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Commentary

Understanding racial diversities in Kaposi's sarcoma

Kaposi's sarcoma (KS) is a tumour of endothelial cell origin caused by the human herpesvirus-8 (HHV-8). There are four types of histologically indistinguishable KS: classic, endemic, iatrogenic and epidemic[1]. With the advent of the HIV era, epidemic KS was noted increasingly and was ascribed to HIV-induced immunological dysfunction resulting in inability to control HHV-8 co-infection[2], particularly in countries where HHV-8 is widely prevalent. With improved access to highly active antiretroviral therapy (HAART), a significant decline in incidence was noted in late 1990s by Multicenter AIDS Cohort Study (MACS)[3] and later registry match studies[4]. However, MACS reported that although the incidence of KS decreased with age, older HIV-infected persons who did not receive HAART continued to have an increased risk of KS[5].

KS has also been recognized in men who have sex with men (MSM), are HIV seronegative and have no identifiable immunodeficiency. This variant of KS has been mentioned as non-epidemic KS and resembles classic KS in presentation and prognosis[6]. It may be noted that reporting of this variant of KS is much less compared to that of epidemic KS in most of the available databases.

It is believed that the risk of KS among HIV-infected individuals varies geographically, probably due to differences in prevalence of HHV-8, HIV burden, local drivers of the HIV epidemic and access to care for the populations at risk of HIV infection. A recent multicentre multiregional analysis in the Asia-Pacific, South Africa, Europe, Latin and North America regions provided data on risk of KS[7]. The study reported that the risk of KS was highest in South Africa with cases reported even in women. However, in North America and Europe, although reporting of KS was lower than in South Africa, men had a high-risk of KS acquisition. In contrast, incidence of KS was very low in the Asia-Pacific regions[7].

In an analysis of population-based cancer incidence and survival spanning over four decades in this issue, Kumar *et al*[8] present trend data on racial differences in incidence of KS and survival in the United States of America highlighting the changes observed after the introduction and increasing availability of HAART. The analysis showed higher and continued incidence of KS in certain regions of USA particularly among African-Americans (AA). The analysis also showed higher incidence and one-year mortality among AA in USA compared to non-Hispanic Whites (NHW). Disparities among races with regard to HIV incidence, access to care and burden of KS have been discussed as likely reasons for observing disproportionately higher incidence particularly at younger ages among AA. The lower one-year survival rates among AA, noted in this study, also probably reflect gaps in linkage to care in a stage of advanced HIV disease in this population. In addition to late diagnosis and inadequate access to care and treatment, the authors have also commented on inadequate retention in care as possible attributable factors affecting survival. It is also important to note that even among persons with better access to care and ART, as well as older persons, KS is increasingly reported, probably reflecting changing cancer biology and immune senescence in the backdrop of higher longevity with HIV infection[9]. However, robust data need to be generated to confirm that the higher incidence of KS among AA could also be due to increasing access by AA to HIV care.

The global evidence on the risk of KS among people with different ethnic origins has several dimensions resulting in variations in reporting[10-12]. A report from the Swedish cancer registry showed that persons of African origin had the highest risk of KS among immigrants followed by those from Latin America[13]. It has also been reported that due to several limitations to this analysis, alternative hypotheses for explaining racial predisposition need to be tested[13]. Studies should

be conducted in other countries, like South Africa, with significant population level variation in ethnicity and notable burden of HIV/AIDS to demonstrate racial variation in incidence and burden of KS in the context of access to health care in general and to ART in particular.

There is now ample evidence from developed countries to demonstrate effectiveness of ART on incidence of KS and improved survival after introduction of ART[14-19]. A recently published meta-analysis has reported annual decrease of 3.6 per cent in the KS incidence after introduction of HAART worldwide[20]. A report reviewing published literature from 1996 to 2012 that assessed the impact of ART on KS incidence documents that at an individual patient level, effectiveness of ART on KS incidence in resource-limited settings is comparable to that of resource-rich settings[21]. However, this study also recommended the need for more data from diverse settings to bridge knowledge gaps such as effectiveness of ART at an individual patient level as well as at the population level[21]. The scenario remains challenging in Africa where high burden of KS persists probably due to inadequate access to health care and high HHV-8 co-infection rates[7,20]. Ideally, models should be developed for predicting the susceptibility of HIV-infected people to KS based on access to care and ART in various geographic settings and varied economies.

A significant limitation of the study by Kumar *et al*[8] was that the Surveillance, Epidemiology and End Results (SEER) database covered only a proportion of the AA and NHW populations. Hence, if there are differences between the data in SEER database and the actual real life data on KS in the health systems, estimates of incidence and survival among AA as well as NHW would have some bias. Furthermore, because of lack of precise data on definitive diagnosis of HIV and treatment access, KS reports among the younger people are almost invariably presumed to be due to HIV infection and that may not always be the case. It has been reported that patients with higher CD4 counts and history of receiving HAART for more than six months had a lower risk of developing KS as compared to those with lower CD4 counts and no HAART exposure or HAART for less than six months[20]. This substantiated the findings in the current report that KS incidence among NHW was higher at older age groups who presumably had better and continued access to care compared to AA. However, the overall KS incidence as well as incidence at younger ages were reported to be higher in AA, and this probably reflected the disparity not only in HIV burden between NHW and AA in USA but also lower rates of access to care among AA, particularly in the South and West. This is probably one of the key findings in this paper.

Countries with high burden of KS report high prevalence of HHV-8. Screening of HIV-infected individuals for the presence of HHV-8 genotypes should be given due importance. The virus is characterized by high genetic variability across the entire genome and has been classified into different genotypes. A systematic review in Africa from 1998 to 2017 has identified the need for a harmonized testing protocol for better understanding of HHV-8 seropositivity in HIV-infected individuals. Specific genotypes of HHV-8 will have to be considered while designing and developing anti-HHV-8 vaccine candidates as part of an overall strategy of prevention of KS[22].

In India, KS has been reported sporadically in low numbers, and the risk is considered to be extremely low overall. A population-based registry match study in Pune demonstrated that while the overall cancer risk among people living with HIV (PLHIV) was 11.5 times higher than in the general population (1996-2008), there was not a single case of KS reported[23]. Large community-based prospective studies in different parts of the country covering the key subpopulations of men having sex with men and female sex workers will be able to document HHV-8 prevalence and genotype/s that is/ are responsible for development of KS in low HIV-burden settings and identify epigenetic and immune factors that can be causally associated with HIV and KS link. It will also be possible to plan suitable interventions to prevent incidence of KS among HIV-infected people. Data on HIV-infected individuals, their disease profile, uniform periodic workup including key laboratory investigations, data on co-morbidities, long-term complications and on various AIDS-defining illnesses collected through multiple sites in different geographical locations in diverse settings in India will help to measure the incidence of KS and associated risk factors among HIV-infected individuals. Moreover, coverage of ART in HIV-infected individuals should show a continuous improvement. This will help in avoiding long-term complications and AIDS-defining illnesses such as KS in Indian patients.

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