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

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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.

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

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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 2010.5 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 literature1-6,14-60 (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...
| 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 | – | – |
| (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)  | 15, F       | Netherlands | Heart transplant | Pred, Tacrolimus, MMF | 1 year | Histo       | Topical ammonium lactate + triamcinolone, tretinoin 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 acitretin + 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) |
| Ref. | Age, Gender | Country | Medical History | Immunosuppressant(s) | TS Onset | Diagnostics | Treatment(s) | Outcome |
|------|-------------|---------|----------------|----------------------|----------|-------------|-------------|---------|
| 73   | 46, F       | USA     | Kidney transplant | –                    | 4 months | Histology   | Topical steroids, antibiotics, antihistamines & valganciclovir | Good effect valganciclovir. Improved 7 weeks later |
| 23   | 62, M       | USA/Romania | Bilateral lung transplant | Pred, Tacrolimus, MMF | 6 years  | Histology, EM, PCR | Oral calcitriol | Poor effect. Relapses following years |
| 22   | 48, M       | USA     | Kidney transplant | Pred, Tacrolimus, MMF | 2–3 months | Histology, PCR | Oral valganciclovir | Partial effect valganciclovir |
| 37   | 63, F       | USA/Romania | Heart transplant | Tacrolimus, MMF | 8 months  | Histology, EM, PCR | Oral valganciclovir | Good effect. Improved 7 weeks later |
| 48   | 57, F       | USA     | CLL | Rituximab, CP, Cytoxan, allopurinol | 6 months | Histology, PCR | Oral valganciclovir | Partial effect valganciclovir |
| 13   | 5, M        | Spain   | – | Pred, Tacrolimus, MMF | 3 months | Histology | Oral valganciclovir | Partial effect. Healed 4 months later |
| 24   | 14, F       | USA     | Lung transplant | Pred, Tacrolimus, MMF | 6 months  | Histology, PCR | Oral acyclovir | Unknown effect. Healed 2.5 years later |
| 26   | 26, F       | France  | – | Pred, Tacrolimus, MMF | 6 months  | Histology | Oral acyclovir | No effect. Healed with topical keratolytics & reduced immunosuppression |
| 21   | 7, M        | Japan   | – | Pred, Tacrolimus, MMF | 8 months  | Histology | Oral acyclovir | Partial effect valganciclovir |
| 29   | 1.5, F      | Spain   | Multivisceral transplant | Pred, Tacrolimus, MMF | 6 months  | Histology | Oral acyclovir | Reduced immunosuppression |
| 30   | 36, M       | USA     | Kidney transplant | Pred, Tacrolimus, MMF | 8 months  | Histology | Oral acyclovir | Partial effect valganciclovir. Healed 3 months later |
| 32   | Middle aged | Canada  | Kidney transplant | Pred, Tacrolimus, MMF | 11 months | Histology | Oral acyclovir | Partial effect. Healed after discontinuation of immunosuppression |
| 33   | 1,5, F      | Spain   | Multivisceral transplant | Pred, Tacrolimus, MMF | 6 months  | Histology | Oral acyclovir | Reduced immunosuppression |

**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        | Chemo (not specified) | –        | PCR         | Manual extraction of spicules with tweezers | Good effect. Virtually healed 2 months later |
| (39) | 7, M        | Australia | Pre-B ALL          | Chemo (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 x 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              | Chemo (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 x 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 doxycline | Diseased (colorectal 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     | Intestinal 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 |
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 intra-cellular small viral particles in cells from patients with TS using
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. 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. 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. The

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**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.

**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.
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, faces, conjunctiva, tonsils, upper respiratory tract, heart and gastrointestinal organs.\(^22,27,38,62,64,65\) 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 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.\(^5\) 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.\(^69,69\)

### 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.

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

| Treatment                                | n  | %    |
|------------------------------------------|----|------|
| Good                                     | 23 | 23.5 |
| Oral valganclovir                        | 23 | 23.5 |
| Reduced immunosuppression                | 11 | 11.2 |
| 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 antistaminines                     | 2  | 2.0  |
| Topical calcineurim inhibitors           | 2  | 2.0  |
| Benzoyl peroxide                         | 1  | 1.0  |
| Oral glucocorticoids                    | 1  | 1.0  |

**Note:**

- \(n\) = total number of treatments.
- †Other than cidofovir.
- Other than valganclovir.
- Bold values are the sum of \(n\) and % for each category and in total.

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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. To our knowledge, there is however no scientific support for an effect in vivo nor in vitro of valganciclovir on HPyVs. Notably, however, prophylaxis with valganciclovir to kidney transplant recipients did not decrease HPyV viraemia nor development of polyoma-associated nephropathy. 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. This holds true primarily for cidofovir and reduced immunosuppression, whereas, as previously mentioned, the mechanism of action for valganciclovir in HPyV infection remains unknown. 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. 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.

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