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SHORT COMMUNICATION

Effective Palliation of Intractable Bleeding from Noonan Syndrome-associated Lymphatic Malformations by Radiotherapy

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Noonan syndrome is an autosomal dominant genetic disorder with an estimated prevalence of 1 in 1,000–2,500 (1). It is typically caused by mutations in the *PTPN11* gene although mutations of the *SOS1*, *RAF1*, *KRAS*, and *BRAF* genes have been implicated as well. Patients with Noonan syndrome exhibit a constellation of findings including minor facial dysmorphism, short stature, and heart disease, most commonly pulmonic stenosis and hypertrophic cardiomyopathy (1). Lymphedema is another common manifestation, but diffuse cutaneous lymphatic malformations are extremely rare in Noonan syndrome according to Evans et al. (2). We report a case of intractable bleeding from diffuse lymphatic malformations of the scrotum and perirectal region that improved dramatically with external beam radiation therapy.

CASE REPORT

A 33-year-old man with a past medical history of Noonan syndrome complicated by pulmonic stenosis with congestive heart failure and profound brawny edema of the abdomen and lower extremities presented to the hospital with intractable bleeding from innumerable cutaneous lymphatic malformations of the scrotum, groin, and perirectal region (Fig. 1A).

He first developed these cutaneous lymphatic malformations approximately two years prior as a complication of his Noonan syndrome and chronic lymphedema, and the lesions progressed. For 1.5 years, he had chronic intermittent bleeding from these lesions requiring frequent blood transfusions when his hemoglobin would decrease to 5–6 g/dl from his usual baseline hemoglobin of 8 g/dl. He required hospitalizations almost monthly for complications associated with bleeding and super-infection of his cutaneous lesions. His severe anemia from these bleeding lymphatic malformations significantly compromised his already tenuous cardiopulmonary function, resulting in multiple extended admissions to the medical and cardiac intensive care units. His lesions were also associated with significant pain requiring high-dose narcotics that further compromised his respiratory function.

His cutaneous lymphatic malformations were previously treated with a variety of topical therapies, including Monsel's solution (basic ferric sulfate), aluminum chloride, silver nitrate, surgical hemostatic polymer, heat stick, electrocautery, extensive curettage and cauterization, and scar induction with electrocoagulation, all with little-to-no reduction in his bleeding. Because of his refractory, ongoing blood loss from these lesions, his case was presented at Dermatology Grand Rounds to solicit additional treatment options. Timolol and rapamycin were considered but not ultimately employed. Ablative CO_2 laser therapy was limited by the patient's MRSA carriage, colonization, and superficial skin infections requiring contact isolation.

During one of his admissions for bleeding, radiation was considered as a local treatment option to reduce his bleeding. After consulting with the primary care team and the medical dermatologists, the patient decided to proceed with radiation treatments.

He was treated to a dose of 20 Gy in 2 Gy fractions treating once daily over a two-week period. For the lesions on the upper abdomen, he was treated with 6 MV photons using volumetric modulated arc therapy (VMAT), a form of intensity modulated radiation therapy (IMRT) that delivered a homogeneous, conformal dose to the skin lesions while minimizing dose to the underlying normal tissues. The cutaneous lesions on the scrotum, perineum, and perirectal regions were encompassed within a field covered by opposing anterior and posterior portals. More superiorly in the pelvis, the lesions on the anterior skin were treated with opposing lateral beams using half-beam blocking to minimize divergence of the beams into the underlying tissues while the lesions on the posterior pelvic skin were treated with a similar beam arrangement using opposed lateral portals. This beam configuration minimized radiation dose to the inner pelvis. Custom bolus was used to ensure adequate dose build-up to the cutaneous lesions. Treatment was designed to deliver the prescribed dose to a depth of 2 cm below the skin surface. His radiation treatment plan is shown in Fig. S1[1].

The original plan was to deliver 30 Gy in 15 fractions of 2 Gy per fraction, a dose known to be effective for achieving objective responses in multiple different lymphomatous neoplasms,

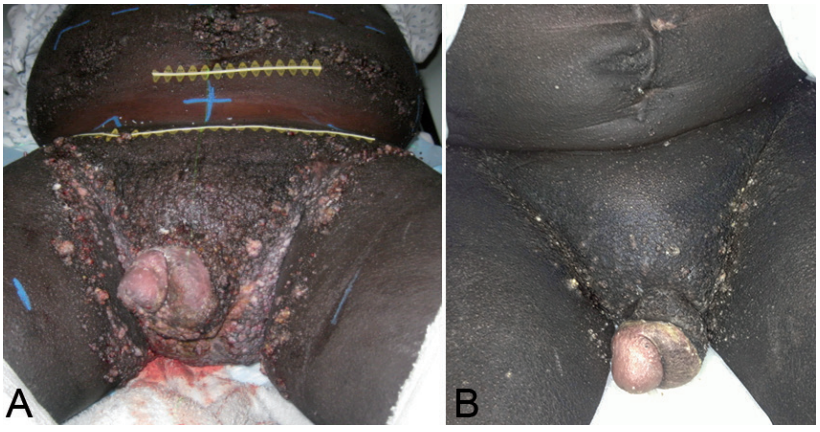

Fig. 1. (A) Innumerable lymphatic malformations of the scrotal, perineal, perirectal, pelvic, and lower abdomen, as they appeared just prior to the start of radiation treatment. (B) Appearance 10 months following completion of radiation therapy. The size of the lesions and the degree of bleeding was significantly improved. A written permission from the patient is given to publish these photos.

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but his radiation treatments were aborted after only 10 fractions because of an episode of cardiopulmonary compromise that prevented him from lying flat on the treatment table for his subsequent radiation treatments. The radiation therapy was not thought to have contributed to the cardiopulmonary compromise. Because of the large treatment volume, he was treated with a conventional fractionation regimen of 2 Gy per fraction to minimize the risk of radiation-related complications rather than being treated with a hypofractionated radiation regimen using larger doses per fraction.

After completing radiation, the patient experienced a significant, durable improvement in his bleeding as well as dramatic shrinkage in the size of his lesions (Fig. 1B). He reported a 7-month interval following radiation during which he did not require any blood transfusions, a marked contrast to his monthly transfusion requirement prior to radiation therapy. The pain associated with his lesions also improved following radiation.

DISCUSSION

Cutaneous lymphatic malformations associated with Noonan syndrome are a very rare skin manifestation of this genetic disorder, and to our knowledge have not been reported on the scrotum or associated with such severe bleeding in the literature. Pootrakul et al. (3) recently reported the first case of cutaneous lymphatic malformations of the vulva in a patient with Noonan syndrome, but the lesions did not bleed.

There is limited evidence in the literature to guide treatment of lymphatic malformations in the setting of Noonan syndrome. In this patient, a wide array of topical and locally destructive treatments were tested but found to be of limited efficacy. Ablative CO_2 laser therapy has been used with success to treat lymphangioma circumscriptum and other lymphatic malformations (4), including a case of lymphangioma circumscriptum of the scrotum (5), but the patient was not a candidate for this approach because of his MRSA carriage, colonization, and superficial skin infections requiring contact isolation. Radiation therapy was considered because of its long established efficacy for arresting bleeding associated with a variety of malignancies. Radiation therapy is frequently employed for the palliative treatment of hemoptysis from lung cancer, GI bleeding associated with esophageal or gastric cancers, and vaginal bleeding from gynecologic malignancies and has been known to stop cutaneous bleeding from skin cancers. The mechanism of action is thought to be mediated by damage to the DNA of the endothelial cells which results in endothelial cell loss as these cells enter mitosis. The loss of endothelial cells along the surface of blood vessels leads to thrombosis and capillary necrosis. The net effect is sclerosis and obliteration of small blood vessels that results in improved hemostasis according to Hall & Giaccia (6). The choice of radiation for this patient's lymphatic malformations was also influenced by a case report from Turkey by Yildiz et al. (7) that demonstrated the effectiveness of radiation therapy in the treatment of congenital vulvar lymphangioma circumscriptum (although our patient's lesions were felt to penetrate more deeply than lymphangioma circumscriptum).

As a result of the modest dose of radiation delivered to his skin lesions, this patient enjoyed a prolonged interval during which he no longer required transfusions and experienced improvement in his pain. Because of the large treatment volume encompassing the pelvis and lower abdomen, he was treated with conventional fractionation (2 Gy per fraction) rather than hypofractionated radiation using a higher dose per fraction. Hypofractionated radiation may provide more durable palliation of bleeding than conventionally fractionated radiation (8), but at the expense of additional radiation-related toxicity, especially when treating large target volumes. For patients with more limited lesions, hypofractionated radiation is a reasonable option and may be preferred because it reduces the total number of fractions and may increase endothelial damage resulting in a more prolonged treatment effect.

To our knowledge, this is the first case reported in the literature of cutaneous lymphatic malformations of the scrotum in a patient with Noonan syndrome and the first case of refractory bleeding from Noonan syndrome associated cutaneous lymphatic malformations. The case also highlights the utility of radiation treatments as a novel method to achieve durable hemostasis and shrinkage of lesions in patients with such lesions that are refractory to traditional treatment modalities. Radiation therapy may also be an effective treatment for intractable bleeding from lymphatic malformations or lymphangiomas associated with other underlying conditions.

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