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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Kaposi Sarcoma-Associated Herpesvirus and Primary and Secondary Pulmonary Hypertension*

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Background: Kaposi sarcoma-associated herpesvirus (KSHV) has been implicated as a factor in the pathogenesis of primary pulmonary hypertension (PPH). We conducted a case-control study of patients with PPH and pulmonary hypertension (PH) associated with other disorders (secondary PH) to look for evidence of KSHV infection.

Materials and methods: The study population was composed of patients with a diagnosis of PH at the University of California San Francisco Medical Center Department of Cardiology between July and November 2003. Serologic testing for KSHV was performed using enzyme-linked immunosorbent assays based on peptides from open reading frame-65 and K8.1, using sera from 19 patients with PPH, 29 patients with secondary PH, and 150 control subjects

Results: The overall seroprevalence of KSHV among all study participants was 2.0%. The rate among control subjects was 0.7% (1 of 150 subjects); among the study participants with PPH, we found no evidence of KSHV infection (0 of 19 patients). There was no significant difference between the observed seroprevalence of KSHV among patients with PPH compared to control subjects ($p = 0.89$). Of the 29 patients with a diagnosis of secondary PH, 3 patients (10.3%) were KSHV seropositive. Significantly, two of the three KSHV-infected secondary PH patients were also HIV positive, a known independent risk factor for KSHV infection and secondary PH.

Conclusion: Our data do not support KSHV infection having a significant role in PPH or non-HIV-associated secondary PH compared to age- and gender-matched control subjects.

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Key words: enzyme-linked immunosorbent assay; human herpesvirus-8; K8.1; Kaposi sarcoma-associated herpesvirus; open reading frame-65; pulmonary hypertension

Abbreviations: CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; IHC = immunohistochemical staining; KSHV = Kaposi sarcoma-associated herpesvirus; OD = optical density; OR = odds ratio; ORF = open reading frame; PCR = polymerase chain reaction; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; UCSF = University of California San Francisco; UPCI = University of Pittsburgh Cancer Institute

Pulmonary hypertension (PH) is a progressive disorder characterized by elevated mean pulmonary artery pressure that may result in right ventricular failure. Primary PH (PPH) is idiopathic, whereas secondary PH results from conditions known to increase pulmonary artery pressure.^{1,2}

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PPH is most prevalent in persons 20 to 40 years of age and is three times more frequent in women than in men. This has led some to hypothesize that hormonal dynamics or an X-linked genetic locus may be involved with disease development.³ More recently, it has been reported that infection with Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus type 8, is associated with PPH.⁴ The hypothesis that an infectious agent may play an etiologic role in this idiopathic disorder

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Table 1—Demographic and Clinical Characteristics of Study Subjects*

Characteristics	PPH (n = 19)		Secondary PH (n = 29)		Control Subjects (n = 150), No. (%)
	No. (%)	p Value	No. (%)	p Value	
Gender					
Male	5 (26.3)		12 (41.4)		54 (36.0)
Female	14 (73.7)	0.29‡	17 (58.6)	0.36‡	96 (64.0)
Ethnicity					
White	11 (57.9)		13 (44.8)		127 (84.7)
Black	2 (10.5)	0.01‡	3 (6.9)	<.001‡§	2 (1.3)
Hispanic	3 (15.8)		9 (31.0)		8 (5.3)
Asian	3 (15.8)		4 (17.2)		13 (8.7)
Age, yr†	47.4 ± 15.5	0.44	50.9 ± 10.1	0.69	49.9 ± 13.1
Mean pulmonary artery pressure, mm Hg†	46.4 ± 14.5		42.4 ± 14.0	0.35¶	

*p values are calculated using control subjects as a referent group.

†Mean ± SD.

‡Fisher exact test one-sided p value.

§White vs nonwhite.

||Student *t* test, pooled variance estimator.

¶PPH vs secondary PH; pulmonary artery pressure not available for control subjects.

is intriguing, and has potentially profound implications for its diagnosis, prevention, and treatment.

Since the discovery of KSHV in 1994,⁵ a number of diseases and disorders have been hypothesized to be associated with KSHV. To date, the diseases in which KSHV plays an etiologic role are limited to Kaposi sarcoma (KS), primary effusion lymphoma, and a subset of multicentric Castleman disease.⁶ Epidemiologic studies have described potential modes of viral transmission,^{7–11} rates of infection in different populations,^{12–18} and demographic and social risk factors associated with KSHV.^{8,14,19–22} Because KSHV is a relatively new virus, much is still unknown regarding its role as a potential etiologic agent or cofactor in diseases other than KS, primary effusion lymphoma, and multicentric Castleman disease. It is plausible that a number of rare idiopathic disease states could have a viral etiology or be influenced by a viral agent such as KSHV.

As the reported association between PPH and KSHV has been questioned,²³ we sought to examine whether an association exists between PPH and secondary PH and KSHV infection in a robust manner, using different methods than those previously employed. We designed a matched case-control study with sufficient power to examine whether KSHV infection differed between individuals with and without PH using highly specific and sensitive serologic assays based on both lytic and latent KSHV antigens.

MATERIALS AND METHODS

Subjects

The study population included patients with a diagnosis of PH at the University of California San Francisco (UCSF) Medical

Center Department of Cardiology between July and November 2003. Patients were enrolled and blood was drawn at the UCSF Cardiovascular Research Institute. PH was defined as right-heart catheterization with a mean pulmonary artery pressure > 25 mm Hg at rest. To elucidate the etiology of the PH and segregate patients to the PPH group and the secondary PH group, patients underwent diagnostic studies, including echocardiography, ventilation-perfusion scans, pulmonary function testing, and blood sampling to evaluate for the presence of collagen vascular disease, liver disease, thyroid disease, and HIV. High-resolution CT scanning, sleep studies, and coronary angiography were performed as indicated by the history and physical examination.

The PPH group included patients with idiopathic PH without a demonstrable cause or association. The secondary PH group included all other patients who met the above definition for PH. In total, the study population included 19 subjects with PPH, 29 subjects with secondary PH (Table 1), and 150 control subjects (130 healthy individuals, 19 patients with coronary artery disease, and 1 patient with meningioma). Control subjects were matched to cases with respect to gender and age (\pm 5 years).

Prior to patient selection, sample size calculations were performed to establish the minimum sample size required to observe a significant difference in infection rates between cases and controls. Assuming the KSHV infection rate among patients with PPH was 32%, half the rate previously reported,⁴ and the rate among control subjects was 3.3%, the rate of KSHV seroprevalence observed among US blood donors,²⁴ a minimum sample size of 19 cases and 57 controls should allow a significant effect to be observed between cases and controls with 95% confidence and 80% power. If the actual rate of KSHV infection among patients with PPH is 63% as reported by Cool et al,⁴ then our sample size should allow a significant effect to be observed between cases and controls with 99% confidence and 99% power.

Blood was drawn from each subject, and serum was separated and frozen at -70°C . Prior to KSHV testing, case and control specimens, as well as 10 positive and 10 negative laboratory controls from the University of Pittsburgh Cancer Institute (UPCI) were blinded. The blinding was performed and maintained by UCSF until the completion of all serologic testing at UPCI. Informed consent was obtained from all study participants, and institutional review board approval was obtained in accordance with the guidelines for human experimentation of the UCSF and the University of Pittsburgh.

Serologic testing was performed at the UPCI at the Hillman Cancer Center, Pittsburgh, PA. Antibody testing was performed using enzyme-linked immunosorbent assay (ELISA) based on peptides from the open reading frame (ORF)-65 and K8.1 with sequences ASDILTTLSSTTETAAPAVADARKPPSGKKK and RSHLGFWQEGWWSGQVYQDWLGRMNCSYENMT, respectively, as previously described^{25,26} with modifications. In brief, serum at a dilution of 1:100, was added to four wells: two wells coated with peptide (5 µg/mL) and the remaining two wells without peptide. Optical density (OD) values were read on a plate reader (MRX ICXA0716; Dynatech Laboratories; Chantilly, VA) at 405-nm wavelength after reaction with rabbit anti-human IgG horseradish peroxidase (1:6000; DAKO; Carpinteria, CA) and development in 3,3',5,5'-tetramethylbenzidine (Bio-Rad; Hercules, CA). ODs for a given sample were calculated as the mean OD of the wells containing peptide minus the mean OD of the wells containing no peptide.

The assay cutoff for each peptide was determined *a priori* to be 0.04 based on receiver operator characteristic curve analyses. Specimen results were considered positive if the OD of both ELISA assays was >0.04, negative if both assays had ODs ≤ 0.04, and equivocal if the two assays were discordant. Concordance for the ELISA assays was 96% (Fig 1), and all internal

controls were correctly identified by both assays. Samples with discordant ELISA results (positive for one antigen and negative for the other) were retested using an indirect immunofluorescence assay as previously described.²⁷ Patients reactive in two of the three seroassays were classified as KSHV seropositive. The algorithm for defining seropositivity was determined to be 99% specific and 88% sensitive based on quality control panels (data not shown). To elucidate the relationship between KSHV and secondary PH, the following statistical tests and measures of association were utilized where appropriate: Fisher exact test, Student *t* test, exposure odds ratios (OR), and exact 95% confidence limits.

RESULTS

Patients and control subjects were similar with respect to age and gender; at the time of enrollment, patients with PPH and secondary PH had similar pulmonary artery pressures ($p = 0.35$; Table 1). The overall seroprevalence of KSHV among all study participants was 2.0%. The rate among control subjects was 0.7% (1 of 150 subjects), and among the study participants with PPH we found no evidence of

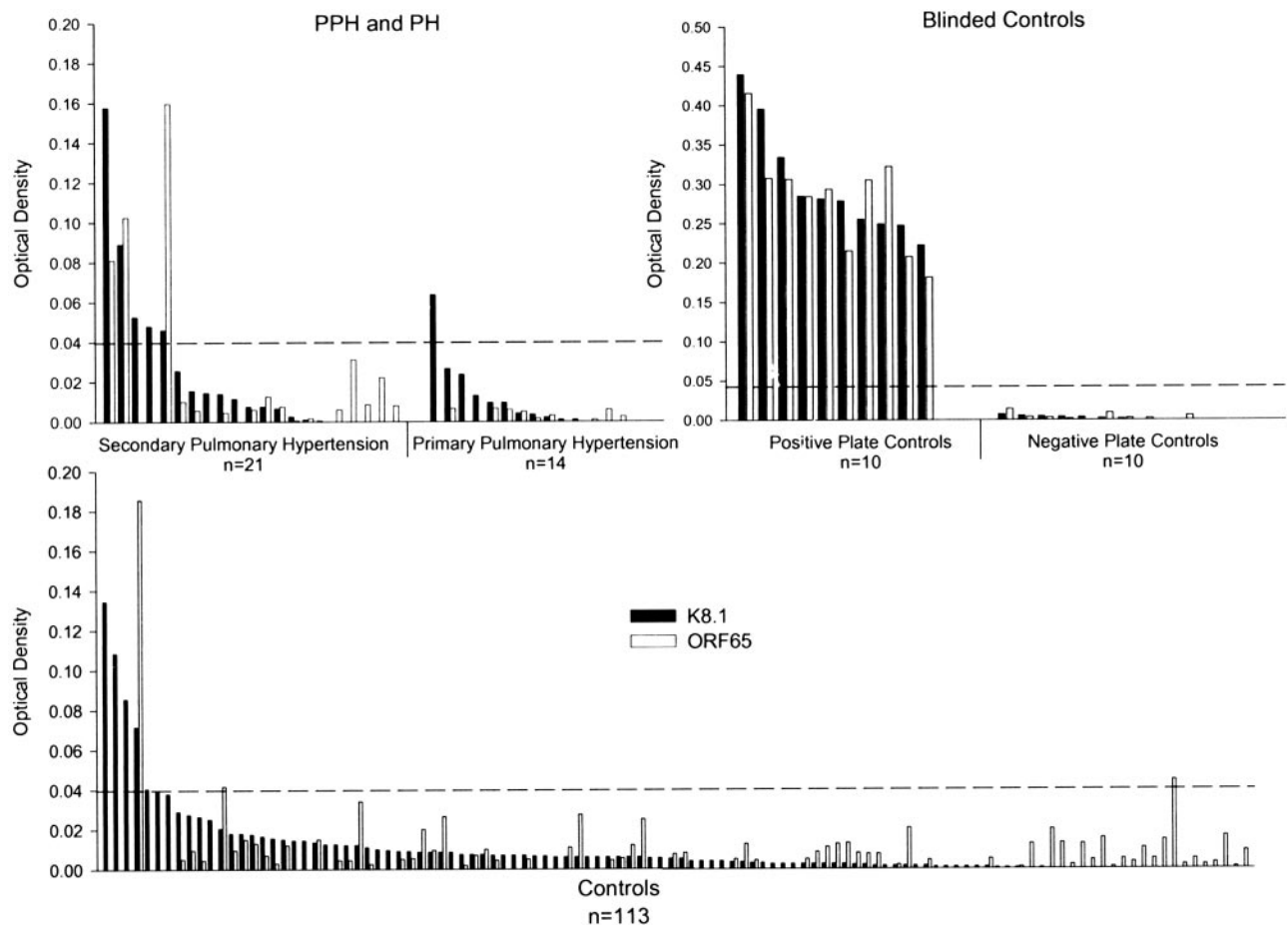


FIGURE 1. OD values from patients with PPH and secondary PH and control subjects. Dashed line indicates OD cut-off (0.04) for defining seropositivity. A total of 51 specimens (5 PPH, 9 secondary PH, and 37 controls) with OD values < 0 for K8.1 and ORF-65 are not represented.

KSHV infection (0 of 19 patients) [Table 2]. Of the 29 patients with secondary PH, 3 patients (10.3%) were KSHV seropositive (2 with PAH secondary to HIV infection and 1 with scleroderma). There was no significant difference between the observed seroprevalence of KSHV among patients with PPH compared to control subjects ($p = 0.89$) or patients with secondary PH ($p = 0.21$). A significant KSHV association was present between patients with secondary PH and control subjects ($p = 0.01$), with an OR of 17.3% and 95% confidence interval (CI) of 1.3 to 908.

DISCUSSION

We found no association between KSHV and PPH. Patients with secondary PH had elevated KSHV seroprevalence compared to healthy control subjects (10.3% vs 0.7%), an observation that was previously found among patients with secondary PH (11.8%) and blood donor control subjects (2.7%).²³ The present findings of no association between KSHV and PPH (0 of 19 PPH patients were KSHV seropositive) are in contrast to those of Cool et al,⁴ who reported a positive association between KSHV and PPH. Using immunohistochemical staining (IHC) for LANA1, and a polymerase-chain-reaction (PCR) assay on lung DNA to detect the KSHV viral cyclin gene, they found 63% of PPH patients were KSHV infected. In contrast, we observed an association between secondary PH and KSHV ($p = 0.01$), whereas Cool et al⁴ found no evidence of infection among patients with secondary PH using IHC (one patient [6.3%] tested positive by PCR). Cool et al⁴ did not include a control group without PH. How-

ever, using the findings from their patients with secondary PH as a comparison group, their data suggest the odds of KSHV infection among patients with PPH are increased > 23 times that of patients with secondary PH (OR, 23.3; 95% CI, 2.2 to 1,082), a finding we could not replicate with our serologic methods (OR, 0; 95% CI, 0.0 to 3.7).

These disparate results may have several explanations. Some of the difference may be explained by different methods used to establish KSHV infection. The techniques, PCR and immunohistochemistry, used by Cool et al⁴ are prone to false-positive reactions in epidemiologic studies and have contributed in the past to spurious associations between KSHV and multiple myeloma,^{28,29} various skin cancers,³⁰ and sarcoidosis.³¹ In their reported sequencing of PCR products generated from PPH lesions (see Fig 3 in the article by Cool et al⁴), all of the products are either too short or too long to be actual amplification products from the virus and show far higher sequence variation than previously reported, indicating either the detection of novel herpesviruses or that some of these case results are false-positive. Similarly, special care is needed for immunostaining glandular and epithelial tissues since edge artifact can be mistakenly interpreted for positivity. It is possible that a similar problem will be encountered with alveolar spaces, which can be easily determined through blinded testing of tissues with appropriate control antibodies.

Although it is conceivable that any or all of these issues played a role in the differing results, an alternative to our explanation for why the present results differ from those previously reported, has already been put forth. Cool et al²⁴ have suggested

Table 2—Subjects Seropositive for KSHV by Assay

Variables	No.	K8.1 Positive	ORF-65 Positive	KSHV Positive
Experimental control subjects				
Positive	10	10 (100)	10 (100)	10 (100)
Negative	10	0 (0)	0 (0)	0 (0)
Study subjects				
PPH	19	1 (5.3)	0 (0)	0 (0)
Secondary PH	29	5 (17.2)	3 (10.3)	3 (10.3)
Control subjects	150	5 (3.3)	3 (2.0)	1 (0.7)
Secondary PH-associated condition				
Collagen vascular disease	12	2 (16.7)	1 (8.3)	1 (8.3)
Congenital systemic-to-pulmonary shunts	2	0 (0.0)	0 (0.0)	0 (0.0)
Portal hypertension	4	0 (0.0)	0 (0.0)	0 (0.0)
HIV infection	4	2 (50.0)	2 (50.0)	2 (50.0)
COPD	1	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	4	1 (0.3)	0 (0.0)	0 (0.0)
Sarcoidosis	2	0 (0.0)	0 (0.0)	0 (0.0)

*Data are presented as No. (%) unless otherwise indicated.

that KSHV serologic tests cannot detect organ-specific infection, which we feel is particularly implausible given the high degree of vascularity present in the plexiform lesions characteristic of PH, and the lack of evidence for the lung as an immunologically privileged site. Furthermore, KSHV is a γ -2 herpesvirus that is resident as a lifelong infection of circulating B cells.

Our findings of no association between KSHV and PPH are robust for several reasons: first, the known epidemiology of KSHV is inconsistent with the known epidemiology of PPH. In the United States, KSHV infection is most common in HIV-infected homosexual male subjects; however, PPH is significantly more common among young, otherwise healthy, female subjects. KSHV is more common in Mediterranean and African populations and rare in many Asian populations. One would expect the risk group and demographic and geographic distributions of KSHV and PPH to be similar, but there is no evidence that this is the case. Second, serologic detection of KSHV infection has the advantage that past and current infection can be established irrespective of the site of infection. In addition, properly established serologic assays that have been developed for KSHV since 1998 are less prone to false-positive results than other methods such as IHC and PCR. In fact, estimates of KSHV infection rates based on PCR testing among non-Kaposi sarcoma populations widely vary and range from $< 1\%$ to $> 90\%$,³² and determinations of KSHV infection using IHC are often subjective and prone to nonspecific binding that can lead to misdiagnosis of uninfected individuals. Third, our study was of sufficient size to detect a significant effect of KSHV between patients with PPH and control subjects even if KSHV infection is only associated with one third of patients with PPH, a rate far below that reported by Cool et al.⁴ In sum, our findings of no association between KSHV infection and PPH are robust and are likely generalizable to patients with PPH in the United States.

Although we found no evidence of an association between KSHV seropositivity and PPH, we did observe a correlation between secondary PH and KSHV infection. This may reflect a causal link between KSHV and secondary PH, but it is also likely that these results simply reflect the high rate of KSHV infection among HIV-positive individuals. For example, between 26% and 48% of homosexual men with HIV infection in the United States are KSHV seropositive.^{9,33} Because our study was not specifically designed to address HIV-related secondary PH, which requires testing of appropriate HIV-positive control subjects, we are unable to distinguish among these possibilities. However, if the

HIV-associated cases are excluded from analysis, the rate of KSHV seroprevalence among the secondary PH group (3.7%) is remarkably similar to that observed in US blood donors (3.3%)²⁴ and does not significantly differ from that observed in the control subject ($p = 0.27$, Fisher exact test) or in those with PPH ($p = 0.58$, Fisher exact test).

In conclusion, we find no association between KSHV and PPH and that at most KSHV may be an uncommon contributor to secondary PH. Further, we find no association between KSHV and non-HIV-associated secondary PH. We are unable to exclude the possibility that HIV-associated PH is associated with KSHV, but our observations strongly suggest that KSHV does not play an etiologic role in PPH. Furthermore, our findings support that patients with secondary PH or PPH do not have an increased susceptibility to KSHV infection compared to healthy control subjects.

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