REVIEW ARTICLE

Trichodysplasia spinulosa: a comprehensive review of the disease and its treatment

P. Curman,[1,2,*] A. Näsman,[3,4] H. Brauner[2,5,*]

[1]Dermatology and Venereology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[2]Dermato-Venereology Clinic, Karolinska University Hospital, Stockholm, Sweden
[3]Department of Clinical Pathology and Cytology, Karolinska University Hospital, Stockholm, Sweden
[4]Department of Oncology and Pathology (OnkPat), Karolinska Institutet, Stockholm, Sweden
[5]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
*Correspondence: P. Curman and H. Brauner, E-mail: hanna.brauner@ki.se (HB); philip.curman@ki.se (PC)

Abstract

Trichodysplasia spinulosa (TS) is a rare dermatological disease caused by TS-associated polyomavirus (TSPyV) in immunosuppressed patients. The seroprevalence of TSPyV in immunocompetent adults is high and the number of immunosuppressed patients developing TS remains low, suggesting that TS is underdiagnosed and/or that additional unknown factors are needed in order to develop TS. There is no well-established treatment for TS, and to date a majority of reported cases have consequently received ineffective therapies, likely due to the unavailability of reviews and recommendations of treatments for TS. The few treatments reported in case reports to be effective include topical cidofovir 3%, reduction of immunosuppression and oral valganciclovir. In this comprehensive review, we present all published cases to date, together with a summary of all treatments for TS categorized by overall clinical efficacy, thus addressing this rare disease and what appears to be its clinically efficacious treatment.

Received: 17 April 2020; revised: 16 October 2020; Accepted: 27 October 2020

Conflicts of interest

HB has received personal fees from Kyowa Kirin, outside the submitted work. PC and AN declare no conflict of interest.

Funding sources

HB is supported by the Swedish Society for Medical Research, the Swedish Cancer Foundation, the Swedish Medical Association, Region Stockholm (clinical research appointment), and Clas Groschinsky, Åke Wiberg and Karolinska Institutet foundations. AN is supported by grants from stiftelsen Åke Wibergs stiftelse, Jeanssons stiftelser, Stockholms Läns Landsting, stiftelsen Tornspiran, Karolinska institutet, Cancer och Allergifonden and Magnus Bergvalls stiftelse.

Introduction

Trichodysplasia spinulosa (TS) is a rare folliculocentric disease, first reported in 1995,[1,2] and later named in 1999.[3] The key clinical manifestation of TS is keratin spines protruding through follicular openings, which have been termed spicules.[2] The centre of the face is the most frequently affected body site, but spicules can develop virtually anywhere or be disseminated throughout the skin.[4,5] TS appears to occur exclusively in immunocompromised patients, most commonly following solid organ transplantation or immunosuppressive treatment for leukaemia. TS is caused by TS-associated polyomavirus (TSPyV), first isolated and characterized in 2010.[6] Seroepidemiological studies have however found that TSPyV is ubiquitous and that the seroprevalence in healthy, immunocompetent adults is around 65–80%.[7–13] It is still incompletely known why some immunocompromised patients develop TS while the majority do not. Given the rarity of the disease, no gold standard treatment exists. To date (until end of April 2020), 60 clinical cases and their treatments have been described in published literature[1–6,14–60] (Table 1). Several different treatment modalities have been tested and more or less thoroughly assessed through clinical case studies. The clinical efficacy of the different treatments however varies greatly, motivating the need for this systematic review of all published cases.

To the best of our knowledge, no comprehensive or up-to-date review of TS and its treatment exists. We herein present an in-depth review of TS, including an evaluation of different treatments, together with a previously unpublished case of TS to illustrate its clinical features.

Methods

We aimed to include in this review all cases of TS published and available on PubMed on April 2020. The initial search

Table 1 Trichodysplasia spinulosa: summary of all published cases

Ref.	Age, gender	Country	Medical history	Immunosuppressant(s)	TS onset	Diagnostics	Treatment(s)	Outcome
(1)	31, M	Germany	Kidney transplant	Pred, CsA	9 months	Histo	Reduced immunosuppression	Virtually healed 3 months after reduced CsA
(2)	79, M	Spain	Multiple myeloma	Pred, Melphalan	–	Histo	Topical urea 10%	Healed after ~ 1 year
(3)	44, M	USA	Kidney/pancreatic transplant	Pred, Tacrolimus, AZA	2.5–3 years	Histo, EM	–	–
(4)	13, F	USA	Bilateral lung transplant	Pred, CsA, MMF, MTX	2.5 years	Histo	Benzoyl peroxide	No effect
(47)	34, F	USA	Kidney transplant	Pred, Tacrolimus, CsA, MMF	2.5 years	Histo	Topical steroids, antibiotics, calcineurin inhibitors & tretinoin 0.05%	No effect
(15)	13, F	USA	Kidney transplant	Pred, Tacrolimus, MMF	9 months	Histo, EM	Topical steroids, imiquimod & cidofovir 3%	Partial effect cidofovir
(16)	8, M	USA	Kidney transplant	Pred, Tacrolimus, MMF	8 months	Histo, EM	–	–
	19, M	USA	ALL	Pred, CP, Vincristine	2.5 years	Histo, EM	–	–
(48)	48, F	USA	Kidney transplant	Tacrolimus, MMF	8–9 years	Histo	Topical tretinoin 0.05% & tazarotene gel 0.5%	Partial effect tazarotene gel
(14)	68, M	USA	Non-Hodgkin's lymphoma	Fludarabine, Rituximab	1–1.5 years	Histo, EM	Topical cidofovir 1%	Good effect cidofovir, improved within months
(17)	8, M	Australia	ALL	Vincristine, 6-MP, MTX	2 years	Histo, EM	Topical salicylic acid 4%, Ammonium lactate 17.5%, tretinoin 0.05% & oral acitretin 10 mg x 2	No effect. Healed spontaneously 2 years later
	6, M	Australia	ALL	Pred, CP, Vincristine	2 years	Histo, EM	–	Healed spontaneously 9 months later
(18)	70, M	Australia	CLL	Fludarabine, Rituximab, CP	4 years	Histo	Topical urea 10% + lactate 5%	No effect. No regression 15 months later
(49)	37, F	USA	Heart transplant	Pred, CsA, MMF	8 months	Histo	Topical imiquimod, tazarotene gel, acyclovir & oral valganciclovir	Good effect valganciclovir. Healed 1 year later
(50)	5, M	USA	Heart transplant	Pred, Tacrolimus, MMF	1 year	Histo	Topical ammonium lactate + triamcinolone, tretioin 0.025%, Urea & cidofovir 3%	Good effect valganciclovir, unknown effect cidofovir
(19)	5, F	Canada	Heart transplant	Tacrolimus, MMF	9 months	Histo, EM	Topical retinoid, oral isotretinoin 0.5 mg/kg & valganciclovir	Good effect valganciclovir
(6)	15, M	Netherlands	Heart transplant	Pred, Tacrolimus, MMF	1 year	Histo, EM, PCR	Topical cidofovir 1%	Partial effect. Virtually healed after 3 months
(51)	27, F	USA	Kidney transplant	Tacrolimus, MMF	–	–	Topical acyclovir + 2-deoxyglucose + green tea extract	Good effect
(20)	9, F	Canada	Pre-B ALL	Vincristine, 6-MP, MTX, dexamethasone	–	Histo	–	–
(21)	7, F	USA	Pre-B ALL	Chemotherapy (not specified)	2–4 months	Histo, EM, PCR	Topical steroids	Diseased (sepsis)

Table 1 *Continued*

Ref.	Age, gender	Country	Medical history	Immunosuppressant(s)	TS onset	Diagnostics	Treatment(s)	Outcome
(73)	46, F	USA	Kidney transplant	–	4 months	Histo	Topical steroids, antibiotics, retinoids, oral antibiotics, antihistamines & valganciclovir	Good effect valganciclovir. Improved 7 weeks later
(23)	62, M	USA/Romania	Bilateral lung transplant	Pred, Tacrolimus, MMF	6 years	Histo, EM, PCR	Oral valacyclovir	Poor effect. Relapses following years
	37, F	USA/Romania	Heart transplant	Pred, Tacrolimus, MMF	8 months	Histo, EM, PCR	Oral valganciclovir	Good effect
(22)	48, M	USA	Kidney transplant	Tacrolimus, MMF	2–3 months	Histo, EM, PCR, cytology	–	–
(52)	57, F	USA	CLL	Rituximab, CP, Cytarabine	6 months	Histo, EM, PCR	Topical imiquimod, salicylic acid, steroids, cidofovir 1% & oral cimetidine	Partial effect cidofovir
(45)	14, F	USA	Lung transplant	Pred, Tacrolimus, MMF, CsA, Muromonab, Tobramycin	3 years	Histo	Topical keratolytics, cryo therapy & reduced immunosuppression	Unknown effect. Healed 2.5 years later
(25)	5, M	Spain	ALL	6-MP, MTX	3–4 months	Histo	Topical emollients & keratolytics	No effect. Healed spontaneously 3 years later
(53)	62, M	USA	Kidney transplant	Pred, Tacrolimus, MMF	6 months	Histo	Topical cidofovir 1%	Partial effect
(28)	Middle aged	Canada	Kidney transplant	Pred, Tacrolimus, MMF	11 months	Histo	Oral valganciclovir	Good effect. 90% healed 1 year later
(26)	49, F	Australia	Kidney transplant	Pred, Tacrolimus, MMF	11 months	Histo, PCR	Topical tretinoin 0.05% & oral valganciclovir	No effect. No regression 4 months later
(24)	26, F	France	SLE with complications	Pred, CP, MMF	1–1.5 years	Histo, PCR	–	Diseased (cardiac arrest)
	40s, M	USA	Gorlin syndrome	Vismodegib	3 months	Histo	Topical anti-fungals, steroids, valacyclovir & imiquimod	Poor effect. Healed after discontinuation of vismodegib
(27)	7 months, F	Japan	Myocarditis	–	–	PCR	–	Diseased (myocarditis)
(30)	42, F	Canada	Kidney transplant	Pred, Tacrolimus, MMF	8 months	Histo	Topical acyclovir & retinoids	No/poor effect
(31)	36, M	USA	Kidney transplant	Pred, Tacrolimus, MMF	8 months	Histo, PCR	Topical anti-fungals, metronidazole, imiquimod, cidofovir 1 & 3% & oral valganciclovir	Good effect cidofovir 3%. Virtually healed 3 months later
(29)	62, M	USA	Kidney transplant	Pred, Tacrolimus, MMF	6 months	Histo	Topical cidofovir 1 & 3%	Partial effect cidofovir 3%. Improved 3 months later
(32)	7, M	USA	Pre-B ALL	Vincristine, 6-MP, MTX	3 months	Histo, EM	Topical cidofovir 3%	Partial effect. Healed 1 month after discontinued immunosuppression
(33)	1.5, F	Spain	Multivisceral transplant	Pred, Tacrolimus	5–6 months	Histo	Topical cidofovir 1%	Good effect. Healed 1.5 years later
(35)	35, M	USA	Kidney transplant	Tacrolimus, MMF	6 months	Histo	Reduced immunosuppression	Good effect. Healed 2 years later

Table 1 *Continued*

Ref.	Age, gender	Country	Medical history	Immunosuppressant(s)	TS onset	Diagnostics	Treatment(s)	Outcome
(34)	12, M	France	Kidney transplant	Tacrolimus, MMF	6 months	Histo, PCR, serology	Topical steroids, emollients & oral acyclovir	No effect
(40)	7, M	USA	Pre-B ALL	Chemotherapy (not specified)	–	PCR	Manual extraction of spicules with tweezers	Good effect. Virtually healed 2 months later
(39)	7, M	Australia	Pre-B ALL	Chemotherapy (not specified)	33 months	PCR	–	Virtually healed 12 months later
(41)	11, M	USA	Kidney transplant	Pred, Tacrolimus, MMF	14 months	Histo	Reduced immunosuppression & topical cidofovir 1%	Good effect both. Virtually healed at 7 months & 4 years later
(36)	6, M	USA	ALL	–	6 months	Histo, PCR	–	Healed 6 months after discontinuation of immunosuppression
(5)	37, M	Canada	Liver transplant	Cyclosporine	16.5 years	Histo	Reduced immunosuppression, topical retinoids & oral leflunomide 20 mg × 1 for 3 months	Good effect leflunomide. Healed 3 months later
(37)	79, M	Spain	AML	Cytarabine, Glasdegib	3 months	Histo	–	–
(42)	52, F	USA	Kidney transplant	Pred, Tacrolimus, MMF	4 years	Histo, PCR	–	–
(38)	54, M	Netherlands	ALL	Chemotherapy (not specified), Cyclosporine	–	Histo, PCR	Topical cidofovir 1%	Good effect. Healed 14 weeks later
	62, F	Netherlands	Kidney transplant	Tacrolimus, MMF	1.5–2 years	Histo, PCR	Oral valganciclovir	Partial effect. Improved 5 months later
(43)	52, F	France	HIV, B-cell lymphoma	R-CHOP	–	Histo, PCR, confocal microscopy	Oral acitretin 20 mg × 1 & valganciclovir	Good effect valganciclovir. Healed 4 months later
(46)	37, F	Chile	Myelodysplastic syndrome	–	–	Histo	–	–
(44)	82, F	USA	Non-Hodgkin's lymphoma	–	–	Histo	Topical metronidazole & oral doxycycline	Diseased (colon cancer)
(54)	9, F	USA	Kidney transplant	Pred, Tacrolimus, MMF, Alemtuzumab	44 months	Histo	Reduced immunosuppression, i.v. cidofovir & topical cidofovir 1%	Good effect reduced immunosuppression & i.v. cidofovir. Improved 4 months later
(57)	7, M	Italy	Bilateral kidney transplant	Pred, Tacrolimus, MMF	–	Histo, PCR	–	–
(56)	6, F	USA	Intenstinal transplant	Pred, Tacrolimus, Sirolimus	'Several months'	Histo, PCR	Topical cidofovir 1%	–
(55)	7, M	USA	Pre-B ALL	– (MTX?)	6 months	Histo, IHC	Topical steroids & oral prednisone	No effect
(59)	65, F	Brazil	Kidney transplant	Pred, Tacrolimus, MMF	6 months	Histo, PCR	Oral valacyclovir, topical acyclovir, i.v. cidofovir & oral leflunomide	Good effect leflunomide. Improved 4 months later
(58)	6, M	Lebanon	Heart transplant	Pred, Tacrolimus, MMF	15 months	Histo	Topical valacyclovir	–
(60)	25, F	USA	Kidney transplant	Pred, Tacrolimus, MMF	6 months	Histo	Topical imiquimod, oral valganciclovir	Good effect valganciclovir. Healed 7 weeks & 10 months later

Table 1 *Continued*

Ref.	Age, gender	Country	Medical history	Immunosuppressant(s)	TS onset	Diagnostics	Treatment(s)	Outcome
This article	68, F	Sweden	CLL	Alemtuzumab, Ofatumumab	5 months	Histo, PCR	Topical steroids, anti-fungals, calcineurin inhibitors, adapalene gel, & oral antibiotics & acyclovir	No effect

6-MP, mercaptopurine; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; AZA, azathioprine; CLL, chronic lymphocytic leukaemia; CP, cyclophosphamide; CsA, cyclosporine A; EM, electron microscopy; Histo, histopathology; i.v. , intravenous; IHC, immunehistochemistry; MMF, mycophenolate mofetil; MTX, methotrexate; PCR, polymerase chain reaction; Pred, prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SLE, systemic lupus erythematosus; TS, trichodysplasia spinulosa.

query was 'Trichodysplasia spinulosa'. All relevant articles were evaluated and included if they clearly described a case of the disease. Articles not unquestionably depicting TS were excluded. The reference lists of the identified articles were thereafter thoroughly reviewed in search for new articles to include, and the process was repeated until no new articles were found in the reference lists of included papers. Due to the initial diversity in naming the disease (see 'History'), all different names for the disease went through the same process and searches were continued until no new articles were found on PubMed or in reference lists. The literature searches were focused on medical literature in English; however, one article in German and one in Spanish were also included after being translated. One case with a misspelling of the word 'Trichodysplasia' in the title ('Trichoydsplasia') was also identified and included since the word was correctly spelled in the abstract.

History

Except a few descriptions of follicular hypertrophy of unknown origin in the second half of the 20th century, TS is first described and associated with immunosuppression in 1995.[1,2] The name 'Trichodysplasia spinulosa' was coined in 1999,[3] and the disease-causing human polyomavirus (HPyV) TSPyV was ultimately characterized in 2010.[6] Previous names for the disease include 'Follicular spicules of the nose',[2] 'Pilomatrix dysplasia',[4] 'Virus-associated trichodysplasia of immunosuppression',[15] 'Trichodysplasia of immunosuppression'[48] and 'Cyclosporine-induced folliculodystrophy'.[47]

Trichodysplasia spinulosa-associated polyomavirus

Human polyomaviruses constitute a group of small viruses with a non-enveloped double stranded DNA genome. The genome is divided into a non-coding region, and an early and a late region. The early region encodes the large T-antigen and the small T-antigens, which are all involved in viral replication and cell transformation. The late region encodes the capsid proteins, VP-1, VP-2 and VP-3.[61]

The BK and JC viruses were identified in 1971 and were for a long time the only two HPyVs known. However, in 2007, a third HPyV was discovered at Karolinska Institutet – the KI polyomavirus (KIPyV) – and a couple of months later a fourth virus – the Washington University polyomavirus – was discovered. Thereafter, the number of identified HPyV species has increased dramatically and today 13–14 different HPyVs have been described. Another name for TSPyV is HPyV 8.[61]

Trichodysplasia spinulosa-associated polyomavirus in Trichodysplasia spinulosa

The first evidence of a potential link between a HPyV and TS was published in 1999, when Haycox *et al.*[3] demonstrated intracellular small viral particles in cells from patients with TS using

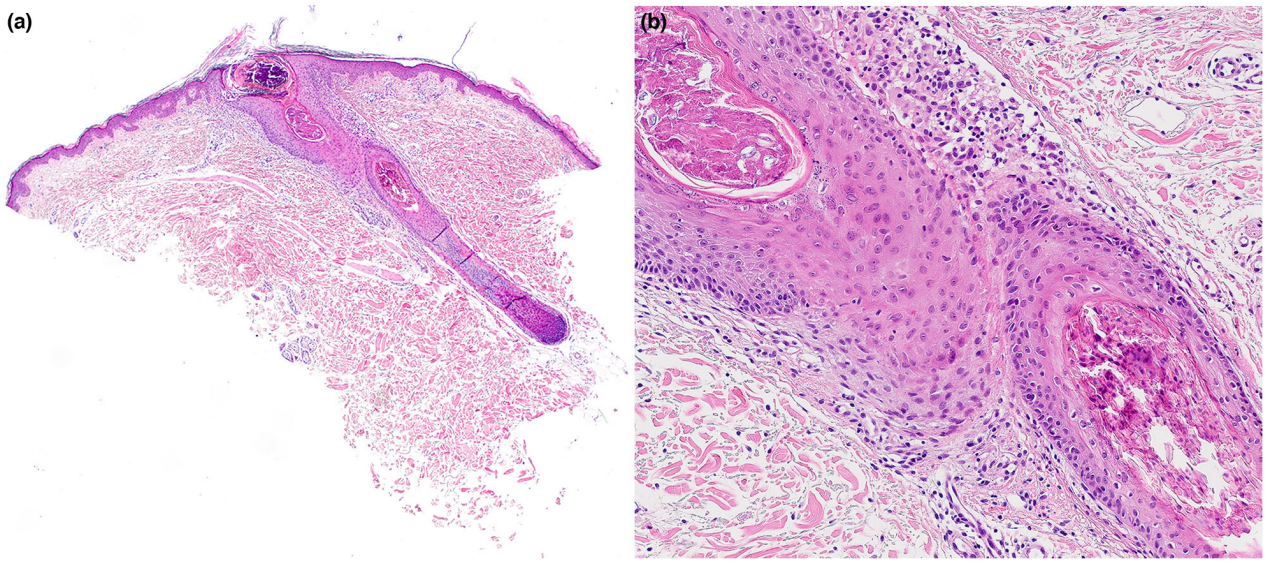

Figure 1 Trichodysplasia spinulosa: histo-morphological appearance, as identified in the patient described. (a) 40× magnification showing a dilated hair follicle with keratin plugging and (b) 400× magnification showing eosinophilic trichohyalin protein deposits.

electron microscopy. However, it was not until 2010 that the TSPyV was identified specifically in lesional skin by van der Meijden and colleagues, utilizing a rolling-circle amplification method followed by treatment with restriction enzymes and sequencing.[6] The infection appears to be causative for TS since high viral loads are found solely in lesional skin (~10^6 copies/cell) but not in non-lesional skin (<10^2 copies/cell) and control samples.[62] Today, the 'gold standard' detection method of TSPyV is PCR. For a complete diagnosis of TS, however, TSPyV PCR together with typical histo-morphological changes and clinical presentation should be included.

Epidemiology of Trichodysplasia spinulosa-associated polyomavirus

Transmission of TSPyV seems to occur in early childhood, primarily from mother to child and between siblings.[63] The

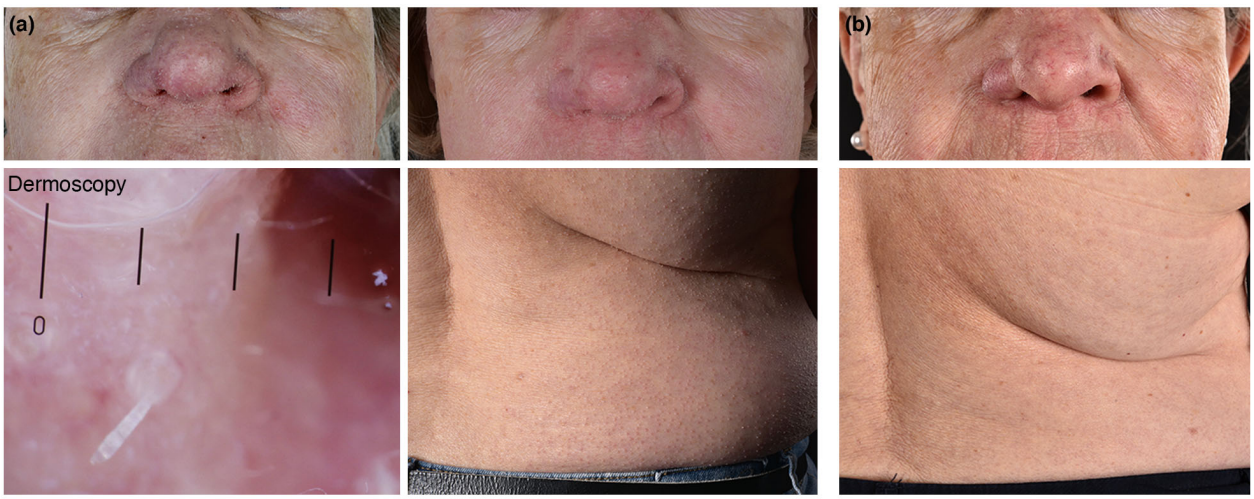

Figure 2 Trichodysplasia spinulosa: clinical features. (a) Early presentation showing keratin spines, or spicules, protruding through follicular openings in the central facial area and the trunk. Dermoscopy illustrating a spicule. (b) Complete resolution 3 years after discontinuation of immunosuppression.

Table 2 Trichodysplasia spinulosa: summary of all treatments categorized by reported efficacy, sorted after number of treatments.

Reported overall efficacy	*n*	%
Good	**23**	**23.5**
Oral valganciclovir	11	11.2
Reduced immunosuppression	5	5.1
Cidofovir 3%	4	4.1
Oral leflunomid	2	2.0
Manual extraction	1	1.0
Partial	**12**	**12.2**
Cidofovir 1%	10	10.2
I.v. cidofovir	2	2.0
No/poor	**63**	**64.3**
Topical retinoids	12	12.2
Topical steroids	9	9.2
Topical imiquimod	6	6.1
Topical keratolytics	5	5.1
Emollients	5	5.1
Topical anti-virals†	5	5.1
Oral anti-virals†	4	4.1
Oral retinoids	3	3.1
Topical antibiotics	3	3.1
Topical anti-fungals	3	3.1
Oral antibiotics	2	2.0
Oral antihistamines	2	2.0
Topical calcineurin inhibitors	2	2.0
Benzoyl peroxide	1	1.0
Oral glucocorticoids	1	1.0
Total treatments	**98**	**100**
No/unknown treatment or unreported effect	**23**	–

n = total number of treatments.
†Other than cidofovir. ‡Other than valganciclovir.
Bold values are the sum of *n* and % for each category and in total.

seroprevalence is high from birth until 2 months of age, after which it rapidly decreases, suggesting the presence of maternal antibodies early in life. At around 3 years of age, the seroprevalence starts to increase until it reaches adult levels at 11 years of age,[7,8,12] indicating that infection occurs in childhood. TSPyV has been found in many body sites in addition to skin, including blood, urine, faeces, conjunctiva, tonsils, upper respiratory tract, heart and gastrointestinal organs.[22,27,38,56,64,65] However, so far there is no evidence that TSPyV plays a role in the pathophysiology of any other disease.[66,67]

The seroprevalence of TSPyV in healthy and immunocompetent adult populations is high and varies in studies between 63% and 80%.[7–13] The fact that TS is a fairly rare condition in immunosuppressed patients despite the high seroprevalence is paradoxical and suggests that additional factors, other than immunosuppression alone, are needed for the development of clinical disease.[11] An alternative possibility, supported by recent data, is that TS may be caused by a primary infection with TSPyV in immunosuppressed individuals, rather than a re-activated latent viral infection.[38,39]

The histo-morphology of Trichodysplasia spinulosa

A typical histo-morphological picture of TS (Fig. 1a) consists of enlarged, expanded, dilated hair follicles with keratin plugging the infundibula and absence of hair shafts.[3,16,50,62,68] The inner root sheath epithelium demonstrates dystrophy and eosinophilic trichohyalin protein deposits (Fig. 1b). Numerous apoptotic cells and acanthosis are often observed.[3,68] If present, inflammation is often mild.[3] Immunostaining suggests that the primary target for TSPyV is follicular keratinocytes.[34] in line with studies trying to elucidate the molecular pathways behind TSPyV. These pathways have been shown to involve protein phosphatase 2, pRB phosphorylation and upregulation of p16 and p21, ultimately leading to hyperproliferation.[68,69]

Clinical features

The typical clinical features of TS are here illustrated by a previously unpublished case. A 68-year-old woman with a diagnosis of chronic lymphocytic leukaemia (CLL) for three years presented to our dermatology clinic. The CLL had initially not required any treatment, but progression of the disease had motivated immunosuppressive treatment with two rounds of alemtuzumab together with a total of eight infusions of ofatumumab. Around 5 months after commencing the immunosuppressive treatment, she had started to develop superficially desquamating slightly erythematous rashes around the eyebrows, nose and cheeks. Over the following months she developed a mild, spiky rash over the whole abdomen, back and upper arms, together with worsening of the condition in the face with additional slight erythema and loss of eyebrow hair (Fig. 2a). The rash was asymptomatic, as in the majority of reported cases; however, it has also been described as mildly pruritic. The diagnosis was initially unclear but TS was later confirmed by a skin punch biopsy showing the typical histo-morphological signs and a PCR with very high copy numbers of TSPyV. Treatments attempted prior to correct diagnosis included topical glucocorticoids, topical anti-fungals, tacrolimus ointment, adapalene gel and oral antibiotics. After the diagnosis was set, the patient was given oral acyclovir for 2 months. All treatments were essentially without effect. At follow-up over 3 years after discontinuation of immunosuppression, she displayed complete resolution of TS (Fig. 2b). The CLL also remains in complete remission.

Treatment

Currently, no well-established treatment for TS exists. Several different treatment modalities have been reported but are limited to case reports or small case series and commonly lack clear statements of efficacy and long-term follow-up (Table 1). All reported treatments for TS are summarized in Table 2.

Treatments are arranged in three groups depending on reported efficacy: good, partial or no/poor effect. The total number of treatments exceeds the total number of patients since with several patients more than one treatment had been attempted over time.

Our conclusion based on reviewing these 60 clinical cases is that topical cidofovir appears to be the most effective treatment, particularly in the 3% formulation. Usage of cidofovir 3% is however limited due to lack of availability in many countries. Oral valganciclovir is also reported to be efficient against TS and is more widely available. Cidofovir has proven to inhibit HPyV replication *in vitro*, but its potential effects on TSPyV and other HPyVs *in vivo* remain unclear.[70] To our knowledge, there is however no scientific support for an effect *in vitro* nor *in vivo* of valganciclovir on HPyVs. Notably, however, prophylaxis with valganciclovir to kidney transplant recipients did not decrease HPyV viraemia nor development of polyoma-associated nephropathy.[71,72] Reducing patient immunosuppression is effective but often unfeasible due to the risk of organ rejection or flaring of underlying disease. The majority of treatments display no or poor effect, including widely used topical treatments such as retinoids, glucocorticoids, keratolytics, imiquimod and antibiotics, and systemic treatments such as retinoids and antibiotics (Table 2).

A common denominator for the treatments proven efficacious is that they reduce the causative agent, either by reducing the viral load of TSPyV by anti-viral effect or by a reduction of immunosuppression.[70] This holds true primarily for cidofovir and reduced immunosuppression, whereas, as previously mentioned, the mechanism of action for valganciclovir in HPyV infection remains unknown.[71] Further studies are warranted to elucidate the mechanistic bases for these treatments. A limitation of the conclusions reachable in this review is that it is impossible to firmly know whether the patients would have improved even without treatment, since many cases of TS show spontaneous regression over time.[17,25,38,39] However, a spontaneous regression generally requires longer time compared to an efficacious medication (Table 1).

Conclusion

We conclude that a reduction or inhibition of immunosuppressive treatment is an effective treatment for TS, but is unfortunately often not possible due to other clinical considerations. As an alternative, several case reports support the usage of topical cidofovir or oral valganciclovir. Available literature reviewed here support the use of topical cidofovir 3% if available as first-line treatment of TS, whenever reduced immunosuppression is unfeasible. Oral valganciclovir is also reported to be effective; nevertheless, no scientific evidence of this practice exists to date. Many less efficient treatment regimens are however still used in the cases reported to date, urging for the considerations provided in this review to help avoid such unnecessary and ineffective treatments in the future. Nonetheless, it is important to remember that the knowledge to date is limited to case reports and smaller case series, and larger studies are needed in order to make conclusions firm. In addition, further mechanistic studies of these suggested treatments are needed.

Acknowledgements

We would like to thank our colleagues MD PhD Maria Karlsson for aid in narrowing in on the correct clinical diagnosis of our case and for valuable comments on the manuscript, and MD PhD Britta Krynitz for help with initial histopathology. We also thank the patient for granting us permission to publish this information. The patient in this manuscript has given written informed consent to the publication of her case details.

References

1 Izakovic J, Büchner SA, Düggelin M, Guggenheim R, Itin PH. [Hair-like hyperkeratoses in patients with kidney transplants. A new cyclosporin side-effect]. *Hautarzt* 1995; **46**: 841–846.
2 Requena L, Sarasa JL, Ortiz Masllorens F *et al.* Follicular spicules of the nose: a peculiar cutaneous manifestation of multiple myeloma with cryoglobulinemia. *J Am Acad Dermatol* 1995; **32**(5 Pt 2): 834–839.
3 Haycox CL, Kim S, Fleckman P *et al.* Trichodysplasia spinulosa–a newly described folliculocentric viral infection in an immunocompromised host. *J Investig Dermatol Symp Proc* 1999; **4**: 268–271.
4 Chastain MA, Millikan LE. Pilomatrix dysplasia in an immunosuppressed patient. *J Am Acad Dermatol* 2000; **43**(1 Pt 1): 118–122.
5 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. *Transpl Infect Dis* 2017; **19**.1–4.
6 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 Pathog* 2010; **6**: e1001024.
7 Fukumoto H, Li TC, Kataoka M *et al.* Seroprevalence of trichodysplasia spinulosa-associated polyomavirus in Japan. *J Clin Virol* 2015; **65**: 76–82.
8 Chen T, Mattila PS, Jartti T, Ruuskanen O, Söderlund-Venermo M, Hedman K. Seroepidemiology of the newly found trichodysplasia spinulosa-associated polyomavirus. *J Infect Dis* 2011; **204**: 1523–15236.
9 Nicol JT, Robinot R, Carpentier A *et al.* Age-specific seroprevalences of merkel cell polyomavirus, human polyomaviruses 6, 7, and 9, and trichodysplasia spinulosa-associated polyomavirus. *Clin Vaccine Immunol* 2013; **20**: 363–368.
10 Šroller V, Hamšíková E, Ludvíková V, Musil J, Němečková Š, Saláková M. Seroprevalence rates of HPyV6, HPyV7, TSPyV, HPyV9, MWPyV and KIPyV polyomaviruses among the healthy blood donors. *J Med Virol* 2016; **88**: 1254–1261.
11 van der Meijden E, Kazem S, Burgers MM *et al.* Seroprevalence of trichodysplasia spinulosa-associated polyomavirus. *Emerg Infect Dis* 2011; **17**: 1355–1363.
12 van der Meijden E, Bialasiewicz S, Rockett RJ, Tozer SJ, Sloots TP, Feltkamp MC. Different serologic behavior of MCPyV, TSPyV, HPyV6, HPyV7 and HPyV9 polyomaviruses found on the skin. *PLoS One* 2013; **8**: e81078.
13 Gossai A, Waterboer T, Nelson HH *et al.* Seroepidemiology of Human Polyomaviruses in a US Population. *Am J Epidemiol* 2016; **183**: 61–69.
14 Osswald SS, Kulick KB, Tomaszewski MM, Sperling LC. Viral-associated trichodysplasia in a patient with lymphoma: a case report and review. *J Cutan Pathol* 2007; **34**: 721–725.

15 Sperling LC, Tomaszewski MM, Thomas DA. Viral-associated trichodysplasia in patients who are immunocompromised. *J Am Acad Dermatol* 2004; **50**: 318–322.
16 Wyatt AJ, Sachs DL, Shia J, Delgado R, Busam KJ. Virus-associated trichodysplasia spinulosa. *Am J Surg Pathol* 2005; **29**: 241–246.
17 Sadler GM, Halbert AR, Smith N, Rogers M. Trichodysplasia spinulosa associated with chemotherapy for acute lymphocytic leukaemia. *Australas J Dermatol* 2007; **48**: 110–114.
18 Lee JS, Frederiksen P, Kossard S. Progressive trichodysplasia spinulosa in a patient with chronic lymphocytic leukaemia in remission. *Australas J Dermatol* 2008; **49**: 57–60.
19 Schwieger-Briel A, Balma-Mena A, Ngan B, Dipchand A, Pope E. Trichodysplasia spinulosa–a rare complication in immunosuppressed patients. *Pediatr Dermatol* 2010; **27**: 509–513.
20 Burns A, Arnason T, Fraser R, Murray S, Keratotic WN. "spiny" papules in an immunosuppressed child. Trichodysplasia spinulosa (TS). *Arch Dermatol* 2011; **147**: 1215–1220.
21 Matthews MR, Wang RC, Reddick RL, Saldivar VA, Browning JC. Viral-associated trichodysplasia spinulosa: a case with electron microscopic and molecular detection of the trichodysplasia spinulosa-associated human polyomavirus. *J Cutan Pathol* 2011; **38**: 420–431.
22 Fischer MK, Kao GF, Nguyen HP *et al*. Specific detection of trichodysplasia spinulosa–associated polyomavirus DNA in skin and renal allograft tissues in a patient with trichodysplasia spinulosa. *Arch Dermatol.* 2012; **148**: 726–733.
23 Elaba Z, Hughey L, Isayeva T *et al*. Ultrastructural and molecular confirmation of the trichodysplasia spinulosa-associated polyomavirus in biopsies of patients with trichodysplasia spinulosa. *J Cutan Pathol* 2012; **39**: 1004–1009.
24 Moktefi A, Laude H, Brudy Gulphe L *et al*. Trichodysplasia spinulosa associated with lupus. *Am J Dermatopathol* 2014; **36**: e70–e74.
25 Celeiro-Muñoz C, González-Vilas D, Sánchez-Aguilar D, Suárez-Peñaranda JM. Viral-associated trichodysplasia secondary to antineoplastic treatment in a patient with lymphoblastic leukemia. *Am J Dermatopathol* 2014; **36**: e105–e107.
26 Lee YY, Tucker SC, Prow NA, Setoh YX, Banney LA. Trichodysplasia spinulosa: a benign adnexal proliferation with follicular differentiation associated with polyomavirus. *Australas J Dermatol* 2014; **55**: e33–e36.
27 Tsuzuki S, Fukumoto H, Mine S *et al*. Detection of trichodysplasia spinulosa-associated polyomavirus in a fatal case of myocarditis in a seven-month-old girl. *Int J Clin Exp Pathol* 2014; **7**: 5308–5312.
28 Kirchhof MG, Shojania K, Hull MW, Crawford RI, Au S. Trichodysplasia spinulosa: rare presentation of polyomavirus infection in immunocompromised patients. *J Cutan Med Surg* 2014; **18**: 430–435.
29 Richey JD, Graham TA, Katona T, Travers JB. Development of trichodysplasia spinulosa: case report of a patient with Gorlin syndrome treated with vismodegib. *JAMA Dermatol* 2014; **150**: 1016–1018.
30 Laroche A, Allard C, Chababi-Atallah M, Masse M, Bertrand J. Trichodysplasia spinulosa in a renal transplant patient. *J Cutan Med Surg* 2015; **19**: 66–68.
31 Leitenberger JJ, Abdelmalek M, Wang RC, Strasfeld L, Hopkins RS. Two cases of trichodysplasia spinulosa responsive to compounded topical cidofovir 3% cream. *JAAD Case Rep* 2015; **1**: S33–S35.
32 Nguyen NV, Burgos A, Prok L. Spiny papules in an immunosuppressed child. *Pediatr Dermatol* 2015; **32**: e296–e297.
33 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**: e1646–e1649.
34 Rouanet J, Aubin F, Gaboriaud P *et al*. Trichodysplasia spinulosa: a polyomavirus infection specifically targeting follicular keratinocytes in immunocompromised patients. *Br J Dermatol* 2016; **174**: 629–632.
35 DeCrescenzo AJ, Philips RC, Wilkerson MG. Trichodysplasia spinulosa: a rare complication of immunosuppression. *JAAD Case Rep* 2016; **2**: 307–309.
36 Kadam P, Pan T, Gates R *et al*. Detection of beta-human papillomavirus in a child with polyomavirus-associated trichodysplasia spinulosa. *Am J Dermatopathol* 2017; **39**: 928–931.
37 López-Lerma I, Ferrer B, Zarzoso I, Hernández-Losa J, García-Patos V. Spiny hyperkeratosis (trichodysplasia spinulosa-like eruption): a cutaneous adverse effect of Hedgehog pathway inhibitors involving expression of p16. *J Eur Acad Dermatol Venereol* 2017; **31**: e182–e184.
38 van der Meijden E, Horváth B, Nijland M *et al*. Primary polyomavirus infection, not reactivation, as the cause of trichodysplasia spinulosa in immunocompromised patients. *J Infect Dis* 2017; **215**: 1080–1084.
39 Bialasiewicz S, Byrom L, Fraser C, Clark J. Potential route of transmission for trichodysplasia spinulosa polyomavirus. *J Infect Dis* 2017; **215**: 1175–1176.
40 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. *Pediatr Dermatol* 2017; **2**: e74–e76.
41 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. *Pediatr Transplant* 2017; **21**: e12849.
42 Rosenstein RK, Ko CJ, Colegio OR. Trichodysplasia spinulosa. *Transplantation* 2017; **101**: e314.
43 Aleissa M, Konstantinou MP, Samimi M *et al*. Trichodysplasia spinulosa associated with HIV infection: clinical response to acitretin and valganciclovir. *Clin Exp Dermatol* 2018; **43**: 231–233.
44 Thomas RS, Lear W, Bohlke A. Trichodysplasia spinulosa in the setting of colon cancer. *Cutis* 2018; **102**: 262–264.
45 Berk DR, Lu D, Bayliss SJ. Trichodysplasia spinulosa in an adolescent with cystic fibrosis and lung transplantation. *Int J Dermatol* 2013; **52**: 1586–1588.
46 Navarrete-Dechent C, Cevallos C, Manríquez JJ, Salazar C, González S. [Trichodysplasia spinulosa. Report of one case]. *Rev Med Chil* 2018; **146**: 107–110.
47 Heaphy MR, Shamma HN, Hickmann M, White MJ. Cyclosporine-induced folliculodystrophy. *J Am Acad Dermatol* 2004; **50**: 310–315.
48 Campbell RM, Ney A, Gohh R, Robinson-Bostom L. Spiny hyperkeratotic projections on the face and extremities of a kidney transplant recipient. *Arch Dermatol* 2006; **142**: 1643–1648.
49 Holzer AM, Hughey LC. Trichodysplasia of immunosuppression treated with oral valganciclovir. *J Am Acad Dermatol* 2009; **60**: 169–172.
50 Benoit T, Bacelieri R, Morrell DS, Metcalf J. Viral-associated trichodysplasia of immunosuppression: report of a pediatric patient with response to oral valganciclovir. *Arch Dermatol* 2010; **146**: 871–874.
51 Blake BP, Marathe KS, Mohr MR, Jones N, Novosel T. Viral-associated trichodysplasia of immunosuppression in a renal transplant patient. *J Drugs Dermatol* 2011; **10**: 422–424.
52 Wanat KA, Holler PD, Dentchev T *et al*. Viral-associated trichodysplasia: characterization of a novel polyomavirus infection with therapeutic insights. *Arch Dermatol* 2012; **148**: 219–223.
53 Jawa P, Jain K, Allen R, Bradauskaite G, Kung SC. Trichodysplasia spinulosa. *Kidney Int* 2014; **85**: 715.
54 Barone H, Brockman R, Johnson L *et al*. Trichodysplasia spinulosa mimicking lichen nitidus in a renal transplant patient. *Pediatr Transplant* 2019; **4**: e13394.
55 Frigerio A, Toptan T, Chang Y, Abbott J, Cipriano SD, Bowen AR. Widespread keratosis pilaris-like eruption in an immunocompromised child. *JAAD Case Rep* 2019; **5**: 352–354.
56 Chamseddin BH, Tran BAPD, Lee EE *et al*. Trichodysplasia spinulosa in a child: Identification of trichodysplasia spinulosa-associated polyomavirus in skin, serum, and urine. *Pediatr Dermatol* 2019.**5**: 723–724.
57 Borgogna C, Albertini S, Zavattaro E *et al*. Primary trichodysplasia spinulosa polyomavirus infection in a kidney transplant child displaying virus-infected decoy cells in the urine. *J Med Virol* 2019; **91**: 1896–1900.
58 Stephan C, Kurban M, Khalil S, Bitar F, El-Rassi I, Assy J. Viral-associated trichodysplasia spinulosa in a paediatric cardiac transplant recipient. *Clin Exp Dermatol* 2019; **2**: 244–246.

59 Pierrotti LC, Urbano PRP, Nali LHDS *et al*. Viremia and viruria of trichodysplasia spinulosa-associated polyomavirus before the development of clinical disease in a kidney transplant recipient. *Transpl Infect Dis* 2019; **21**: e13133.
60 Shah PR, Esaa FS, Gupta P, Mercurio MG. Trichodysplasia spinulosa successfully treated with adapalene 0.1% gel and oral valganciclovir in a renal transplant recipient. *JAAD Case Rep* 2020; **6**: 23–25.
61 Dalianis T, Hirsch HH. Human polyomaviruses in disease and cancer. *Virology* 2013; **437**: 63–72.
62 Kazem S, van der Meijden E, Kooijman S *et al*. Trichodysplasia spinulosa is characterized by active polyomavirus infection. *J Clin Virol* 2012; **53**: 225–230.
63 Pedergnana V, Martel-Jantin C, Nicol JTJ *et al*. Trichodysplasia spinulosa polyomavirus infection occurs during early childhood with intrafamilial transmission, especially from mother to child. *J Invest Dermatol* 2017; **137**: 1181–1183.
64 Sadeghi M, Aaltonen LM, Hedman L, Chen T, Söderlund-Venermo M, Hedman K. Detection of TS polyomavirus DNA in tonsillar tissues of children and adults: evidence for site of viral latency. *J Clin Virol* 2014; **59**: 55–58.
65 Bagasi AA, Khandaker T, Clark G *et al*. Trichodysplasia spinulosa polyomavirus in respiratory tract of immunocompromised child. *Emerg Infect Dis* 2018; **24**: 1744–1746.
66 Fava P, Merlino C, Novelli M *et al*. HPyV6, HPyV7 and TSPyV DNA sequences detection in skin disease patients and healthy subjects. *J Eur Acad Dermatol Venereol* 2016; **30**: 624–627.
67 Toptan T, Yousem SA, Ho J *et al*. Survey for human polyomaviruses in cancer. *JCI Insight* 2016; **1**: 1–14.
68 Kazem S, van der Meijden E, Wang RC *et al*. Polyomavirus-associated Trichodysplasia spinulosa involves hyperproliferation, pRB phosphorylation and upregulation of p16 and p21. *PLoS One* 2014; **9**: e108947.
69 Nguyen HP, Patel A, Simonette RA, Rady P, Tyring SK. Binding of the trichodysplasia spinulosa-associated polyomavirus small T antigen to protein phosphatase 2A: elucidation of a potential pathogenic mechanism in a rare skin disease. *JAMA Dermatol* 2014; **150**: 1234–1236.
70 Andrei G, Topalis D, De Schutter T, Snoeck R. Insights into the mechanism of action of cidofovir and other acyclic nucleoside phosphonates against polyoma- and papillomaviruses and non-viral induced neoplasia. *Antiviral Res* 2015; **114**: 21–46.
71 Jehn U, Schütte-Nütgen K, Bautz J, Suwelack B, Reuter S. Valganciclovir is not a risk factor of BK polyomavirus viremia. *Am J Transplant* 2019; **19**: 3436–3437.
72 Reischig T, Kacer M, Hes O *et al*. Cytomegalovirus prevention strategies and the risk of BK polyomavirus viremia and nephropathy. *Am J Transplant* 2019; **19**: 2457–2467.
73 Brimhall CL, Malone JC. Viral-associated trichodysplasia spinulosa in a renal transplant patient. *Arch Dermatol* 2012; **148**: 863–864.