

Implantable venous access device associated complications in patients with hereditary angioedema

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Clinical Implications

- This report describes 2 patients with hereditary angioedema, treated with C1 esterase inhibitor prophylaxis via implantable venous access devices (IVADs), who developed complications of superior vena cava syndrome and *Candida* fungemia related to these devices.
- Allergy/immunology specialists and patients should be aware of the risks and complications when they choose IVADs for administration of long-term intravenous medications.

TO THE EDITOR:

Increasingly in the United States, long-term intravenous access has become an important part of medical therapy. Some of the therapies these devices are used to administer include chemotherapy, antibiotics, and blood products. Implantable venous access devices (IVADs), also commonly known as “ports,” are one example of such access devices. In patients with hereditary angioedema (HAE), C1 esterase inhibitor (C1INH) has been shown to be effective as long-term prophylactic therapy.^{1,2} C1INH, when used as a long-term prophylactic therapy, is administered intravenously and not infrequently has been administered via ports. However, having these devices for a prolonged period of time can lead to complications such as blood stream infections and thrombosis.³⁻⁶ The incidence of IVAD complications are well documented in other patient populations such as in patients with cancer, sickle cell disease, and HIV. However, IVAD-associated complication rates have not been studied in patients with HAE. We report two patients with HAE receiving C1INH intravenous prophylactic therapy who developed IVAD-associated complications.

A 37-year-old woman was diagnosed with type I HAE at the age of 13 on the basis of low C1INH antigenic and functional levels. She has had multiple HAE flares of bilateral extremity edema and gastrointestinal symptoms at a rate of about 1 to 2 per month. She had failed androgen therapy with danazol, stanozolol, and oxandrolone and had required intubation on at least 8 different occasions because of laryngeal edema. Her past medical history is also significant for hepatitis C infection, diabetes mellitus, depression, anemia, and allergic rhinitis and no prior history of intravenous drug abuse. Because of frequent admissions for HAE attacks which required parenteral fluids and medications and poor venous access, an IVAD was recommended by the hospitalist service and was placed in her right upper chest. Because of failure of multiple other prophylactic regimens and a high frequency of serious HAE attacks and hospitalizations, C1INH prophylaxis therapy was prescribed

through our clinic and resulted in a reduction in HAE attacks. Four months later, she presented with fever, tachycardia, tachypnea, and bilateral pulmonary infiltrates, and *Candida albicans* was cultured from blood. She was treated with micafungin for 14 days which was continued at a long-term acute care facility. The port was not removed on the recommendation of infectious disease specialists who wished to salvage her port while treating the infection.

A 34-year-old woman with past medical history of allergic rhinitis, gastroesophageal reflux disease, and bipolar disorder had a 20-year-history of type I HAE diagnosed by low C1INH antigenic and functional levels. She had failed therapy with androgens (stanozolol, danazol) and epsilon aminocaproic acid. She continued to have frequent extremity and abdominal attacks on a monthly basis. She also had several episodes of laryngeal edema that required intubation on 3 different occasions. The patient, in conjunction with her primary care physician, decided that an IVAD would be best to receive C1INH prophylaxis. She had 4 different IVADs placed in anticipation of C1INH prophylactic therapy. Because it was placed too deeply in her right upper chest, the first port could not be used and had to be replaced after only a few months. Because of failure of multiple other prophylactic regimens and a high frequency of attacks and hospitalizations, when C1INH prophylaxis therapy became available, it was prescribed through our clinic. The second port was also placed in the right upper chest, but she could not receive C1INH therapy regularly due to its limited availability because of financial constraints and it was only used for acute attacks. However, this second port malfunctioned after 6 months and could no longer be used. A third port was placed in her left chest, and she continued intermittent C1INH therapy. Because of her financial constraints, she could only receive <10 doses in a 6-month-period. After 6 months with the third port, deep vein thrombosis was found within her superior vena cava (SVC) which resulted in removal of her third port. This eventually led to SVC syndrome for which she underwent SVC bypass surgery. Approximately 2 years later, she was diagnosed with recurrent SVC syndrome and subsequently underwent balloon angioplasty. She is currently receiving C1INH prophylactic therapy every 3 days via her fourth port which is in her right femoral vein that was placed after her SVC bypass surgery.

Major complications of long-term IVADs, as indicated by these 2 cases, are blood stream infections and thrombosis. Various rates of infectious complications have been shown in many prospective observational studies with different types of intravascular access devices. Specifically, infection rates seen with IVADs are generally associated with lower rates of blood stream infection than other devices such as cuffed and tunneled central venous catheters and hemodialysis catheters.³

The literature is robust on IVAD-associated complications in patients with various malignancies. For example, a complication rate of up to 51% has been observed with central venous catheters in children with solid and hematologic malignancies.^{5,6} Another well-studied, but less immunosuppressed, population of IVAD complications is in patients with sickle cell disease. In these patients who need long-term red cell transfusion therapy for

stroke prevention, IVADs are often used. Studies have shown rates of blood stream infections ranging from 0 to 5.5 per 1000 days with central venous access devices in this population.^{7,8} These infections were defined as growth of bacteria or fungi in cultures obtained through central venous catheters or peripherally while the implanted devices were in place.

Another main IVAD-associated complication is thrombosis. When the rates of thrombotic complications were studied in the same sickle cell population, they ranged from 0.16 to 0.99 per 100 days with central venous access devices.^{7,8} Thrombotic complications were identified by radiologic studies and did not include minor occlusion that could be successfully treated with thrombolytic agents.

In addition, there have been reports of thromboembolic complications directly associated with plasma-derived C1INH. In one series, in which neonates developed thrombotic complications during cardiac surgery after C1INH administration, these complications were attributed to C1INH.⁹ This thrombogenic effect has also been reported in an animal study.⁹ Although it is difficult to attribute all thrombotic events to C1INH, this potential risk needs to be considered.

Our cases indicate that patients with HAE may be at risk for development of blood stream infection and thrombosis from complications of IVADs used to deliver HAE-specific therapy. The first case, although the patient may have had an increased risk due to diabetes mellitus and hepatitis C infection, resulted in a hospital admission with a long-term intravenous antifungal therapy. The second case resulted in placement of multiple ports, repeated procedures, and SVC syndrome. Complications of IVADs have not been examined in patients with HAE who require long-term C1INH prophylactic therapy. Because these complications can and often lead to serious patient morbidity and possibly mortality, it is important to consider potential risks of IVADs for long-term prophylaxis in patients with HAE. Avoidance of IVADs in conjunction with C1INH replacement or use of androgens as prophylaxis should be considered. Although not approved by the Food and Drug Administration, subcutaneous administration of C1INH for prophylaxis would eliminate the need for IVADs and associated risks. Yet IVADs are often viewed as a convenient option for delivery of frequent intravenous medications. Therefore, allergy/immunology specialists and patients should still be aware of the risks and complications when they choose IVADs, that it is not the standard of care, that caution should be exercised when

considering these devices, and, in our opinion, that these devices should be avoided if possible.

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