Viral-Associated Trichodysplasia of Immunosuppression

Report of a Pediatric Patient With Response to Oral Valganciclovir

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Background: Viral-associated trichodysplasia of immunosuppression is an increasingly recognized entity characterized by follicular-based papules, primarily in the central part of the face, that produce variable degrees of alopecia and dysmorphic features. It has been primarily described in transplant recipients but has recently been recognized in patients receiving chemotherapy for leukemia and lymphoma. It is associated with distinctive histologic features such as dilated anagen hair follicles, absent hair papillae, and abrupt cornification of the inner root sheath.

Observations: A 5-year-old boy presented with spiny follicular papules that caused thickening of the skin of the face 1 year after cardiac transplantation. He had been exposed to several immunosuppressive agents, including mycophenolate mofetil, tacrolimus, intravenous immunoglobulin, rituximab, cyclophosphamide, and prednisone. Despite the failure of multiple topical treatments, our patient's eruption improved with systemic valganciclovir therapy.

Conclusions: We describe the youngest patient (to our knowledge) with viral-associated trichodysplasia of immunosuppression and discuss the characteristic clinicopathologic features. Our report supports the theory that immunosuppression is the predisposing factor to a folliculotropic papovavirus that alters follicular maturation.

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IRAL-ASSOCIATED TRICHO-
dysplasia of immuno-
suppression (VATD), an in-
creasingly recognized
entity, was first reported
by Haycox et al1 in 1999. The report
described a folliculocentric viral infection,
originally termed trichodysplasia spinu-
losa, in a patient who was receiving cy-
closporine after renal and pancreas trans-
plantation. Sperling et al2 first used the
term VATD in a 2004 article describing a
kidney transplant recipient on a multi-
drug immunosuppression regimen. Most
recently, VATD has been recognized in pa-
tients receiving chemotherapy for acute
and chronic lymphocytic leukemia and
non-Hodgkin lymphoma.3-5

REPORT OF A CASE

A 5-year-old boy with a history of Kabuki syndrome and hypoplastic left heart syndrome underwent cardiac transplantation in June 2007 because of intravenous inotropic dependence. After the transplantation, he was placed on a regimen of mycophenolate mofetil, tacrolimus, and prednisone. In December 2007, he developed donor-specific antibodies. To combat antibody-mediated rejection, he received plasmapheresis, intravenous immunoglobulin, rituximab, and cyclophosphamide. After this therapy, treatment with tacrolimus and prednisone was restarted.

Approximately 1 year after the transplantation, in May 2008, the patient developed an eruption on his face that progressed to involve his trunk and extremities. The transplantation team had concerns that the eruption might be a manifestation of graft-vs-host disease because the timing of the rash corresponded to the discontinuation of oral prednisone therapy. On presentation to the dermatology service in August 2008, the patient had numerous spiny, follicular papules primarily involving his trunk, the central area of his face, and the proximal aspect of his thighs. At that time, there was mild thickening of the nasal ala and lobules. The patient's only complaint was mild pruritus. Clinically, the eruption was consistent with keratosis pilaris. A biopsy specimen was obtained from the patient's right thigh. Histologic sections demonstrated follicles with dilated infundibula, hyperkeratosis, perifollicular fibro-
sis, and a sparse perifollicular infiltrate consisting of lymphocytes and histiocytes. The findings were interpreted as consistent with keratosis pilaris, with no evidence of graft-vs-host disease. The patient was initially treated with ammonium lactate cream and triamcinolone cream, 0.1%. The initial treatment had minimal effects; tretinoin cream, 0.025%, and urea cream, 40%, were added to the patient’s topical regimen.

The patient was referred to one of us (D.S.M.) for further evaluation. Out-of-state insurance permitted evaluation but no procedures. A diagnosis of VATD was suspected, and a recommendation was made to obtain a biopsy specimen from a lesion on a thickened area of the face. In the interim, the eruption progressed, with thickening of the skin of the face, particularly the nose, chin, and ears, eventually becoming leonine in appearance (Figure 1). In November 2008, while the patient was under general anesthesia for another procedure, a single 4-mm punch biopsy specimen was taken from the submental region.

Histologic sections revealed numerous enlarged, bulbous anagen hairs (Figure 2). No hair papillae were identified. A thin layer of basophilic, germinative cells transitioned to inner root sheath–like cells containing several enlarged trichohyaline granules. The inner root sheath–like cells abruptly cornified without the presence of a granular layer. The inner root sheath–type cornification was confirmed by staining with toluidine blue. No hair

Figure 1. Patient’s eruption demonstrates confluence of spiny papules and dramatic thickening of the skin. Note the leonine features of the face.

Figure 2. Large bulbous anagen follicles are evident. Follicles lack dermal papillae and hair shaft production (hematoxylin-eosin, original magnification ×4).

Figure 3. Transition from a thin basophilic germinative layer to larger eosinophilic cells with numerous large trichohyalin granules. Note the abrupt cornification of inner root sheath–like cells (hematoxylin-eosin, original magnification ×20).

Figure 4. Patient’s dramatic improvement in skin texture and thickening during systemic valganciclovir therapy.
shafts were present. Outer root sheath–type epithelium was present only at the upper half of affected bulbs. The upper segment of the follicle showed a dilated, hyperkeratotic, and shaftless infundibulum (Figure 3). Vacuolated keratinocytes with pyknotic nuclei and coarse keratohyaline granules, findings consistent with viral cytopathic effects, were seen in the upper layers of the perifollicular epithelium. Because of the limited amount of tissue remaining after the initial hematoxylin-eosin sections and recuts, the specimen was not submitted for electron microscopy. The clinical and histopathologic findings were consistent with those of previous reports, and a diagnosis of VATD was made.1,3 Topical therapy with twice-daily application of cidofovir ointment, 3%, resulted in little change in the eruption. Oral valganciclovir therapy was subsequently initiated, with significant improvement (Figure 4).

COMMENT

First reported after immunosuppression from cyclosporine therapy, VATD has been linked to various other immunosuppressive medications, including tacrolimus, azathioprine, prednisone, mycophenolate mofetil, cyclophosphamide, methotrexate, rituximab, and vincristine (Table).1-8 Our patient’s immunosuppressive regimen included mycophenolate mofetil, tacrolimus, and prednisone. Because of the development of host antibodies to the graft heart, our patient was also exposed to intravenous immunoglobulin, rituximab, and cyclophosphamide.

Electron microscopy offers insight as to the causative agent. The intranuclear, icosahedral viral particles identified by electron microscopy are morphologically suggestive of a papovavirus. Of the Papovaviridae, human papillomavirus, BK polyomavirus, and JC polyomavirus have been the primary focus. All attempts by investigators to isolate a causative agent have been negative to date.1,3,5-7

 Clinically, patients who have VATD develop multiple flesh-colored to erythematous follicular-based papules. Lesions have a predilection for the central part of the face and impart an infiltrated appearance to the skin that can produce dysmorphic features, most commonly distorting the contours of the nose. Variable degrees of alopecia have been reported with spinelike projections replacing hairs, most commonly of the eyebrows and occasionally the eyelashes and other hair-bearing areas of the face.1,4 The scalp is less commonly involved. Lesions typically progress to involve the trunk and extremities.

### Table. Reported Cases of Viral-Associated Trichodysplasia of Immunosuppression (VATD)

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Medical History</th>
<th>Immunosuppressive Agents</th>
<th>Duration of Immunosuppression Before Onset of Eruption, mo</th>
<th>Progress of Eruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/5/M (present case)</td>
<td>Cardiac transplant</td>
<td>Cyclophosphamide, rituximab, intravenous immunoglobulin, tacrolimus, prednisone</td>
<td>12</td>
<td>No improvement with cidofovir cream, 3%; significant improvement with systemic valganciclovir</td>
</tr>
<tr>
<td>2/6/M²</td>
<td>ALL (T-cell)</td>
<td>Cyclophosphamide, vincristine, prednisolone</td>
<td>24</td>
<td>Chemotherapy completed 4 mo before onset of eruption; resolution after 9 mo</td>
</tr>
<tr>
<td>3/8/M²</td>
<td>Renal transplant</td>
<td>Tacrolimus, mycophenolate mofetil, prednisone</td>
<td>8</td>
<td>Severe persistent eruption</td>
</tr>
<tr>
<td>4/8/M³</td>
<td>ALL (T-cell)</td>
<td>Vincristine, mercaptopurine, methotrexate</td>
<td>24</td>
<td>Eruption regressed 6 mo after chemotheraphy was completed; no improvement with topical salicylic acid, ammonium lactate, tretinoin, or oral acitretin</td>
</tr>
<tr>
<td>5/13/F²</td>
<td>Renal transplant</td>
<td>Mycophenolate mofetil, prednisone, tacrolimus</td>
<td>9</td>
<td>Minimal improvement with topical imiquimod cream; slow improvement with topical cidofovir cream, 3%</td>
</tr>
<tr>
<td>6/19/M³</td>
<td>ALL (B-cell)</td>
<td>Cyclophosphamide, vincristine, prednisolone, intrathecal methotrexate</td>
<td>22</td>
<td>Chemotherapy completed 3 mo after onset of eruption</td>
</tr>
<tr>
<td>7/37/F²</td>
<td>Cardiac transplant</td>
<td>Cyclosporine, mycophenolate mofetil, prednisone</td>
<td>8</td>
<td>Improvement after 5 mo of systemic valganciclovir; no evidence of VATD at 1-y follow-up</td>
</tr>
<tr>
<td>8/44/M¹</td>
<td>Renal-pancreatic transplant</td>
<td>Tacrolimus, azathioprine, prednisone</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td>9/68/M⁴</td>
<td>Recurrent NHL</td>
<td>Fludarabine, rituximab</td>
<td>Not reported</td>
<td>Relapse of NHL corresponds to onset of VATD; marked improvement with cidofovir cream, 1%</td>
</tr>
<tr>
<td>10/70/M⁶</td>
<td>CLL</td>
<td>Cyclophosphamide, fludarabine, rituximab</td>
<td>48</td>
<td>Eruption continued for 15 mo after chemotheraphy was discontinued; no improvement with oral minocycline, topical urea, 10%, or lactic acid cream, 5%</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; NA, not available; NHL, non-Hodgkin lymphoma.
ties. Patient symptoms may range from an asymptomatic eruption to mild pruritus. The age range reported is between 5 and 69 years. The duration of immunosuppression at the time of the development of the lesions varies from 8 to 48 months. The disease course appears to be intimately linked to immunosuppression, and lesions remain persistent in patients who are receiving ongoing immunosuppression. The time of onset in a patient with acute lymphocytic leukemia correlated with the chemotherapy course and tended to spontaneously resolve as the immune status improved.

The histologic features are unique and indicate that the portion of the follicle responsible for producing the hair shaft is replaced with inner root sheath material. The resultant abrupt inner root sheath–type cornification, as indicated by toluidine blue staining, produces the spine-like projections from the follicular-based papules.

Treatment options remain limited. Topical steroids, topical tacrolimus, topical antibiotics, minocycline, imiquimod cream, and topical as well as systemic retinoids have been used without success. Improvement with cidofovir cream, 3%, and cidofovir, 1%, in a moisturizing skin cream (Vanicream; Pharmaceutical Specialties Inc, Rochester, Minnesota) has been reported. Our patient was placed on a twice-daily topical regimen of cidofovir cream, 3%. This topical regimen had little effect on our patient’s eruption. One case report describes the observation of the discontinuation of oral valganciclovir therapy with the onset of VATD; empirically restarting valganciclovir therapy led to the resolution of the eruption. Based on that report, our patient was placed on systemic valganciclovir therapy. Although there was no temporal relationship between the discontinuation of oral valganciclovir therapy after transplantation and the onset of VATD in our case, this systemic therapy has dramatically improved our patient’s VATD. However, it has not provided total resolution. Our patient unfortunately developed bone marrow suppression as a result of the therapy. Initially, the dose of valganciclovir was decreased to alleviate some bone marrow suppression; however, the VATD recurred with disfiguring disease around the nares.

To date, 10 cases of VATD have been reported in the literature. At the age of 5 years, our patient represents the youngest reported case of VATD, to our knowledge. This case adds to the growing body of literature and provides further support to the theory that a chronic state of immunosuppression is the predisposing factor to a folliculotropic papovavirus that alters follicular maturation.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data: Benoit, Bacelieri, Morrell, and Metcalf.
Drafting of the manuscript: Benoit, Bacelieri, and Morrell.
Critical revision of the manuscript for important intellectual content: Benoit and Morrell.
Administrative, technical, or material support: Benoit, Bacelieri, and Morrell.
Study supervision: Morrell.
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REFERENCES