commentaries

25 Years of Kaposi Sarcoma Herpesvirus: Discoveries, Disparities, and Diagnostics

Devon E. McMahon, BA[1]; Toby Maurer, MD[2]; and Esther E. Freeman, MD[1]

Twenty-five years ago, a novel sequencing technique performed on skin biopsies from a man with AIDS-associated Kaposi sarcoma (KS) revealed two tiny fragments of herpesvirus-like DNA. Although these sequences represented less than 1% of what is now known as KS–associated herpesvirus (KSHV), this discovery was the first molecular evidence of the viral origin of KS.[1] In this commentary, we provide an overview of the origin of global KS disparities and evaluate the role of KSHV in developing inexpensive, point-of-care diagnostics. We argue that developments in resource-limited settings will inform knowledge and practices worldwide as reciprocal innovation becomes a reality.

KS first made headlines in July 1981 after the Centers for Disease Control and Prevention reported 26 cases of the cancer in men who have sex with men. KS rapidly became synonymous with AIDS and carried immense stigma—a mark of an unidentified, deadly disease. Curiously, KS appeared more commonly in men who have sex with men than in other groups, leading to speculation that the cancer was an unidentified sexually transmitted disease.[2] It was known that hepatitis B increased the risk of hepatocellular carcinoma by 100-fold, but the scientific community remained perplexed by how a T-cell–depleting virus could be so tightly linked to a cutaneous and visceral cancer.

The veil of mystery surrounding this opportunistic cancer was lifted 13 years later in December 1994 when Yuan Chang, MD, and Patrick Moore, MD, discovered KSHV, also known as human herpesvirus 8 (HHV-8), in New York City. This finding was the first clue that viruses—specifically the oncoviruses KSHV, Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus (HTLV), and molluscum contagiosum virus (MCV)—caused most of the HIV-associated cancers.[3] In fact, these seven viruses are estimated to cause 15% to 20% of all cancers.[3] The detection of this cancer-virus link provided insight into the role of immune surveillance in virally mediated cancers, which completely changed the landscape of cancer biology. In October 2019, Chang and Moore received the National Cancer Institute Director's Career Achievement Award for their discovery.

Of course KS was not a new disease. It was first described in 1872 by Hungarian dermatologist Moritz Kaposi. Although it was initially identified in men of Mediterranean and Eastern European descent, by the 1950s, physicians increasingly recognized that an endemic version of KS was highly prevalent in sub-Saharan Africa. A 1971 publication from Uganda reported that KS constituted 9% of malignant tumors in males.[4] The heterogeneous global distribution of KSHV explains the magnitude of endemic KS in sub-Saharan Africa. The seroprevalence of KSHV in North America, Europe, and Asia is $< 10\%$, but $> 40\%$ in most parts of sub-Saharan Africa.[5]

Although the reason for this asymmetric distribution of KSHV remains unknown, what is clear is that the dual burden of HIV and KSHV has created an epidemic of HIV-associated KS in sub-Saharan Africa (Fig 1).[6] Today, KS is the leading cause of cancer in both men and women in Botswana and Mozambique and the second leading cause of cancer in Malawi, Uganda, Namibia, Zambia, Lesotho, and Eswatini.[7] Just as KS was the first sign of a soon-to-be explosive HIV epidemic, it has also cast light on an emerging cancer epidemic in sub-Saharan Africa.[8] Given that $> 80\%$ of cancers in sub-Saharan Africa are diagnosed at an advanced stage, we believe that earlier diagnosis of cancers such as KS must become a global health priority.[9]

A major challenge in the diagnosis and treatment of KS in sub-Saharan Africa is the lack of resources for histopathologic diagnosis, including biopsy supplies, technicians, reagents, and pathologists.[10] For patients with HIV-associated KS, the diagnostic delay may partially explain the strikingly high mortality rate of KS in sub-Saharan Africa, with one study estimating 1-year mortality at 40%.[9] Challenges with diagnostic delay have compelled our cross-disciplinary team in Uganda and the United States to create novel point-of-care diagnostics for KS. Quantifying the amount of KSHV DNA present in biopsy samples that are suggestive of KS could allow for rapid diagnostic confirmation. One such device being piloted in Uganda is called the Tiny Isothermal Nucleic Acid Quantifications System (TINY; Cornell Engineering, Ithaca, NY,

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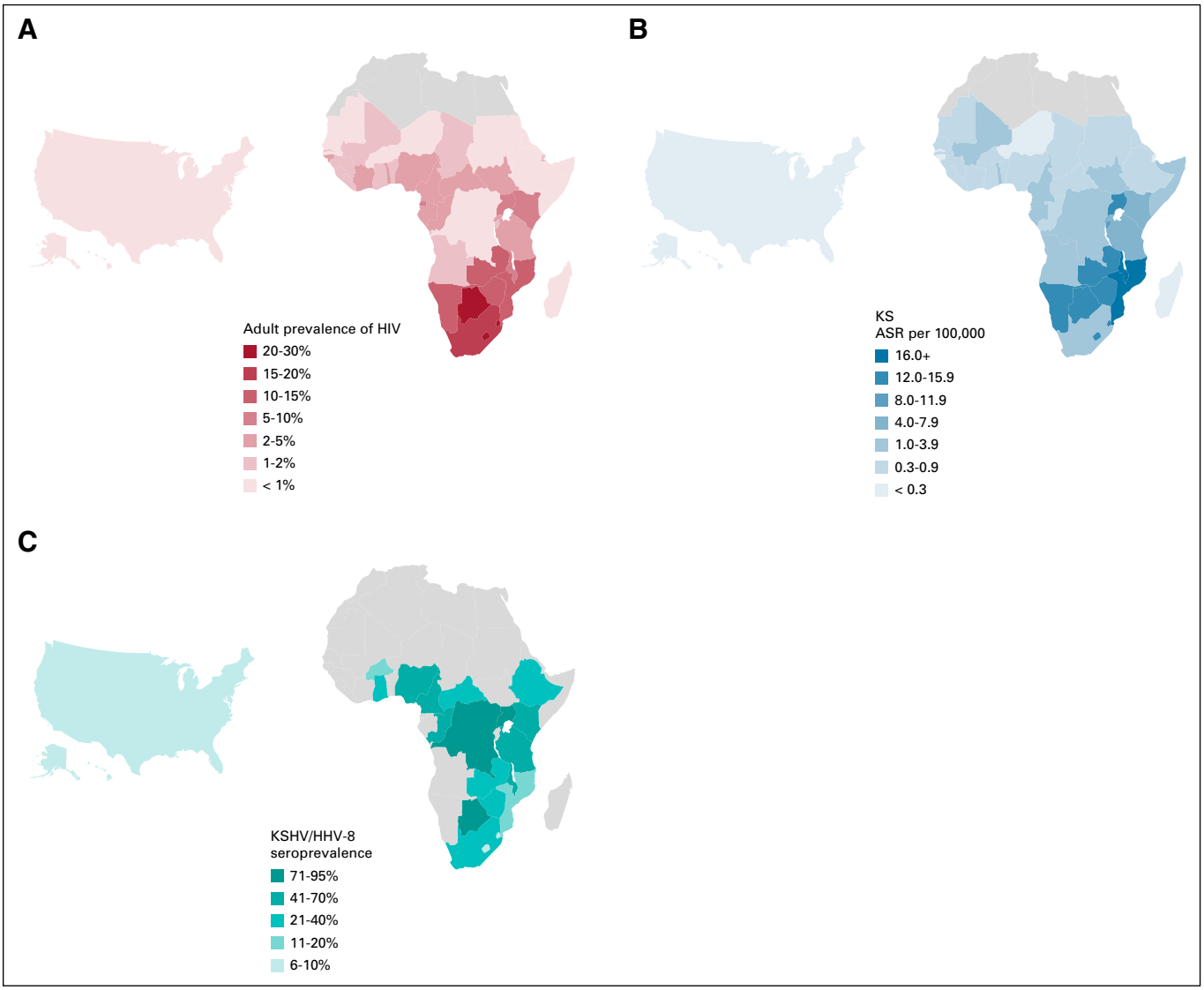

FIG 1. Comparisons of (A) HIV prevalence for adults age 15 to 49 years,[6] (B) age-standardized rates (ASRs) for Kaposi sarcoma (KS) incidence for all sexes and ages,[7] and (C) seroprevalence of KS–associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) among the United States and continental sub-Saharan African countries.[5]

and Weill Cornell Medicine, New York, NY), which can amplify the KSHV DNA found in a skin biopsy via electricity, sunlight, or flame.[11] The device has a turnaround time of less than 3 hours, with a sensitivity of 93% and specificity of 94%.[12]

KS is a unique cancer in that the global distribution primarily affects countries in sub-Saharan Africa, where cancer research, diagnostics, and therapeutics have often been overshadowed by the HIV epidemic.[8] Just as for HIV and other infectious diseases, point-of-care diagnostics could begin to reduce the poor outcomes that have been documented in oncology patients. We propose that nucleic-acid identification methods similar to those performed 25 years ago could be harnessed in a low-cost device for the diagnosis of KS in resource-limited settings. Although they were originally designed for resource-limited settings, these technologies may have important effects on the diagnosis of virus-mediated cancers worldwide.

AFFILIATIONS

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA
[2]Indiana University School of Medicine, Indianapolis, IN

CORRESPONDING AUTHOR

Esther E. Freeman, MD, Massachusetts General Hospital, Department of Dermatology, 50 Staniford St, Boston, MA 02114; Twitter: @DrEstherFreeman; e-mail: efreeman@mgh.harvard.edu.

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