BRIEF ARTICLES

Hyperpigmentation Associated with the Use of Topical Cidofovir for Treatment of Trichodysplasia Spinulosa in an Immunosuppressed Adult: Case Report and Review of the Literature

Roya S. Nazarian BA[1], Nikki S Vyas MD[2], John Evans MD[3], Robert G. Phelps MD[2,3]

[1]Icahn School of Medicine at Mount Sinai, New York, NY
[2]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY
[3]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT

Trichodysplasia spinulosa (TS) is a rare, opportunistic infectious skin disease caused by the polyoma virus. Clinically, TS is characterized by follicular papules, keratin spicules, and alopecia most classically in a midfacial distribution. Since its discovery in 2010, no standard of treatment has been established, though use of oral acitretin, valganciclovir, lefludomide, topical cidofovir, physical extraction, and modification of immunosuppressive medications have been reported in the literature. We describe the case of a 52-year old female with a painful midfacial eruption and alopecia of the bilateral eyebrows ultimately diagnosed with TS and treated with topical cidofovir 3%. Though the TS eruption resolved, treatment resulted in hyperpigmentation of the affected area. Hyperpigmentation associated with cidofovir use has been reported in cases of molluscum contagiosum, however no such association has been described in the treatment of TS to our knowledge. Therefore, we report this case to highlight an underreported adverse effect of topical cidofovir in the setting of this rare disease.

INTRODUCTION

Trichodysplasia spinulosa (TS) is a rare, infectious skin disease seen in severely immunocompromised hosts.[1] This unusual disease is caused by infection with the polyoma virus, a small DNA virus in the polyomaviridae virus family. Multiple treatments exist including oral acitretin, valganciclovir, lefludomide, topical cidofovir, physical extraction, and modification of immunosuppressive medications. Clinically, TS is characterized by follicular papules, keratin spicules, and alopecia most classically in a midfacial distribution.[2] Since its discovery in 2010, no standard of treatment has been established. Proper diagnosis and treatment is crucial to prevent painful and potentially disfiguring lesions.

CASE REPORT

We report the case of a 52-year-old African American female with a one-year history of a painful eruption on her face. Her past medical history was significant for renal transplant from an unknown childhood illness, HIV infection controlled with highly active antiretroviral therapy (HAART), hypertension, thyroid nodules, and uterine

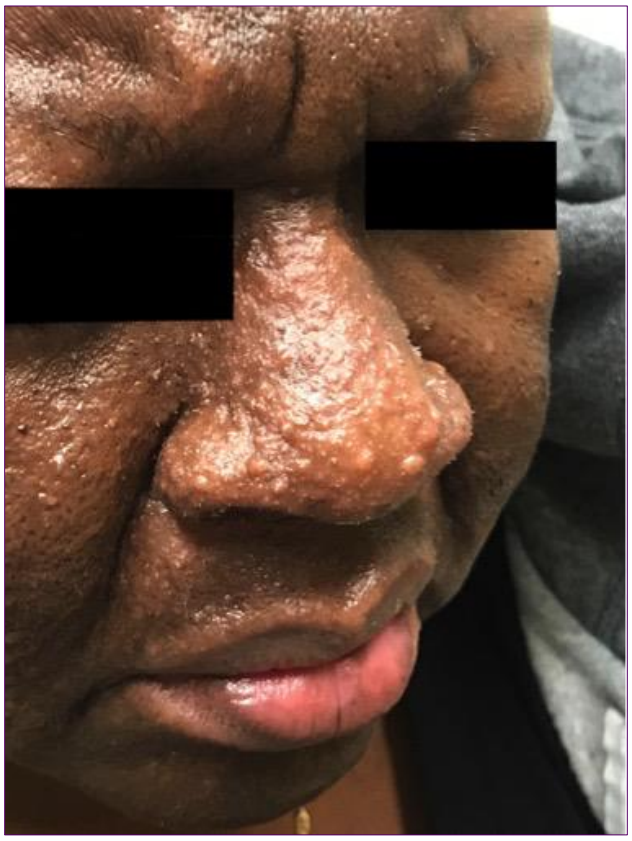
fibroids. Her medications included Betalacept (5mg/kg IV every 4 weeks), Tacrolimus (1 mg daily), prednisone (5mg daily), oxybutynin (15mg daily), gabapentin (300mg daily), dolutegravir (50mg daily), and Emtricitabine-tenofovir (200-25mg daily).

Laboratory findings were notable for a white blood cell count of 3,200 (4,000-11,000), Hemoglobin of 10.5 (12-15.5), hematocrit of 32.9 (36.1-44.3), platelets of 195 (150-450), BUN of 27 (10-15), creatinine of 1.79 (0.6-1.1mg), calcium of 10.6 (8.5-10.5mg/dl), LDL of 107 (100-120 mg/dL), and total cholesterol of 239 (<200mg/dL). All other laboratory values were normal.

Physical exam was significant for multiple skin colored, erythematous, firm papules, with spicules on the mid-face. Concomitant eyebrow alopecia was also appreciated. The patient endorsed occasional pain but no pruritus, burning or other symptoms. The differential diagnosis included acne vulgaris, trichodysplasia spinulosa, lichen spinulosus, trichoepitheliomas, colloid milium, and milia. She was treated for presumed acne vulgaris with salicyclic acid chemical peels, adalapene gel, benzoyl peroxide wash, and ultimately oral isotretinoin; however this resulted in no significant improvement.

A curettage biopsy subsequently demonstrated dilated, distended hair follicles within the dermis, without obvious shaft formation (Figure 1). The hair shaft was effaced and lacked true hair formation. Follicles were filled with abnormal, dense keratinization and excessive inner root sheath production. No outer root sheath or hair bulb papillae were present (Figures 2 and 3). The constellation of findings was most consistent with a diagnosis of trichodysplasia spinulosa.
The patient was treated with once daily compounded topical cidofovir 3% cream (with Versabase® Cream). After 8 months of therapy, the facial eruption completely resolved, however residual hyperpigmentation of the affected area was noted at the one-year follow-up. Ingredients of the cream base were reviewed with the compounding pharmacy and included the common contact allergens methylchloroisothiazolinone, methylisothiazolinone, ethylhexyl stearate, cyclopentasiloxane, sorbitol, aloe barbadensis leaf juice, tocopheryl acetate, and disodium EDTA.

Figure 1. Erythematous follicular papules and spicules of the mid-central face associated with alopecia of the eyebrows were appreciated on examination.



In order to rule out contact dermatitis, the patient underwent patch testing with the topical cidofovir cream and specifically methylchloroisothiazolinone and methylisothiazolinone. However, the results were negative for hypersensitivity. The patient discontinued topical cidofovir cream, which resulted in mild improvement of hyperpigmentation but recurring TS lesions. She chose to resume topical cidofovir, and the hyperpigmentation persists at the16-month follow-up.

Figure 2A. A curettage biopsy shows a disrupted, dilated, distended hair follicle within the dermis (H&E, 100x). No hair shaft formation is evident.

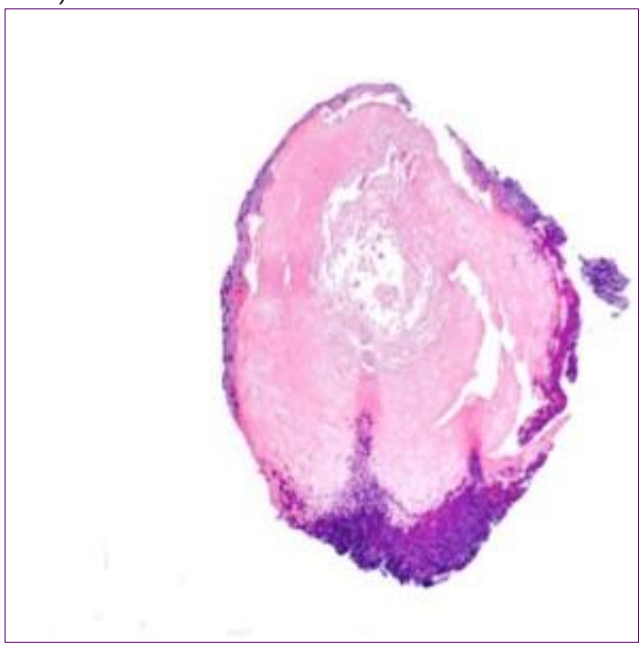


Figure 2B. The hair shaft is effaced without true hair formation. The follicle (H&E, 40x) shows abnormal, dense keratinization and excessive inner root sheath production. No outer root sheath is seen. The hair bulb lacks a papilla.

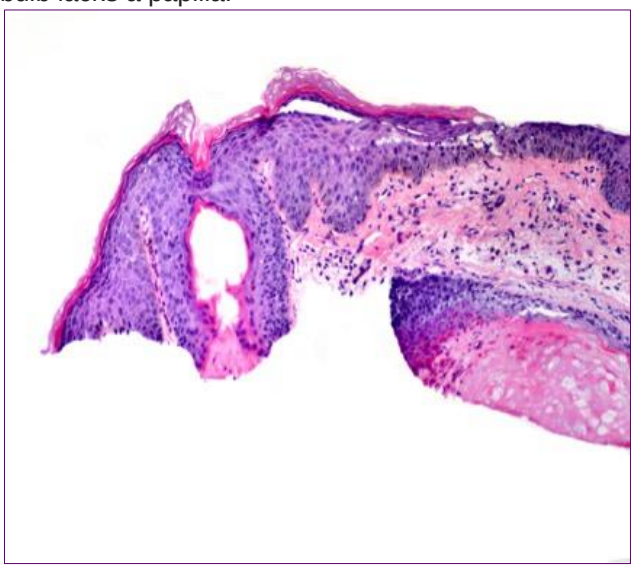
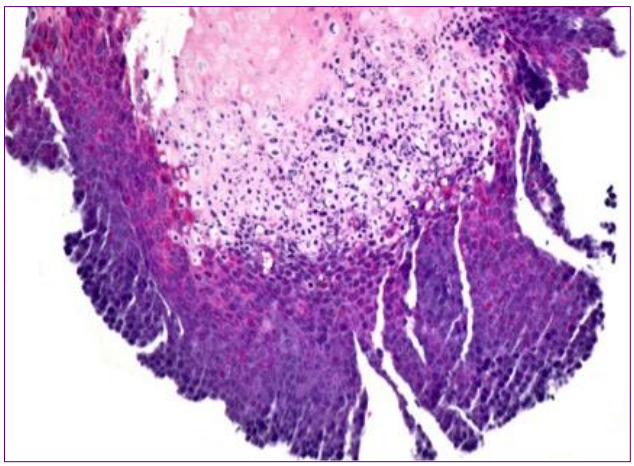


Figure 2C. Nucleated eosinophilic cells (H&E, 40x) with excess trichohyaline and intraepithelial viral inclusions can be seen.



DISCUSSION

The polyomaviridae virus is a small, non-enveloped double stranded DNA virus. Long-term infection with this virus is usually asymptomatic, but immunosuppression can lead to primary infection or reactivation, resulting in infection of the central nervous

system, urinary tract, respiratory tract, and skin.[1] In 2010, a new polyoma virus called Trichodysplasia Spinulosa-Associated polyomavirus (TSPyV) by Van der Meijden et al was reported to be the cause of TS.[1] This rare disease is known to affect immunocompromised hosts, most commonly after solid organ transplant. One recent review of 20 patients with TS found it to be associated with solid organ transplants in 13 cases and with leukemia or non-Hodgkin lymphoma in 7 cases.

TS is very rarely diagnosed in patients with HIV, perhaps because the degree of immunosuppression seen in patients treated with highly active antiretroviral therapy (HAART) is not sufficient for disease progression. Still, TSPyV was found to be elevated on the skin of men with known HIV compared to controls.[3] The current case is unique in that TS was diagnosed in an immunocompromised patient in the setting of both HIV infection and post-transplantation immunotherapy.

Clinically TS presents with follicular, erythematous, hyperkeratotic papules most often located on the central face, however it may also be found on the trunk and upper extremities. Skin thickening and alopecia have also been noted.[4] Histologically, TS is characterized by abnormal hair follicles often without a formed hair shaft. Excessive and disorganized inner root sheath cells, intraepithelial viral inclusions, and nucleated eosinophils containing excess trichohyaline can also be appreciated.[5]

Management of TS is challenging, as this disease entity is newly described and rare. Treatment options include topical cidofovir, topical acitretin, oral leflunomide, and manual extraction of keratin spicules (table I). This case highlights the safe use of topical cidofovir in a patient with a history of renal disease and transplant, though the oral antiviral counterpart is associated with nephrotoxicity. Furthermore, this case highlights hyperpigmentation as a rare adverse event associated with the use of topical cidofovir. Post-inflammatory hyperpigmentation was reported after the use of topical cidofovir for the treatment of molluscum contagiosum in 6 out of 14 patients with HIV.[6] However, after a thorough review of the literature in Pubmed, this case is the first to our knowledge to highlight a similar outcome in the setting of polyoma virus infection. Though the patient presented here did not test positive for contact dermatitis related to the topical cidofovir, it should be noted that the preservative ingredients found in topical cidofovir base, mainly methylchloroisothiazolinone and methylisothiazolinone, have been increasingly associated with a delayed hypersensitivity reaction.[7] Dermatologists should be aware of this potentially common adverse event and counsel patients with TS accordingly.

CONCLUSION

TS is a rare disease that affects immunosuppressed individuals. Topical cidofovir appears to be the most commonly used treatment (Table I). However, this unique case highlights a new and unreported adverse effect of hyperpigmentation in the setting of TS. Dermatologists should be aware of this potential consequence and counsel patients appropriately.

Table I. Review of reported treatments for trichodysplasia spinulosa.

Treatment	Mechanism of Action	Evidence	Adverse Events
Topical Cidofovir (1-3%)	Antiviral, which selective inhibits viral DNA polymerase.	Successful resolution of TS lesions after 2-4 months.[8-11]	Current case described hyperpigmentation adverse reaction. Use of topical cidofovir for the treatment of molluscum contagiosum has been associated with hyperpigmentation in several cases.[6]
Topical or Oral Acitretin	Speculated modulation of keratinocyte differentiation and hyperproliferation.	Minimal improvement of TS lesions after use of 20mg acitretin daily and tretinoin 0.05% daily, in a patient who ultimately improved due to recovered immune function.[12]	Limited evidence of efficacy.
Oral Leflunomide	Tyrosine kinase inhibitor, which inhibits replication of DNA viruses.	Modification of immunosuppressive medications and leflunomide 100 mg daily orally for 5 days, followed by 40 mg daily for 1 month resulted in resolutions of lesions after 3 months.[13]	None reported.
Oral Valganciclovir	Gancylcovir competitively inhibits dGTP incorporated in viral DNA, thereby inhibiting viral replication.	Successful resolution of TS lesions in a case report with the use of 900mg valganciclovir BID.[14]	None reported.
Manual Extraction	Physical removal of facial TS papules.	Successful resolution in a child after 2 months of repeated manual extraction.[15]	Pain associated with manual extraction.

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Corresponding Author:
Robert G Phelps, MD
Department of Dermatopathology
Department of Dermatology
Icahn School of Medicine at Mount Sinai
One Gustave L Levy Place, New York, NY 10029
Phone: 212-241-6500
Email: robert.phelps@mountsinai.org

References:

1. van der Meijden E, Janssens RW, Lauber C, Bouwes Bavinck JN, Gorbalenya AE, Feltkamp MC. Discovery of a new human polyomavirus associated with trichodysplasia spinulosa in an immunocompromized patient. *PLoS pathogens.* 2010;6(7):e1001024.
2. An P, Saenz Robles MT, Duray AM, Cantalupo PG, Pipas JM. Human polyomavirus BKV infection of endothelial cells results in interferon pathway induction and persistence. *PLoS pathogens.* 2019;15(1):e1007505.
3. Wieland U, Silling S, Hellmich M, Potthoff A, Pfister H, Kreuter A. Human polyomaviruses 6, 7, 9, 10 and Trichodysplasia spinulosa-associated polyomavirus in HIV-infected men. *The Journal of general virology.* 2014;95(Pt 4):928-932.
4. Haycox CL, Kim S, Fleckman P, et al. Trichodysplasia spinulosa--a newly described folliculocentric viral infection in an immunocompromised host. *The journal of investigative dermatology Symposium proceedings.* 1999;4(3):268-271.
5. DeCrescenzo AJ, Philips RC, Wilkerson MG. Trichodysplasia spinulosa: A rare complication of immunosuppression. *JAAD case reports.* 2016;2(4):307-309.
6. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2000;14(6):484-488.
7. Scherrer MA, Rocha VB, Andrade AR. Contact dermatitis to methylisothiazolinone. *Anais brasileiros de dermatologia.* 2015;90(6):912-914.
8. Nguyen NV, Burgos A, Prok L. Spiny Papules in an Immunosuppressed Child. *Pediatric dermatology.* 2015;32(6):e296-297.
9. Coogle LP, Holland KE, Pan C, Van Why SK. Complete resolution of trichodysplasia spinulosa in a pediatric renal transplant patient: Case report and literature review. *Pediatric transplantation.* 2017;21(2).
10. Leitenberger JJ, Abdelmalek M, Wang RC, Strasfeld L, Hopkins RS. Two cases of trichodysplasia spinulosa responsive to compounded topical cidofovir 3% cream. *JAAD case reports.* 2015;1(6):S33-35.
11. Santesteban R, Feito M, Mayor A, Beato M, Ramos E, de Lucas R. Trichodysplasia Spinulosa in a 20-Month-Old Girl With a Good Response to Topical Cidofovir 1%. *Pediatrics.* 2015;136(6):e1646-1649.
12. Digiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro JR. Systemic retinoids in the management of ichthyoses and related skin types. *Dermatologic therapy.* 2013;26(1):26-38.
13. Kassar R, Chang J, Chan AW, Lilly LB, Al Habeeb A, Rotstein C. Leflunomide for the treatment of trichodysplasia spinulosa in a liver transplant recipient. *Transplant infectious disease : an official journal of the Transplantation Society.* 2017;19(4).
14. Holzer AM, Hughey LC. Trichodysplasia of immunosuppression treated with oral valganciclovir. *Journal of the American Academy of Dermatology.* 2009;60(1):169-172.
15. Barton M, Lockhart S, Sidbury R, Wang R, Brandling-Bennett H. Trichodysplasia Spinulosa in a 7-Year-Old Boy Managed Using Physical Extraction of Keratin Spicules. *Pediatric dermatology.* 2017;34(2):e74-e76.