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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 infection[1-8]. As a matter of fact, cancer incidence as a whole and especially for some kinds of cancers[9-16]. 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 therapy[17-19]. 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[9]. 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 increased[10, 11, 20-23].

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Hodgkin lymphoma (HL) is a curable malignancy which is thought to be associated with Epstein-Barr virus infection[24, 25]. Classical HL is characterized by lymphatic spread and late involvement of adjacent and distant[26]. 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[27] 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[17, 28-31]. 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[29, 32-34].

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[35, 36]. 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[36].

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[25, 37]. 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[27, 38, 39].

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[40, 41]. 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[42]. 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[43].

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[23, 24, 44].

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% formal-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[24, 45].

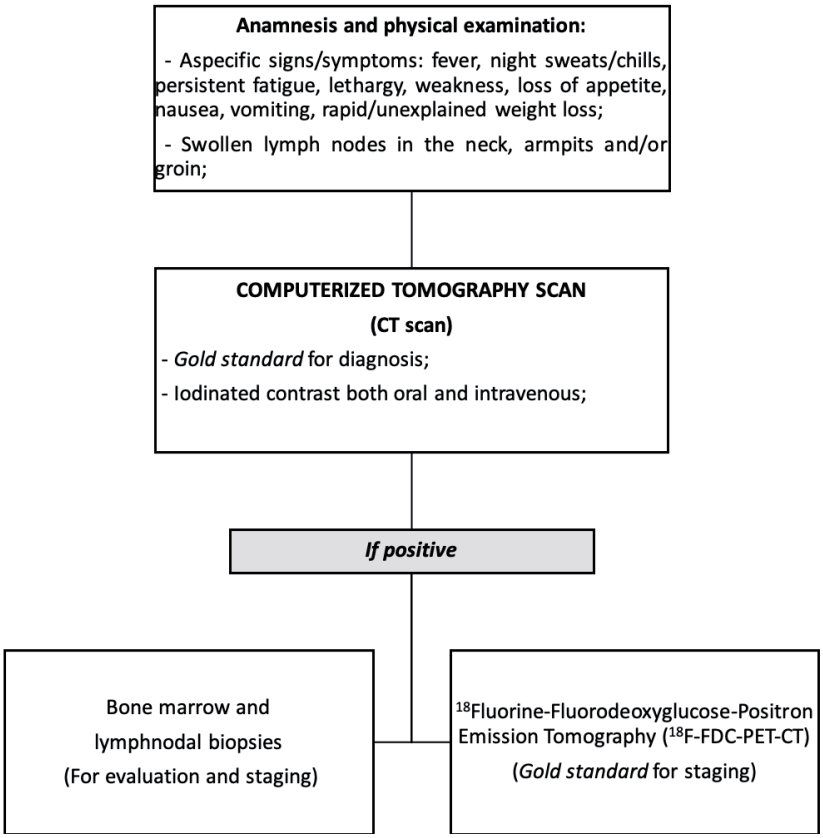

Fig. 1. Diagnostic algorithm for Hodgkin's lymphoma.

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[46-50].

^{18}F-FDG-PET

^{18}F-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[51, 52]. 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[51,53,54]. ^{18}F-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[55].

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[35,56]. Several studies showed that lower-dose chemotherapy was preferable in HIV-associated HL[41,57]. 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[50,58,59]. 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 inhibition effect on CYP3A, could cause a deeper myelotoxicity and prolonged neutropenia[27,60,61]. The improved outcomes in patients with HIV-HL highlight the important role played by cART in improving the patients' immunological status and by the possibility to treat on schedule at full dose intensity in the modern era. New therapeutics chances have been developed in the treatment of LH among which high-dose chemotherapy with stem cell transplant and targeted therapy. High doses of chemotherapy kill cancer cells but also healthy ones, including blood-forming cells. Stem cell transplant is a method to replace the blood-forming cells. Particularly, stem cells are obtained from the blood or bone marrow of the patient or a donor and are frozen and stored. After the patient completes chemotherapy, the stored stem cells are introduced to the patient through infusion in order to restore the blood cells pool. Targeted therapy is a kind of therapy using drugs or other substances able to destroy cancer cells causing less damage to normal cells than chemotherapy or radiation. The use of monoclonal antibody represents one type of targeted therapy being studied in the treatment of primary CNS lymphoma. Monoclonal antibodies are made in laboratory from a single type of immune system cell and can identify substances on cancer cells or normal substances able to induce the growth of cancer cells. The antibodies, attaching these substances, kill cancer cells blocking their growth or keeping them from spreading. Monoclonal antibodies are administered by infusion. They may be used alone or combined with drugs, toxins, or radioactive material. Particularly, a recent trial to study the combination between doxorubicin, vinblastine, and dacarbazine (AVD) and the monoclonal antibody Brentuximab vedotin (BV) (AVD-BV) was carried out in the upfront setting of HIV-HL. This phase I trial demonstrated the safety of the AVD-BV regimen with standard BV 1.2 mg/kg dosing in HIV-HL. Response to treatment was encouraging, with 83% of the patients achieving complete remission by PET/CT post cycle 2, and all in complete remission by end of therapy, with 100% PFS at a median follow up of 25 months[62].

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

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