Human papillomavirus (HPV) and cervical dysplasia in adult female cystic fibrosis (CF) lung transplant recipients

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ABSTRACT

Human papillomavirus (HPV) is the principal risk factor for cervical cancer. Transplant recipients are at a disproportionate risk of HPV complications. We conducted a single-centre, retrospective study of adult female cystic fibrosis (CF) lung transplant recipients between 2008 and 2021. We observed 12 of 34 (35.3%) with ≥1 abnormal pap smear (median age: 26.7 years). Complications included refractory anogenital warts (n=3), vulvectomy (n=2) and cervical cancer (n=4), with two deaths from metastatic disease. None with HPV morbidity was vaccinated. Lung transplant recipients had greater odds of cervical dysplasia relative to controls (OR, 3.98; 95% CI 1.17 to 11.82). CF care providers must prioritise HPV vaccination to attenuate potential future morbidity and mortality.

INTRODUCTION

Cervical cancer is the fourth leading cause of female cancer deaths worldwide, with >90% attributable to human papillomavirus (HPV).[1] There is a high lifetime probability of acquiring HPV, with ≥80% of sexually active individuals developing ≥1 HPV infection by age 45.[2] Whereas many are familiar with the respiratory infection sequelae of cystic fibrosis (CF), few data exist on HPV. Given the predisposition towards lung transplantation and consequent immunosuppression in CF, understanding factors impacting the outcomes is of utmost importance. Recent studies on women with CF have highlighted a high proportion of abnormal Papanicolaou (pap) smears (33% of non-transplanted and 25% of transplanted women with CF), cervical dysplasia or fulminant cancer (12.8%).[3] Following clinical observations of disproportionate HPV-associated morbidity and mortality in women with CF post-transplant, we formally audited our population and determined the prevalence and sequelae of HPV-related disease.

METHODS

We performed a retrospective chart review from the Southern Alberta Adult CF Clinic of all women between January 2008 and April 2021 with a lung transplant. Collected patient demographics are detailed in table 1. Specific gynaecological history included time of first pap smear, details around pap smears, colposcopy and surgical procedures, presence of cervical cancer, cervical intraepithelial neoplasia (CIN), and/or refractory anogenital warts. Controls were randomly identified female adult patients with CF without lung transplantation (age ±1 year) attending our clinic from the same time period of interest. Individuals who met the above criteria were identified through chart review and a random number generator was used to match controls with cases in a 2:1 ratio. Statistical analysis comparing cohort characteristics was performed using Student's t-test for continuous variables, and χ^2 test or Fisher's exact test depending on sample size for categorical data at a two-sided α of 5% using R V.4.04 (R Core Team, 2021).

RESULTS

Characteristics of female CF lung transplant recipients

Thirty-four transplanted women were identified. We found 12 patients (35.3%) with at least one abnormal pap smear (preceding (n=1, 8.3%) or following (n=11, 91.7%) lung transplantation). Among these (median age 26.7 years (IQR 23.5–32.3) at first abnormal pap), nine (75.0%) were found to have cervical dysplasia and three (25.0%) with refractory anogenital warts. The period prevalence during the study (13 years) was 35.3% for abnormal pap smears, 8.8% for anogenital warts, 26.4% for cervical dysplasia and 11.8% for cervical cancer. The median time from lung transplantation to first abnormal pap smear was 6.17 years (IQR 3.99–7.75). There were no clinically significant differences in comorbidities and demographics between those who had HPV-associated morbidity and those who did not (table 1). Individuals who had received HPV vaccination (median age at series completion 19.4 years (IQR 17.3–25.4), with 8 of 9 being vaccinated prior to transplantation) were significantly less likely to have HPV-associated complications than unvaccinated individuals (0% (0 of 9) vs 48% (12 of 25), p=0.01).

HPV-associated morbidity and mortality in CF

To evaluate the risk of HPV complications among our cohort of CF female lung transplant recipients (n=34), we compared them with a cohort of age-matched, randomly identified CF female controls (n=64) who had not received a lung transplant. There were greater odds of cervical dysplasia (OR, 3.98; 95% CI 1.17 to 11.82) in transplanted women with CF compared with non-transplanted CF controls. Among our cohort of transplanted women with HPV complications (n=12), there were a total of 58 colposcopies performed. Two individuals (17%) required surgical vulvectomy after repeatedly failing salvage therapy. In total, four (33%) developed cervical cancer. Two (17%)

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Table 1 Demographics of female adult CF lung transplant recipients

	Transplanted without HPV complications (n=22) n (%)	Transplanted with HPV complications (n=12) n (%)
CF-related factors		
Genotype, n (%)		
ΔF508 homozygous	11 (50)	5 (42)
ΔF508 heterozygous	7 (32)	7 (58)
Other	4 (18)	0 (0)
CF comorbidities, n (%)		
Pancreatic insufficiency	19 (86)	11 (92)
CF liver disease	4 (18)	1 (8)
Gastrointestinal reflux disease	10 (45)	6 (50)
Distal intestinal obstruction syndrome	10 (45)	7 (58)
CF arthropathy	5 (23)	0 (0)
Sinus disease (polyps or nasal congestion)	11 (50)	7 (58)
Pretransplant factors		
Age at the time of transplant/cohort inclusion, years, median (IQR)	29.7 (23.7–33.9)	26.7 (23.5–32.3)
Body mass index at the time of transplant (kg/m^2), median (IQR)	20.6 (18.2–21.1)	19.8 (18.2–20.9)
FEV_1 predicted at the time of transplant, median (IQR)	24.8 (17.1–29.3)	26.5 (22.0–31.5)
CF-related diabetes pretransplant	7 (32)	4 (33)
Chronic *Pseudomonas aeruginosa* infection (%)	20 (91)	9 (75)
Post-transplant factors		
CF-related diabetes post-transplant	12 (55)	7 (58)
CMV status, n (%)		
Donor +, Recipient –	6 (27)	4 (33)
Donor +, Recipient +	9 (41)	5 (42)
Other	7 (32)	3 (25)
Maintenance immunosuppression, n (%)*		
Tacrolimus	17 (77)	11 (92)
Corticosteroids	22 (100)	12 (100)
Mycophenolate	19 (86)	10 (83)
Azathioprine	3 (14)	1 (8)
Sirolimus	2 (9)	1 (8)
Ciclosporin	1 (5)	0 (0)
Aspergillus infection, n (%)	5 (23)	2 (17)
Patients with ≥1 acute cellular rejection episode, n (%)	12 (55)	5 (42)
BOS-free survival, without BOS, n (%)†		
5 years	9 (60)	5 (50)
10 years	4 (50)	2 (33)
Overall survival, alive, n (%)		
5 years	15 (68)	10 (83)
10 years	8 (36)	6 (50)

*Patients were often on multiple drug regimens and thus the numbers are greater than the total sum of patients. Immunosuppression regimen at the time of abnormal first pap smear is reported.
†Numbers calculated from the total population of patients alive at the time of assessment.
BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; CMV, cytomegalovirus; HPV, human papillomavirus.

individuals died from metastatic cervical cancer complications (74 and 115 months after first abnormal pap, and 131 months and 167 months after transplantation, respectively). There was no difference between rejection-free and total survival at 5 and 10 years in this small cohort.

DISCUSSION

Those at highest risk of HPV-related complications are individuals with profound immune suppression. There is a twofold to sixfold higher rate of CIN,[4] threefold higher rate of cervical cancer,[4] and 20-fold to 50-fold higher rate of vulvar carcinoma[4 5] in renal transplants compared with age-matched controls.[6] Our retrospective review similarly identified higher rates of HPV-related complications in CF female lung transplant recipients. The results from our study stress the importance of regular gynaecological follow-up and cervical screening in transplanted women with CF. While immunosuppression has been identified as key risk factor for the development of HPV, CF in of itself may be a confounding risk factor as chronic inflammation resulting in thick cervical mucus may increase susceptibility to HPV. Our study is provocative in identifying these correlations; however, larger cohorts would need to be analysed to develop meaningful conclusions around the type and intensity of immunosuppression and risk of HPV-related sequelae.

HPV is associated with other malignancies including those affecting the head and neck, penis, and anus. Indeed, anal dysplasia and cancer risk are 10-fold higher in transplanted patients.[7 8] Furthermore, mucosal HPV infections have been reported in renal transplants to be higher than controls (32.5% vs 17.0%).[9] It is important to note that, aside from cervical cancer screening, there is no other routine screening programme for other HPV-related malignancies. As these non-cervical malignancies generally manifest at a slower rate, their rates will likely increase over time.

Among high-risk populations, recommendations include yearly cervical cancer screening and administration of HPV vaccination. Multiple large, international, randomised controlled trials have consistently demonstrated HPV vaccinations are safe and effective for prevention of HPV infections, external genital lesions, abnormal pap smears and high-grade cervical dysplasia. A systematic review evaluating population-level impact of girls-only HPV vaccination programmes observed an 83% decline in HPV-16 and HPV-18 (the strains most associated with cancers), a 51% decline in CIN2+ lesions, and a statistically significant decline in anogenital warts, with greater reductions seen in countries with higher uptake rates.[10]

In CF, there is limited knowledge on factors associated with HPV vaccine uptake. A recent study of paediatric patients with CF identified healthcare providers' positive advice and fear of HPV-related disease were the main rationale justifying vaccination uptake, with insufficient knowledge and concerns about potential side effects as barriers.[10] At present, no consensus guidelines regarding HPV vaccination specifically prior to lung transplantation exist apart from those in the general population. Notably, none of the patients included in our study with HPV complications was vaccinated either prior to or following transplantation, identifying a gap in clinical care in this population that merits further exploration.

This was a small exploratory retrospective study with all limitations inherent in such methodology, including a small sample size which may limit generalisability of our findings, but highlights the prevalence and potentially devastating impact of HPV in CF after lung transplantation. Routine universal HPV vaccination of all eligible children and adults with CF should be prioritised by CF providers to prevent future morbidity and mortality given the high rate of lung transplantation in this population. To survive end-stage CF lung disease and lung transplantation only to experience life-altering morbidity (affecting sexual health, personal confidence, relationships, etc) and potential mortality of HPV—a highly vaccine-preventable disease—is now unacceptable.

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Contributors CT performed clinical chart reviews and collected the relevant data. RS assisted in statistical calculations. AC provided guidance related to the relevant

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literature in the area. MDP envisioned and supervised the project and serves as its guarantor. CT created the first draft of the manuscript, and all authors assisted in the creation of the final manuscript.

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Competing interests CT is supported by a Cystic Fibrosis Foundation Fellowship. RS has no conflicts relevant to this work but serves on Cystic Fibrosis Foundation and Cystic Fibrosis Canada advisory committees. AC has worked with Merck in an advisory capacity and serves an advisory role for Immunize Canada. MDP has no conflicts relevant to this work but serves as Vice Chair for Cystic Fibrosis Canada's Research Advisory Committee.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Conjoint Regional Health Ethics Board (REB20_2040A). Waiver of consent was provided by the REB. As several patients had passed away, it was not appropriate to seek individual consent.

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