Trichodysplasia spinulosa: a presentation of polyomavirus infection in immunosuppressed patients

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Abstract

Trichodysplasia spinulosa (TS) is a rare skin condition that occurs mainly in immunosuppressed patients. Although initially postulated to be an adverse effect of immunosuppressants, TS-associated polyomavirus (TSPyV) has since been isolated from TS lesions and is now considered to be the causative agent. Trichodysplasia spinulosa presents with folliculocentric papules with protruding keratin spines, most commonly on the central face. Trichodysplasia spinulosa can be diagnosed clinically, but the diagnosis can be confirmed with histopathological examination. Histological findings include the presence of hyperproliferating inner root sheath cells containing large eosinophilic trichohyaline granules. Polymerase chain reaction (PCR) can also be used to detect and quantify TSPyV viral load. Owing to the paucity of reports in the literature, TS is frequently misdiagnosed and there is no high-quality evidence to guide management. Herein, we present a renal transplant recipient with TS that did not respond to topical imiquimod but improved upon treatment with valganciclovir and reduction of the mycophenolate mofetil dose. Our case highlights the inverse relationship between immune status and disease progression in this condition.

Keywords: immunosuppression, mycophenolate mofetil, transplant, trichodysplasia spinulosa, valganciclovir

Introduction

Trichodysplasia spinulosa (TS) presents almost exclusively in immunosuppressed patients [1]. Trichodysplasia spinulosa was first reported in 1995 in a renal transplant recipient treated with cyclosporine [2]. The term trichodysplasia spinulosa was then coined in 1999 by Haycox et al. in their report of a combined renal and pancreatic transplant recipient on tacrolimus, azathioprine, and prednisone [3]. Although initially believed to be an adverse effect of cyclosporine, in 2010, the causative agent of TS, TS-associated polyomavirus (TSPyV), was isolated and characterized from the keratotic spicules of a patient [4]. To date, approximately 60 cases of TS have been described in the literature [1]. Trichodysplasia spinulosa presents characteristically with a folliculocentric papular eruption with keratin spine formation, most frequently on the face [5,6]. Owing to its rarity, this condition is often misdiagnosed and there is a lack of evidence to support any gold standard treatment. Herein, we report a renal transplant recipient with TS and the significant improvement upon administration of valganciclovir and reduction of the dose of mycophenolate mofetil.

Case Synopsis

A 71-year-old-woman presented to our dermatology clinic with a 5-month history of asymptomatic skin-colored follicular papules on her face. She reported her rash had started while travelling through Southeast Asia, where she had significant amounts of sun exposure. She had previously been diagnosed by two different dermatologists as having rosacea and seborrheic dermatitis. She had tried and failed doxycycline, metronidazole 0.75% cream, sulfur-

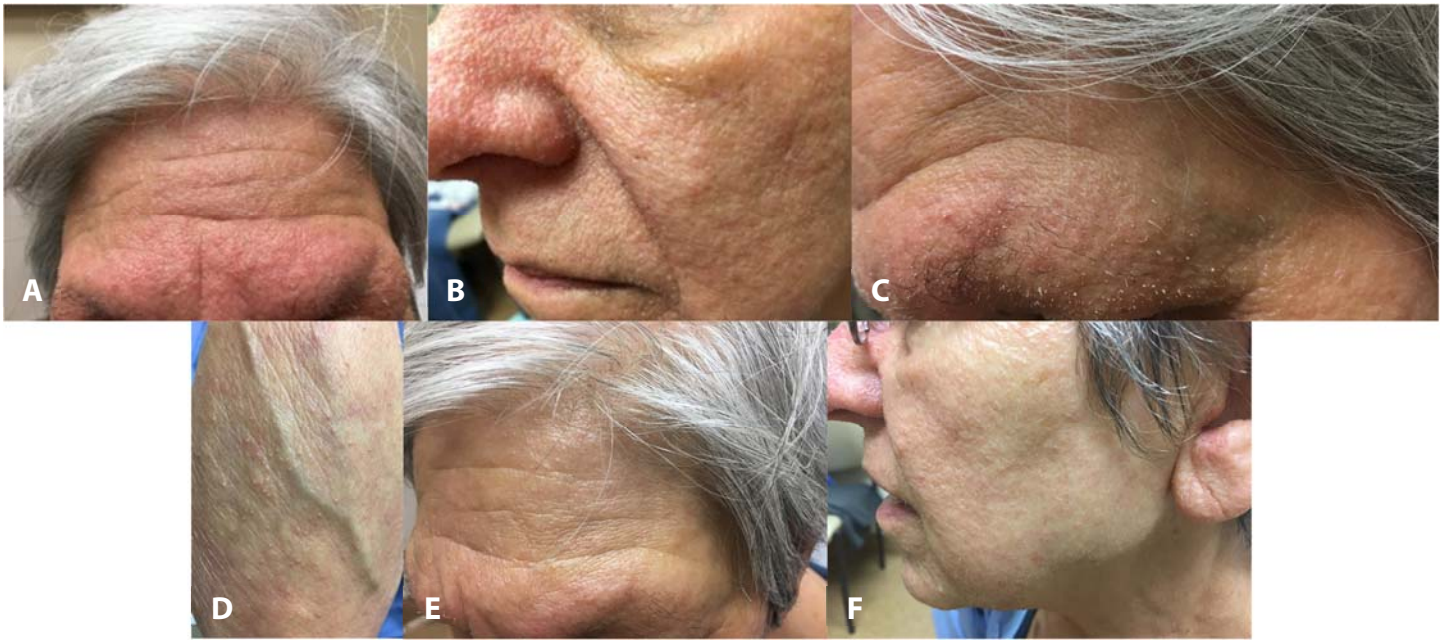

Figure 1. ***A-D****) Diffuse folliculocentric papules with white spiny projections over the forehead, nose, medial cheeks, and forearms.* ***E-F****) Marked clinical improvement upon introduction of valganciclovir and reduction in the dose of mycophenolate mofetil.*

containing face wash, ketoconazole 2% cream, ketoconazole 2% shampoo, tacrolimus 0.1% ointment, and hydrocortisone 2.5% cream. Of note, she had undergone an unrelated kidney transplant a year prior to her presentation, for which she was taking mycophenolate mofetil 720mg twice daily, prednisone 5mg once daily, and oral tacrolimus 1mg once daily.

Examination revealed diffuse papules with white spiny projections over the forehead, eyebrows, nose, medial cheeks, chin, upper arms, and trunk (**Figure 1**). She also had bilateral loss of the lateral eyebrows, but no alopecia elsewhere. The clinical differential diagnosis mainly centered on trichodysplasia spinulosa because of the distinctive eruption of keratin spines in the setting of immunosuppression.

Two 4mm punch biopsies taken from the left medial and right lateral eyebrow revealed dysmorphic terminal-sized follicles with expanded outer root sheaths containing coarse trichohyalin granules along with an absence of formed hair shafts or follicular papillae, diagnostic of TS (**Figure 2**). She was started on oral valganciclovir 450mg twice a day and the renal team halved the dose of mycophenolate mofetil to 360mg twice daily to reduce immunosuppression. She was also started on imiquimod 5% cream three times a week. Despite reporting slight improvement with imiquimod, she self-discontinued this after three weeks because of dryness. She was then offered acitretin or a topical retinoid but declined due to concern for side effects. After an initial flare related to sun exposure during a vacation, she experienced gradual and continued improvement over the next several months; valganciclovir was tapered and stopped approximately one year after her initial presentation. On her last follow-up two years after presentation, she was satisfied with her current condition and had minimal skin involvement.

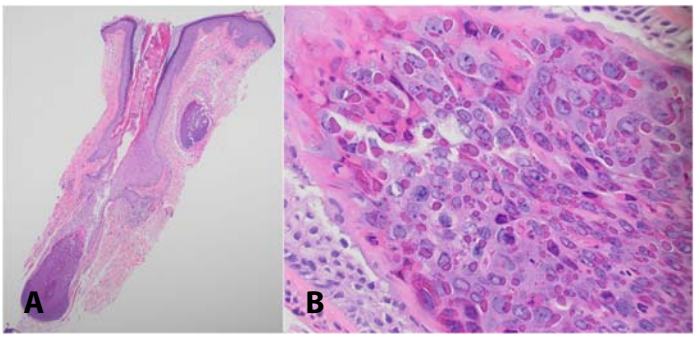

Figure 2. *Histological sections stained with H&E show the bulbar/stem portions of superficial dysmorphic terminal-sized follicles with expanded inner root sheaths containing coarse trichohyalin granules, along with absence of formed hair shaft or follicular papillae.* ***A)*** *40×;* ***B)*** *200×.*

Case Discussion

Trichodysplasia spinulosa is a folliculocentric skin infection that occurs chiefly in immunosuppressed patients. It has been reported in ages 5 to 70 and does not appear to have any sex predilection [5]. Although initially described in association with cyclosporine use in solid organ transplant patients [7,8], TS was subsequently reported in association with other immunosuppressants [9,10] and hematological malignancies [11,12]. Trichodysplasia spinulosa has also been reported in one patient with no history of immunosuppression that was treated with vismodegib for basal cell carcinomas arising from Gorlin syndrome [13].

As exemplified by the improvement in our patient's condition when immunosuppression was reduced, there is an inverse relationship seen between immune status and disease progression in TS. This supports the increasingly accepted hypothesis that infection with TSPyV is the likely driving agent in this condition. TSPyV was first isolated from plucked spicules of TS patients using DNA amplification [4]. However, given that TSPyV infection is largely prevalent in the general population, with seropositivity rates of 70% in healthy adults [14,15], it is likely that factors other than immunosuppression are involved in the pathophysiology of TS. Recent data suggests that primary infection, rather than reactivation of latent infection, may be necessary for the development of TS [16]. Interestingly, in our patient, both the initial presentation and a later flare were attributed to sun exposure. Ultraviolent (UV) radiation is known to be a trigger for reactivation of viral infections, most prominently herpes simplex virus, but also possibly varicella zoster virus, human papillomavirus, and human immunodeficiency virus [17]. The effect of UV radiation on TSPyV remains to be studied. Recently, another human polyomavirus, human polyomavirus 9 (HPyV9) has been reported to cause a widespread eruption characterized by hyperkeratotic papules and plaques in solid organ transplant recipients [18]. These findings suggest that the manifestations of various human polyomavirus infections in immunosuppressed patients remain incompletely understood.

Trichodysplasia spinulosa can be diagnosed clinically but histopathological findings and molecular testing provide diagnostic confirmation. The features seen in TS relate to disruption of normal hair maturation. Trichodysplasia spinulosa characteristically presents with skin-colored or erythematous follicular papules with protruding white-yellowish keratin spines [1,5,19]. It most commonly affects the central face, but can also occur on the neck, trunk, and extremities. As the disease progresses, varying alopecia and leonine facies can occur. Alopecia most commonly involves the eyebrows but can also involve the eyelashes and scalp [1,5,19]. On dermatoscopy, TS can be distinguished from other hyperkeratotic disorders by the presence of long, bright white spicules that protrude peripherally from follicular openings, compared to the dark, confined keratin plugs seen in other hyperkeratotic conditions [20]. The differential diagnosis of TS includes folliculitis, keratosis pilaris, ulerythema, lichen spinulosus, lichen planopilaris, multiple minute digitate hyperkeratosis, spiculate demodicosis, alopecia mucinosa, trichostasis spinulosa, follicular graft-versus-host disease, and follicular spicules of multiple myeloma [5,9].

Histologically, the hallmark of TS is the presence of hyperproliferating inner root sheath cells containing large eosinophilic trichohyaline granules. Other features include abnormally large hair follicles with dilated infundibula, along with small or absent papillae owing to hair bulb hyperplasia. On immunostaining, high expression of the proliferative marker Ki67 is common [1,5]. The diagnosis of TS can also be confirmed with a "pull test," by removing keratin spicules with tweezers and using light microscopy to visualize inner root sheath keratin accumulation [21]. Electron microscopy can also be used to demonstrate the presence of intranuclear polyomavirus particles within inner root sheath cells [21]. Alternatively, real-time polymerase chain reaction (RT-PCR) can provide both diagnostic confirmation and TSPyV viral load quantification. TSPyV can be found in low amounts (i.e., $<10^4$ copies per cell) in non-TS tissues [5,22]. However, it remains unknown whether viral load correlates with disease severity.

There is limited data regarding the optimal treatment of TS. Topical cidofovir 1-3% cream, applied twice daily, is a reasonable first-line option when available. Topical cidofovir has been shown to result in clinical improvement and reduction in TSPyV viral loads [1,5]. Studies have shown that cidofovir inhibits human polyomavirus replication in vitro, but its potential effects on TSPyV replication remain uninvestigated [23]. Although nephrotoxicity is a side effect of cidofovir when administered intravenously, no renal complications from topical cidofovir have been reported so far [5,24]. However, the availability of topical cidofovir is limited in many countries. Another antiviral, oral valganciclovir, is more widely available and has also been shown to result in improvement in multiple cases [1,19,25,26]. Other therapies, including topical and oral retinoids, topical imiquimod, topical corticosteroids, keratolytics, and antibiotics have exhibited more mixed results [1,5]. Reduction of immunosuppression is also effective, but should only be attempted in the appropriate clinical scenario and in consultation with transplant specialists because of the risk of organ rejection [1]. In our patient, introduction of valganciclovir and reduction in mycophenolate mofetil resulted in marked clinical improvement.

Conclusion

Trichodysplasia spinulosa is a rare condition that is commonly misdiagnosed in immunosuppressed patients. Herein, we report a renal transplant recipient with TS that was initially diagnosed as rosacea and seborrheic dermatitis. Our patient improved upon use of valganciclovir and reduction of immunosuppression. Given the high seropositivity of TSPyV infection in the general population, it is possible that TS is underdiagnosed. Our case illustrates the importance of having a high index of suspicion for TS in immunosuppressed patients presenting with a hyperkeratotic follicular eruption on the central face.

Potential conflicts of interest

The authors declare no conflicts of interest.

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