicians must remain vigilant in identifying medications in this patient population and performing a thorough medication review prior to transplant.

Conclusion. ACEi-induced angioedema is a serious side effect that can lead to airway compromise and death. Patients who undergo SCT are highly immunocompromised, and this immunocompromised state may predispose one to ACEi-related angioedema, particularly with obligatory administration of tacrolimus or sirolimus, which also are implicated when combined with ACEi. Clinicians must be thorough in evaluating medications administered prior to, during, and after SCT, not only with relation to immune suppression, but with management of comorbid medical issues. Additional research is needed to understand underlying mechanisms of commonly used medication classes in causing complications.

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