Challenges in the management of the transgender patient with sickle cell disease

To the Editor:

Patients with sickle cell disease (SCD) who identify as transgender pose a management challenge. Standard care for transgender patients is cross-sex hormone therapy (CSHT), but treatment may increase the risk of thrombosis1–3 and stroke.1,3,4 Approximately 1.4 million adults in the US identify as transgender,5 and many experience gender dysphoria.1 Treatment with CSHT stimulates secondary sex characteristic development and facilitates physical, emotional, and social alignment with the patient’s gender identity.1 CSHT reduces mental health disorders1–2 and suicide. For transgender patients who have SCD, the benefits of CSHT are balanced against increasing the risk of SCD complications. We present three transgender patients with SCD and highlight fundamental treatment considerations. The Johns Hopkins Institutional Review Board acknowledged this work.

Clinical data are in Table 1. Patient 1 is a 22-year-old transgender female with hemoglobin SS (HbSS), mild protein S deficiency (61%), and Moyamoya syndrome complicated by bilateral ischemic strokes at age 12. She received chronic partial exchange transfusions (CT) and aspirin and underwent bilateral pial synangiosis. Her care was complicated by tobacco use and treatment nonadherence. At age 20, she was referred to a transgender health surgical center. She wanted estrogen treatment. An interdisciplinary team including hematology, adolescent medicine, endocrinology, and psychology developed a CSHT plan initially including endogenous testosterone suppression with spironolactone (25 mg daily), leuprolide (3.75 mg intramuscular injections approximately every 6–40 weeks) and transdermal 17-beta estradiol (estradiol). Adherence to CT with a goal sickle hemoglobin ≤30% was the sine qua non for prescribing CSHT because of her stroke history. The patient reached a maximum estradiol dose of 50 mcg; nonadherence to CT (sickle hemoglobin 29.8–64.3%) precluded prescribing higher estrogen doses. She reported, then denied, taking nonprescribed estrogen. Mild feminization of her features improved her mood. She had no venous thromboembolism (VTE) or stroke since starting transdermal estradiol over 16 months ago.

Patient 2 is a 49-year-old transgender female with hemoglobin SC (HbSC), multiple pulmonary emboli (PE), bilateral hip avascular necrosis, and frequent painful crises. She has antiretroviral suppressed HIV. Her care was complicated by treatment nonadherence, depression, tobacco use, illicit drug use, homelessness, and limited family/peer support. A specialty clinic for transgender patients prescribed her oral estradiol (4 mg daily) and spironolactone (25 mg twice daily). She developed recurrent PE while prescribed anticoagulation concerning for anticoagulation nonadherence. Estradiol was discontinued. She was referred to a transgender health surgical center.

Patient 3 is a 21-year-old transgender male with HbSS previously on CT for abnormal transthoracic Dopplers. A transgender health center prescribed him testosterone cypionate (subcutaneous injection, 70 mg weekly). While receiving CSHT, he switched from CT to hydroxyurea which he took inconsistently. He reported voice deepening, increased body hair, and irregular menses after over 25 months of CSHT. Brain MRI performed after initiating CSHT was stable. His hemoglobin remained in his usual range. He was referred for bilateral mastectomy.

These cases highlight how treatment for transgender patients with SCD requires balancing the gender-affirming benefits of CSHT against thromboembolic1–3 and cardiovascular risks.1,3,4 Denying transgender patients CSHT may worsen their gender dysphoria. Alienated patients often disengage from care and may pursue nonprescribed CSHT. Our patients wanted CSHT intensely despite significant risks; we suspected patients 1 and 2 pursued illicit estrogen. Pre-existing thrombotic and neurologic complications, adherence, and psychosocial stability must be incorporated into treatment recommendations.

Evidence on exogenous hormone use in patients with SCD is limited. There are no studies of transgender patients with SCD receiving CSHT. The risks of exogenous estrogen or testosterone administration in transgender patients with SCD is extrapolated from studies in natal-sex females and males, respectively. Even these data are sparse.

For transgender females, CSHT with estradiol is recommended1,2 because it is bioidentical to estrogen produced by human ovaries1 and serum levels can be monitored.1,2 However, patients with SCD are at increased risk for VTE,6 and exogenous estrogen administration can provoke VTE.1,2 VTE risk depends on the estrogen preparation, route of administration, and dose prescribed.1–3 Ethinyl estradiol1–3 and conjugated equine estrogen1,2 increase thrombotic risk. Transdermal estrogen may have a lower VTE risk.1–3 Transgender patients with activated protein C resistance taking no anticoagulation (n = 11) were treated with transdermal estradiol without developing VTE.1 Studies of estrogen in patients with SCD do not address estrogen for transgender SCD patients because these studies include natal-sex females receiving oral contraceptives which

Abbreviations: CSHT, cross-sex hormone therapy; CT, chronic partial exchange transfusions; estradiol, 17-beta estradiol; GnRH, gonadotropin-releasing hormone; HbSC, hemoglobin SC; HbSS, hemoglobin SS; PE, pulmonary emboli; SCD, sickle cell disease; VTE, venous thromboembolism
typically contain ethinyl estradiol which is not recommended for CSHT.1,2 Less thrombogenic estradiols used in CSHT have not been studied in patients with SCD.

For transgender males, exogenous testosterone is prescribed. Testosterone causes dose-dependent increases in hemoglobin, and increases the risk of erythrocytosis,3 priapism, and cardiovascular complications.4 These side effects are concerning for patients with SCD because SCD is associated with cardiovascular and viscosity-related complications. In the US, available testosterone formulations are bioidentical to testosterone produced by human testicles.1 Testosterone enanthate and testosterone cypionate are commonly prescribed. Testosterone undecanoate has a longer half-life than other preparations. Its use is restricted to participants in a monitoring program because of rare reports of pulmonary microembolism and anaphylaxis.1 The literature on testosterone in patients with SCD is limited. Seven natal-sex males with SCD were treated for hypogonadism with testosterone undecanoate without changes in hemoglobin, painful crises, priapism frequency, or cardiovascular events.7 These data cannot be easily extrapolated to predict the effects of exogenous testosterone in transgender males.

No studies specifically guide CSHT for transgender patients with SCD. Given the risks of CSHT for this population, we utilized management principles based upon known evidence-based strategies to reduce SCD morbidities. We used disease-modifying therapy in conjunction with CSHT for patients with HbSS. Modest evidence suggests hydroxyurea and CT improve abnormal coagulation system activation in patients with SCD. Patients 1 and 3 received disease-modifying therapy with CSHT and experienced problems with treatment adherence but did not have a thrombosis or stroke.

For patients with HbSC, there is not strong evidence to support disease-modifying therapy; however, patient 2’s recurrent PEs make anticoagulation an appropriate precondition to CSHT with estradiol. If VTE occurs in patients with SCD on CSHT, indefinite anticoagulation may be indicated, especially while the patient takes CSHT. Estradiol is not currently recommended for patient 2 because of her recurrent PE, suspected nonadherence to anticoagulation, and tobacco use. Her chronic HIV is an additional acquired VTE risk.8

A standard aim of CSHT is to achieve physiologic hormone levels and/or satisfy patient goals of treatment.1 Given the theoretical risks of exogenous hormone administration, we utilized a strategy to minimize the doses necessary for treatment. Gonadotropin-releasing hormone (GnRH) analogs, like leuprolide, suppress unwanted endogenous hormones1,2 and can reduce exogenous hormone doses needed to achieve a therapeutic effect. Patient 1 took leuprolide and reported benefit before starting estradiol. Surgery, a definitive intervention, may limit the need for pharmacologic intervention for some patients, but patients may not want surgery and patients with SCD are at increased risk of perioperative complications. Nevertheless, orchiectomy and oophorectomy eliminate endogenous hormone production and may be considered with gender reassignment surgery.

These cases highlight the complexities of treating transgender patients with SCD. Both transgender identity and SCD are associated with stigma and increased morbidity and mortality. Nonadherence is common and may compromise care teams’ confidence that CSHT can be safely prescribed. Yet patients with gender dysphoria may pursue nonprescribed therapy, so a collaborative, harm-reduction approach to managing CSHT must be considered. Engaging an interdisciplinary team with expertise in SCD, transgender health, and CSHT may help

| TABLE 1 | Clinical data for case patients |
|---|---|---|
| **Patient 1** | **Patient 2** | **Patient 3** |
| Age | 22 | 49 | 21 |
| Sickle Cell Genotype | HbSS | HbSC | HbSS |
| Sex at Birth | Male | Male | Female |
| Gender Identity | Female | Female | Male |
| SCD Modifying Treatment | Chronic partial exchange transfusions | None | Previously chronic partial exchange transfusions, now hydroxyurea |
| # Painful crises per year | 2-4 | > 10 per year | 2-4 |
| History of Acute Chest Syndrome | Yes | No | No |
| History of Cerebral Vascular Accident | Right frontal lobe anterior cerebral artery territory infarction; patchy infarction of the right periventricular white matter in the right frontal lobe, centrum semi ovale and corona radiata; and left frontal operculum infarction. | No | No |
| Comorbidities | Moyamoya syndrome, asthma, frequent sexually transmitted infections, secondary hemochromatosis | HIV, history of multiple pulmonary embolisms, history of multiple suicide attempts, high emergency department utilization | Asthma, secondary hemochromatosis |
| Smoking History | Prior history | Current smoker | Negative |
| Anticoagulation and/or Antiplatelet Medication | Aspirin | Warfarin | No |
| Adult or pediatric hematologist | Pediatric | Adult | Pediatric |
| Participation in Transgender Clinic | Yes | No | Yes |

**CORRESPONDENCE**

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incorporate complex medical and psychosocial concerns into treatment recommendations. Conclusions from this case series are limited by the real-world problems of treatment nonadherence, small sample size, and short duration of follow-up. These cases highlight the need for more research in this area.

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CONFLICT OF INTERESTS

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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A common functional PIEZO1 deletion allele associates with red blood cell density in sickle cell disease patients

To the Editor:

PIEZO1 encodes a large mechanosensitive cation channel expressed in multiple cell types, including red blood cells (RBCs). In humans, rare gain-of-function mutations in PIEZO1 cause hereditary xerocytosis (HX), characterized by RBC dehydration and anemia. Recently, Ma et al. identified an in-frame PIEZO1 deletion allele (rs572934641) that is common in individuals of African ancestry. In vitro, the deletion increased PIEZO1 inactivation time, mimicking other gain-of-function mutations found in HX patients. RBCs from nine healthy African Americans heterozygotes for rs572934641 were dehydrated when compared to erythrocytes from noncarriers.

RBC dehydration has been implicated in the clinical variability observed in patients with sickle cell disease (SCD), a multiorgan disorder caused by mutations in the β-globin gene. Increased RBC density, a hallmark of SCD, is independently correlated with hemolysis, priapism, leg ulcer, and renal dysfunction in patients. Here, we investigated the association between the common functional PIEZO1 deletion allele and RBC density, hemolytic parameters, estimated