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Trichodysplasia of immunosuppression successfully treated with oral valganciclovir

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Abstract

Trichodysplasia of immunosuppression (TOI) is a newly described rare clinicopathologic entity usually found in transplant patients on chronic immunosuppressive medications or with hematologic malignancies. TOI consists of a cutaneous eruption of spiny papules predominantly affecting the face and arms. The distinct histopathologic picture includes abnormally maturing anagen follicles with hyperkeratotic infundibula and excessive inner root sheath differentiation. Given that intranuclear viral particles have been noted on electron microscopy of skin biopsy in several patients, a viral etiology is suspected. These viral particles are similar in shape and size to a polyoma virus, however, the virus has not been identified to date. There are reports of improvement of TOI with topical cidofovir or tazarotene 0.5% gel, but to our knowledge there has not been a report of near-complete resolution with oral valganciclovir. We report a case of TOI in a heart transplant patient on a chronic immunosuppressive regimen of sirolimus, mycophenolic acid and prednisone that demonstrated almost complete response to treatment with systemic valganciclovir.

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Trichodysplasia of Immunosuppression is a rare entity described in transplant patients which consists of follicular spiny papules distributed primarily over the face. We report a 37 year old caucasian female status post orthotopic heart transplant who began noticing facial papules eight months post-transplantation. Her medications after transplant included cyclosporine, mycophenolic acid and prednisone as well as a 100 day course of oral valganciclovir for CMV prophylaxis at 900mg daily dose which was replaced with oral acyclovir as per post-transplant anti-viral prophylaxis protocol. The papules grew in size and number and subsequently spread to the trunk and extremities over several months. The patient additionally noted hair loss of the affected areas. The patient's exam confirmed almost complete alopecia of the face, trunk and upper extremities, as well as partial madarosis. Erythematous to skin-colored, follicular, spiny, hyperkeratotic papules were noted on the face, upper trunk, arms and legs. The facial papules were larger and coalesced leading to disfigurement of the nose (Figure 1). Histopathology (Figure 2A, 2B) was consistent with the diagnosis of TOI and revealed dilated anagen hair follicles with absent hair shafts, discontinuous inner root sheath, and abnormal corneocytes filling the infundibula of the follicles, with some containing apoptotic nuclei and others containing prominent trichohyaline granules (excessive inner root sheath differentiation). Electron microscopy, however, revealed no viral inclusions, and PCR for all known HPV types was negative. After the development of the lesions, cyclosporine was

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discontinued and replaced with sirolimus; however, this medication change did not lead to improvement of the papules. In addition, the patient received no benefit after three months of topical imiquimod therapy used three nights per week. She also tried topical tazarotene therapy but was unable to tolerate the gel secondary to severe stinging and discomfort of the skin. Based on the observation that the papules arose after the discontinuation of valganciclovir, we empirically restarted oral valganciclovir at a dose of 900mg twice each day combined with the brief use of topical acyclovir therapy twice each day for two months, and the patient demonstrated dramatic improvement over a five month period. She was then continued on valganciclovir at a dose of 900mg once each day and has not had a resurgence of her papules over a year later (Figure 3).

Discussion

Trichodysplasia of immunosuppression (TOI),¹ also known in the literature as trichodysplasia spinulosa,² viral-associated trichodysplasia spinulosa,³ pilomatrix dysplasia,⁴ and cyclosporine-induced folliculodystrophy,^{5,6,7} is a newly described rare clinicopathologic entity. TOI was first reported in 1995 in the context of drug-induced immunosuppression in the setting of organ transplantation,⁸ but has since been described in non-transplant patients with pre-B-cell leukemia,⁴ acute⁹ as well as chronic lymphocytic leukemia,¹⁰ and low-grade follicular-type non-Hodgkin's lymphoma.¹¹ TOI is an eruption of spiny papules associated with a distinct histologic picture of abnormally maturing anagen follicles with hyperkeratotic infundibula and excessive inner root sheath differentiation. Histopathologic evaluation of a biopsy specimen has been the standard for diagnosis, but a spicule pull-test has recently been described¹⁰ which allows for a minimally invasive diagnosis via microscopic assessment of spicules for inner root sheath keratinization.

The precise etiology of this condition remains uncertain, although a viral etiology is suspected given that intranuclear polyhedral inclusions were noted in six of eight TOI patients described in the literature whose biopsy specimens were examined by electron microscopy. These inclusions are suspicious for papovavirus^{2,9} or, more specifically, polyomavirus¹¹ particles given the approximately 40-nm size. Polyomaviruses are double-stranded DNA viruses with low infectivity in the general population and tend to only cause severe disease and occasionally malignancy,^{12,13} in immunosuppressed patients. PCR studies in TOI patients have been negative for the highly seroprevalent¹⁴ JC and BK, two of the five known polyoma viruses, as well as papilloma viruses in the past.^{2,9} Perhaps future studies such as high-throughput pyrosequencing technologies combined with computational subtraction¹⁵ may find the causative agent in TOI.

We suggest that optimal treatment strategies should include antivirals to target the proposed causative agent. Topical cidofovir, a nucleotide analogue which inhibits viral DNA polymerase has been noted to demonstrate efficacy in therapy of two polyoma viral syndromes,^{16,17} and has proven useful in the management of TOI;^{3,11} however, its use is limited by high cost. The employment of other agents that have recently proven useful in polyomavirus-associated nephropathy (PVAN), such as leflunomide and fluoroquinolone antibiotics,¹⁶ have not been reported in this entity. IVIg has been tried in TOI with negative results.⁹ Another strategy is reduction of immunosuppression,¹⁸ and indeed, there are reports of TOI in patients on cyclosporine improving or resolving with cessation of cyclosporine therapy;^{5,7,8} Tazarotene 0.5% gel proved effective for TOI in one renal transplant patient on tacrolimus and mycophenolic acid, however, topical tretinoin was not helpful in several other case reports.^{3,8,19} Interestingly, innate immune response to polyoma viruses appears to be linked to activation of Toll-like receptors 2 and 4²⁰ which may explain why tretinoin, a TLR-2 downregulator,²¹ was not useful. Similarly, topical imiquimod, a specific TLR-7 stimulator, did not demonstrate much beneficial effect.³ Perhaps agents more specific for TLR-2 and 4,

such as modified heat-shock proteins and topical sensitizers,²² will prove useful in this condition in the future. Other therapies reported not to show efficacy in this condition have included minocycline,^{5,10} keratolytics,¹⁰ topical corticosteroids,^{5,3} topical tacrolimus and topical antibiotics.⁵ There have been a few reports of spontaneous improvement in leukemia patients when their immune system is reconstituted after discontinuation of chemotherapy; however, there are no reports of spontaneous improvement in the transplant population who remain on high doses of chronic immunosuppressive regimens.⁹

To our knowledge, this is the first report of successful treatment of TOI with oral valganciclovir, and the efficacy of an antiviral is all the more interesting in light of the fact that our patient's electron microscopy did not reveal any viral particles. The utility of valganciclovir in polyomaviruses is established by a recent study of reactivation of viruses in solid organ transplant patients receiving CMV prophylaxis²³ which noted a significantly lower incidence of BK polyomavirus viremia in patients receiving valganciclovir than in those receiving ganciclovir prophylaxis. Considering that valganciclovir is thought to be merely a more bioavailable prodrug of ganciclovir, apparently exerting its effect in much the same way, the increased efficacy of the former for control of BK polyomavirus is not clearly explained by its putative mechanism. The increased efficacy of this class of drugs against polyomaviruses may be related to an interaction between CMV and BK polyoma viral replication.²⁴ Herpesvirus infection appears to cause significant amplification of simian polyomavirus SV40 in in-vitro studies²⁵ such that the treatment with the antiherpesvirus drug class may treat coinfection with herpesviruses leading to decreased replication of polyomavirus by both direct and indirect mechanisms. Whatever the mechanism, valganciclovir seems to be an effective new entry in the dermatologic armamentarium for trichodysplasia of immunosuppression.

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Figure 1.
Clinical image of patient immediately prior to initiation of valganciclovir therapy.

Figure 2.

A. Low power view (20X) demonstrating abnormally maturing anagen hair follicles with excessive inner root sheath differentiation, no normal hair papillae and hyperkeratotic, slightly dilated infundibula. **B.** Intermediate power view (100X) demonstrating the hyperkeratotic infundibula and the absence of mature hair sheaths.

Figure 3.
Clinical image of patient one year subsequent to initiation of valganciclovir therapy.