HODGKIN’S LYMPHOMA IN PEOPLE LIVING WITH HIV: EPIDEMIOLOGY AND CLINICAL MANAGEMENT

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Abstract. After the introduction of combination Antiretroviral Therapy (cART), survival of people living with HIV/AIDS (PLWH) has improved, bringing to the appearance of new health problems. Among these problems, there is an increased risk to develop malignancies. Hodgkin’s lymphoma (HL) is a curable malignancy, suspected to be associated with Epstein-Barr Virus (EBV) infection. Median age of HL incidence in PLWHs is 30 years, after approximately 7 and a half years from the HIV infection diagnosis. HL is significantly more frequent in PLWHs than in the general population. As a matter of fact, the incidence of this disease is 8-fold higher than the general population during the pre-cART era, and the difference worsened, reaching a 13-fold higher incidence during the cART era. Early diagnosis is crucial. The detection of cancer in an early stage improves the outcome of patients, indeed. The aim of this paper was to review the epidemiological characteristics and the diagnostic and therapeutic management of HL in HIV infected patients.

KEYWORDS: HIV-associated Hodgkin’s lymphoma

INTRODUCTION

Due to the introduction of effective HIV therapy, we observed nowadays an increase in life expectancy of people living with HIV (PLWH). However, this increase highlighted many health problems connected to the infection11. As a matter of fact, cancer incidence as a whole and especially for some kinds of cancers9-16. This could be related to the basal virus-mediated immune suppression, which leads to a consequent increase of cancer risk despite the positive effects of antiretroviral therapy17-19. The positive effects of cART are undeniable, though. As a matter of fact, there has been a substantial change in the malignancies occurring in PLWHs. In particular, classical AIDS-defining cancers (ADCs) incidence such as Kaposi’s sarcoma (KS) and non-Hodgkin’s lymphomas (NHL) has declined significantly while others, and especially non-AIDS-defining cancers (NADCs) as Hepatocarcinoma (HCC) HCV-related, is increased20, 11, 28-23.
Hodgkin lymphoma (HL) is a curable malignancy which is thought to be associated with Epstein-Barr virus infection. Classical HL is characterized by lymphatic spread and late involvement of adjacent and distant lymph nodes. The aim of this paper was to review the diagnostic and therapeutic management of HL in HIV infected patients.

**Epidemiology**

The mortality rate of HL is progressively decreasing. However, the incidence has remained mostly unchanged during the past two decades in the UK and US, where it is approximately 2.7-2.8 per 100,000 persons per year. It is estimated that during the 2018, approximately 8,800 new diagnosis of HL will be made in the US, leading to 1,300 deaths. Women are more affected than men, incidence peaks are reported in young adults and in older people.

The median age of HL presentation in PLWH is around 30 years, approximately after 7 and a half years from the HIV infection diagnosis. HL is significantly more frequent in PLWHs than in the general population. It has been demonstrated that the incidence of this disease was 8-fold higher than the general population during the pre-cART era, and it increased significantly, reaching 13-fold, during the cART era.

**Pathogenesis**

A severe immunosuppression, like the one we observe in advanced HIV/AIDS, could lead to a disruption within the host microenvironment, resulting in a decreased incidence of HL. This disruption could explain why the higher incidence of HL in HIV is higher when the CD4+ count decrease. Moreover, several studies have shown a significant difference in the distribution of HL subtypes in HIV-infected people compared to HL in a HIV-negative population.

Viral oncogenesis, especially supported by Epstein-Barr virus (EBV), seems to play a most important role in HIV-HL than HL of the general population. In fact, it is possible to detect EBV only in about one-third of cases of non-HIV-associated HL, compared to almost all cases of HIV-HL. This finding, published in several papers, suggests that EBV is directly involved in lymphomagenesis.

**Staging**

The 2008 WHO classification of HL recognizes two histological types of HL: classical and nodular lymphocyte-predominant.

The classical form includes four different clinical entities: lymphocyte depletion, nodular sclerosis, mixed cellularity and lymphocyte-rich forms. Histologically, the malignant Hodgkin Reed-Sternberg (HRS) cells represent less than 1% of cancer cellularity, with the most part made up of surrounding polyclonal lymphocytes, eosinophils, neutrophils, macrophages, plasma cells, fibroblasts and collagen. Most patients with HL present asymptomatic superficial lymphadenopathy. The histological subtypes pattern of HL observed in HIV-infected patients differs from the general population, with higher proportion observed for the mixed cellularity (MC) and lymphocyte depletion (LD) forms. MC and LD subtypes of classical HL are correlated with worse immunosuppression, while the nodular sclerosis (NS) form increases with higher CD4+ counts and use of cART.

The most common involved sites of disease are cervical, supraclavicular and mediastinal lymph nodes, while sub-diaphragmatic presentations, bone marrow and hepatic involvement are less frequent. Splenic involvement is usually concomitant with hepatic disease and systemic symptoms; however, extra-nodal presentations are quite rare. Classic HL usually spreads by contiguity within the lymphatic tissue network, with late extension to adjacent and distant viscera. Most of the patients arrive at the diagnosis with an advanced-stage disease, i.e. stage III/IV of Ann Arbor Staging Classification for HL. Despite the cART therapies, the incidence of early-stage disease appears to be increasing.

**Diagnosis (Figure 1)**

About two-thirds of patients show an advanced lymphoma stage with extranodal and unusual sites involvement.

Diagnosis is made through physical examination and diagnostic interventions as bone marrow biopsy, Computer Tomography (CT), Fluorodeoxyglucose-positron emission tomography (FDG-PET) that should be performed in accordance with guidelines.

**Bone Marrow Biopsy**

Bone marrow (BM) examination is considered essential in the evaluation and staging of HL, at the time of initial diagnosis as well as after therapy. Biopsies, performed under local anesthesia, were obtained using the conventional technique from the posterior superior iliac spines, fixed in 10% of formalin solution and/or decalcified using 10% formol-formic acid for 4-6 h followed by serial sections of 4-6 µm of thickness that are cut and stained by hematoxylin and eosin (HE) for histological examination. The histological classification of HL was based on the WHO classification as previously reported.
HIV-ASSOCIATED HODGKIN’S LYMPHOMA

Malignant cells have an increased rate of aerobic glycolysis, compared to normal tissue. Fluorine-18 is a positron emitter. The emitted positron penetrates only a few millimeters into tissues before combining with an electron. Detection of both photons is the principle by which PET operates. Fluorine-18 has a half-life of 110 min, allowing acquisition of images over 30-120 min. The biodistribution of FDG can be affected by various physiologic factors but a level of less than 150 mg/dl is desirable. Because the primary route of FDG excretion is renal, good hydration is required. PET imaging is initiated approximately 60 min following the injection of FDG.

18F-FDG PET can highlight abnormal foci of increased FDG accumulation in HIV-infected people with suspected malignancy by localizing to malignant or inflammatory cells such as neutrophils and macrophages. Activated lymphocytes consume an increased amount of glucose and it has been demonstrated that in HIV-infected individuals, lymph nodes have higher accumulation of FDG compared to those of the uninfected patients. In the case of lymphoma, the nodes are often swollen, with a more intense FDG uptake than those present in reactive lymphadenopathy without malignancy. However, there are no rigorously defined quantitative PET methods to differentiate these entities.

**Computer Tomography**

Computer tomography (CT) is currently the gold standard for staging malignant lymphoma; before the CT era, patients with a diagnosis of HL underwent many radiologic studies. CT technology has been more and more developed and refined; major improvements include the introduction of spiral CT in the early 1990s and the advent of multidetector-row CT in 1998.

Nowadays, CT for staging malignant lymphoma is performed on at least 4-section multidetector-row CT scanners. Patients receive an intravenous injection of iodinated contrast medium and, usually, an oral contrast agent prior to scanning. Determination of nodal involvement is based on size criteria.

**18F-FDG-PET**

18F-FDG PET is a diagnostic method using Fluorodeoxyglucose (FDG) that, through glucose transporters, is absorbed by cells where it is phosphorylated by hexokinase into FDG-6-phosphate that undergoes no further metabolism within cells. Moreover, its dephosphorylation by glucose-6-phosphatase is a relatively slow process in comparison to that of glucose-6-phosphatase. This, combined with the fact that FDG-6-phosphate cannot easily cross the cell membrane, results in entrapment of FDG-6-phosphate within viable cells. Malignant cells have an increased rate of aerobic glycolysis, compared to normal tissue. Fluorine-18 is a positron emitter. The emitted positron penetrates only a few millimeters into tissues before combining with an electron. Detection of both photons is the principle by which PET operates. Fluorine-18 has a half-life of 110 min, allowing acquisition of images over 30-120 min. The biodistribution of FDG can be affected by various physiologic factors but a level of less than 150 mg/dl is desirable. Because the primary route of FDG excretion is renal, good hydration is required. PET imaging is initiated approximately 60 min following the injection of FDG.

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Fig. 1. Diagnostic algorithm for Hodgkin’s lymphoma.
THERAPY

The treatment of HIV-associated HL was improved over the past 30 years in line with higher control of HIV replication and preservation of immune system. In the pre-CART era, patients with HIV-associated HL had poor life expectancy with a median survival of about 5-6 months. The introduction of cART, about 20 years ago, produced good effects on the outcome of HIV-associated HL determining increases in median survival. This finding can be definitely attributed to beneficial effects of cART on immune function. Several studies showed that lower-dose chemotherapy was preferable in HIV-associated HL. Worldwide therapy for HL consists of the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Several investigations show that the ABVD therapy in conjunction with cART was associated with improved outcomes. Another study shows the utility of the use of epirubicin, bleomycin, vinorelbine, cyclophosphamide, and prednisone (VEBEP) in patients with advanced-stage. Combined modality therapy with chemotherapy and radiation has been the standard of care, but late complications of radiotherapy, including secondary malignancies and cardiovascular and respiratory diseases, have induced to consider the chemotherapy treatment alone in selected patients. Several authors demonstrate that HIV-HL patients with concurrent cART achieved similarly positive results as those observed in general population. However, interactions between antiretroviral and chemotherapeutic drugs could result in increased levels and toxicity of some agents while others could become subtherapeutic. Moreover, it was demonstrated that the combined use of chemotherapy, with its side effect on myelopoiesis, and zidovudine and/or protease inhibitors, with their strong therapy, with its side effect on myelopoiesis, and zidovudine and/or protease inhibitors, with their strong effect on the outcome of HIV-associated HL determining increases in median survival. This finding can be definitely attributed to beneficial effects of cART on immune function. Several studies showed that lower-dose chemotherapy was preferable in HIV-associated HL.

CONCLUSIONS

HL continues to be an important complication in PLWHAs with a high incidence and mortality, independently from their HIV serological status. For all these reasons, this disease represents a major worldwide public health problem. Early diagnosis is crucial, as the detection of cancer in an early stage improves the outcome of the patients. Furthermore, when a HL is detected at an early stage, an effective curative treatment is possible. A pharmacological approach in advanced stage cancers is now, possible thanks to new experimental drugs such as combined chemotherapy and use of monoclonal antibodies.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

REFERENCES


