

Detection of Beta–Human Papillomavirus in a Child With Polyomavirus-Associated Trichodysplasia Spinulosa

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Abstract: Viral associated trichodysplasia spinulosa (VATS) is a rare cutaneous eruption characterized by folliculocentric papules, keratin spicules, and alopecia associated with trichodysplasia spinulosa-associated polyomavirus (TSPyV) infection. We report a case of a 6-year-old male child who presented with a generalized papular eruption during chemotherapy for acute lymphoblastic leukemia. The papules were tested for human papillomavirus (HPV) DNA by nested polymerase chain reaction (PCR) and TSPyV using PCR and gene sequencing studies. The lesions were positive for TSPyV by PCR combined with sequencing and showed high copy number with real-time PCR, and beta-papillomavirus was identified by PCR and sequencing. Immunohistochemistry revealed inner root sheath keratinocytes expressing nuclear HPV L1 capsid antigen. To our knowledge, this is the first case of concomitant productive HPV and TSPyV infection in a VATS-affected patient. The presence of HPV may be coincidental, however, further studies are needed to establish whether specific HPV genotypes influence the development of abnormal inner root sheath trichohyalin granules found in VATS.

Key Words: viral associated trichodysplasia, human papillomavirus, trichodysplasia spinulosa polyomavirus, trichohyalin granules, beta-papillomavirus

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INTRODUCTION

Viral associated trichodysplasia spinulosa (VATS) is a rare folliculocentric process seen in immunocompromised individuals,¹ particularly in solid organ transplants or hematological malignancies.² It presents as keratotic, spiny papules frequently involving the central face and rarely involving the trunk, extremities, and scalp. Alopecia of the eyebrows and eyelashes is frequent. The characteristic histopathological 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.³ Electron microscopy, polymerase chain reaction (PCR), immunohistochemistry, and viral load findings confirm that active trichodysplasia spinulosa-associated polyomavirus (TSPyV) infection plays an etiological role in the pathogenesis of VATS.⁴

Here, we report the clinical and histopathological findings in a 6-year-old male child with acute lymphoblastic leukemia affected with VATS that clinically resembled keratosis pilaris. Both HPV and TSPyV DNA were detected in the skin biopsy specimens. Antibody to HPV L1 capsid antigen showed evidence of active HPV (virion-producing) infection. The patient was affected with VATS during chemotherapy, consistent with the occurrence of VATS in severely immunocompromised patients. Coinfection of TSPyV and beta-papillomavirus (PV) is novel and has been previously described in a poroma.⁵ The presence of HPV in VATS affected tissue may reflect a coincidental phenomenon. Likewise, productive HPV infection in the setting of depressed immunity may work together with TSPyV to produce the characteristic VATS findings in this case.

CASE REPORT

A 6-year-old white male child with acute lymphoblastic leukemia on chemotherapy presented with a 6-month history of a generalized papular eruption beginning on his face and gradually spreading to his entire body. The eruption displayed a waxing and waning pattern and was associated with fevers. Cutaneous examination revealed numerous 1-mm skin-colored papules distributed throughout the face, trunk, and extremities (Fig. 1). Two skin biopsies were obtained from the left arm and right forearm over a 2-month interval, during which time the patient's papules worsened.

Histopathological analysis supported a follicular-based disorder that correlated with the clinical findings. Biopsies revealed a cystically dilated follicular infundibulum with islands of debris and keratin plugging. In the mid to deep reticular dermis, dilation of the lower third of affected hair follicles was also found. The enlargement was due to eosinophilic cytoplasmic inclusions and degenerated keratinocytes, which distended the inner root sheath region of affected hair follicles (Fig. 2). The adjacent dermis and epidermis did not exhibit inflammatory infiltrates or alterations in other adnexa.

Regionally, in the area affected by VATS, inner root sheath keratinocyte nuclei faintly expressed HPV L1 capsid protein (Fig. 3). Nuclear expression is considered a marker of active HPV infection and decreased immune function.^{6,7}

Beta-globin PCR was positive in both specimens. The NCBI-BLAST analysis of the sequence information obtained from clones of putative HPV-PCR products revealed the presence of different HPV types in the samples. In one sample, EV-HPV PCR and FAP-PCR detected the presence of HPVX4B/RTRX4 and HPV

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FIGURE 1. Trichodysplasia spinulosa exhibiting a keratosis pilaris-like eruption. Left panel shows myriad, very small, slightly red papules scattered over arm skin that had a fine, sandpaper-like texture. The right panel shows numerous scaly papules and some keratotic spicules, typical of VATS.

113. EV-HPV PCR detected the presence of HPV 124 in the other specimen. PGMY-GP PCR was negative in both specimens.^{7–10} TSPyV PCR products were detected in 2 samples.³ TSPyV-specific real-time PCR (TSPyV Genesig Kit; Primerdesign Ltd, Eastleigh, United Kingdom) revealed the presence of high copy number of virus in both lesions (estimated 2129 and 4231 copies/cell).

Most VATS eruptions resolve spontaneously as immune reconstitution occurs.¹¹ No active treatment was initiated in our patient. The eruption cleared in 6 months once chemotherapy was ceased and immunity improved. At the time of follow-up, a year later, he remained in remission with no further VATS episodes.

DISCUSSION

This case demonstrates the occurrence of productive HPV infection in a TSPyV-positive VATS-affected patient. The coinfection of HPV in TSPyV-positive VATS is heretofore undescribed. TSPyV has been identified as the etiological agent in VATS, and its increasing incidence in VATS-affected tissue affirms its pathogenic role.^{12,13}

HPV is found in normal skin, hair follicles, and perilesional skin,¹² thus making it a commensal organism.¹⁴ Active HPV infections are denoted by HPV capsid antigen expression and production of HPV particles.¹⁵ There is growing evidence suggesting that the bulge area of the outer root sheath of the hair follicle serves as an endogenous reservoir for HPV particularly beta-PV. The detection of HPV DNA in hair follicles is therefore frequently used as a marker of cutaneous infection.¹⁶ Likewise, asymptomatic infection with human polyomaviruses may be acquired early in life. Depressed immunity can reactivate these viruses from latency and produce detectable viremia and disease manifestation. In contrast, evidence also exists that VATS may represent a primary TSPyV infection during immunosuppression.¹³

Several types of HPV DNA were detected in our patient: HPVs 113, 124, and 4B/RTRX (84% similar to HPV 118). Biopsy revealed numerous enlarged red keratohyalin granules within the inner root sheath (Fig. 3). It should be noted that some HPV have type-specific keratohyalin granules and/or intracellular inclusions; however, the data on HPV genotype-specific phenotypes is poorly documented (Fig. 2). One of the hallmarks of HPV infection is the

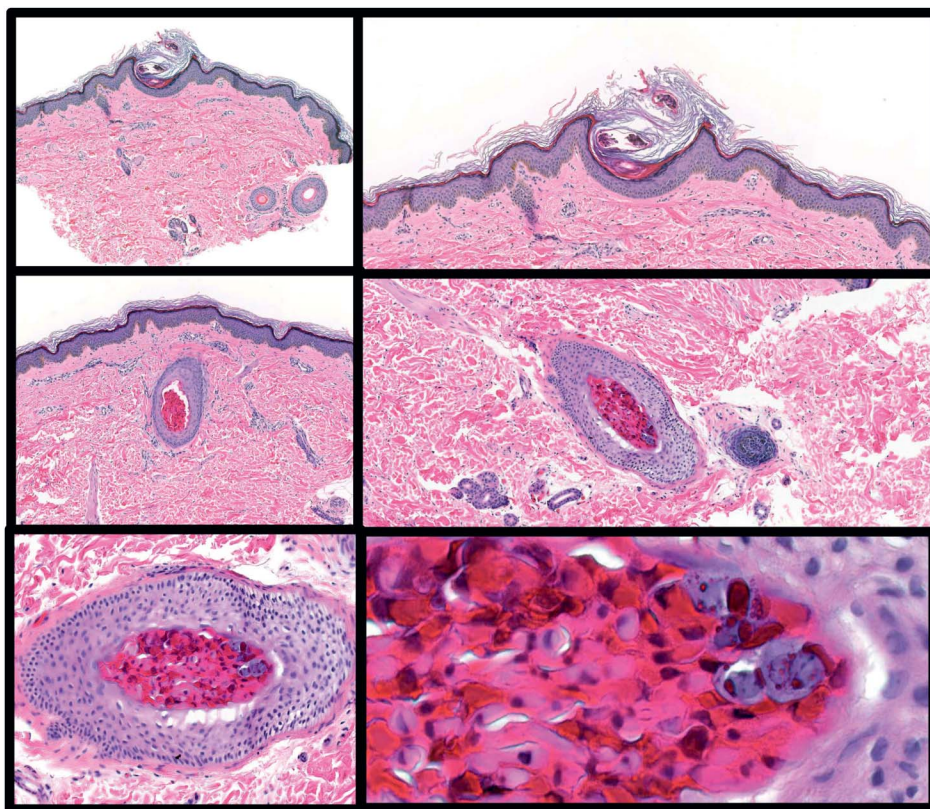


FIGURE 2. VATS histopathology. Top panels show keratosis pilaris-like changes seen as keratotic plug obstructing the follicular infundibulum and rising above the surface of the skin. The mid and bottom panels show level sections with increasing magnification of dilated follicle. The bottom panels show abnormally large, eosinophilic trichohyalin granules replacing the inner root sheath. The outer root sheath is unaffected, and no hair cortex is found.

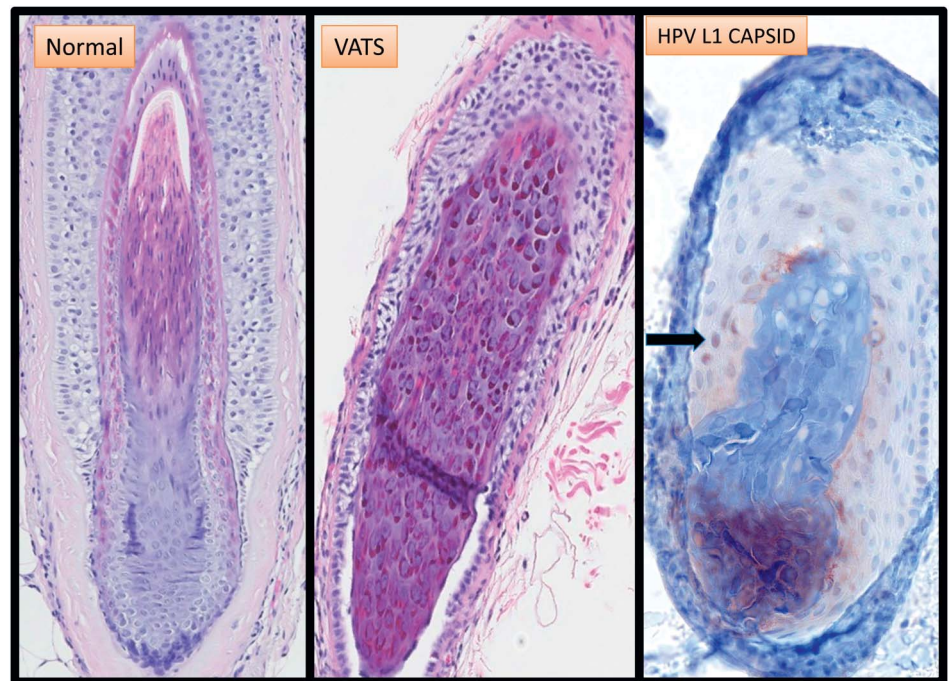


FIGURE 3. Comparison of normal and VATS inner root sheaths and illustration of HPV L1 capsid expression. Compared with normal, VATS shows expansion and dilation of the lower half of hair follicles with cornified eosinophilic cells containing large trichohyalin granules and viral inclusions (30 nm in diameter).²² HPV L1 capsid faintly labeled the inner root sheath keratinocyte nuclei, a pattern attributed to active HPV (virion-producing) infection.^{6,7}

presence of clumped keratohyalin granules representing the cytopathic viral effect.¹⁵ Based on this HPV-specific histological clue, the keratohyalin granules detected within the inner root sheath in our patient may partly be a consequence of productive HPV infection. Moreover, as previously mentioned, HPV in hair follicles is a marker for cutaneous HPV infection. Indeed, there is morphologic overlap between myrmecia/HPV 1 eosinophilic cytoplasmic inclusions and those of VATS.¹⁵

Both positive and negative controls were performed for immunohistochemistry and PCR for all samples. These controls support the presence of beta-PV. This novel detection of productive HPV infection in VATS is noteworthy. To our knowledge, this is the first case whereby productive HPV infection has been detected in VATS-affected tissue. The copathogenic role of HPV in the histopathogenesis of TSPyV-positive VATS is unknown. The production of intracytoplasmic inclusions is a typical finding in some HPV displaying productive infection. It is uncertain whether HPV plays a pathogenic role in VATS; however, it certainly cohabitates in the same skin lesions.

VATS presents as multiple erythematous follicular papules that affect the central face and may create dysmorphic features.¹⁷ In our patient, the papules displayed a keratosis pilaris-like presentation, causing a diagnostic dilemma. Although the initial skin biopsy favored a diagnosis of keratosis pilaris, infundibular plugging, level sections of the specimen demonstrated the lower follicle changes, diagnostic of VATS-dilated follicle with abnormally large trichohyalin granules enlarging the inner root sheath/lower one-third of the hair follicle.

Our patient developed VATS during chemotherapy. VATS generally develops during immunosuppressed states, typically during or soon after chemotherapy.¹⁷ Improving

immune status by reducing immunosuppression plays a pivotal role in the resolution of VATS.¹⁸ HPV infections are controlled by intact cell-mediated and humoral immune systems.¹⁹ Patients with cell-mediated immunodeficiencies, such as in hematological malignancies, are at a higher risk of developing HPV infections as seen in our patient.²⁰ A year after his disease remission, he remains free of any VATS eruptions. Disease onset, TSPyV mediated, coincided with HPV infection as a consequence of the low immunity levels, and as the immune system reconstituted, the cutaneous papules of VATS diminished.

CONCLUSIONS

Our case study confirms the etiological role of the TSPyV in VATS. Waxing and waning keratosis pilaris-like changes heralded VATS, whose disease activity correlated with the immune status and the histopathological presence of abnormal, enlarged inner root sheath filled with irregular keratohyalin granules and inclusion bodies. Similarly, for HPV, immune deficiency promotes productive HPV infections that manifest in some genera as epidermal growths associated with keratohyalin granules and inclusion bodies.^{15,21} In this patient, 3 HPV genotypes were detected, HPVX4B/RTRX4, HPV 113, and HPV 124, in punch biopsies of keratosis pilaris lesions, where inner root sheath keratinocytic nuclei expressed capsid L1 protein, evidence of productive HPV infection. This constellation of phenotypic and viral findings may be accidental. However, the productive HPV infection implicates an influential role in the histopathology of VATS in this case. Further case studies are warranted to ascertain a definite association.

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