Contents lists available at ScienceDirect

# Gynecologic Oncology Reports

Case report

# Concurrent nonavalent human papillomavirus (HPV) vaccination and immune stimulation with imiquimod to treat recalcitrant HPV-associated high grade vaginal intra-epithelial neoplasia

R. Farrell [a,b,*], J. Zaunders [c,d], IM. Poynten [d], L. Anderson [b,e], L. Evans [f,g]

[a] *Chris O'Brien Lifehouse Hospital, Camperdown, Sydney, New South Wales 2050, Australia*
[b] *Sydney Medical School, University of Sydney, New South Wales 2006, Australia*
[c] *NSW State Reference Labaoratory for HIV, Centre for Applied Medical Research, St Vincents Hospital, New South Wales, Australia*
[d] *HIV Epidemiology and Prevention Program, The Kirby Institute, University of NSW Kensington, Sydney, New South Wales 2052, Australia*
[e] *NSW Health Pathology, Royal Prince Alfred Hospital, Camperdown, Sydney, New South Wales 2050, Australia*
[f] *University of NSW Kensington, Sydney, New South Wales 2052, Australia*
[g] *Department of Clinical Immunology, Allergy and HIV, Liverpool Hospital, South Western Sydney Local Health District, Liverpool Sydney, New South Wales 2170, Australia*

## ARTICLE INFO

## ABSTRACT

This is the first report describing detailed T cell responses to viral-like proteins contained in an HPV specific vaccine given in combination with Imiquimod for treatment of persistent VAIN2/3. We postulate that stimulation of the innate immune system with Imiquimod and the specific CD4 and CD8T cell responses following HPV vaccination with Gardasil9[@] combined to induce clinical remission in a woman with treatment-refractory disease.

## 1. Objective

We aimed to induce clinical remission in a woman with recalcitrant, widespread high grade vaginal intraepithelial neoplasia (HSIL, VAIN2 or 3) using immune modulator therapy (Imiquimod) in combination with nonavalent HPV vaccination, and to study the HPV-associated T cell responses to determine therapeutic action of this combined modality.

## 2. Background

High-grade vaginal intra-epithelial neoplasia is a precursor to vaginal cancer and is caused by infection with human papillomavirus (HPV) in at least 96 % of cases. (Serrano et al., 2015) Treatment is therefore recommended for VAIN2 or 3, and more common modalities include surgical excison and/or ablation (using CO2 laser, electro-coagulation, photodynamic therapy), and in selected cases topical treament (Imiquimod or 5-Fluorouracil). (Kesic et al., 2023) Despite treatment, the rate of persistent disease is reported as 6.4–13.9 %, recurrence rates up to 59 %, and risk of progression to vaginal cancer between 2 and 15.4 %. (Dodge et al., 2001; Sopracordevole et al., 2016)

The risk of developing invasive disease is dependent on the presence of VAIN3 and length of follow-up, with a mean time interval from treatment of HSIL to progression to squamous cell carcinoma reported as 54.6 months (4–146 months). (Sopracordevole et al., 2016).

Adjuvant HPV vaccination in unvaccinated women has been shown to reduce the risk of new high grade dysplasia of the cervix by 64 % (from 5.9 % to 1.9 %) when given immediately following treatment of CIN2 or 3. (Lichter et al., 2020) However, the role of adjuvant HPV vaccination in the management of recurrent or persistent VAIN2/3 is unclear. (Bryan et al., 2019) Whereas HPV vaccination leads to prevention of future infection by inducing neutralising antibodies to the viral L1 capsid proteins, avoidance of persistent infection would additionally require induction of co-ordinated CD4 and CD8 T-cell responses leading to cytotoxicity of virus-infected cells. Data investigating the T cell responses to adjuvant HPV vaccination in high grade dysplasia of the lower genital tract (LGT) are limited and few studies have investigated the association between T-cell response and HPV vaccination when used in combination with immunomodulator therapy. (van Poelgeest et al., 2016).

The aims were therefore to assess the effect of HPV vaccination,

combined with topical imiquimod, on a case of persistent VAIN2/3 despite previous surgical treatment, and to measure the cellular HPV-specific response to this combination treatment.

## 3. Case report

We present the case of a 32 year old nulliparous woman with a history of cervical hr-HPV and possible HSIL (pHSIL) found on routine screening, with CIN1 on cervical biopsy. Approximately 12 months later, biopsies showed CIN3 and multi-focal VAIN3. (Table 1). Past gynaecological history included imperforate hymen with haematometra requiring surgical excision at age 14 years. Three doses of quadrivalent HPV vaccine (Gardasil®, active against HPV6,11,16,18) were received at age 15 years. The patient reported first vaginal coitus at age 27 years, less than 3 lifetime sexual partners (monogamous with current partner for 4 years), and first Papanicolou smear 3 years previously (negative). The patient is planning conception.

Initial treatment was surgical resection of CIN3 (involving all four cervical quadrants) by large loop excision, and excision and/or diathermy of 8 separate sites of VAIN3 located throughout the vagina. Pathology of the vaginal lesions is shown in Fig. 1.

Due to the rapid progression of HPV-related disease in this Case, referral to an immunologist for investigation of a possible immune deficiency was undertaken. Results showed normal lymphocyte subsets

and surface markers, IgG/A/M and E within the normal range, negative HIV serology, and normal mitogen response.

Four months following initial surgical treatment, a repeat examination under anaesthesia (EUA) and biopsies were performed, which confirmed recurrent/residual VAIN2/3 in multiple areas of the right side of the vagina.

HPV DNA genotyping by polymerase chain reaction (PCR) was performed on vaginal and cervical specimens, and HPV52 was detected at both sites.

A 16-week course of Imiquimod 5 % (Aldara™ 5 % cream) was commenced, initially with half recommended dose of 125 mg on a tampon inserted vaginally 3 days per week. The patient experienced systemic flu-like symptoms and some vaginal bleeding after the first 4 weeks, necessitating a one week break from treatment. It was then possible to introduce full dose treatment of 250 mg 3 times per week, with some intermittent reductions to half dose due to flares in systemic symptoms.

Nonavalent HPV vaccine (HPV9v vaccine, Gardasil9®, active against HPV6,11,16,18,33,45,52 and 58 was administered 3 months prior to commencement of Imiquimod and the final (third) dose given 3 months following first dose of Imiquimod.

Fig. 2 **Case CD4 (A) and CD8 (B) T cell in vitro responses to HPV52 E6 and E7 peptide pools and to nonavalent Gardasil.** Post-vaccination lack of HPV52 E6- and E7-, but presence of Gardasil-

**Table 1**

Historical Sequence of Investigations, Treatment and Results.

| Date | Investigation/Treatment | Result |
|---|---|---|
| 07/2017 | Papanicolaou smear | Negative |
| 03/2020 | Cervical screening test | hr-HPV non 16/18 detected, pHSIL |
| 03/2020 | Colposcopy, Cervical biopsies | Colposcopy: CIN 1, Pathology: CIN 1 |
| 01/2021 | Cervical screening test | hr-HPV non 16/18 detected, pHSIL |
| 01/2021 | Colposcopy | widespread cervical/vaginal HSIL |
| 01/2021 | EUA, LLETZ cervix, excision and diathermy multiple vaginal lesions | Pathology: Cervix: CIN 3 extends to ectocervical margins (endocervix clear) Vagina: VAIN 2/3 all lesions |
| 03/2021 | Immunology consultation **\* Serum Assays for in vitro immune tests** | No obvious primary immune deficiency: normal lymphocyte subsets and surface markers, IgG/A/M and E, negative HIV serology, and normal mitogen response |
| 03/2021 | HPV vaccination with nonavalent Gardasil9® 3 doses commenced | |
| 05/2021 | EUA, biopsies cervix and vagina | No CIN. Pathology: VAIN 3 right vagina (upper and lower) |
| 06/2021 | Cervical and Vaginal HPV subtyping by PCR | HPV52 |
| 06/2021 | Imiquimod vaginal application commenced (16 week course) | |
| 09/21 | Cervical co-test Cervical Biopsy Vaginal co-test Colposcopy | hr-HPV non 16/18 detected, LSIL and cellular changes of regeneration and repair CIN 1/HPV hr-HPV non 16/18 detected, HSIL Right upper vaginal lesion 0.5 cm |
| 10/21 | EUA, Cervical biopsy, vaginal biopsies, Laser to upper vaginal lesion | Pathology: Cervix anterior and posterior CIN 1. Vagina: Right upper vagina VAIN 3, all other areas VAIN 1 |
| | **\*T cell responses to HPV52 E6 and E7** | **Undetectable CD4 or CD8 T cell response** |
| 12/21 | Vaginal dilator therapy | |
| 06/22 | Cervical co-test Vaginal Co-test | hr-HPV negative, cytology negative hr-HPV negative, cytology negative |
| | **\*T cell responses to nonavalent Gardasil9®** | **Vigorous CD4 and CD8 T cell response** |
| 04/23 | Cervical co-test Vaginal co-test | hr-HPV negative, cytology negative hr-HPV negative, cytology VAIN 1 |
| 05/23 | TV US | Viable pregnancy 8 weeks |

hr-HPV- high risk HPV detected, using PCR (polymerase chain reaction), pHSIL- possible high grade squamous lesion, CIN- cervical intraepithelial neoplasia, EUA-examination under anaesthesia using colposcope, 5% acetic acid and Lugols iodine, LLETZ- large loop excision of the transformation zone, VAIN- vaginal intra-epithelial neoplasia.

\* serum assays for in vitro immune tests- AIM (activation induced marker) assay using CD25/OX40 (CD134) and CD25/CD137 for measurement of CD4 and CD8 T cell response, respectively, to HPV 52 E6 and E7 peptides, or nonvalent Gardasil, as specified.
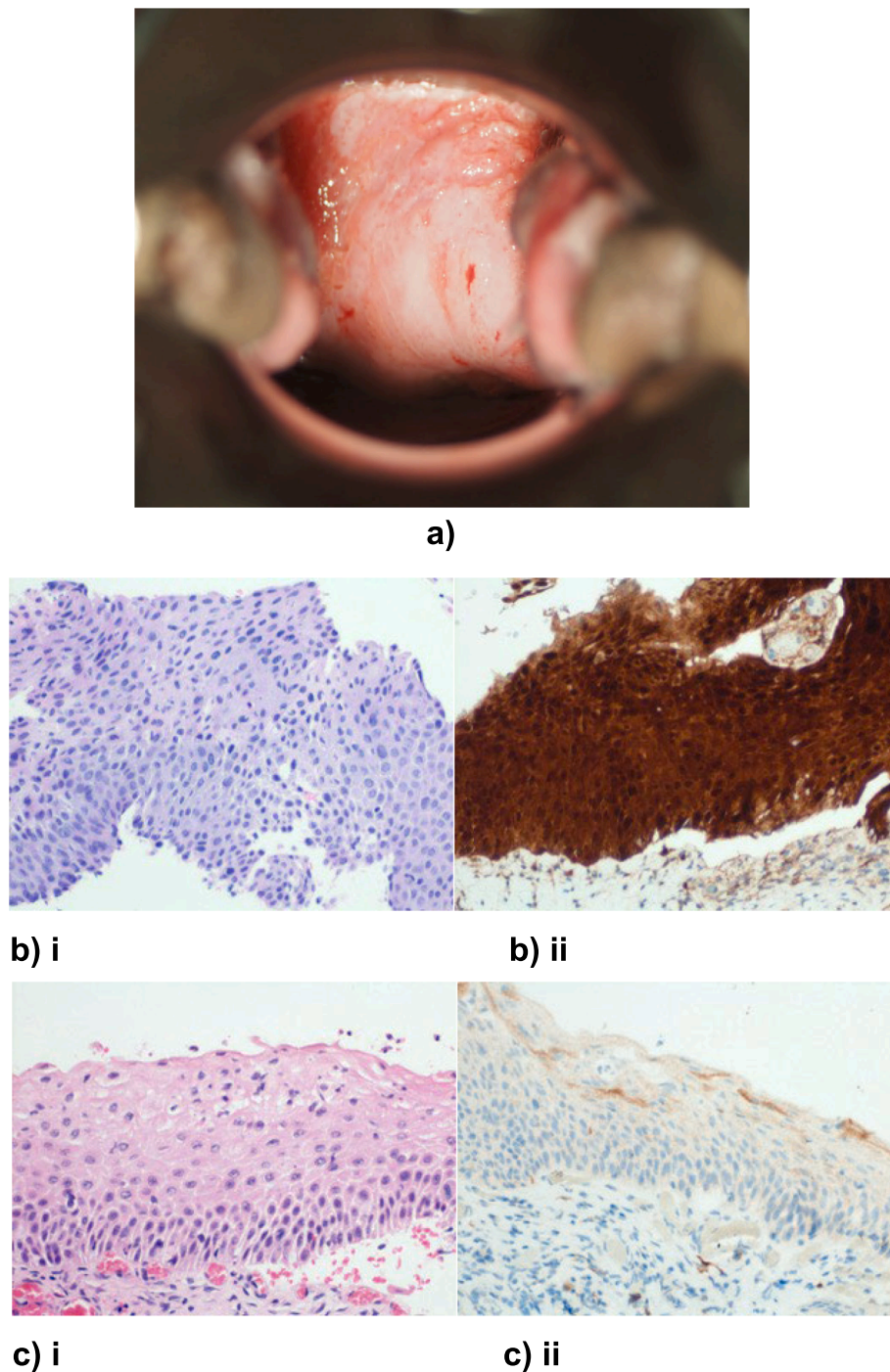
**Fig. 1.** Clinical photos of cervix and vagina. a) Macro 01/2021: before treatment showing CIN 3 of cervix contiguous with VAIN 3 of anterior vagina (lower- anterior cervix, upper- anterior upper vaginal wall). b) Micro 01/2021: Right lateral vaginal biopsy at initial surgical excision, pre- Gardasil9® vaccine and pre-Imiquimod treatment. i) Haematoxylin and eosin stained section showing VAIN 3. ii) p16 immunohistochemistry showing block positivity. c) Micro 10/2021: Right lateral vaginal biopsy after Gardasil9® vaccine ×3 courses and vaginal Imiquimod 16 weeks treatment i) Haematoxylin and eosin stained section showing subtle HPV/VAIN 1. ii) p16 immunohistochemistry showing limited staining on surface of no significance.

specific CD4 T cells using the CD25/OX40 AIM assay (A, upper) and 7 day proliferation assay (A, lower). Similarly, there was a lack of HPV52 E6- and E7-specific CD8 T cells using the CD25/CD137 AIM assay (B, upper) or 7 day proliferation assay (B, lower). However, there were Gardasil-specific CD8 T cells detected in the CD25/OX40 AIM assay (B, upper) and in the 7 day proliferation assay (B, lower).

## 4. Post-vaccination HPV52 T cell response studies

Following identification of HPV52 by PCR, we used overlapping peptide pools from the respective sequences of HPV52 E6 and E7 to investigate specific T cell responses following vaccination with non-avalent Gardasil9®. HPV52 E6- and E7-specific T cells in peripheral blood mononuclear cells (PBMC) were measured using AIM (activation induced marker) CD25/OX40 (CD134) upregulation on CD4 T cells and CD25/CD137 on CD8 T cells, after 2 days of incubation with HPV 52 E6
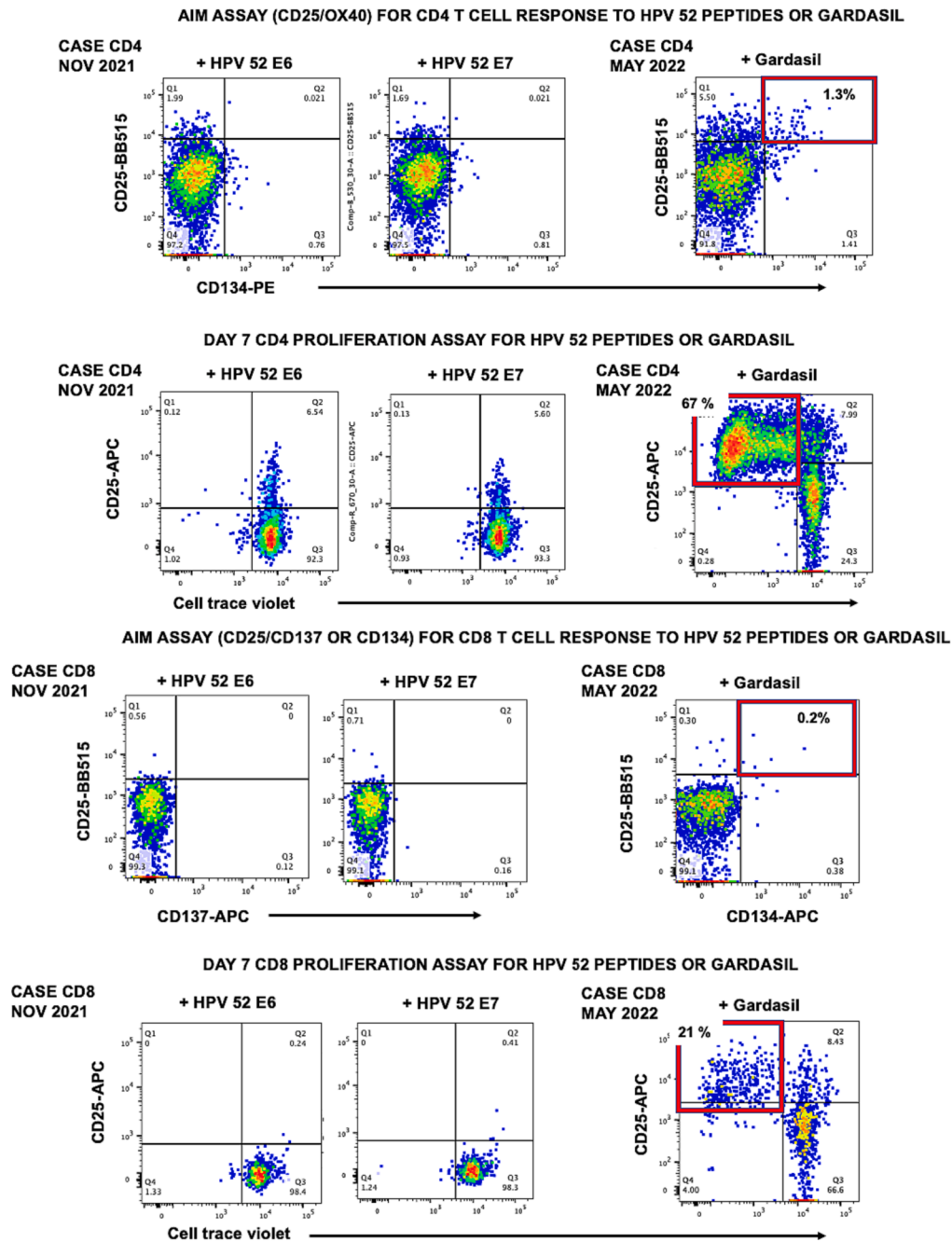
**Fig. 2.** Post vaccination HPV52 specific T cell assays.

and E7 peptide pools (Fig. 2). The results show that neither HPV52 E6- and E7-specific CD4 T cells (Fig. 2A), nor CD8 T cells (Fig. 2B), were detectable at this time point. Similarly, using the day 7 in vitro proliferation assay, neither HPV52 E6- and E7-specific CD4 T cells nor CD8 T cells were detectable. Altogether, these results suggested that E6- and E7-specific CD4 and CD8 T cells were **not** involved in clinical regression following Gardasil immunization.

Due to the lack of responses to E6 and E7, by the time that the VAIN cytology had been cleared, we then tested CD4 and CD8 T cell responses to Gardasil itself, using the OX40 AIM assay (Fig. 2A and B, red boxes). Since the virus-like particles (VLPs) used in Gardasil9® are comprised of recombinant proteins, and not peptides, we hypothesized that we may see CD4 responses, but not see any CD8 responses, since recombinant proteins do not usually access the HLA Class I cell surface presentation pathway in vitro. As shown in Fig. 2A, there was a significant CD4

response to Gardasil9® in the OX40 AIM assay, but no response by CD8 T cells (Fig. 2B), as expected.

However, when we measured the longer day 7 proliferation responses to Gardasil9®, we saw a very large CD4 proliferation response (Fig. 2A) and also a very clear, although smaller, CD8 proliferation response to Gardasil9® (Fig. 2B). These results are consistent with uptake of VLP's and access to the HLA Class I presentation pathway, in addition to the access of recombinant proteins for HLA Class II presentation pathway for CD4 T cell responses.

Following completion of Imiquimod and immediately following the third dose of Gardasil9® vaccine, an examination under anaesthesia (EUA), vaginoscopy and colposcopy were performed and multiple cervical and vaginal biopsies were taken. Results showed a small 0.5 cm residual area of VAIN2/3 in the right upper vagina, and residual CIN1 of the posterior cervix. All other areas of CIN and VAIN3 (over 90 % of

lesions) had resolved, with biopsies showing inflammation only. There was a moderate degree of upper vaginal stenosis noted. Laser treatment was performed on the right upper vaginal VAIN2/3 following biopsy.

The patient commenced the use of regular vaginal dilator therapy post-operatively and continued regular follow-up. At 6 and 18 months post laser treatment, no hr-HPV was detected, cytology of the cervix was negative, and cytology of the vagina was VAIN1.

The patient achieved a successful pregnancy following last co-test, 2 years after treatment commenced. Ongoing close follow-up with colposcopy, cervical and vaginal co-test +- biopsy is planned.

## 5. Discussion

VAIN is an uncommon disease, with an incidence of 0.2–2/100 000 women/year and accounts for 0.4 % of all premalignant lesions of the female lower genital tract. (Kesic et al., 2023) As in the case presented, VAIN is associated with CIN in around 65 % of cases. (Dodge et al., 2001) The overall rate of progression of VAIN2/3 to cancer despite treatment and follow-up is reported as 2–15.4 %. (Dodge et al., 2001; Sopracordevole et al., 2016; Hodeib et al., 2016) In a series of 205 women with VAIN2/3 on biopsy, Soprocordevole et al (Sopracordevole et al., 2016) found a siginificantly higher risk of progression to cancer in women diagnosed with VAIN3 than VAIN2 (15.4 % vs 1.4 %, p < 0.00011) following ablative or excisional treatment at a mean post-treatment time of 54.6 (range 4–146) months. This confirms the importance of accurate histological diagnosis, adequate treatment, close post-treatment monitoring, and long-term follow up of these patients.

Treatment of VAIN2/3 should be individualised for each case, with consideration of patient characteristics such as age, parity, immunedeficiency status, sexual activity, site and extent of disease, and previous VAIN treatment. (Kesic et al., 2023) Histology obtained by biopsy is required prior to treatment to both avoid overtreatment of LSIL (HPV/VAIN 1) or inadequate treatment of VAIN2/3 or invasive disease. This may require EUA and mutiple biopsies of multifocal disease, as in this Case.

Treatment options for VAIN2/3 include surgical excision or ablation, and medical therapies. Excision methods are preferred as first-line treatment to provide a complete specimen for histopathological diagnosis and exclusion of occult malignancy, which is present in 2.6–30 % of patients. (Kesic et al., 2023) The risk of recurrent disease after initial treatment of VAIN2/3 is high but may be lower for excisional than ablative treatments. Recurrence rates after surgical excision range from 7.2 to 20.8 %. (Kesic et al., 2023) However, as in our case, excision may not be possible for all lesions if there is widespread mutifocal disease. In this situation, ablative techniques such as CO2 laser, electrocoagulation (diathermy), photodynamic therapy, or plasma energy ablation may be utilised. The incidence of treatment side effects such as scarring, vaginal stenosis, and dysparuenia following excision or ablation, as in our case, highlights the need for alternative effective treatment options, especially for recurrent or peristent disease.

Imiquimod is now more widely used as a treatment for VAIN2/3 following a number of studies showing acceptable response rates of around 76 %. (Inayama et al., 2020) Inayama et al found recurrence after complete response to imiquimod in one of eight patients (13 %). (Inayama et al., 2020) An RCT comparing Imiquimod with laser therapy and observation in 30 women with VAIN2/3 showed a histological regression to less than VAIN1 in 80 % (8/10) treated with Imiquimod, 100 % (10/10) treated with laser, and 67 % (6/9) in the observation arm at 16 weeks followup. (Tainio et al., 2016) Further studies are required to compare longer term response rates following imiquimod with surgery and other available treatment options.

As with our patient, adverse effects of vaginal imiquimod 5 % include flu-like symptoms, vaginal irritation, and localised pain. (Tainio et al., 2016) Overall, most symptoms can be controlled with use of simple oral analagesia and result in temporary cessation or dose-reduction, but uncommonly require complete cessation of treatment.

To date, HPV vaccination has been used primarily as prophylaxis. High protection rates that correlate with the induction of an antibody response have been shown to result in reduced rates of both detectable cervical HPV and cervical cancer. (Lei et al., 2020) Recent systematic reviews have also suggested a decrease in CIN 2/3 recurrence/new disease rates post HPV vaccination. (Kechagias et al., 2022) In a real-world study of a cohort of 514,537 women aged 17–26 years living in Denmark between 2006 and 2019, HPV vaccination at age 16 years or younger resulted in a decrease in incidence of vaginal HSIL + of 84 % compared to women who were unvaccinated. (Dehlendorff et al., 2021).

The combined intervention with Imiquimod and nonavalent Gardasil9® vaccine (including the HPV52 subtype) appears to have enhanced the anti-HPV cell mediated immune response in this Case. We did not detect any CD4 or CD8 in vitro response to peptide pools from E6 or E7 from HPV52, using our sensitive AIM or proliferation assays. Post-vaccination, however, vigorous CD4 responses to the HPV VLP's were detected in vitro, at least comparable to those in other healthy adult vaccinees. We propose that the concurrent administration of imiquimod might stimulate the innate immune system to up-regulate cytokines such as IFN-a, IL-6 and TNF-a that then activate antigen-presenting T cells to target HPV infected cells. However, a larger study is needed to assess the relative contributions of innate immune activation with or without a therapeutic vaccine. It is also possible that much of the CD4 response to HPV9v vaccine may be memory cells or boosted memory cells from the original quadrivalent vaccination 17 years earlier. Therefore, a limitation of the study is that pre-vaccination in vitro responses to Gardasil9® vaccine were not performed. Overall though, the post-vaccination response was vigorous, notably the clear proliferation response of CD 8T cells to Gardasil9®.

It is plausible that the CD4 response to vaccination in this study contributed to subsequent control of the HPV52 lesions by boosting T cell immunity. This is supported by previous studies that have shown CD4 cytotoxic T lymphocytes playing an important role in human antiviral and anti-tumour immunity. (Juno et al., 2017) However, few previous studies have investigated the T cell response to HPV-specific vaccination and the effect on high grade pre-cancers of the lower genital tract. (van Poelgeest et al., 2016; Shibata et al., 2021) Furthermore, no previous study has reported T cell response to HPV specific vaccine given concurrently with Imiquimod directly to such lesions. It is also unknown if adjuvant HPV vaccine can reduce the risk of recurrent VAIN. Further studies are required to investigate possible individual and/or synergistic roles of CD4 and CD8 T cells in regression of HPV-infected lower genital tract lesions.

## 6. Conclusion

This is the first report describing cellular responses to viral-like proteins contained in an HPV specific vaccine given in combination with Imiquimod for treatment of persistent VAIN. We postulate that stimulation of the innate immune system with Imiquimod and specific HPV cellular responses following vaccination combined to induce clinical remission in a woman with treatment-refractory disease. CD4 and CD8 T cell responses to HPV were demonstrated in association with the remission.

Further investigation of treatment-refractory VAIN patients for such cellular responses may help to establish a role of cellular immunity in controlling and eradicating HPV. In particular, the role of HPV vaccination therapeutically with or without innate immune system stimulation should be explored.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Author Statement**.

**Rhonda Farrell** conceptualisation of the study, designing the clinical methodology together with Evans L, clinically managed the case,

provided resources, literature review, writing the paper as main author, reviewing and editing the paper.

**John Zaunders** designing the laboratory methodology, conducting the laboratory studies, writing and editing the paper, providing scientific input and results.

**Isobel Mary Poynten** literature review, clinical methodology, writing and revieweing the paper.

**Lyndal Anderson** conducting the pathology reviews, writing and reviewing the paper, providing the clinical photographs.

**Louise Evans** conceptualisation of the study, designing the clinical methodology with Farrell R, literature review, clinically managing the case, writing and reviewing the paper.

## CRediT authorship contribution statement

**R. Farrell:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **J. Zaunders:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Investigation, Validation, Formal analysis, Methodology, Resources. **IM. Poynten:** Writing – original draft, Writing – review & editing, Visualization, Validation, Formal analysis, Methodology, Supervision. **L. Anderson:** Data curation, Writing – original draft, Writing – review & editing, Visualization, Methodology, Resources. **L. Evans:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Visualization, Investigation, Validation, Formal analysis, Methodology, Supervision, Resources, Project administration.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We thank the patient who has consented to be involved in this study.

*Funding*

## References

Bryan, S., Barbara, C., Thomas, J., Olaitan, A., 2019. HPV vaccine in the treatment of usual type vulval and vaginal intraepithelail neoplasia: a systematic review. BMC Women's Health 19 (3). https://doi.org/10.1186/s12905-018-0707-9.

Dehlendorff, C., Baandrup, L., Kjaer, S.K., 2021. Real-world effectiveness of human papillomavirus vacccination against vulvo-vaginal high-grade pre-cancerous lesions and cancers. JNCI 113 (7), 869–874.

Dodge, J.A., Eltabbakh, G., Mount, S., Walker, S.P., Morgan, A., 2001. Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia. Gynecol. Oncol. 83, 363–369.

Hodeib, M., Cohen, J.G., Mehta, S., Rimel, B.J., Walsh, C.S., Li, A.J., Karlan, B.Y., et al., 2016. Recurrence and risk of progression to lower genital tract malignancy in women with high grade VAIN. Gynecol Oncol 141 (3), 507–510.

Inayama, Y., Yamanishi, Y., Nakatani, E., Aratake, J., Sasagasako, N., Yamada, K., et al., 2020. Imiquimod for vaginal intraepithelial neplasia 2–3: a systematic review and meta-analysis. Gynecol Oncol 160 (1), 140–147.

Juno, J.A., van Bockel, D., Kent, S.J., Kelleher, A.D., Zaunders, J.J., Ling Munier, C.L., 2017. Cytotoxic CD 4 cells- friend or foe during viral infection? Front. Immunol 8. https://doi.org/10.3389/fimmu.2017.00019.

Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, et al. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis, BMJ 2022;378 e070135.

Kesic, V., Carcopino, X., Preti, M., Vieira-Baptista, P., Bevilacqua, F., Bornstein, J., et al., 2023. The european Society of Gynaecological Oncology (ESGO), the International Society for the Study of vulvovaginal disease (ISSVD), the european College for the Study of vulval disease (ECSVD), and the european Federation of Colposcopy (EFC) consensus statement on the management of vaginal intraepithelial neoplasia. Int J Gynecol Cancer (1–16). https://doi.org/10.1136/ijgc-2022-004213.

Lei, J., Ploner, A., Elfstrom, K.M., Wang, J., Roth, A., Fang, F., et al., 2020. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 383, 1340–1348.

Lichter, K., Krause, D., Xu, J., Laurent Tsai, S.H., Hage, C., Weston, E., et al., 2020. Adjuvant human papillomavirus vaccine to reduce recurrent cervical dysplasia in unvacccinated women. a systematic review and meta-analysis. Obstets and Gynecol 135 (5), 1070–1083.

Serrano, B., de Sanjose, S., Tous, S., Quiros, B., Munoz, N., Bosch, X., et al., 2015. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45,52 and 58 in female anogenital lesions. Eur J Cancer. 51 (13), 1732–1741.

Shibata, T., Shah, S., Evans, T., Coleman, H., Lieblong, B.J., Spencer, H.J., et al., 2021. Expansion of human papillomavirus- specific T cells in periphery and cervix in a therapeutic vaccine recipient whose cervical high-grade squamous intraepithelial lesion regressed. Front Immunol 12, 10.3389.fimmu.2021.645299.

Sopracordevole, F., Barbero, M., Clemente, N., Fallani, M.G., Cattani, P., Agarossi, A., et al., 2016. High-grade vaginal intraepithelial neoplasia and risk of progression to vaginal cancer: a multicentre study of the italian society of colposcopy and cervico-vaginal pathology (SICPCV). Eur Rev Med Pharmacol Sci 20, 818–824.

Tainio, M., Jakobsson, K., Louvanto, I., Kalliala, J., Paavonen, P.N., et al., 2016. Randomised trial on treatment of vaginal intraepithelial neoplasia-imiquimod, laser vaporisation and expectant management. Int. J. Cancer 139, 2353–2358.

van Poelgeest, M., Welters, M.J.P., Vermeij, R., Stynenbosch, L.F.M., Loof, N.M., Berends-van der Meer, D.M.A., et al., 2016. Vaccination against oncoproteins of HPV 16 for noninvasive vulvar/vaginal lesions: lesion clearance is related to the strength of the T-cell response. Clin Cancer Res 22 (10), 2342–2350.