Lung cancer in people living with HIV: a different kettle of fish?

Lung cancer remains the leading cause of cancer-related deaths in southern Africa, with an age-standardised incidence rate (ASR) of 3.95/100 000 in females and 10.12/100 000 in males.[1] It is well known that tobacco smoking remains the most common risk factor for the development of lung cancer globally. In South Africa (SA), tobacco smoking, human immunodeficiency virus (HIV) and pulmonary tuberculosis infection (PTB) are all considered components of the so-called 'colliding epidemics'.[2] While we know chronic obstructive lung disease (COPD) predisposes to lung cancer, both local and international data seem to suggest that HIV and PTB may also be associated with the development of lung cancer.[3,4] It is further postulated that these factors may alter disease presentation and progression.[3]

Two large US registry-based studies were possibly the first to indicate a major causal link between HIV and the development of lung cancer. Sigel *et al.*[5] reported that the incidence rate ratios (IRR) for lung cancer in people living with HIV (PLHIV) was 1.7 (95% CI 1.5 - 1.9) after adjusting for age, sex, tobacco smoking, COPD and other factors. Shiels *et al.*[5] reported that two non-acquired immunodeficiency syndrome (AIDS)-related cancers, namely lung and rectal cancer, presented earlier in PLHIV. In this study, the median age for lung cancer in PLHIV was 50 v. 54 years in HIV non-infected persons.[6] HIV is therefore not only an independent risk factor for the development of lung cancer, but it may also be implicated in a younger age of cancer onset. It has also been suggested that PLHIV present with more advanced disease and have a worse prognosis, despite being well controlled on antiretroviral therapy.[7]

In a two-year prospective study performed at our institution, 467 of 609 (76.7%) patients with lung cancer either consented to an HIV test or were known to be HIV-infected at index presentation.[3] In total, 44 of 467 (9.4%) were HIV-positive. We observed both clinical and statistically significant differences in PLHIV diagnosed with lung cancer. PLHIV and lung cancer were found to be younger at index presentation in comparison to those non-infected with HIV (mean age 54.1 v. 60.5 years, with respective standard deviations (SD) of 8.4 and 10 years; p <0.01). Much to the authors' surprise, the most common pathological subtype in PLHIV was squamous cell carcinoma and not adenocarcinoma (43.2% v. 30.1%; p=0.07). By contrast, data from previous studies performed at our institution clearly found adenocarcinoma to be the most common form of lung cancer, comparable with international data.[8] Unlike many AIDS-related malignancies, infective aetiologies have never been implicated in the pathogenesis of lung cancer.[3] It is clear that the pathogenesis of HIV in lung cancer is related to a unique interplay of multiple proposed mechanisms. Further investigation is however required to discover the possible role of previously unidentified infective agents which may trigger lung inflammation, alterations in microbiome and epithelial injury.[9]

Finally, the data showed that PLHIV were more likely to have a poor Eastern Cooperative Oncology Group (ECOG) performance status of ≥3 (47.7% v. 29.4%; p=0.02). This was substantiated by the finding that in non-small-cell lung cancer, PLHIV were less likely to have early-stage lung cancer (0% v. 10.3%; p =0.02) in comparison with HIV non-infected persons.

In the current issue of the *AJTCCM*, Berman *et al.*[10] report findings of a retrospective study comparing lung cancer, in HIV-infected and HIV non-infected populations from a cohort in Johannesburg, South Africa. The retrospective nature, small sample size and late-stage presentation of both population groups with incurable lung cancer are certainly limitations of the study. However, two very important findings echoing both international and local data need to be highlighted namely that PLHIV in this study presented at a significantly younger age (53.9 v. 61.6 years; p=0.0001) and that squamous cell carcinoma was again the most common pathological subtype diagnosed.[10]

Questions remain on how the altered immune system of PLHIV (often despite suppressed viral loads) independently contributes to the younger presentation of lung cancer. Moreover, how the immune response in PLHIV and possible unidentified infective agents may predispose specifically to squamous cell carcinoma development.

What cannot be denied is the fact that the clinical-pathologically manifestations of lung cancer in PLHIV are definitely a different kettle of fish.

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