



Biomarkers Associated with AIDS-Defining Malignancies in Children

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ABSTRACT

AIDs-infected children have an increased cancer risk due to a compromised immune system and an increased susceptibility to oncogenic viruses. Worldwide, a range of children between ages 0-14 years are infected with AIDs and are at an increased risk of developing cancer. However, as a result of immunosuppression, systemic inflammation, persistent HIV viremia and increased susceptibility to oncogenic viruses, children or people with AIDs are at a higher risk of some malignancies which includes those considered as AIDs-defining malignancies (ADM) such as Kaposi sarcoma and non-Hodgkin lymphoma and non-AIDs-defining malignancies (NADM) such as Hodgkin lymphoma. The intricate relationship between AIDs and malignancies in children involves a heightened cancer risk due to immunodeficiency. Biomarkers serve as crucial tools in identifying, understanding, and managing these malignancies by providing valuable information about the underlying biological processes and aiding in personalized treatment strategies. Combined antiretroviral therapy (cART) reduces the risk of cancer development in children infected with AIDs. Starting cART before the development of severe immunosuppression is key in the prevention of cancer in AIDs-infected children. Vaccination against high risk variants of human papilloma virus (HPV) may protect against cancer associated with HPV (e.g cervical cancer) later in life.

Keywords: Cervical cancer, HPV, cART, Biomarkers, AIDs

Introduction

In spite of ongoing HIV/AIDS research and prevention methods, human immunodeficiency virus infection has persisted (Ifeanyichukwu *et al.*, 2011). HIV infection has caused a considerable impact on cancer incidence since the global epidemic of AIDs (Carbone *et al.*, 2022). According to epidemiological data, being infected with HIV increases the risk of acquiring different cancers (Carbone *et al.*, 2022).

HIV-associated malignancies are tumours whose incidence is raised in HIV patients, particularly those whose increased incidence is caused by the HIV infection. These include both AIDs-defining malignancies (cancers that cause AIDs when found in HIV-infected people) and non-AIDs-defining cancers (other cancers whose prevalence rises with HIV infection). Kaposi sarcoma, some high grade B cell lymphomas, and cervical carcinoma are malignancies that are associated with AIDs (Yarchoan, 2014).

Biomarkers are objectively measured qualities that indicate normal biological processes, pathogenic processes, and pharmacological reactions to therapies. Biomarkers are biochemical compounds produced by cancer cells as a result of the malignant process (Lesko *et al.*, 2001). However, cancer biomarkers can only be detected when cancer is present. Cancer biomarkers can be discovered in several samples, including serum, plasma, whole blood, urine, and tissue. Cancer cells may create typical endogenous products at a higher rate or newly activated genes that were inactive in normal cells (Flepisi *et al.*, 2014). Biomarkers, such as intracellular chemicals or proteins in tissues or discharged into the bloodstream, can signal the existence of cancer. A biomarker's value resides in its capacity to provide early indications of illness progression, as well as its simplicity of detection and measurement across populations (Srinivas *et al.*, 2001).

The aim of this review is to critically evaluate the utility of specific biomarkers in the diagnosis and management of childhood HIV-defining malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer.

AIDs-Defining Malignancies

AIDs-defining malignancies include Kaposi sarcoma, non-Hodgkin lymphoma (aggressive B-cell lymphoma), and cervical cancer.

Kaposi Sarcoma

Kaposi sarcoma (KS), a vascular tumor caused by KS-associated herpesvirus (KSHV) infection of endothelial cells (ECs), is dependent on intra-lesion leukocytes' prolonged proinflammatory signals and the infection of new ECs (Ayers *et al.*, 2018). The origins of these cytokines and infectious viruses within lesions are not completely understood. KS has a high concentration of mast cells. The incidence of Kaposi sarcoma (KS) in HIV-infected patients has significantly decreased with the introduction of active antiretroviral therapy (ART) to suppress HIV replication. However, there is growing evidence of a reemergence of Kaposi sarcoma in HIV-positive people, with a risk of development 35–60 times higher than in the general population (Silverberg *et al.*, 2011). This reemergence under successful HAART treatment raises questions about the disease's heterogeneous and complex pathology (Royston *et al.*, 2021). Given this backdrop, recent ACSR-supported studies are significant for gaining new insights into pathophysiology and identifying new treatment targets.

Cervical Cancer

Cervical cancer is the most common malignancy in Sub-Saharan African women, particularly among HIV-positive people. There has been no systematic profiling of cancer genomes, transcriptomes, or epigenomes in this cohort until now. Gagliardi *et al.* (2020) analyzed 118 tumors from Ugandan patients, 72 of whom were HIV+, and did extended mutation analysis on an additional 89 tumors. The study discovered changes in tumor DNA methylation, promoter- and enhancer-associated histone marks, gene expression, and pathway dysregulation based on the HPV clade (Silver and Schmelz, 2023). Changes in histone modification at HPV integration sites were found to be associated with increased expression of adjacent genes and endogenous retroviruses (Gagliardi *et al.*, 2020).

Identification of Biomarkers in Kaposi Sarcoma

Cavallin *et al.* (2018) found that KSHV lytic replication and the KSHV-oncogene vGPCR activate PDGFRA signaling by upregulating its ligands, PDGFA/B. Blocking PDGFRA signaling is anti-tumorigenic, suggesting that stable inhibition of PDGFR signaling may be effective for KS treatment. Kumar *et al.* (2019) found that KSHV infection activated the E3 ligase HACE1 protein, which regulates KSHV-induced oxidative stress by activating Nrf2 and increasing nuclear translocation. The absence of HACE1 enhanced ROS, which facilitated virus entry and cellular death, and decreased nuclear Nrf2, antioxidant, and viral gene expression. Taken together, these constitute the bulk of lymphoma diagnoses and cover a wide range of cancers. The most frequent HIV-NHL is diffuse large B cell lymphoma (DLBCL), which is 17 times more likely to arise. Its clinical course is more aggressive and frequently manifests in advanced stages in HIV-infected patients than in HIV-negative ones. However, the molecular pathophysiology underlying DLBCL's aggressive character remains poorly understood. The following research, which use ACSR specimens and data, shed light on AIDS-defined non-Hodgkin lymphoma (Silver and Schmelz, 2023).

Non-Hodgkin lymphoma

A child living with HIV is 10 to 20 times more likely to develop aggressive non-Hodgkin lymphoma (NHL) despite HAART and 5 to 26 times more likely to develop Hodgkin lymphoma, a non-AIDS-defining neoplasm, than a person without HIV (Shiels *et al.*, 2018). When standard-dose chemotherapy regimens are combined with HAART, the clinical outcomes in HIV-NHL patients have improved to the point that they are equivalent to the general population. HIV-NHLs account for the majority of lymphoma diagnoses and cover a wide spectrum of malignancies (Barta *et al.*, 2015). DLBCL is the most common HIV-NHL, with a 17-fold increase in the chance of incidence. Its clinical course is more aggressive and frequently manifests in advanced stages in HIV-infected patients than in HIV-negative ones. However, the molecular pathophysiology underlying DLBCL's aggressive character remains poorly understood. The following research, which uses ACSR specimens and data, sheds light on AIDS-defined non-Hodgkin lymphoma (Silver and Schmelz, 2023).

Cancer Biomarkers

Cytokines

Cytokines (interferons, interleukins, and tumor necrosis factors) govern immune responses, cellular communication, and have a diverse function in various stages of cancer immunity (Qiu *et al.*, 2021). Because of their numerous roles, cytokines have been studied in a number of clinical trials to determine their potential as immunotherapy drugs. IL-2 was an early candidate for immunotherapy (Gupta *et al.*, 2023). IL-2 injection and adoptive transfer of anticancer T-cells grown *ex vivo* in the presence of IL-2 were efficacious immunotherapy interventions for renal cell carcinoma and melanoma (Rosenberg, 2014). Patients with advanced colorectal, ovarian, or melanoma were given low doses of IL-2 and autologous dendritic cells loaded with tumor lysates for adjuvant therapy (Liu *et al.*, 2016). Treatment with IL-12 resulted in greater cytotoxicity of NK cells, higher production of IFN- γ in cytotoxic CD8+ T cells, increased proliferative activity, and improved differentiation of naïve Th cells to Th1 cells (Mukhopadhyay *et al.*, 2019). However, severe side effects were seen during IL-12 administration, limiting its application in immunotherapy (Chulpanova *et al.*, 2020). Another member of the IL-2 cytokine family, IL-21, has been utilized to increase the proliferation of germinal center B cells and induce the differentiation of CD40L-stimulated B cells into plasma cells. Clinical experiments using recombinant IL-21 have shown that it can increase the number of CD3+CD56+ NKT-like cells in patients with stage IV malignant melanoma and activate T and NK cells in patients with stage IV CRC (Coquet *et al.*, 2013).

Paracrine signaling factors involved in the crosstalk between cancerous and non-malignant cells in the cancer environment have a significant impact on tumor biology (Lacina *et al.*, 2019). The abundant synthesis of IL-6 by CAFs and other cell types (for example, adipocytes in breast cancer) in various types of tumors demonstrates the importance of this factor in cancer cell biology. IL-6 promotes cancer cell proliferation and the epithelial-to-

mesenchymal transition (Goulet *et al.*, 2019). Experimental IL-6 blockade combined with IL-8 suppression effectively reduced cancer cell invasiveness in vitro (Zhang *et al.*, 2022). The activation of STAT3, JAK/STAT, mTOR, sonic hedgehog, and nuclear factor κ B (NF κ B) signaling is crucial for the IL-6 action on cancer cells and supports the metastatic spread of malignant disease (von Ahrens *et al.*, 2017). The involvement of IL-6 in neo-vascularization and, as a result, cancer progression has been proven (Middleton *et al.*, 2014). As widely addressed by Lacina and coworkers (2019), cancer cells, including CMM cells, release IL-6. This cytokine's synthesis via both paracrine and autocrine mechanisms, as well as their complex regulation, must be expected to influence CMM cell biology. Factors of intercellular crosstalk from the cancer site can pass the capillary wall and enter the systemic bloodstream. As a result, these bioactive compounds can be detected in the blood serum of cancer patients (Kučera *et al.*, 2019). This finding shows that these compounds could act as biomarkers, allowing researchers to evaluate illness progression. However, issues may arise due to the specificity of these findings. Furthermore, the patient's overall health status must be carefully considered, as even a small respiratory infection before the examination might drastically alter the serum profile. These factors, produced by the cancer ecosystem and transported by circulation, appear to play a role in shaping the premetastatic tissue landscape, a safe niche that serves as a suitable cradle for cancer cell homing and subsequent metastasis development, as demonstrated in the cases of breast cancer and malignant melanoma (Kolb *et al.*, 2021). High levels of IL-6, IL-10, and TNF- α in serum can predict death in patients with advanced malignant illness (Stoll *et al.*, 2021). Cancer patients typically die in the terminal, therapy-refractive stage of the disease from cancer-related cachexia and wasting. IL-6 and TNF- α play a significant role in this process, affecting adipocytes, hepatocytes, and striated muscle fibers. These hormones cause skeletal muscle atrophy, lipolysis, "browning" of white adipocytes, and ketogenesis in the liver (Lacina *et al.*, 2019). It appears that there is a clear relationship between high IL-6 levels produced by malignant tissue, low skeletal muscle mass, and patient survival (Kays *et al.*, 2020). In addition to these severe metabolic abnormalities, IL-6 can pass the blood-brain barrier and be recognized by hypothalamus and hippocampus neurons that regulate food intake and cause depression (Shimura *et al.*, 2017). A high level of IL-6 has been linked to an increased risk of suicide (Keaton *et al.*, 2019). The combination of metabolic and central nervous system disorders appears to be lethal in the late stages of the disease, once anti-cancer therapy has failed (Brabek *et al.*, 2020).

Tumour Markers

CA-125

A woman with suspected advanced ovarian cancer should undergo a physical examination, ultrasonography, serum cancer antigen (CA-125) measurement, and imaging analysis (CT scan or MRI). These standard techniques demonstrated little accuracy in predicting the results of primary surgery with a tumor resectability deposition of more than 1 cm. Furthermore, the location of the tumor influences metastatic tumor resectability, and optimal cytoreduction is difficult when the cancer spreads into the diaphragm, liver parenchyma, small intestinal surface area, smaller omentum, or hepatic portal (Llueca *et al.*, 2018). Cancer antigen 125 (CA-125) is a protein found in the blood that is widely used to diagnose early ovarian cancer. CA-125 levels are also connected with other cancers, including pancreatic, lung, breast, colorectal, and benign ovarian cysts. The examination of CA-125 has a low specificity for diagnosing ovarian cancer but has the ability to examine, monitor, and evaluate ovarian cancer medication responses (Charkhchi *et al.*, 2020).

CONCLUSION

Cancer biomarkers have the promise to improve the management of cancer across all stages, including screening, diagnosis, detection, staging, prognosis, and treatment response assessment. Biomarkers can help detect cancer early, follow progression, and prevent recurrence. Early identification can increase survival rates for HIV-positive cancer patients by identifying high-risk individuals, distinguishing between aggressive and indolent tumors, and monitoring disease progression. The dawn of a revolutionary era in cancer medicine is upon us, where the individual patient's molecular makeup takes center stage in guiding detection, diagnosis, and treatment. Biomarkers, like beacons illuminating the intricate landscape of cancer, hold the immense potential to identify tumors years before symptoms arise, paving the way for early intervention and improved outcomes. This paradigm shift, driven by the burgeoning field of precision oncology, promises to transform cancer management from a one-size-fits-all approach to a meticulously tailored strategy for each patient.

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