SUBMITTED 24 DEC 22
REVISION REQ. 26 JAN 23; REVISION RECD. 26 FEB 23
ACCEPTED 28 MAR 23
ONLINE-FIRST: MAY 2023
DOI: https://doi.org/10.18295/squmj.5.2023.035

Trichodysplasia Spinulosa

***Ayida Al Khalili,[1] Elsa Maciagowski,[2] Khue Nguyen,[2] Kevin A. Watters[3]**

[1]Dermatology Unit, Department of Family Medicine and Public Health, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman; Departments of [2]Dermatology and [3]Pathology, McGill University Health Center, Montreal, Canada
**Corresponding Author's e-mail: a.alkhalili@hotmail.com*

Abstract:
Trichodysplasia spinulosa (TS) is a unique, rare clinical and histological dermatologic entity described mainly in setting of immunosuppression. It is caused by a novel human polymoavirus, trichodysplasia spinulosa-associated polyomavirus (TSPyV). We report a biopsy-proven case of TS in a renal transplant patient presented to dermatology outpatient clinic in Montreal, Canada in 2015. Reduction of immunosuppression and/or anti-viral therapy is the main therapeutic strategies used to treat such cases. Our patient was managed with valgancyclovir with no obvious response. Subsequently, a trial of topical imiquimod was commenced. Awareness of TS can prompt early diagnosis and management to prevent possible complications.

Keywords: Trichodysplasia spinulosa, immunosuppression, organ-trasplant, human polyomavirus.

Introduction

Trichodysplasia spinulosa (TS) is a rare cutaneous manifestation due to viral infection affecting mainly immunosuppressed hosts. The majority of the patients are solid organ recipients or patients diagnosed with hematological malignancies.[1]

Given its rarity, in most cases there is a potential delay in diagnosis. Moreover, the pathogenesis of TS is not completely understood. Few therapeutic options are suggested by published case reports and no standard therapies are approved yet.[2]

We present a case of TS in a renal transplant recipient and review the main characteristic features of this entity.

Case Report

A male in his 60s presented to the dermatology outpatient clinic in Montreal, Canada in 2015 for evaluation of facial papules. These were of two-month duration and progressively increasing in number, affecting the whole face but more concentrated on the nose. There was mild facial pruritus. The patient was a kidney transplant recipient since July 2014 for hypertensive nephropathy. He was on therapy with mycophenolic acid (Myfortic) and tacrolimus (Advagraf). Medical history was positive for, osteoarthritis, gout and IgA gammopathy (Monoclonal gammopathy of undetermined significance). His other medications include amlodipine, phosphate, magnesium, pantoprazole and ASA.

Skin examination revealed follicular flesh-coloured to pinkish monomorphic papules mainly on central face involving the forehead and nose with central white protruding spines. Scalp, mucosal membranes, palms and soles were not affected (figure 1).

Considering his immunosuppressive status, our differential diagnosis includes mainly infectious etiologies such as molluscum contagiosum, filiform verrucae and trichodysplasia spinulosa of immunosuppression. We have also considered idiopathic follicular hyperkeratotic spicules or other adnexal pathologies such as sebaceous

hyperplasias, trichoepitheliomas, fibrofolliculomas, trichodiscomas and facial fibrous papules (angiofibromas) as possibilities.

Histopathological exam of one of the papules showed dilated follicular infundibulae with keratin plugs and viral-like changes with large irregular eosinophilic/basophilic trichohyalin like granules within the inner root sheath cells consistent with trichodysplasia spinulosa (figure 2). Additional test such as electron microscopy or polymerase chain reaction was not performed.

Based on typical clinical findings in the setting of renal transplantation and suggestive histologic features, the patient was diagnosed with trichodysplasia spinulosa. He was managed initially with oral valganciclovir without adequate response. Subsequently, a trial of topical imiquimod was commenced. Unfortunately, he was lost to follow up in dermatology clinic.

Verbal informed consent was obtained from the patient for publication.

Discussion

Trichodysplasia spinulosa is a rare clinicopathologic skin entity primarily described in immunosuppressed individuals. It is caused by trichodysplasia spinulosa-associated polyomavirus (TSPyV).[2]

The first case of TS was reported in 1995 by Izakovic et al., describing a new entity with spiny follicular hyperkeratosis thought to be related to cyclosporine treatment.[3]

Four years later, possible polyomavirus association with TS was described by Haycox et al. Electron microscopy findings of lesional skin were consistent with polyomavirus-induced changes and the condition was termed trichodysplasia spinulosa.[4]This was confirmed only in 2010 when a novel double-stranded DNA virus was isolated from the hyperkeratotic lesions using a rolling-circle amplification detection method.[5] The

presence of 1 million viral load in lesional skin compared to non-lesional skin further reinforced the causal relationship.[6]

TSPyV is a member of *Polyomaviridae* family. BKPyV and JCPyV are the first members discovered in 1970s to infect human.[7] These are linked to transplant-related kidney disease and progressive multifocal leukoencephalopathy, respectively.[8]

There are four novel members from the same family linked to cutaneous conditions mainly in association with immunosuppression including TSPyV. Merkel cell PolyomaVirus (MCPyV) is linked to a rare neuroendocrine tumour of the skin, Merkel cell carcinoma (MCC) with overall viral prevalence of 80% of the cases. Human PolyomaVirus 6 (HPyV6) and 7 (HPyV7) are associated with unique pruritic dyskeratotic dermatoses in immunosuppressed individuals.[7]

Exposure to TSPyV occurs at a very young age and usually follows an asymptomatic latent course. Seroprevalence of TSPyV in immunocompetent adults is High, reaching up to 80%. Moreover, seroprevalence increases even more in immunocompromised individuals and more in patients with TS.[1, 6] Interestingly, only a minority of immunosuppressed hosts will develop TS clinically. [1] Van der Meijden et al. proposed that the cause of TS is primary polyomavirus infection in immunocompromised hosts rather than reactivation of a latent viral infection which can explain the rarity of this condition.[9] Further studies are required to uncover other variables that cause the disease in specific patient populations. The only evidenced dermatologic clinical phenotype of TSPyV is TS.[1]

Clinically, TS appears as flesh-coloured to erythematous follicular-based papules concentrated on the central face with white spicules protruding from the papules. It can progress to alopecia especially of the eyebrows and thickening of the skin leading to leonine faces.[10] TS can also affect the trunk, extremities and neck.[6]

The distinctive histopathological features of TS involve acanthosis of the epidermis,

aberrant large, distended follicles with dilated infundibulum and presence of large eosinophilic, trichohyaline granules within excessive proliferating inner root sheath cells of the hair bulb.[10, 8]

The classic clinical setting and characteristic histologic findings are usually sufficient to make the diagnosis. Further testing with PCR detection of the virus from the lesions and electron microscopy studies can also be used to confirm the diagnosis.[10]

In a recent review article, Curma et al. reported data of all published cases of TS in PubMed until April 2020. A total of sixty cases were reviewed. Almost all patients were immunosuppressed. The main associated conditions were hematolymphoid malignancies (including multiple myeloma, acute and chronic lymphocytic leukemia, acute myelocytic leukemia, Non-Hodgkin's lymphoma, B-cell lymphoma and myelodysplastic syndrome) or solid organ transplant recipients (including kidney, kidney/pancreatic, heart, lung, liver, intestinal and multivisceral transplant). Other associations include systemic lupus erythematosus on immunosuppressive therapy, Gorlin's syndrome on vismodegib treatment, HIV and B- cell lymphoma and myocarditis.[1]

Interestingly, TS was reported in the setting of remission of lymphoma with a new diagnosis of colon cancer and in the setting of lymphoma relapse. [11, 12] This adds to our limited understanding of the pathogenesis of the disease.

Jose et al. reviewed TS cases associated with solid organ transplant and emphasized that it appears during the first year after transplant with the highest level of immunosuppression.[2] Our patient had developed TS within the first year following his renal transplant. He was diagnosed promptly with characteristic morphology, location of the eruption and histology features.

Managing TS is challenging. However, reduction of immunosuppression is the mainstay of treatment. This might not be always feasible given the risk of organ rejection or flare of the underlying disease. Next line of management is antiviral treatment including

topical cidofovir 1%-3% or oral valganciclovir.[2] Particularly, 3% topical cidofovir might be the most efficient.[1] Topical tazarotene and manual extraction were reported useful in single case reports.[13, 14]Oral leflunomide was reported to dramatically improve the condition in two organ transplant patients.[15] Spontaneous regression has also been described but took longer.[2]

Conclusion

TS is an emerging folliculocentric viral infection that occurs predominantly in immune-altered individuals. Since the rate of organ transplantation and relative immunosuppression are increasing globally, TS may become more prevalent. We present this case to increase awareness of this unique dermatosis to health care providers for early diagnosis and prompt treatment to prevent facial disfigurement. Our knowledge is still inadequate to explain many aspects of TS.

Authors' Contribution

AAK performed the literature review and primary manuscript construction. EM reviewed the case details and edited the manuscript. KN did a general review and edited the entire manuscript. KAW reviewed the histopathology slides, literature review on the pathology section and did a general review and grammatical editing of the manuscript. All authors approved the final version of the manuscript.

References

1. Curman P, Näsman A, Brauner H. Trichodysplasia spinulosa: a comprehensive review of the disease and its treatment. J Eur Acad Dermatol Venereol. JEADV. 2021;35(5):1067-76. doi:10.1111/jdv.17081.

2. Jose A, Dad T, Strand A, Tse JY, Plotnikova N, Boucher HW et al. Trichodysplasia spinulosa: Case reports and review of literature. Transpl Infect Dis 2020;22(5):e13342. doi:10.1111/tid.13342.

3. 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(12):841-6. doi:10.1007/s001050050350.

4. Haycox CL, Kim S, Fleckman P, Smith LT, Piepkorn M, Sundberg JP et al. Trichodysplasia spinulosa--a newly described folliculocentric viral infection in an immunocompromised host. J Investig Dermatol Symp Proc 1999;4(3):268-71. doi:10.1038/sj.jidsp.5640227.

5. 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 One 2010;6(7):e1001024. doi:10.1371/journal.ppat.1001024.

6. Wu JH, Nguyen HP, Rady PL, Tyring SK. Molecular insight into the viral biology and clinical features of trichodysplasia spinulosa. Br J Dermatol 2016;174(3):490-8. doi:10.1111/bjd.14239.

7. Jeles K, Katona M, Csoma E. Seroprevalence of Four Polyomaviruses Linked to Dermatological Diseases: New Findings and a Comprehensive Analysis. Viruses 2022;14(10). doi:10.3390/v14102282.

8. Kazem S, van der Meijden E, Feltkamp MC. The trichodysplasia spinulosa-associated polyomavirus: virological background and clinical implications. APMIS 2013;121(8):770-82. doi:10.1111/apm.12092.

9. van der Meijden E, Horváth B, Nijland M, de Vries K, Rácz EK, Diercks GF et al. Primary Polyomavirus Infection, Not Reactivation, as the Cause of Trichodysplasia Spinulosa in Immunocompromised Patients. J Infect Dis 2017;215(7):1080-4. doi:10.1093/infdis/jiw403.

10. Narayanan D, Rady PL, Tyring SK. Recent developments in trichodysplasia spinulosa disease. Transpl Infect Dis 2020;22(6):e13434. doi:10.1111/tid.13434.

11. Thomas RS, Lear W, Bohlke A. Trichodysplasia spinulosa in the setting of colon cancer. Cutis. 2018;102(4):262-4.

12. 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(9):721-5. doi:10.1111/j.1600-0560.2006.00693.x.

13. 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(12):1643-8. doi:10.1001/archderm.142.12.1643-d.

14. 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;34(2):e74-e6. doi:10.1111/pde.13045.

15. Pierrotti LC, Urbano PRP, Nali L, Romano CM, Bicalho CDS, Arnone M 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(4):e13133. doi:10.1111/tid.13133.

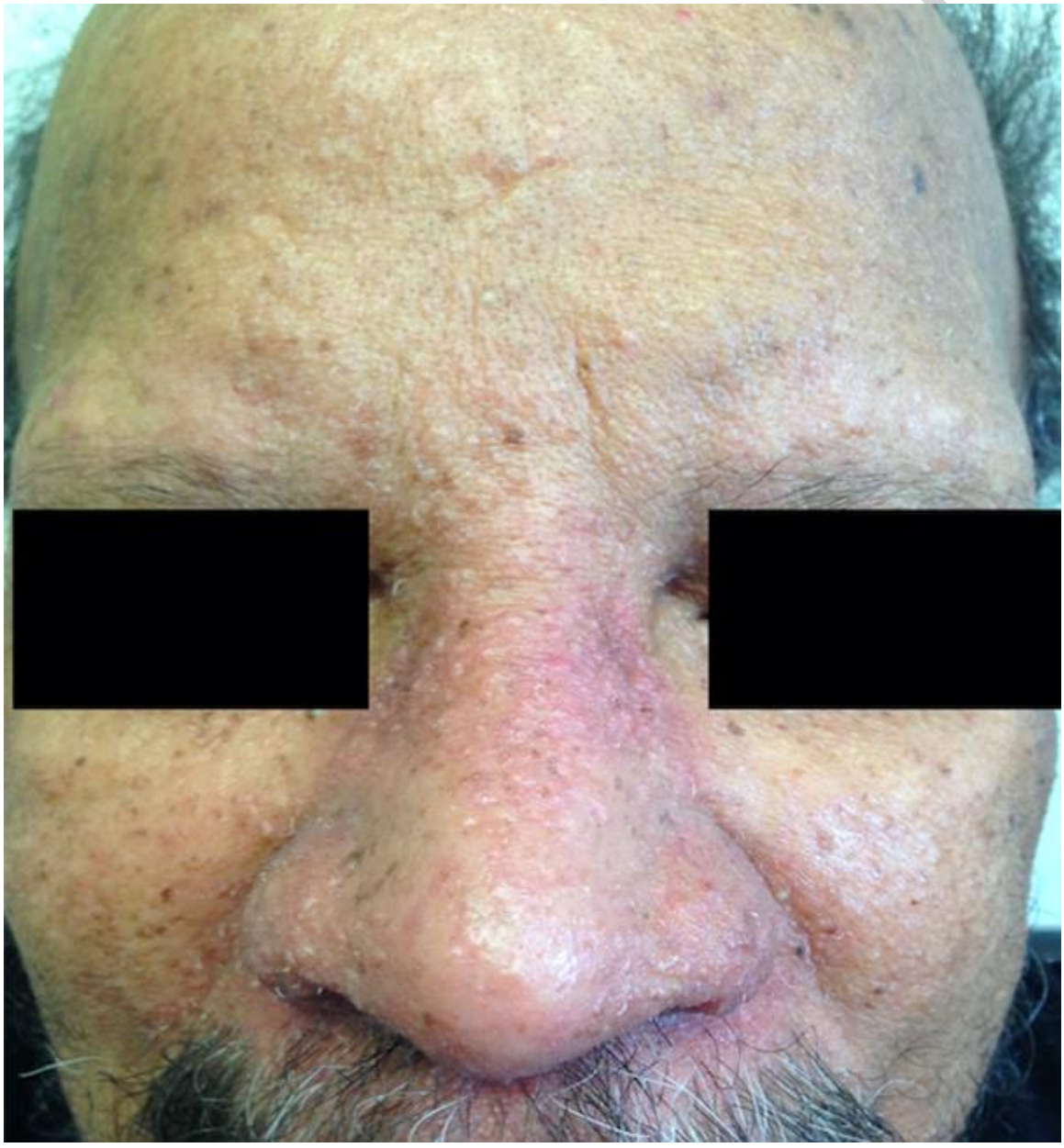

Figure 1A: Skin-coloured monomorphic papules on central face, forehead and nose with protruding central whitish spines.

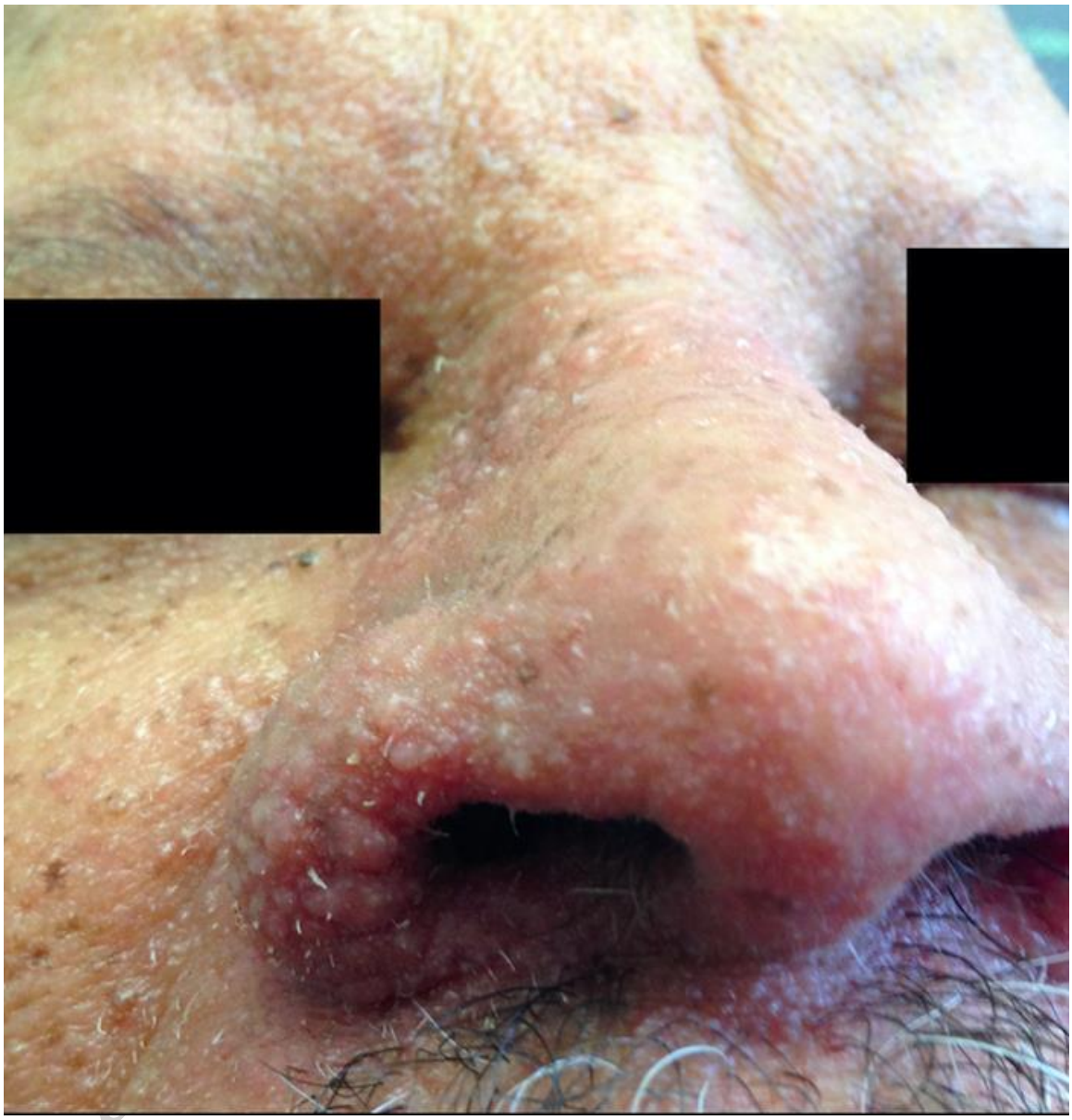

Figure 1B: A close-up image of the papules with white central spines.

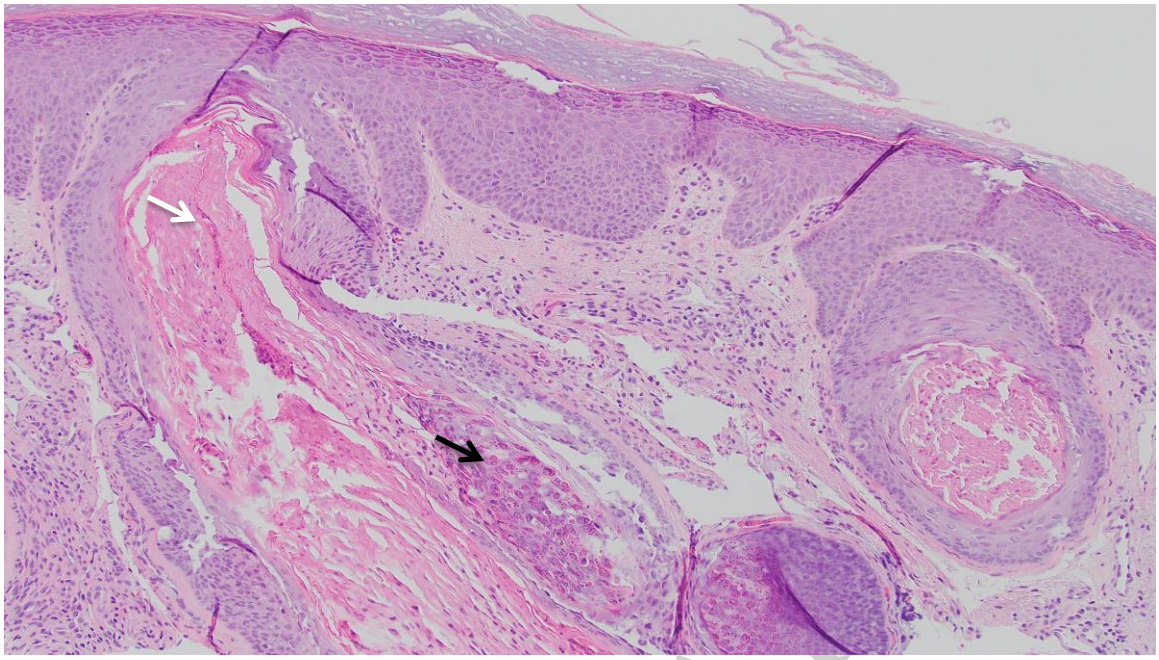

Figure 2A: Dilated follicular infundibulae with keratin plugs (white arrow) and viral epithelial changes (black arrow) consistent with trichodysplasia spinulosa. H&E staining X10

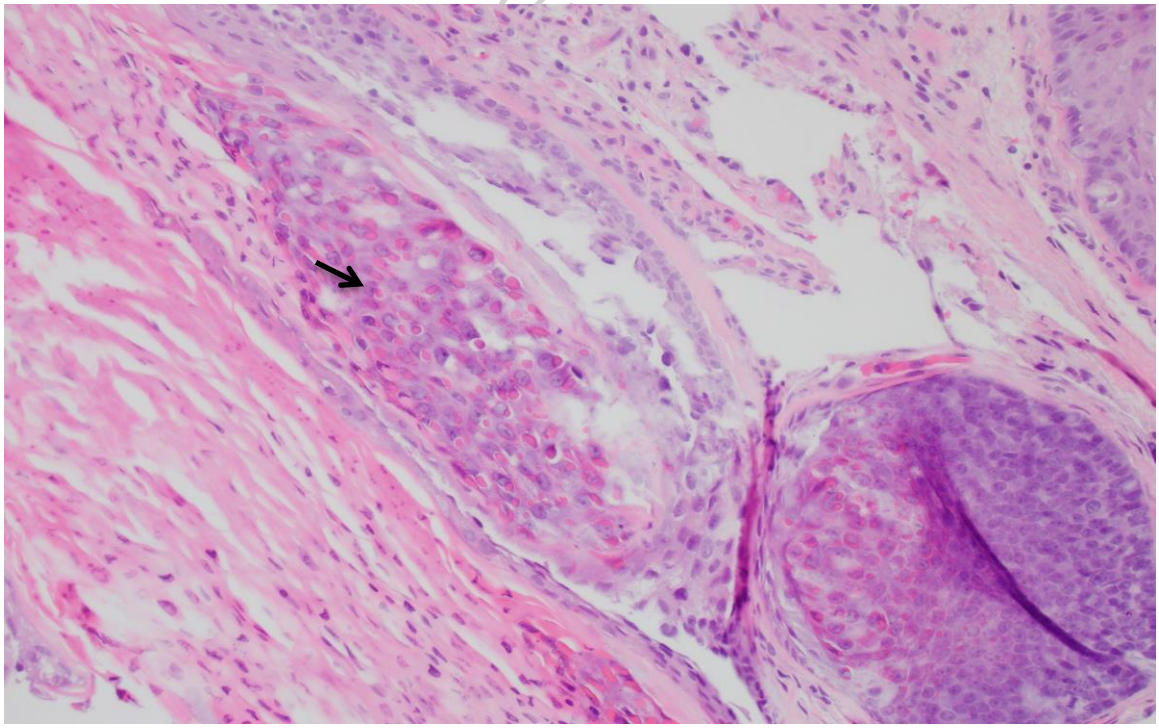

Figure 2B: Higher magnification of the irregular outer root sheath with TSPyV viral epithelial perinuclear eosinophilic/basophilic changes (black arrow). H&E staining X20