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Title page

The prevalence of Human polyomavirus 2 (HPyV2) antibody positivity in psoriasis patients.

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Highlights

- Infection with human polyomavirus 2 (HPyV2) is common.
- Reactivation of HPyV2 in immunocompromised hosts may rarely lead to a serious illness- progressive multifocal leucoencephalopathy (PML).
- HPyV2 induced PML has been reported in association with systemic and biologic treatments for psoriasis, rheumatoid arthritis, haematological malignancy and multiple sclerosis.
- The prevalence of HPyV2 has not been measured in a psoriasis cohort to date.

Background

HPyV2 is a double stranded, deoxyribonucleic acid (dsDNA) human polyomavirus discovered in the 1960s on electron microscopy by Zu Rhein and Chou and cultured in 1971 by Walker et al. [2]. Antibodies to HPyV2 are present in 30-70% of the background population with some reports suggesting an asymptomatic carriage rate of up to 90% [3]. The primary route of transmission for HPyV2 is ingestion, with the tonsils the primary site of viral replication. After resolution of the viremia associated with the primary infection, HPyV2 remains latent in the renal tract. The virus can reactivate in immunosuppressed states. This reactivation can lead rarely to a rapidly progressive neurological condition; progressive multifocal leukoencephalopathy- PML [4]. The background incidence of PML is thought to be < 0.3/100,000 person years [5, 6]. Prior to the advent of combined anti-retroviral therapy

(ART) for treating human immunodeficiency virus (HIV), PML was most commonly associated with HIV infection where it occurs in 3-7% of patients, and is an acquired immunodeficiency syndrome (AIDS) defining illness. [7, 8, 9] Progressive Multifocal Leukoencephalopathy can affect organ transplant recipients, patients with lymphoma, leukaemia, those on long term corticosteroids and other immunosuppressive therapies. Human polyomavirus 2, induced PML has been reported most frequently in association with the use of natalizumab to treat patients with relapsing remitting multiple sclerosis. [10, 11] Many other monoclonal antibodies have been implicated in PML in the setting of MS and other autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis (PsA), psoriasis and haematological disease (see Table 1). [12, 13, 14] The risk of PML occurring in HPyV2 seropositive patients treated with natalizumab ranges from 0.56 to 1.6 per 1000 patients (95% CI) in the first 2 years of treatment. The risk of PML development in patients treated with natalizumab who are seronegative for HPyV2 is estimated at 0.09 per 1000 patients treated (95% CI 0-0.48). As HPyV2 is sine qua non for PML it is presumed that PML in those who are antibody negative represent a false negative antibody test. [11] There has been recent interest in PML in dermatology because of reports linking PML and fumaric acid ester therapy. [15] There have been 19 cases reported to date, 14 of whom had psoriasis. [16] Apart from one case all patients had a lymphocyte count below $0.7 \times 10^9/L$. The other patient was on Psorinovo® (a compounded form of dimethylfumarate/fumaric acid ester) and developed PML at a lymphocyte count of 0.8×10^9 . [17]

There are no data on HPyV2 antibody prevalence in psoriasis patients. HPyV2 testing may be a useful adjunct in determining the risk of PML in psoriasis patients requiring therapy particularly with dimethylfumarate.

Objectives

Our primary aim was to assess the seroprevalence of HPyV2 ~~JCV~~ in psoriasis. The secondary aim was to measure the prevalence of HPyV2 viruria in a psoriasis population. We assessed the treatment and patient specific characteristics in each group.

Study design

We recruited 248 patients with moderate to severe psoriasis after ethical approval and obtained written informed consent. Patients were recruited from a specialist clinic for psoriasis and comprised of three groups. Cohort 1 included moderate to severe psoriasis patients treated with systemic therapies - (95), predominantly methotrexate (25) and biologic agents -predominantly anti-TNF alpha therapies (47), for psoriasis. Cohort 2 included those treated with fumaric acid esters (84) (Fumaderm®) and cohort 3 (69) were psoriasis patients not receiving systemic agents.

Serum was taken for IgG class antibodies against HPyV2. Urine samples for PCR HPyV2 analysis were collected in 89 patients in the systemic/biologics group (cohort 1 (n=95)) of the total group of 248 patients. We recorded lymphocytes counts in all three groups contemporaneously with HPyV2 antibodies.

Baseline demographics of the three cohorts were obtained. At recruitment, baseline PASI (psoriasis area and severity index), DLQI (dermatology life quality index) and current treatment were recorded.

HPyV2 enzyme immunoassay

The HPyV2 IgG enzyme immunoassay was performed at University of Helsinki as previously described by Kardas et al. 2014, with some modifications. The specificity of the assay is

97.78% and a sensitivity of 95.87% as determined previously in an inter- and intra-laboratory comparison. [18] In brief, streptavidin-coated microwell plates, (UniverSA96-Lockwell, Kaivogen Ltd, Finland) were coated with biotinylated HPyV2 virus-like particles (VLPs) (180 ng/well). A streptavidin-coated well served as the streptavidin-background control for each sample and each control. Serum samples were diluted 1:100 and tested in duplicate. Three control sera (negative control, “HPyV2-IgG-Index” control and high positive control) were tested in all assays. After a washing step, horseradish peroxidase conjugated anti-human IgG (Dako, Agilent Technologies) was added for 60 minutes. Substrate (Tetramethylbenzidine, Sigma), 100µl was added to each well. After 15 minutes, 0.5M sulphuric acid was added and the absorbances were measured at 450nm. The reagent blank absorbance and the streptavidin background absorbance were subtracted from the absorbance of the samples and the controls. The results were calculated as an index: the absorbance (OD) of the sample divided by the absorbance of the “HPyV2 IgG Index Control” serum. All positive sera (Index ≥ 0.40) and borderline ($0.16 < \text{Index} < 0.40$) value were re-tested by pre-adsorption with the non-biotinylated VLPs. Briefly, the sera (1:100) were diluted in buffer containing VLP blocking antigen (10 µg/ml) and incubated at 4°C for 90 minutes. The assay was carried out as outlined above. The % inhibition is calculated as the $[(\text{unadsorbed OD} - \text{adsorbed OD}) / \text{unadsorbed OD}] \times 100 = \% \text{ inhibition}$. The result was interpreted as HPyV2 -specific if the inhibition was $>45.0 \%$.

Detection of HPyV2 DNA in urine

The RealStar® HPyV2 PCR Kit (Altona Diagnostics) is a CE marked IVD approved diagnostic test was used for detection of HPyV2 DNA in urine samples obtained from 89 patients in cohort 1. This assay which targets the large T antigen of HPyV2, includes a heterologous

amplification system (internal control) to identify possible PCR inhibition and to confirm the integrity of the reagents of the kit. DNA was extracted from 140µl of urine with the Biomerieux Easy MAG extraction system (bioMerieux) with an elution volume of 60µl. The amplification was performed on the ABI 7500 FAST Analyser using 10µl of eluate and 15µl of the mastermix. The following assay parameters were used: 10 mins at 95°C, 45 cycles at 15s at 95°C and 60s at 58°C. The kit contains 4 quantification standards with concentrations ranging from 10 to 10,000 copies/µl. Furthermore, a QC, HPyV2QC-01 (Qnostics Q control, Scotland) which served as a positive control, was run in all assays.

Results

52% of the systemic/ biologic group were seropositive for HPyV2, 36% were seronegative and 11.5% had equivocal tests. 50% of those receiving fumaric acid esters were seropositive for JCV, 44% seronegative and 5% equivocal. 48% of those not receiving systemic treatment were seropositive for HPyV2, 35% were seronegative and 17% were equivocal. Urinary PCR (n=89) for HPyV2 was positive in 21% of patients on systemic therapy (cohort 1 (n=95)). This figure has been replicated in previous studies. In our group, 95% of those with HPyV2 viruria were also HPyV2 seropositive. HPyV2 viruria is thought to represent active viral replication.

In the systemics and biologic group (n=95), 52% of the group were HPyV2 seropositive. The average age was 49 years (range 21-75 years) and the majority male (59%) versus (41%) female, respectively. The average PASI was 4.4 (range 0-26.2) and 30% of this cohort had a diagnosis of PsA. Of these, 15% were smokers.

In the dimethylfumarate (Fumaderm®) cohort 50% were HPyV2 seropositive. In this group 22.5% smoked, the majority were male (63%) versus (37%) female. The average age was

42.7 years (range 17-75 years). The average PASI was 5.5 (range 0-12.2) and the average weight was 88kgs. In contrast to cohort 1, only 1.6% had a diagnosis of PsA.

In those patients not receiving systemic treatment (Cohort 3), 48% were seropositive for HPyV2. The average age was 41 years (range 19-75 years), with an average PASI of 10.5 (range 5.6-17.4). Once again the majority were (65%) male versus (35%) female. Psoriatic arthritis occurred in 5.7% of this group. One third (32%) of cohort 3 were smokers. The average BMI was 26.6. (See table 2.)

Lymphocyte counts

In cohort 1 (systemics/biologics) the average lymphocyte count was 1.87×10^9 (nadir 0.5, peak 3.5). The average lymphocyte count in cohort 2 (FAEs) was 1.37×10^9 (nadir 0.4, peak 2.8) and in cohort 3 -no systemic therapy- the average lymphocyte count was 2.03×10^9 (nadir 0.6, peak 11.9). HPyV2 seropositivity was present in approximately half of all those lymphopenic patients (table 3). There was no association between HPyV2 seropositivity and lymphopenia. Grades of lymphopenia are outlined in table 4.

Discussion

Active viral replication of HPyV2 in sera has been described previously in a small prospective study of 30 patients with psoriasis (n=15) and psoriatic arthritis (n=15). That study examined a 6 month period of active viral replication using real time PCR to measure HPyV2 DNA in serum and skin rather than lifetime exposure i.e. antibody positivity.. Active viral replication was reported in up to 60% of patients. No viral DNA was detected in skin biopsies. [19]

In our study, we measured IgG HPyV2 seroprevalence in a group of 248 patients with moderate to severe psoriasis. From our data, psoriasis patients showed a similar seroprevalence to that of the normal population. There was no significant difference between those on systemic/biologic agents, fumaric acid esters (Fumaderm®) or those not on systemic immunosuppression for their psoriasis. The prevalence of viruria represents closely the previous reports of HPyV2 viruria. [20, 21] Urinary PCR for HPyV2 was positive in 21% of those patients on systemic therapy (n=89). 95% of these were also HPyV2 seropositive.

Recent reports of PML occurring in patients on fumaric acid esters for psoriasis, led to a directive from the European Medicines Agency outlining more intense monitoring of these patients. [22] They advise monthly monitoring of lymphocyte counts and halving the dose if patients develop grade 1 lymphopenia and stopping treatment if this persists. This contrasts with the guidance issued for multiple sclerosis patients on Tecfidera® or BG-12 dimethylfumarate, whose lymphocytes are monitored on a 3-monthly basis despite the higher annual risk of developing PML of approximately 1 in 1000. [11]

The development of PML in psoriasis patients is dependent on lymphopenia and the presence of HPyV2 infection. Our study showed that approximately 50% of patients with psoriasis are not at risk of PML as they do not have HPyV2 infection. This study also showed that systemic immunosuppression does not increase the risk of HPyV2 infection and that psoriasis per se does not increase this either.

Our study is limited by small numbers. Current studies are assessing the longitudinal risk of developing HPyV2 infection by re-testing psoriasis patients over several time periods to assess the rate of HPyV2 infection.

Conclusion

Psoriasis patients appear to have similar infection rates with HPyV2 compared to the general population. Systemic immunosuppression and/or treatment with fumaric acid esters does not appear to increase the risk of HPyV2 infection in psoriasis patients. The risk of developing PML in HPyV2 negative patients appears to be exceedingly low (false negative rates 2.5-2.7%). [11] Cessation of FAEs necessitates the need for alternative therapy, commonly biologic therapy, which carries a risk of infection requiring hospitalization in 1 per 100 patient years and a risk of death in 1 per 1000 patient years. This is in contrast to the rare occurrence of PML in the background population of <0.3/100,000 patient years [6] and 0.09 per 100 patients treated who are seronegative for HPyV2 virus. [11] Under current clinical prescribing guidelines this common clinical scenario presents a risk/benefit dilemma.

We propose that HPyV2 infection status is relevant in those psoriasis patients with lymphocyte counts between $0.5-0.7 \times 10^{-9}$ who are well controlled on dimethylfumarate.

Further larger studies are needed to ascertain whether HPyV2 infection status may be useful for PML risk stratification in psoriasis patients requiring treatment with DMF.

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^bJ Hassan: Investigation, Writing

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Conceptualization, Resources, Investigation, Writing-review and editing.

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Declaration of conflicts of interest.

none

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PML associated with monoclonal antibodies				
Underlying medical condition	Drug implicated	Molecular target	Risk of PML	
Multiple sclerosis	Natalizumab	α -4 integrin	1 in 1000	
Rheumatoid arthritis	Rituximab	CD20	1 in 32,000	
	Abatacept	CD80, CD86		
Systemic lupus	Belimumab	BAFF, BLys		
Haematological disease				
CLL	Alemtuzumab	CD52	low	
B cell lymphoma	Ibrutonumab tituxen	CD20		
CLL	Obinutuzumab	CD20		
Hodgkin's Lymphoma, ALCL	Brentuximab vedotin	CD30		
Colon cancer/NSCL cancer	Cetuximab	EGF receptor		
Colon cancer	Bevacizumab	VEGF-A		
Acute organ rejection	Muromonab	CD-3		
	Basiliximab	CD-25		
Psoriasis/psoriatic arthritis	Efalizumab	CD11a	Withdrawn in 2009	
	Infliximab Etanercept Adalimumab	TNF- α	low	

Table 1. [12,13,14.]

Patient Demographics	Cohort 1 (n=95)	Cohort 2 (n=84)	Cohort 3 (n=69)
Antibody positivity	52%	50%	48%
Average age	49 (range 21-75 years)	43 (range 17-75 years)	41 (range 19-75 years)
Sex	Male 59% Female 41%	Male 65% Female 35%	Male 65% Female 35%
Average PASI (Psoriasis area and severity index)	4.4 (0-26.2)	5.5 (0-12.2)	10.5 (5.6-17.4)
Average Lymphocyte count	1.86x 10 ⁻⁹ (nadir 0.5, peak 3.5)	1.38 x10 ⁻⁹ (nadir 0.4, peak 2.8)	2.03 x10 ⁻⁹ (nadir 0.6, peak 11.9)
Smoking status	21.8%	22.5%	32%
Presence of PsA	30%	1.6%	5.7%
PsA: Ps	3:7	1:61	1:22
Urinary JCV	(n=89) uJCV pos in 21%	(n=1) uJCV pos in 1%	

Table 2.

Grades of lymphopenia	Systemics/biologics Cohort 1 (n=95)	Fumaric acid esters Cohort 2 (n=84)	No treatment Cohort 3 (n=69)
1. An ALC of <Lower normal limit to 0.8 x10 ⁻⁹	5.9% (7) 3-JCVpos	6% (4) 2-JCVpos	0%
2. 0.5 to 0.8x 10 ⁻⁹	8.5% (10) 5 JCV pos	15% (10) 5-JCVpos	1.4% (1)
3. 0.2-0.5 x10 ⁻⁹	nil	1.5% (1)	nil
4. <0.2 x10 ⁻⁹	nil	nil	nil
5. 0	nil	nil	nil

Table 3.

Grades of lymphopenia	Systemics/biologics Cohort 1 (n=95)	Fumaric acid esters Cohort 2 (n=84)	No treatment Cohort 3 (n=69)
1. An ALC of <Lower normal limit to 0.8×10^{-9}	5.9% (7) 3-JCVpos	6% (4) 2-JCVpos	0%
2. 0.5 to 0.8×10^{-9}	8.5% (10) 5 JCV pos	15% (10) 5-JCVpos	1.4% (1)
3. 0.2 - 0.5×10^{-9}	nil	1.5% (1)	nil
4. $<0.2 \times 10^{-9}$	nil	nil	nil
5. 0	nil	nil	nil

Table 3.