

The role of human immunodeficiency virus in the pathogenesis of vernal keratoconjunctivitis-like disease in adults: A demographic and epidemiological study

Anine Kritzinger, Anthony G Zaborowski, Wilbert Sibanda¹, Linda Visser

Purpose: The purpose was to identify and describe patients with new-onset vernal keratoconjunctivitis-like (VKC-like) disease after puberty. **Methods:** The study consisted of two parts: a prospective observational descriptive study of patients with new-onset VKC-like disease, and a case-control study to determine the relationship of a CD4 count with VKC-like disease in adults, in the setting of human immunodeficiency virus (HIV). Patients were recruited between January 2016 and November 2017 from a Provincial Eye hospital, one of two large referral hospitals in KwaZulu-Natal, South Africa. Patients presenting to the eye clinic were screened and diagnosed at the Primary Eye Care Unit. Inclusion criteria: age 15 years and older with signs and symptoms of new-onset VKC-like disease. Exclusion criteria: a history of childhood atopic diseases, atopic keratoconjunctivitis and patients who declined HIV testing. Data collected included HIV status, CD4 count, antinuclear antibodies and total serum immunoglobulin E. **Results:** Thirty-three patients were included; females $n = 16$ and males $n = 17$. The mean age at presentation was 32.45 ± 9.93 years, 95% CI = 28.94–35.97. Twenty-six patients (78.8%) were HIV positive, 95% CI (62–89). The proportion of HIV positive patients was statistically different from the HIV negative group, Chi-squared = 21.866, P value <0.0001. In the group of HIV positive patients, 72% were classified as immunodeficient according to their CD4 counts. An association was proven between severely immunodeficient patients and the risk of VKC-like disease (Chi-squared = 4.992, P value = 0.0255). **Conclusion:** In this cohort, a statistically significant association was found between VKC-like disease in adults and an HIV positive status. This association calls for more research on the subject.

Key words: Allergy, immunocompromised, ocular manifestations of HIV, vernal keratoconjunctivitis, VKC-like disease in adults

Allergic conjunctivitis in human immunodeficiency virus (HIV) has been well described in the literature.^[1] Epidemiological studies about vernal keratoconjunctivitis (VKC) have noted that it may present as a new disease in young adults aged older than 15 years.^[2-4] In other studies, VKC-like disease in adults has been described as VKC with the onset in patients older than 20 years^[5] and has been noted as very rare. Anecdotal evidence suggests that it is presenting itself regularly in our setting.

The morbidity caused by immune-based hypersensitivity diseases might be a concern to the patient before the other manifestations of an immunocompromised status.^[6] An epidemiological and demographic study on VKC done by Leonardi *et al.* found that VKC-like disease in adults presented as a new disease with an incidence of 0.06/100 000 compared to a mean incidence of 7.2/100 000 of VKC in children.^[2] In our experience, patients present with the signs and symptoms of vernal keratoconjunctivitis in adulthood or after the onset of puberty, with no prior history of any atopic disease.

Research done on atopy and autoimmunity showed that 35% of children tested positive for antinuclear antibodies (ANA) and this group of patients had the most significant clinical

symptoms.^[7] Another study investigating the pathogenesis of VKC found that 30.8% of patients tested positive for ANA.^[8] Nebbioso *et al.* tested total serum immunoglobulin E (IgE) in a study to investigate the role of individual variables in the pathogenesis of VKC. They found that 46.1% of patients had a total IgE >100 UI/ml.^[8] Leonardi *et al.* found that total serum IgE testing done on VKC patients resulted in a wide range of results. Other studies demonstrated a high total serum IgE.^[9]

HIV has not been associated with VKC in previous studies. For this study, a prospective review of patients with VKC-like disease in adults was done with the goal to identify and describe VKC-like disease in adults.

Methods

Design and subjects

This was a prospective, descriptive study. This study was approved by the Biomedical Research Ethics Committee (BREC) of

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Department of Ophthalmology, ¹School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Durban, South Africa

Correspondence to: Dr. Anine Kritzinger, Department of Ophthalmology, University of KwaZulu-Natal, 238 Mazisi Kunene Rd., Glenwood, Durban - 4041, South Africa. E-mail: aninekritzinger@gmail.com

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the University of Kwazulu-Natal (BE519/14), and site permission was obtained from the medical manager of the participating hospital. The population sampled for this study was all patients presenting to the participating eye clinic at a Provincial Eye Hospital in Durban, South Africa. This is a public hospital with a catchment area that includes referrals from the rural coastal areas of KwaZulu-Natal, as well as inland areas, excluding Pietermaritzburg. The study population included any person aged 15 years and older with a diagnosis of new-onset vernal keratoconjunctivitis.^[2-4] Vernal keratoconjunctivitis is a disease that mostly subsides at or just before puberty.^[10] Patients older than 15 years are grouped as adults and are no longer part of the pediatric population.^[2-4] The screening sister and doctor, as well as the sorting officer at the eye clinic, screened and sorted patients, identifying VKC-like disease in adults among patients. The sampling strategy was a consecutive sample that met the inclusion criteria. The sampling period was January 2016 to November 2017.

Patients who presented with a typical history, as well as signs and symptoms of vernal keratoconjunctivitis, were counseled regarding voluntary participation in this study. Each patient gave written informed consent, assisted by a translator where appropriate, to participate in this study, to provide blood samples and demographic as well as clinical data. Participants aged 15–18 years gave written assent to be a participant and a parent or guardian gave written informed consent. A data collection form, designed for use in this study and randomly numbered, was filled in by the consulting doctor. The data were collected on a single visit while follow-up visits were documented in the patient's hospital file and did not form part of the data collection. The following information was collected: age, sex, race, general medical and atopic history, drug history including the use of antiretroviral medication and HIV status. KwaZulu-Natal is the province with the highest HIV prevalence (16.9%) in South Africa.^[11]

Investigations done included ANA and total serum IgE. Serum specific IgE and skin prick tests were not done as availability of these allergen-specific tests are limited at an Eye hospital. HIV testing was done if the patient's status was unknown and a CD4 count was done for HIV positive patients. Each patient's HIV status was treated as confidential by the investigator as well as the test counsellor. All patients received the routine management and treatment for vernal keratoconjunctivitis.

The inclusion criteria were age 15 years and older,^[2-4] signs and symptoms of vernal keratoconjunctivitis, including: tearing, itching eyes, conjunctival papillae (>1 mm/giant papillae), limbal follicles, Trantas' dots, as well as any complications occurring secondary to vernal keratoconjunctivitis, such as a corneal shield ulcer. The exclusion criteria were any patient younger than the age of 15 years, any patient with a history of childhood atopic diseases, such as allergic conjunctivitis, vernal keratoconjunctivitis, asthma, eczema, allergic rhinitis and any patient with atopic keratoconjunctivitis. Patients who were unwilling to undergo HIV testing at the time of counselling were excluded from the study.

The HIV positive patients were grouped according to CD4 counts using the WHO system for immunological classification of an established HIV infection.^[12] Patients were also grouped according to age. The total serum IgE levels were classified as normal or raised based on reference ranges according to age.^[13]

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or medians, and these were compared using the

Student's *t*-test. Proportions and categorical variables were compared using Pearson's Chi-squared test or Fisher's exact test as appropriate. A linear correlation was assessed using Pearson's correlation coefficient (*r*). All analyses were done using IBM SPSS version 25 (SPSS Inc. Released 2017. SPSS for Windows version 25. Armonk, NY: IBM Corp). The level of significance was set at $P < 0.05$.

Results

The study cohort included a total of 33 patients. The study consisted of 16 females (48.5%), 95% CI (32.5–64.8) and 17 males (51.5%), 95% CI (35.2–67.5). All the demographic characteristics are shown in Table 1. All of the patients were black Africans.

The youngest patient was 15 years old, and the oldest patient was 56 years old. The mean age of onset of VKC was 32.45 ± 9.93 years, 95% CI (28.94–35.97). The median age was 32 years [interquartile range (IQR) = 12] and modal age of 26 years. The patients were divided into five groups according to their age [Table 1]. At the time of diagnosis, more than 50% of the patients were older than 32 years, and 39.4% of patients were 30–40 years old. Females ($n = 16$) presented at an average age of 34.69 ± 8.11 years, 95% CI (30.36–39.01). The median age of presentation for females was 32.50 years (IQR = 7). The youngest female was 24 years, and the oldest was 56 years old. Males ($n = 17$) presented at an average age of 30.35 ± 11.21 years. The median age of males at presentation was 28 years (IQR = 16). The youngest male was 15 years old, and the oldest male was 53 years old. The average age of presentation with VKC was higher in females (34.69 ± 8.11 years) than in males (30.35 ± 11.21 years), but this difference was not statistically significant at 95% CI, $t = -1.802$; P value = 0.0763.

The results of all investigations done are summarized in Table 2.

Patients were tested for ANA and one patient out of 33 tested ANA positive. All patients were tested for total serum IgE levels with an average IgE of 1862 ± 2007.13 . 51.5% of patients had a raised IgE level, 42.4% had an IgE result that was within the normal range for their age, and the rest, 6.1%, did not have data (test results not available). In determining the mean, only those patients who had IgE values were included. 13 out of 25 HIV positive patients (52%) had a raised IgE while four of the six HIV negative patients (66.7%) had a raised serum IgE level.

HIV testing was done if a patient did not know their status and seven patients were HIV negative; this is 21.2% of the cohort, 95%

Table 1: Demographic characteristics

Variable	<i>n</i>	Percentage	95% CI
Sex			
Female	16	48.48	33.5-64.8
Male	17	51.52	35.2-67.5
Age (Years)			
<20	3	9.1	3.1-23.6
20-30	11	33.3	19.8-50.4
>30-40	13	39.4	24.7-56.3
>40-50	3	9.1	3.1-23.6
>50	3	9.1	3.1-23.6
Race			
Black African	33	100	89.6-100.0

CI (11–38). 26 patients were HIV positive; this is 78.8%, 95% CI (62–89). The proportion of HIV positive patients was statistically different from the HIV negative group, Chi-squared = 21.866, $P < 0.0001$. CD4 counts were done on all the HIV positive patients if their CD4 counts were unknown to them and grouped according to the WHO staging. The CD4 counts ranged between 33 and 1252. The average CD4 count was 383.90 ± 367.32 . The median for the CD4 count was 233 (IQR = 467).

The risk of VKC was associated with any HIV-associated immunodeficiency (Chi-squared = 9.486, $P = 0.0021$), with a total of 26 patients of 33 testing HIV positive; however, only 25 of the 26 had a CD4 count result available. In the group of HIV positive patients, 18 (72%) of these patients were grouped as immunodeficient according to their CD4 counts. In this group, ten patients (40%) had the lowest CD4 count (severely immunodeficient), and three patients (12%) were mildly immunodeficient. An association was found between the severely immunodeficient group and the risk of VKC (Chi-squared = 4.992, P value = 0.0255). There was a weak negative correlation between CD4 count and IgE (Pearson’s $r = -0.2492$), which was not statistically significant ($P = 0.285$). There was no association found between sex and the risk of VKC, Chi-squared = 0.06 and $P = 0.8064$. This study did not find a statistically significant association between HIV status and IgE levels (P value = 0.485).

At the time of consultation and enrolment in this study, it was noted that one patient had a pterygium and another had a conjunctival papilloma. No other co-morbidities related to a positive HIV status and a low CD4 count were noted.

Discussion

VKC-like disease in adults is relatively rare compared to childhood VKC^[2] and as a result, a group of only 33 patients met the criteria for inclusion in this study. The ocular features are detailed in Table 3.

Numerous studies have been done on VKC in children, but very few studies have been conducted on VKC in adults. An example of a study is by Leonardi *et al.* (2013) where 49 adult patients with a VKC-like disease were found among 600 consecutive VKC patients and clinical data, demographic information, and quality of life assessments were done. Immunologic data was collected and tests such as allergen sensitivity and tear cytokines were done. HIV status was not included in their data collection. Our study was done at a provincial hospital and patients may have been treated at their local clinics or hospitals for VKC, without a referral, possibly resulting in a lower number of patients seen at the provincial hospital.

VKC is typically a disease of males in childhood,^[10] but this study did not show a male predominance in adults, which may demonstrate a possible hormonal component in childhood VKC, as previously suggested in the literature.^[2] However, this has not been proven yet and it calls for further study to determine the basis of this finding.

The incidence of HIV in KwaZulu-Natal is 2.3% and the prevalence is 16.9%.^[11] Comparing this to the developed world, the WHO statistics indicates a prevalence rate of HIV in the Americas and Europe of 0.4%.^[14] In our study, 78.8% of patients in the cohort tested HIV positive and there was an association between VKC-like disease, which was statistically significant. Therefore, it can be inferred that an HIV positive status is associated with a higher risk of VKC. The literature showed that some ocular manifestations of HIV in an immunocompromised patient could include atopic disease

Table 2: Results of investigations

Variable	n	Percentage	95% CI
HIV Status			
Negative	7	21.2	10.7-37.8
Positive	26	78.8	62.3-89.3
ANA			
Negative	30	90.9	76.4-96.9
Positive	1	3.3	0.5-15.3
Equivocal*	1	3.3	0.5-15.3
Not done	1	3.3	0.5-15.3
CD4 Count			
None	7	21.2	10.7-37.8
Mild	3	9.1	3.1-23.6
Advanced	5	15.2	6.7-30.9
Severe	10	30.3	17.4-47.3
Not Applicable [†]	7	21.2	10.7-37.8
Not done	1	3.0	0.5-15.3
IgE			
Normal	14	42.4	27.2-59.2
Raised	17	51.5	35.2-67.5
Not done	2	6.1	1.7-19.6

*Equivocal ANA result: fluorescence is borderline and needs further testing such as antinuclear factor. [†]Not applicable: pertaining to patients who are HIV negative

Table 3: Clinical features of ocular findings

Ocular feature	Number of patients (%)
Total number of patients	33 (100)
Limbal papillae	1 (3)
Conjunctival/tarsal papillae (>1 mm/giant)	14 (42.4)
Limbal and tarsal papillae	18 (54.5)
Shield ulcer	0 (0)
Corneal scar	2 (6.1)
Trantas dots	8 (24.2)

such as allergic conjunctivitis.^[1] The small number of patients in our study could be due to the new Universal Test and Treat protocol^[11] that South Africa implemented for HIV patients in 2016, whereby antiretroviral treatment is initiated immediately for all HIV positive patients, regardless of their CD4 count. This will leave fewer patients with a compromised immune system and manifestations of HIV.

The association between allergy and an HIV positive status is still incompletely understood.^[1] A recent case report noted new-onset VKC in a child, with symptoms only manifesting when the patient’s CD4 count dropped below 500 cells/ μ l. In this patient, an improvement in symptoms and signs was only seen once the CD4 count improved. It has been hypothesized that HIV initiates a change in the expression of cytokines and T-helper cells which leads to an increased likelihood for atopic diseases, such as VKC.^[15] In our study, a correlation was seen between a lower CD4 count (clinically immunocompromised patients) and the risk of VKC-like disease. This may correlate with existing knowledge that ocular manifestations of HIV may be the presenting complaint while the patient may be otherwise well, and also that the frequency of ocular manifestations of HIV will increase as the patient’s CD4 count decreases.^[16] Other

studies have noted an increased serum IgE level in HIV positive patients,^[17] but in this study, there was no statistically significant difference between the serum IgE level in HIV positive and HIV negative patients. This could be because patients were already on highly active antiretroviral therapy (HAART) when presenting to the Eye clinic. It has also been shown in the literature that VKC itself could be associated with a raised serum IgE level in at least 40% of patients^[18] which could account for the raised serum IgE level in the HIV negative patients.

At the time of diagnosis, more than 50% of the patients were older than 32 years, and 39.4% of patients were 30–40 years old. The prevalence of HIV was highest among women aged 30–34 (36%) and among men aged 35–39 (28.8%). The HIV prevalence rate by sex and age in South Africa shows the highest rate in women aged 30–34 years and in men aged 35–39 years.^[19]

Several questions have been raised and need more investigation, such as the incidence and prevalence of VKC-like disease in adults, the role of HIV in the pathogenesis of VKC, and the role of antiretroviral treatment in the onset and resolution of VKC. Further research is needed with a larger cohort of patients with VKC-like disease in adults. The monitoring of a response to treatment with antiretroviral medications and associating CD4 counts with symptomatic VKC could prove valuable. This study is limited by the small number of patients.

Conclusion

In this cohort of patients, an association was found between VKC-like disease in adults and HIV. This study also found a statistically significant association between an immunocompromised status and the risk of VKC. These findings support the hypothesis that HIV not only causes an immune deficiency but also an immune dysregulation. Based on our findings, we could recommend that clinicians working in a setting with a high HIV prevalence rate consider offering HIV testing if patients present with new-onset VKC-like disease in adulthood, without any prior atopic history. This could prove to be significant if the patient falls into the high-risk age group for HIV.

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Conflicts of interest

There are no conflicts of interest.

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