ONLINE FIRST

Specific Detection of Trichodysplasia Spinulosa–Associated Polyomavirus DNA in Skin and Renal Allograft Tissues in a Patient With Trichodysplasia Spinulosa

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Background: Trichodysplasia spinulosa (TS) is a rare, disfiguring skin condition that affects immunosuppressed patients, universally involving the central face. New data point to the recently discovered TS-associated polyomavirus (TSPyV) as the causative agent.

Observations: We report a case of TS in a 48-year-old African American man after renal transplant; via polymerase chain reaction and sequencing, confirm the detection of TSPyV in lesional skin; and report the novel detection of TSPyV DNA in renal allograft tissue. Results of polymerase chain reaction analysis were negative for Merkel cell polyomavirus in lesional skin. Fifteen months later, urine cytologic findings showed morphologic evidence of a urinary tract polyomavirus infection. Results of SV40 immunohistochemical analysis were negative in lesional skin, renal allograft, and urine specimens.

Conclusions: To our knowledge, this is the first reported case in which TSPyV DNA has been detected in extracutaneous tissues and the third with combined ultrastructural and molecular confirmation of the presence of TSPyV in lesional skin. Lack of detection of other pathogenic human polyomaviruses in this patient’s skin supports the specific role of this polyomavirus in the genesis of TS. Further basic science studies are needed to determine the exact pathomechanisms of this polyomavirus and to explore possible tumorigenic roles in other skin diseases.


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In 1999, Haycox et al1 introduced the term trichodysplasia spinulosa (TS) to describe a folliculocentric papular eruption with central spiny excrescences in a patient who had received a heart transplant. The eruption began with eyebrow alopecia and facial lesions and progressed to the development of leonine facies and generalized alopecia. This disease, also termed viral-associated trichodysplasia,2 trichodysplasia of immunosuppression,3,4 cyclosporine-induced folliculodystrophy,5 and pilomatrix dysplasia,6 has a distinctive histologic appearance. The characteristic histopathologic findings include dilated hair follicles, proliferation of inner root-sheath cells with enlarged trichohyalin granules, infundibular keratin plugs, and absence of well-formed hair shafts. In the seminal report,1 transmission electron microscopy (TEM) revealed intranuclear virions within inner root-sheath cells that were morphologically consistent with a papovavirus. Additional reports have expanded the at-risk immunosuppressed patient population beyond solid-organ transplant recipients3,13 to include those with hematologic malignant neoplasms.2,7,14,16-22 The potential diagnostic utility of sampling plucked spicules has also been suggested.19 In 2010, van der Meijden and colleagues7 were the first to sequence this virus, termed trichodysplasia spinulosa–associated polyomavirus (TSPyV). It was the eighth described human polyomavirus after the identification of human polyomaviruses (HPy) 6 and 7 in 1971,27,28 Merkel cell polyomavirus (MCPyV) in 2008,24 WU polyomavirus (WUPyV) and KI polyomavirus (KIPyV) in 2007,25,26 and BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV) in 1971.29,30 Since then, HPyV9 has been identified without known pathogenicity, isolated from the serum and skin of renal transplant recipients.20,30

METHODS

Institutional review board–exempt status was obtained for this study at the University of Maryland. As part of standard diagnostic procedures, a 3-mm skin punch biopsy specimen...
A 48-year-old African American man with type 1 diabetes mellitus, hypertension, and end-stage renal disease who had undergone a living-donor renal transplant 1 year earlier was admitted to the University of Maryland Medical Center with progressive shortness of breath due to a recurrent pericardial effusion. At the time, the patient was receiving mycophenolic acid and tacrolimus (FK-506) for immunosuppression. Approximately 2 to 3 months after the kidney transplant, the patient had begun to develop a gradual onset of extensive asymptomatic papules, which at the time of presentation involved his entire central face and ears. Results of a physical examination revealed multiple 1- to 2-mm flesh-colored papules over the glabella, nose, nasolabial folds, philtrum, chin, and ears. Near the center of the face, the papules demonstrated central white spiny excrescences (Figure 1). In addition, patchy alopecia involved both eyebrows. Diffuse skin thickening resulted in a leonine face appearance. Although no other similar skin lesions were noted involving other parts of the body, perifollicular papules with associated postinflammatory hyperpigmentation were present on the patient’s back, most consistent with the clinical impression of acneform folliculitis.

A 3-mm punch biopsy of one of the lesions with a central spine was taken from the left nasolabial fold skin. Microscopic examination revealed striking dilatation of anagen and telogen hair follicles with an expanded inner root-sheath cell population replacing the follicular lumina (Figure 2A). Hair shafts were absent in the affected follicles, with plugging of the infundibula (Figure 2A). Focal mild perifolliculitis and a sparse lymphocytic interface dermatitis were noted in the infundibular portions of intervening vellus hair follicles (Figure 2B). The inner root-sheath keratinocytes contained enlarged, deeply eosinophilic trichohyaline granules (Figure 2C). The epidermis, outer root-sheath epithelium, sebaceous lobules, and eccrine structures were unremarkable. Results of SV40 immunohistochemical analysis were repeatedly negative in the altered follicles.

Transmission electron microscopy confirmed the presence of intranuclear viral inclusions within affected inner root-sheath keratinocytes composed of nonenveloped, icosaheiral viral particles measuring 33 to 38 nm in diameter (Figure 2D), morphologically consistent with polyomavirus infection. No intracytoplasmic or extracellular viral particles were identified.

Concurrent urine cytologic findings were negative for viral cytopathic changes, although a subsequent voided urine specimen more than 1 year later (Figure 3A) was positive for polyomavirus cytopathic changes (decoy cells), whereas casts, as often seen in nephropathy, were notably absent. Results of SV40 immunohistochemical analysis failed to reveal evidence of BKPyV or JCPyV infection in these cells (Figure 3B). There were no associated urologic symptoms or significant changes in serum creatinine level, and all subsequent urine cytologic specimens were negative for viral cytopathic effects. A renal allograft biopsy near the time of the diagnostic skin biopsy yielded morphologically unremarkable findings, also with negative findings on SV40 immunohistochemical analysis. Viral cultures performed on a bronchial wash specimen at the time of dermatologic presentation were negative for adenovirus; influenza A and B viruses; parainfluenza viruses 1, 2, and 3; and respiratory syncytial virus.
The expected 597-bp putative TSPyV-PCR fragment was generated in the DNA sample extracted from this TS lesion (Figure 4A). The BLAST analysis of the cloned sequences obtained from the putative TSPyV-PCR product revealed a 99% identity to the prototype TSPyV sequences deposited in the NCBI-GenBank (GU989205.1). The applied PCR assay did not detect MCPyV in this TS lesion.

On further analysis, the expected 597-bp putative TSPyV-PCR fragment was also generated in the DNA sample extracted from the patient’s renal allograft biopsy specimen (Figure 4B). The BLAST analysis of the DNA sequences obtained from the putative TSPyV-PCR product again revealed a 99% identity to the prototype TSPyV sequences deposited in the NCBI-GenBank (GU989205.1).

After the skin biopsy, the patient was followed up as an outpatient by the transplant medicine service and continued his baseline immunosuppressive therapy regimen with stable renal allograft function through 3 years of follow-up. No additional dermatologic consultations were obtained; therefore, no antiviral medication therapy was initiated to treat his skin lesions.

**COMMENT**

Trichodysplasia spinulosa is being increasingly recognized among immunosuppressed patients. Cases that had been attributed to an adverse effect of cyclosporine treatment in which TEM was not performed are now believed by multiple authors to represent the same
Figure 3. Urine cytologic and immunohistochemical analysis findings in the patient with trichodysplasia spinulosa. A, Isolated polyomavirus (PyV)–infected cells with enlarged, round, hyperchromatic, smudgy nuclei (decoy cells) seen on urine cytologic examination more than 1 year after the patient’s dermatologic presentation (Papanicolaou, original magnification ×400). B, An SV40 immunostain fails to reveal evidence of BKPyV or JCPyV infection; the positive control (inset) shows strong nuclear staining (SV40, original magnification ×400).

Figure 4. Results of DNA analysis in the patient with trichodysplasia spinulosa (TS). A, Detection of TS-associated polyomavirus (TSPyV) DNA and absence of Merkel cell PyV (MCPyV) DNA by means of polymerase chain reaction (PCR) analysis in a TS lesion. For TSPyV detection, lane M contains FX174RF DNA marker (Promega Corporation); lane 1, TS lesion; lane 2, TSPyV negative control DNA extracted from peripheral blood mononuclear cells (PBMCs) (Promega Corporation); and lane 3, reagent control. In lane 1, an expected 597–base pair (bp) TSPyV-PCR product can be seen. For MCPyV detection, lane M contains FX174RF DNA marker (Promega Corporation); lane 1, TS lesion; lane 2, MCPyV positive control (plasmid with MCPyV DNA insert from small T antigen viral gene); lane 3, MCPyV negative control DNA extracted from PBMCs (Promega Corporation); and lane 4, reagent control. No MCPyV-PCR product was detected in lane 1 (TS lesion). In lane 2 (positive control), the expected 150-bp MCPyV-PCR fragment can be seen. B, Detection of TSPyV DNA by PCR in a renal allograft biopsy specimen from the TS patient. Lane M contains FX174RF DNA marker (Promega Corporation); lane 1, kidney biopsy specimen; lane 2, TSPyV negative control DNA extracted from PBMCs (Promega Corporation); lane 3, positive control, cloned DNA of TSPyV small T gene; and lane 4, reagent control. In lanes 1 and 3, the expected 597-bp TSPyV-PCR product can be seen.
specifically described or if demonstrated in available photographs, resulting in cases reported under different names, were identified as TS on the basis of common clinicopathologic features. Twenty-five cases of TS, including the present entity as TS on the basis of common clinicopathologic features. Twenty-five cases of TS, including the present entity, were identified in a patient with TS.17

In regard to certain cases of TS associated with leukemia or lymphoma, it has been postulated that the onset or worsening of TS lesions may predict impending relapse of the underlying hematolymphoid malignant neoplasm,2,3,10 although this remains unclear owing to a paucity of cases, lack of long-term follow-up, and uncertainty about the latency period of infection. Although no correlate has been suggested among patients with TS who underwent solid-organ transplant in terms of allograft function or secondary malignant tumors, the initial onset of lesions in one patient occurred in temporal proximity to renal allograft rejection.3

Treatment options are summarized in Table 2. Oral valganciclovir hydrochloride has shown efficacy in TS in all 4 informative reported cases.1,3,10,12 Topical cidofovir has been used with success in 4 of 5 cases in which response to treatment was described.2,3,7,10,17 One patient’s lesions were controlled by shaving to the level of uninvoluted skin followed by treatment with tazarotene gel,9 and another patient’s lesions improved with a topical compound of acyclovir, 2-deoxy-D-glucose, and epigallocatechin (green tea extract).13 Modifications in immunosuppressant regimen among transplant patients with TS have demonstrated improvement in half these cases.4,8,10,15,18 The overall disease course of TS is somewhat unpredictable owing to the lack of reported long-term follow-up, although lesions may persist or recur for years,12 and the virus is known to perpetuate in hair follicles in the absence of visible lesions.3 Moreover, TSPyV DNA has been identified in a small subset of immunosuppressed patients without clinical evidence of TS.7

Most published cases of TS2,3,4,10,14,16 have closely matched the histopathologic and ultrastructural descriptions of Haycox et al.1 Less typical histologic findings include multiple small hair shafts or hair shaft–like material within affected follicles,7,9,10,17,19 vacuolated keratinocytes with pyknotic nuclei and coarse keratohyalin granules in the upper layers of the perifollicular epithelium,3,10,15,17 gray-blue cytoplasmic material in the proliferative inner root sheath cells,17 and, as demonstrated in this case, focal perifolliculitis22 and a sparse lymphocytic interface dermatitis. Lee et al.23 characterized the pathologic findings in the plucked spicules, which may be used to validate a diagnosis of TS at another anatomic site in patients with histologically confirmed TS and to use for molecular detection of TSPyV.2 Positive findings on polyoma middle T antigen immunohistochemical analysis have recently been described in a patient with TS.17

<p>| Table 1. Summary of Clinical, Histopathologic, Ultrastructural, and Molecular Findings in TS |</p>
<table>
<thead>
<tr>
<th>Finding</th>
<th>Dataa</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reported cases, 1995-2011b</td>
<td>25</td>
</tr>
<tr>
<td>Age, median (IQR) [range], y</td>
<td>27 (8-48) [5-70]</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1:1.1</td>
</tr>
<tr>
<td>No. Male/Female</td>
<td>13/12</td>
</tr>
<tr>
<td>Race/ethnicityc</td>
<td>Non-Hispanic, non-Arab white 18 (72) Non-Hispanic black 3 (12) Asian 2 (8) Hispanic 1 (4) Arab 1 (4)</td>
</tr>
<tr>
<td>Cause of immunosuppression</td>
<td>Solid-organ transplant 14 (56) Hematolymphoid malignant neoplasm 10 (40) Bothd</td>
</tr>
<tr>
<td>Anatomic sites of involvementd</td>
<td>Central face 25 (100) Extremities 21 (84) Eyebrows 16 (64) Trunk 14 (56) Ears 12 (48) Eyelashes 9 (36) Scalp 3 (12) Mucous membranes 0</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Asymptomatic 16 (64) Pruritus 8 (32) Tenderness 1 (4)</td>
</tr>
<tr>
<td>Physical findings</td>
<td>Follicular papules 25 (100) Spiny excrescences 21 (84) Alopecia 16 (64) Skin thickening 13 (52)</td>
</tr>
<tr>
<td>Histopathologic featuresd</td>
<td>Distended hair follicles 25 (100) Infundibular plugging 25 (100) Enlarged, irregular trichohyalin granules 23 (92) Absent hair shafts 19 (76) Abrupt cornification of inner root sheath cells 17 (68) Thin layer of germinative cells at base 13 (52) Keratotic debris predominate inner root sheath cells 13 (52) Inner root sheath cells predominate keratotic debris 12 (48) Abortive hair shaft–like material 6 (24) Vacuolated keratinocytes with coarse keratohyalin granules in perifollicular epithelium 4 (16) Keratotic spines protruding from follicular ostia 2 (8) Apoptotic cells within center of follicle 2 (8) Gray-blue cytoplasmic material in inner root sheath cells 2 (8) Mild lymphocytic perifolliculitis 2 (8) Sparse lymphocytic interface dermatitis 1 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; TS, trichodysplasia spinulosa; TSPyV, TS-associated polyomavirus.

a Unless otherwise indicated, data are expressed as number (percentage) of patients.
b Includes all cases with clinical and histopathologic features commensurate with TS, including those reported in oral abstract and poster form.11,12,17,20,21

c Where unreported, available clinical photographs5,6,8,11,13,16,21 or personal communications20 were used for categorization.
d Clinical and histopathologic features were only counted as present if specifically described or if demonstrated in available photographs, resulting in probable underestimation of the prevalence of some of these features in TS.
e One case demonstrated intranuclear and intracytoplasmic virions.14
Ultrastructural detection of viral particles may vary in localization, and this modality may not be adequately sensitive; in 4 of 13 cases in which TEM was successfully performed, no viral particles were identified. This is likely the manifestation of differing phases of infection within the inner root-sheath keratinocytes in the areas sampled for TEM. During the replication cycle of BKPyV within renal tubular cells in polyomavirus allograft nephropathy, localization of virions supports the specific role of TSPyV in the viral genesis of TS. Seven of the nine human polyomaviruses have been identified in human skin, whereas only TSPyV and other recently identified HPys—KIPyV, WUPyV, MCPyV—are currently believed to be linked to cutaneous diseases.

Table 2: Positive Response to Treatment in Reported Cases of TS and Presumed TS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Source</th>
<th>Anatomic Sites of Identification</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral valganciclovir hydrochloride</td>
<td>Holzer and Hughey, 2009; Benoit et al, 2010; Elaba et al, 2010; Schiewer-Briel et al, 2010</td>
<td>Skin, blood, central nervous system, kidney, urine, lymphoid tissues</td>
<td>Polyomavirus allograft nephropathy, hemorrhagic cystitis</td>
</tr>
<tr>
<td>Topical cidofovir</td>
<td>van der Meijden et al, 2010; Wanat et al, 2010; Osswald et al, 2007</td>
<td>Skin, blood, central nervous system, cerebrospinal fluid, kidney, urine, lymphoid tissues</td>
<td>Progressive multifocal leukoencephalopathy, polyomavirus allograft nephropathy (rare)</td>
</tr>
<tr>
<td>Topical tazarotene with shaving of lesions</td>
<td>Campbell et al, 2006</td>
<td>Blood, brain, central nervous system, lungs, tonsils</td>
<td>Uncertain (pneumonia?)</td>
</tr>
<tr>
<td>Topical compounded acyclovir, 2-deoxy-D-glucose, and epigallocatechin (green tea extract)</td>
<td>Blake et al, 2011</td>
<td>Blood, brain, central nervous system, lungs, tonsils</td>
<td>Uncertain (pneumonia?)</td>
</tr>
<tr>
<td>Change in immunosuppressant regimen</td>
<td>van der Meijden et al, 2010; Holzer and Hughey, 2009; Heapth et al, 2004; Chastain and Millikan, 2000; Izakovic et al, 1995; Benoit et al, 2010; Schiewer-Briel et al, 2010; Wyatt et al, 2005; Sadler et al, 2007</td>
<td>Skin, blood, nasopharynx, lungs, tonsils/lymphoid, hepatobiliary and gastrointestinal tracts</td>
<td>Merkel cell carcinoma</td>
</tr>
</tbody>
</table>

Table 3: Summary of Human Polyomaviruses Identified to Date

<table>
<thead>
<tr>
<th>Human Polyomavirus</th>
<th>Source</th>
<th>Anatomic Sites of Identification</th>
<th>Disease Associations</th>
</tr>
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<tbody>
<tr>
<td>BK polyomavirus</td>
<td>Gardner et al, 1971; Moens et al, 2003</td>
<td>Skin, blood, central nervous system</td>
<td>Polyomavirus allograft nephropathy, hemorrhagic cystitis</td>
</tr>
<tr>
<td>JC polyomavirus</td>
<td>Padgett et al, 1971; Moens et al, 2003</td>
<td>Skin, blood, central nervous system, cerebrospinal fluid</td>
<td>Progressive multifocal leukoencephalopathy, polyomavirus allograft nephropathy (rare)</td>
</tr>
<tr>
<td>KI polyomavirus</td>
<td>Allander et al, 2009; Mourez et al, 2009; Debiaggi et al, 2010</td>
<td>Blood, brain, central nervous system, lungs, tonsils</td>
<td>Uncertain (pneumonia?)</td>
</tr>
<tr>
<td>WU polyomavirus</td>
<td>Gaynor et al, 2007; Mourez et al, 2009; Debiaggi et al, 2010</td>
<td>Blood, brain, central nervous system, lungs, tonsils</td>
<td>Uncertain (pneumonia?)</td>
</tr>
<tr>
<td>Merkel cell polyomavirus</td>
<td>Schowalter et al, 2010; Feng et al, 2009; Moens et al, 2011</td>
<td>Skin, blood, nasopharynx, lungs, tonsils/lymphoid</td>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>Human polyomavirus 6</td>
<td>Schowalter et al, 2010</td>
<td>Skin</td>
<td>Unknown</td>
</tr>
<tr>
<td>Human polyomavirus 7</td>
<td>Schowalter et al, 2010</td>
<td>Skin</td>
<td>Unknown</td>
</tr>
<tr>
<td>TS-associated polyomavirus</td>
<td>van der Meijden et al, 2010; Matthews et al, 2011</td>
<td>Skin, kidney (allograft), urine (presumptive)</td>
<td>TS</td>
</tr>
<tr>
<td>Human polyomavirus 9, including IPPyV strain</td>
<td>Scuda et al, 2011; Sauvage et al, 2011 (IPPyV strain); Moens et al, 2011</td>
<td>Skin, blood, urine</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Abbreviations: IPPyV, Institut Pasteur polyomavirus; TS, trichodysplasia spinulosa.

Abbreviation: TS, trichodysplasia spinulosa.

a Excludes cases with no reported follow-up (cidofovir) or early discontinuation owing to adverse effects (tazarotene).
Our findings of TSPyV DNA in the renal allograft biopsy specimen and subsequent evidence of a productive polyomavirus infection in the urinary tract of our patient that failed to react with antibody to SV40 strongly suggest that TSPyV may be tropic to the urinary tract in addition to skin. Another possibility is that the SV40 immunostain lacked sufficient sensitivity to detect reactivation of latent BKPyV or JCPyV infection in this patient’s urine cytologic material; however, the paired urine cytospin positive control specimen reacted strongly.

Recent epidemiologic data indicate a high seroprevalence of TSPyV in at-risk and general populations that increases with age. Further basic science studies are needed to determine the exact pathomechanisms of TSPyV, particularly concerning the universal predilection for facial skin and relative sparing of the scalp. Given some similarities between epidermotropic polyomaviruses and papilomaviruses, regional skin specificity may represent yet another similarity. Determination of a possible tumorigenic role of TSPyV in other skin lesions also warrants study.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fischer, Kao, Drachenberg, Rady, Tyring, and Gaspari. Acquisition of data: Fischer, Kao, Nguyen, Drachenberg, Rady, Tyring, and Gaspari. Analysis and interpretation of data: Fischer, Kao, Nguyen, Drachenberg, Rady, Tyring, and Gaspari. Drafting of the manuscript: Fischer, Kao, Nguyen, Drachenberg, Rady, Tyring, and Gaspari. Critical revision of the manuscript for important intellectual content: Fischer, Kao, Nguyen, Drachenberg, Rady, Tyring, and Gaspari. Statistical analysis: Kao and Gaspari. Administrative, technical, and material support: Kao, Drachenberg, Rady, Tyring, and Gaspari. Study supervision: Kao, Tyring, and Gaspari.

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REFERENCES
Attribution of Syphilis to the Celts, the Gaus, and the French

In August 1494, King Charles VIII came to Italy in command of his French army, traveling from North to South on the Italian mainland, to conquer the Neapolitan kingdom in February 1495. The French soldiers, who were generally mercenaries, were affected by a new disease, syphilis. In Rome, the disease was named malattia gallica as a token of Gaul, which was the ancient Roman name for France. The first documented synonym for syphilis was morbo gallico, designated by Nicola Leoniceno in his work “De epidemia quam Itali morbiturum preservatio ac Cura.” Philippe de Vigneulles emphasized that syphilis spread so widely across all France that any city could call the disease by its own name, eg, mal de Niort, mal du Carrefour de Poitier, mal de Bordeaux. Some other synonyms attributing the disease to the French were morbues francicas, male francioso, male frasso, male francosso, male francos, mayl francosse, male de fransosi, mala de fransos, mala de fransoszen, mala de fransosae, mala francisches, mala fränsiskrankheth, and bösen (pox) francos.4

Before the end of the 15th century, the gallic adjective was used by Antonio Cammelli,5 a farcical poet, to define his gallica aegritudine. He and his son attributed their own syphilis to the fact that they had modified their sexual practice from homosexuality to heterosexuality, because at that time it was common thinking that women spread syphilis. In the 16th century, syphilis was also attributed to the French by the synonyms malum francicum, morbus francicum, morbus francisci, and malo franco.6 Finally, a new term, lue, which was derived from Latin lues (meaning disease, plague, endemy, and contagion), was followed by celtic, thus recognizing the Celts, an ancient people from Western Europe, especially France, Spain, Germany, and the British Isles. The term lue celtica was first used by Francesco Roncalli Parolini in 1720. Lue defined syphilis until the first half of the 20th century.7

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