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Surgical Pathology in HIV Infection in the Era of Antiretroviral Therapy

Mónica Belinda Romero-Guadarrama
Hospital General De México,
O.D., Medicine School National Autonomous University of Mexico (Unam)
Mexico City

1. Introduction

The natural history of infection with human immunodeficiency virus (HIV) has changed with the introduction of antiretroviral therapy (Fischl et al 1987), these drugs have the ability to inhibit viral replication and immune recovery of infected patients (Lalezari et al 1999). This has resulted in reduced mortality and morbidity caused by this viral infection (Mellors et al 1996). The human immunodeficiency viruses have extraordinary structural and evolutionary complexity since its original identification and description for over 25 years. Nine subtypes are known and three different subtypes, a total of 12, with subtype C HIV-1 responsible for more than half of infections in the world. The molecular and genetic study of HIV reflects the enormous and increasing variability of these organisms (Hue et al 2005).

The HIV viruses are highly variable and are adapted to the selective pressure of antiretroviral drugs, hence antiviral treatments, which started 19 years ago have selected strains with resistance mutations that complicate or invalidate the continuity of certain treatments and sometimes of all.

The geographical distribution and the percentage in the distribution of transmission pathways of the disease have changed over the past 25 years that have elapsed since the start of the epidemic (CDC, 2002). AIDS is an emerging disease in countries of the former Soviet Union, China, and sub-Saharan countries, the number of children and adults who are being infected is higher, producing a characteristic accelerating effect of prolonged epidemics. The AIDS program of the United Nations estimates that by the end of 2005, the total number of people worldwide living with HIV-/-AIDS was 40.3 million, 64% are in sub-Saharan Africa (WHO, 2005). In Europe 294,571 cases were reported in late 2004, 18.6% were women and 3.7% were children. The main transmission groups in Europe are injecting drug users (38.1%), homosexual contacts (29.5%), and heterosexual contacts (20%), although these parameters are not evenly distributed across the continent. While there has been an overall decrease of 6.7% over the previous year 2004 (HIV EURO 2005). In Mexico, the first case was diagnosed in 1983 and currently the largest number of cases (38.400) live in Mexico City, that is 17% of all HIV cases in the country for 2010. The age of onset is 15 to 49 years, 87% are men and 13% are women. The main route of infection is homosexual practice. In this country, AIDS is the third leading cause of death nationally among men 25 to 34 years and the sixth among women in this age group (http: // www. aid-sida-org/ estadistic05.htlm).

The clinical presentation of AIDS varies from one geographic area to another according to the most prevalent transmission groups.

The purpose of this chapter is to conduct a general review of infectious agents and neoplasmas associated with some viral agents in the era of antiretroviral treatment of HIV-infected patients in specimens obtained by biopsy, surgical resection, or cytology material.

2. HIV infection

HIV infects several human cell types such as macrophages and glial cells, but its real target cell is the lymphocyte $CD4^+$ and the following pathogenic processes divided into three periods can be disthinguished.

Primary infection during which the virus spreads to lymphoid organs. It is characterized by high levels of viremia and lasts between two and six weeks, patients have nonspecific symptoms. A few days after the initial infection occurs, they produce large amounts of viruses in activated lymphocytes from the lymph nodes, causing inflammation in the nodal lymphoid tissue. The first reaction of immunity against infection is provided by CD8+ cytotoxic lymphocytes, or CTL, which lyse infected cells that present viral antigens on their surface. The virus is never removed during primary infection, since it maintains a residual viral replication, which is detected in plasma or lymph nodes. Escape mutants seem to evade, by mutation in certain epitopes, the immune pressure of helper T lymphocytes and memory cells, there by escaping destruction CTL (Stremlau et al 2004). A few weeks after infection, there is a significant depletion of $CD4^+$ cells in the digestive tract, long before $CD4^+$ levels in blood are altered. One explanation for this activity in the gastrointestinal tract could be because cells in this area have the co-receptor CCR5, which is used by HIV to infect cells. (Pierson et al 2002)

The second period is the chronic asymptomatic infection, the average duration of this phase is 10 years, it is characterized by stable levels of $CD4^+$ with a tendency to decrease progressively, the viral load drops and may be undetectable, but the virus continues its replication in the lymphoid tissue. The causes of decline in $CD4^+$ cells during this phase of infection are only partially known. The increase in viral load and decreased $CD4^+$ during this phase correlate inversely, but sometimes describe curves of complex kinetics that suggest the presence of multiple factors that influence the lysis of infected lymphocytes and the production of new virus particles. $CD8^+$ lymphocytes remain slightly increased during this phase, indicating the existence of cytotoxic reactions against the virus and viral antigens are detected in follicular dendritic cells. Viral sub-populations become more heterogeneous.

Advanced HIV infection or AIDS. At this stage of the disease, the individual develops opportunistic infections, as $CD4^+$ lymphocyte counts are lower than 200/µl viral replication is accelerated, the activity of anti-HIV CTL declines, and lymphoid morphology is destroyed. Lymphoid tissue degeneration may be due to replication of the virus, or may be an indirect consequence of chronic immune stimulation. Neurological tropism of the infection is observed and produced viruses are less sensitive to neutralizing antibodies.

3. Opportunistic infections

Among the most common opportunistic infections in Mexico and Spain are tuberculosis, Pneumocystis carinii pneumonia and esophageal candidiasis (Secretariat of the National Plan on AIDS 2005). While the introduction of new triple therapies have increased survival of patients infected with HIV, AIDS remains a disease with high mortality rate. Most

opportunistic infections occur as reactivation of latent infections that reappears when the immune system can no longer control them. The current frequency of opportunistic infections varies in different regions and have declined due to active antiretroviral therapy (HAART) (Kaplan et al 2000). From 15 to 30% of non treated HIV-infected patients develop pneumonia during the course of the disease caused by *Pneumocystis jiroveci*. Today opportunistic infections are less common in patients who respond to treatment with HAART. Among infections not associated with AIDS are some that appear in the general population, and have a higher incidence in patients with HIV infection, such as pneumococcal pneumonia, oropharyngeal candidiasis, or herpes zoster. A list of viral, bacterial, and fungal microorganisms that occur in patients with AIDS exists. These can even occur in patients with antiretroviral treatment and immune imbalance. (Table 1).

There are differences in the prevalence and incidence of some diseases that can be attributed to the characteristics of the population, climate, endemic diseases, to standards of hygiene, and medical care availability and pharmacology, as well as to socioeconomic and cultural factors.

Opportunistic infections in HIV patients
Helminthic and Protozoal Infections:

Cryptosporidiosis or isosporiasis (enteritis)
Toxoplasmosis (CNS Infection or pneumonia)
Fungal Infections
Pneumocystosis (pneumonia or Disseminated Infection)
Candidiasis (esophageal, tracheal, or pulmonary)
Cryptococcosis (CNS Infection)
Coccidioidomycosis (Disseminated)
Histoplasmosis (Disseminated)

Bacterial Infections

Mycobacteriosis ("atypical" Mycobacterim eg avium intracellulare, Disseminated or extrapulmonary; M. tuberculosis, pulmonary or extrapulmonary)
Salmonella Infections, Disseminated
Viral Infections

Cytomegalovirus (pulmonary, intestinal, retinitis or CNS infections)
Herpes simplex virus (localized or disseminated)
Varicella zoster virus (localized or disseminated)
Progressive multifocal leukoencephalopathy

Table 1.

3.1 Description of opportunistic microorganisms
3.1.1 Mycoses
Fungal infections are common in patients with HIV infection. Morbidity and mortality are influenced by antiretroviral treatment because of the close relationship between the degree of immunodeficiency, the frequency, and severity of fungal infections.

The advent of HAART and new antifungal agents, such as voriconazole and caspofungin, have decreased the incidence of fungal infections associated with HIV. Although, the causal agent can be clinically suspected, samples can be collected from some body fluids and other sites for the diagnosis, as for example puncture-/-aspiration of abscesses, puncture of cerebrospinal fluid, and from bile, pericardial, pleural, peritoneal, liquids. Bone marrow aspiration, nails, sputum, biopsies of deep tissues or skin, urine and blood. In tissues, the opportunistic organism can be suspected but to know the etiological agent, cultures must be made. (Romani 2004)

Fungal Yeasts: Candida and Cryptococcus Genera.

Candidiasis is the most common fungal infection in these patients, the most common clinical presentation of oropharyngeal candidiasis and vaginal candidiasis in women, occurs with greater frequency and severity than in the rest of the population and they are recurrent. Usually the diagnosis is clinical, by positive culture or visualization of the yeast through Gram staining. In the cervico-vaginal smears. Candida sp. can be morphologically suspected by the presence of yeasts and spores in the cellular smears and observing abundant inflammatory infiltration of polymorphonuclear cells. When the patient presents oropharyngeal candidiasis and dysphagia, diagnosis can be made by endoscopy and biopsy. Finally, invasive candidiasis is uncommon in AIDS patients, but, when present, bronchial or pulmonary candidiasis is observed in the final stages of the disease. (Whiteway et al, 2004).

Cryptococcus neoformans is a worldwide distributed yeast of, spherical shape produced by a single budding unique and posesses a mucopolysacharide capsule that confers virulence. Depending on the capsular polysaccharides four serotypes named A, B, C, and D have been described. According to these serotypes, there are two varieties: C. neoformans (serotypes A and D), which is the most common in patients with AIDS and C. vargatti neoformans (serotypes B and C). Exposure to the organism is frequent and the route of entry is the respiratory tract. The most common clinical form is meningoencephalitis and two-thirds of patients course with extrameningeal dissemination C. neoformans may disseminate widely to the skin, liver, spleen, adrenals and bones. The fungi induce a chronic granulomatous reaction comprising macrophages, lymphocytes, and foreign body-type giant cells. Suppuration also may occur, as well as a rare granulomatous arteritis of the circle of Willis. The diagnosis is made in the positive culture of cerebrospinal fluid or blood (Fig.1).

When evaluating the cerebrospinal fluid cytology, it is possible to observe the characteristics of encapsulated yeasts. The capsule does not stain with standard dyes, making it necessary to use china ink or Mayer's mucicarmine. The sensitivity of the test can reach 75%. Cryptococcosis is higher among HIV-infected persons with fewer than 100 CD4+ lymphocytes/μl (Eisenman et al 2007).

Aspergillus sp

The incidence of invasive aspergillosis in patients infected with HIV is very low due to the spread of highly active antiretroviral therapy (HAART). Risk factors include neutropenia and steroid therapy. Aspergillus fumigatus is the most common species to cause disease, and it produces severe invasive infections in immunocompromised individuals. The usual location is the lung. Diagnosis is difficult because the isolation of Aspergillus sp from respiratory secretions has little value: when respiratory symptoms and pulmonary infiltrates are present, the value of Aspergillus sp. isolation from respiratory secretions increases. The detection of antigens such as galactomannans by ELISA or beta-1-3 glucan is more valuable. Another diagnostic test with a great potential is the polymerase chain reaction (PCR).

Fig. 1. Cryptococcus neoformans in cerebrospinal fluid. (40X China ink)

Morphology: Colonizing aspergillosis (aspergilloma) usually implies growth of the fungus in pulmonary cavities with minimal or no invasion of the tissues. Invasive aspergillosis is an opportunistic infection that is confined to immunosuppressed hosts. The primary lesions are usually in the lung, but widespread hematogenous dissemination with involvement of the heart valves and brain is common. Definitive diagnosis requires histological demonstration of hyphae in tissue and can be more evident if special stains such as periodic acid-Schiff and silver stains are performed, but the fungus must be isolated from sterile samples.
Sporothirx schenckii.
Sporotrichosis is an uncommon infection. The most common form of infection is cutaneous inoculation by contaminated sharps objects and clinical diagnosis is facilitated by the typical lymphocutaneous lesions. Recommended tests for diagnosis should be a skin biopsy and analysis of the purulent material. The pulmonary, musculoskeletal, and other less common forms occur in patients with cellular immunosuppression. The diagnosis is clinical, morphological, and through cultures.
Histoplasma capsulatum.
This microorganism is distributed in the American continent, but in Africa there is a variant of the disease caused by H. capsulatum, variety duboisii. It is a dimorphic fungus and produces common endemic mycosis in HIV-positive patients. The primary infection occurs by conidia inhalation. There are three clinical forms: acute primary infection, pulmonary cavity and acute disseminated infection, which is the most frequent in AIDS patients. The diagnosis is made by culture of respiratory, bone marrow samples, or by biopsy of lymph node, liver, lung, or skin (Fig.2). Methenamine-silver and PAS stainings are useful for its detection in biological fluids and tissues. It in tissue from patients with AIDS, abundant organisms in macrophages can be observed, in general there is no chronic granulomatous reaction. (Isenberg, 2004)
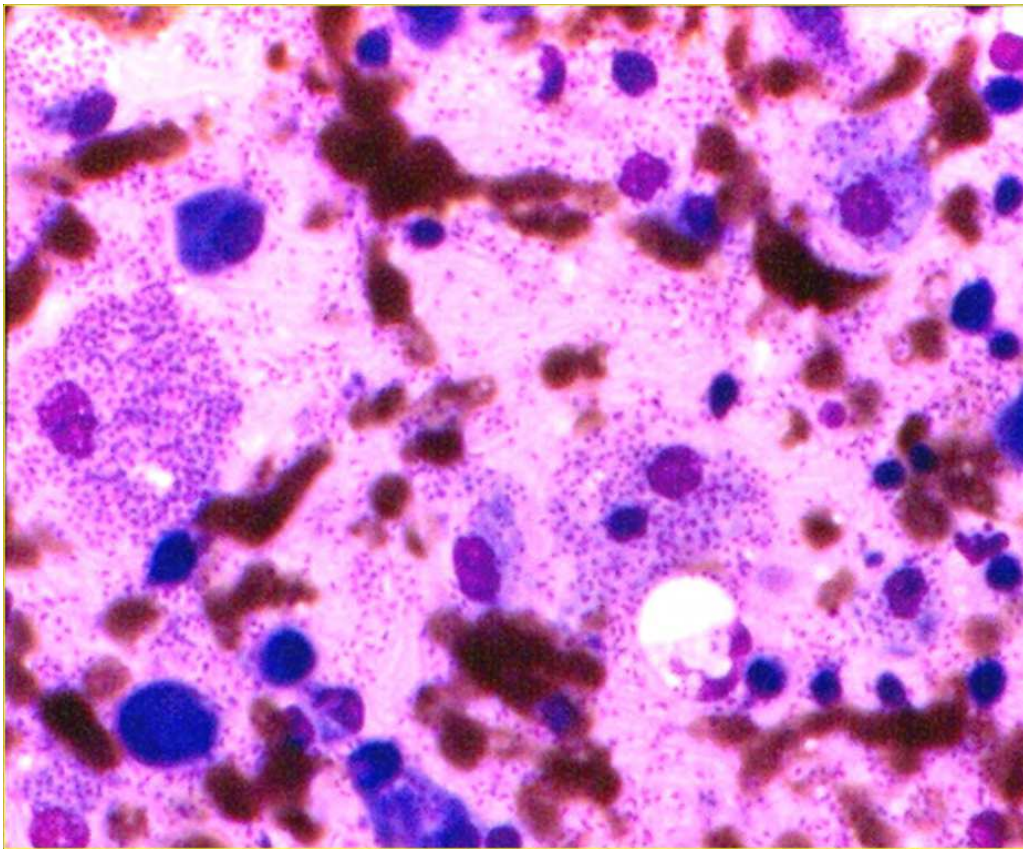
Fig. 2. Histoplasmosis in macrophages in a cervical lymph node. Aspiration biopsy. (PAS stain 40X)

Coccidioides immitis.

It is the causal agent of coccidioidiomicosis. It is a dimorphic fungus and is found in temperate areas of the American continent. The disease is acquired by inhalation of arthroconidia or cutaneous inoculation. There are three clinical forms: cutaneous, asymptomatic, and the disseminated form. The disseminated form was common before the era of HAART in endemic areas. The diagnosis is based on direct examination and culture of sputum, blood, broncho-alveolar lavage, skin and others. In tissue, spherules with endospores are observed and, as in other mycoses, special stains must be performed to identify the organism.

Blastomyces dermatitidis

This is a dimorphic fungus. Its natural habitat is the North American continent, although cases have been reported in Africa, Asia, and Europe. The initial infection is pulmonary, when there is hematogenous spread, it may affect the skin, bones, genitourinary and central nervous systems. In a fresh examination of sputum, skin lesions, or biopsy material characteristic yeast-like elements can be observed that allow for the presumptive diagnosis.

Other dimorphic fungi that occur in HIV patients in specific regions, such as Brazil and China, are Paracoccidioides brasiliensis and Penicillium marneffei, respectively (Patrick, 2003).

3.1.2 Virus infections

Cytomegalovirus.

The diagnosis of cytomegalovirus (CMV) must to rely on laboratory tests. Among the diagnostic tests used are: serological diagnosis, which a little use in HIV-positive patients.

Latex agglutination, or ELISA methods are recommended. Direct detection of the virus or its antigens. Cytological and histological techniques have insufficient sensitivity. However, it is the method of choice for CMV gastrointestinal involvement. If an immunohistochemical technique is used, it can improve the specificity. When there is lung disease, cytopathic changes can be observed in cells obtained from bronchial lavage or sputum. The culture is the gold standard for its specificity for the diagnosis of active infection.

Cytomegalovirus affection caused widespread disease and caused severe damage to the eyes and the gastrointestinal tract, chorioretinitis appeared in 25% of patients with HIV before the advent of HAART, but the condition has declined dramatically (Gerner, et al 1990). The condition of the gastrointestinal tract is observed in 5 to 10% of cases and manifests as ulcerative esophagitis. Detection in biopsies has a positive predictive value, but due to insufficient sensitivity of the samples are should be taken with the diagnosis through this route, ideally tissue should be used, being PCR the most sensitive technique for the diagnosis (Gleaves et al 1984).

Herpes simplex virus and varicella-zoster virus.

The diagnosis of infections with herpes simplex virus (HSV) and varicella zoster virus is basically through clinical criteria, but the severity of some cases or atypical clinical presentation warranted to confirm the diagnosis with laboratory tests (Ashley 1989).

The samples for diagnosis of viral infection are obtained by scraping and taking smears of mucocutaneous lesions, but also by biopsies and respiratory samples.

The affection caused by the herpes simplex virus is manifested by mucocutaneous ulcers in lips, esophagus, external genitals and perianal region. It is possible to see the cytopathic effect on a smear of the mucocutaneous ulcer (Fig. 3)
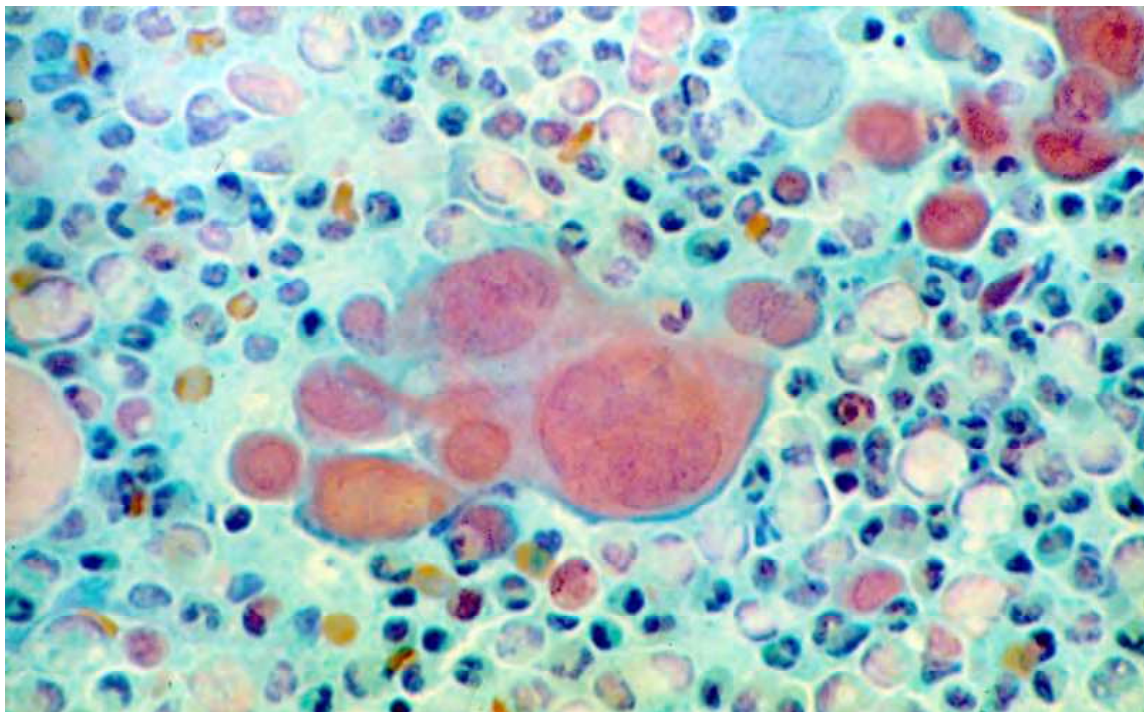

Fig. 3. Herpex simplex virus with cell inclusions or cytophatic effect in perianal region. (40X Papanicolaou stain)

Amplification by PCR is the method of choice for the diagnosis of central nervous system infections in the case of infection with varicella zoster virus. (Gerson et al 1991)

JC polyomavirus.

Compared to other opportunistic infections, new antiretroviral therapies have not had much impact on the occurrence of progressive multifocal leukoencephalopathy. It is possible to observe this complication even in patients virologically stable and the prognosis remains unfavorable. The diagnosis is clinical, supplemented by imaging studies and, at times, with histopathologic examination. Virological diagnosis is restricted to few laboratories and to the use of molecular techniques and electron microscopy.

The samples for the diagnosis are obtained from cerebrospinal fluid biopsies or from autopsies of patients who died from the disease (Athur et al 1989).

3.1.3 Mycobacterial infections: Mycobacterium tuberculosis and non tuberculous mycobacteria

The diagnosis of tuberculosis in HIV-infected patients may be difficult for many reasons, for the multiple atypical clinical and radiological presentations, negative value of the PPD cutaneous reaction, less sensitive bacilloscopies, and on the other hand by the appearance of multidrug-resistant M. tuberculosis strains, possible malabsorbtion, and the disturbing interaction between protease inhibitors and rifampicin. Besides the infection caused by tuberculosis mycobacteria (M.tuberculosis and M. bovis), infection caused by non-tuberculous mycobacteria are frequent in AIDS patientes. Of these the mycobacteria of the avium-intracellulare complex, which constitute the most important pathogen group, where disseminated disease was one of the most common opportunistic infections in these patients. Treatment with antiretrovirals has greatly decreased the disseminated disease mainly in the United States. Diagnosis is made in the following samples: simple or spontaneous sputum tissues (lymphoid tissue biopsies or lung) in sterile liquid such as pleura, pericardium and urine (Pfyffer et al 2003). Molecular biology techniques increases diagnostic sensitivity. In the tissue numerous acid-fast bacilli in alveolar macrophages or tissue are identified, and chronic granulomatous reaction in patients with advanced disease is absent (FTAA and Telent, 1997) (Fig. 4 and Fig. 5).

Other bacterial infections in HIV patients are syphilis caused by Treponema pallidum that causes ulcerative lesions and papules in the genital and anorectal areas.

Biopsy specimens of tissue or lymph node involvement may reveal the presence of treponema, which are apparent with the help of special stains for bacteria or by direct immunofluorescence. (Musher et al 1990).

Some antiretroviral drugs cause other diseases, such as, lipodystrophy and immune reconstitution syndrome, the clinical manifestations are mainly cutaneous (Mudroch et al 2008)

More than half of the manifestations of immune reconstitution syndrome occur in the skin. It has been reported that 10 to 25% of patients starting antiretroviral treatment suffer from this syndrome 90 days later (Rodwell, et al 2008). The most common diagnoses are folliculitis for any reason, reactivation of herpes virus infections, and molluscum contagiosum. Fungal infections, such as ringworm infections of the body and head, as well as systemic mycoses caused by Cryptoccocus (Lehloenya and Mentjes 2006).

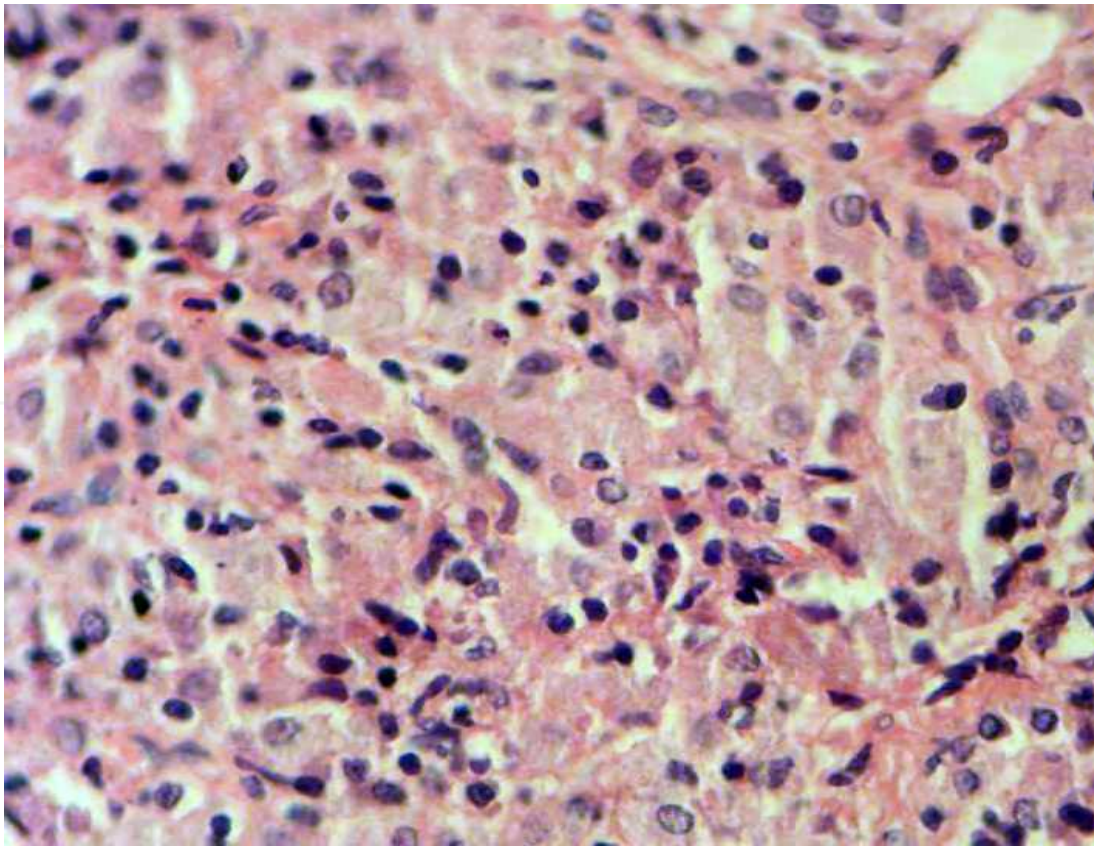It is important to take into account the latter cutaneous manifestations in patients with AIDS.

Fig. 4. Lymph node histologic section with histiocytes and lymphocytes in a patient with atypical Mycobacterium. (H-E 10X)
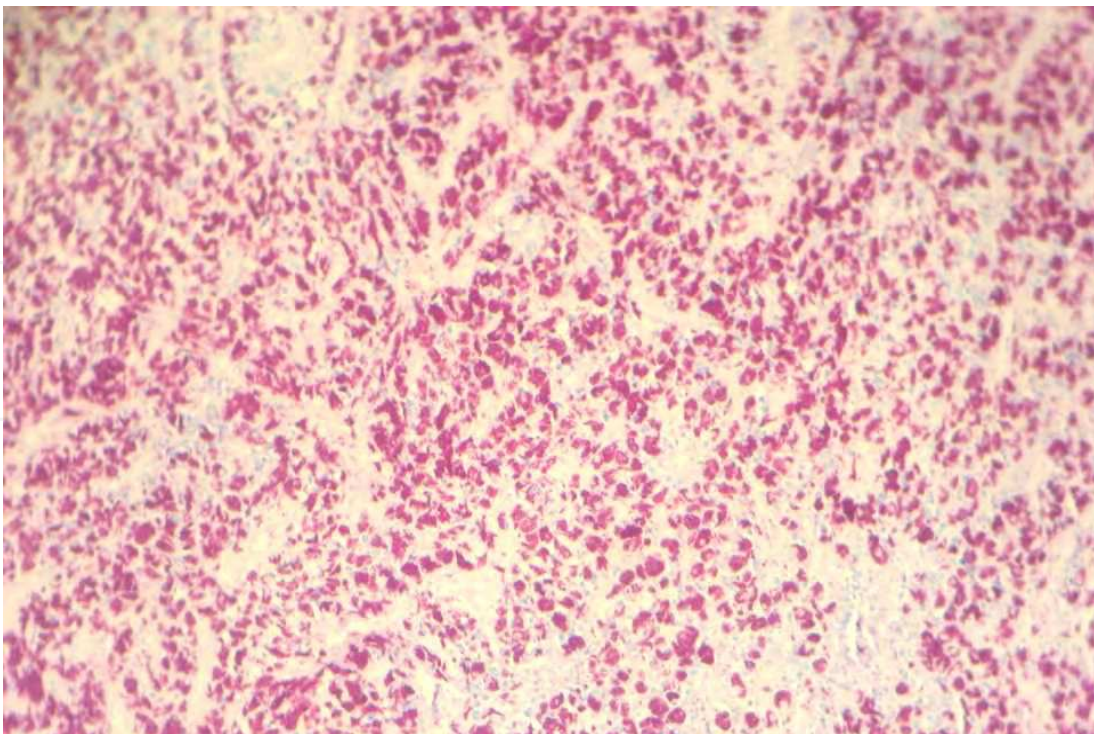

Fig. 5. Sheets of foamy macrophages are seen, which are packed with Mycobacterium demonstrated with acid-fast stains (10X)

4. Neoplasms

The common malignancies in HIV patients are associated with oncogenic DNA viruses like Epstein-Barr virus, Human Herpes virus 8, and human papilloma virus, related to non-Hodgkin and Hodgkin lymphomas, Kaposi's sarcoma, and squamous cell carcinomas such as cervical and anal carcinomas (Table 2).

Lymphoid neoplasms and neoplastic lesions in patients with HIV.
Kaposi sarcoma: cutaneous
and extracutaneous (lung, liver, gastrointestinal tract, lymph node involvement)
 Hodgkin lymphoma
Non-Hodgkin's lymphoma immunophenotype B.
B lymphoma diffuse large cells (immunoblastic morphologic variant)
Primary lymphoma of the central nervous system.
B lymphoma serous cavities.
Plasmablastic lymphoma.
Burkitt lymphoma
B-cell lymphoma, marginal zone MALT
Linfoplasmacitoide lymphoma
Plasma cell neoplasms.
Lymphomas T.
Anaplastic lymphoma.
Specific peripheral T cell lymphoma
Lymphoma T / NK nasal type.
And more rarely others.
Non-neoplastic lesions that may mimic lymphoma in patients with HIV.
Multicentric Castleman disease.
CD 8 lymphocytosis syndrome
Lymphoid interstitial pneumonitis and other
epithelial tumors.
Squamous cell carcinoma of varying degrees of differentiation of the uterine cervix.
Squamous cell carcinoma of anus.
Squamous cell carcinoma of oral cavity

Table 2.

4.1 Kaposi sarcoma

Kaposi sarcoma (KS) is the most common malignancy in these patients, affecting homosexual individuals, but can be seen in any patient with HIV (Mitsuyasu 1990). In recent years, various studies have suggested that the herpes virus HHV-8 plays an important role in the pathogenesis of epidemic, endemic, African, and immunosuppressed Kaposi's sarcoma. It has also been observed in lymphomas cavities (Engels et al 2003). The incidence of KS has declined in recent years with the use of HAART; in most patients it presents with skin lesions, lymph node involvement and less commonly, oral mucosal or gastrointestinal tract lesions. In over 50% of patients with cutaneous KS, visceral involvement can be

detected, such as small intestine and colon. Other affected organs are lung, lymph nodes, liver, heart, and brain.

Histologically, KS lesions are characterized by a proliferation of spindle cells forming vascular channels and expressing markers for endothelial cells and smooth muscle cells (Fig 6). Another change observed is the presence of chronic inflammatory infiltrate. It is believed that the injuries can come from a primitive mesenchymal precursor cell vascular channel. In the pathogenesis of KS, it is believed that spindle cells produce pro-inflammatory and angiogenic factors (Ganem 2006). Clinically, KS is more aggressive in HIV patients than in the sporadic form of the disease.
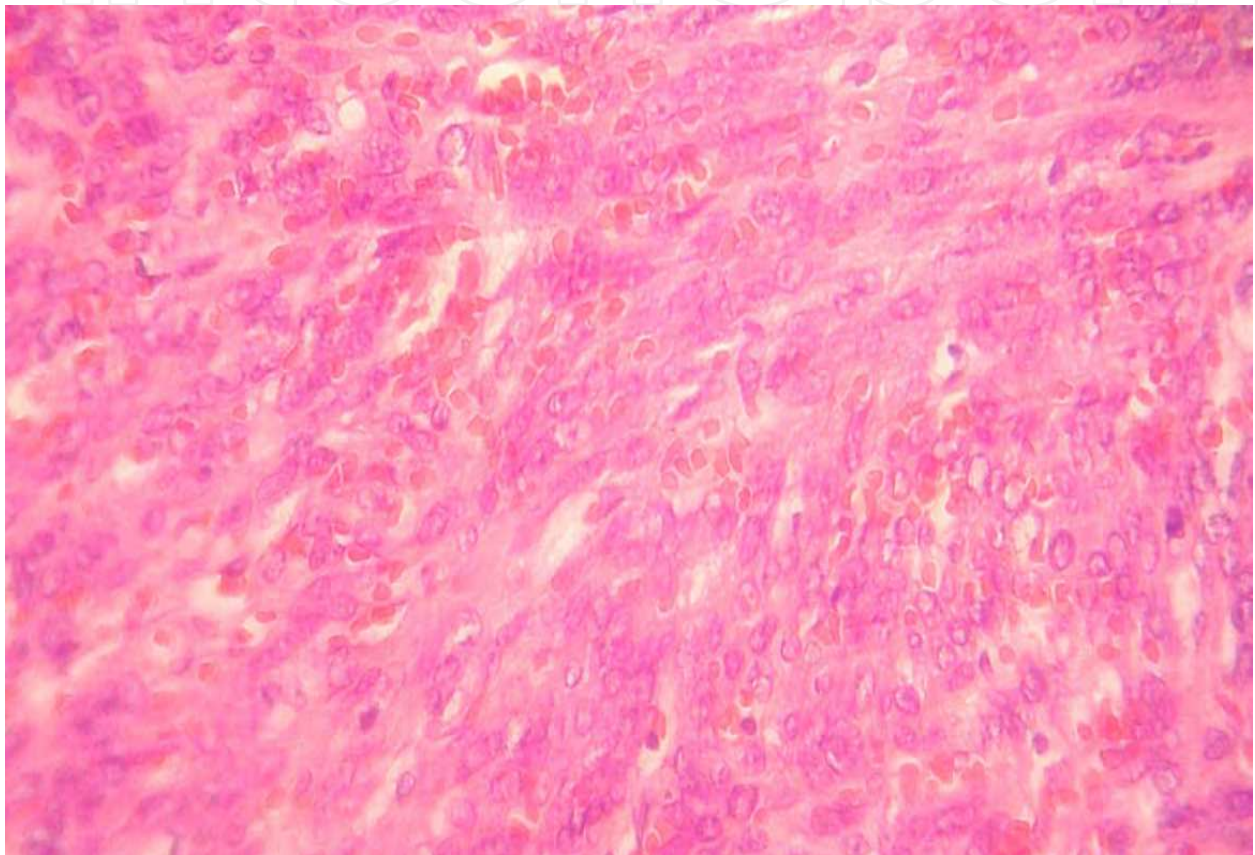

Fig. 6. Kaposi Sarcoma proliferation of spindle cells and vascular channels (H-E10X)

4.2 Lymphomas in HIV patients

The first cases of non-Hodgkin lymphoma (NHL) in patients with HIV infection were reported in homosexual subjects in l982 and the first multicenter study of NHL in patients with HIV infection was published in 1984 (Ziegler et al 1984).

4.3 Non-Hodgkin lymphomas

In recent years we have recognized certain subtypes of uncommon NHL that appears almost exclusively in patients with HIV infection, such as primary effusion lymphoma, other types of lymphomas have peculiar clincopathological characteristics possibly as a result of immunosuppression. (Goedert et al 1998) These include Hodgkin lymphoma (HL), diffuse large B cell lymphomas, plasmablastic lymphoma (Selik and Rabkin 1998). Other

lymphomas described in these patients in which no increased incidence has been described are: MALT-type marginal zone B lymphoma of the digestive tract, lymphoplasmacytoid lymphoma, chronic lymphocytic leukemia, solitary bone and extramedullary plasmacytoma, and immature T lymphomas (lymphoma/ lymphoblastic leukemia) and mature such as the perpheral unespecific T lymphoma, and in our country the nasal type lymphoma T / NK (Gonzalez et al 1998) (Tirelli et al 1995). Other hematological malignancies often described with variable frequencies are some leukemias myeloblastic and chronic myeloproliferative syndromes. Among non-neoplastic lymphoid processes are the multicentric Castleman disease, the CD 8 lymphocytosis syndrome, lymphoid interstitial pneumonitis and the polymorphous polyclonal lymphoproliferative disease B. (Table 2).

Lymphomas in patients with HIV infection are heterogeneous and often result from complex and sequential interaction of several factors (Knowles 1999; Baiocchi1999), such as chronic antigenic activation of B lymphocytes, where maintained stimulation and proliferation of B lymphocytes can be induced by the HIV infection itself, but other mechanisms exist mostly viral, as well as the continuous production of cytokines in response to infection by HIV. High serum concentration are detected of the following interleukins: IL-6, IL-10, and IL-12; it is though that these cytokines are relevant in the polyclonal expansion phase of B lymphocytes. Another factor associated is dysregulation of cytokines and of costimulatory networks, and oncogenic viruses infection.

Of the viruses that have been associated with neoplasmas , there are two implicated in the genesis of NHL, that is, the (EBV) and the human herpes virus type 8 (HHV-8). All viruses with oncogenic capacity share the feature of being in the organism either in their latent stage or as a chronic infection. The mechanisms by which the EBV participates in the genesis of lymphomas is as follows. In normal subjects, when they become infected with EBV they undergo seroconversion during the first decade of life. Primary infection is usually asymptomatic and the virus persists along the whole life. It enters the host by infecting B lymphocytes through the CD 21 (receptor of CD 3d) and persists in latent form after DNA adopts an extra-chromosomal (episome) circular shape (Anagnastopoulos et al 1999). In this stage, nine proteins and two non-coding small RNA, known as EBER 1 and 2, of unknown function can be expressed. Combination of the different proteins yield the three types of EBV latency (Lyons and Liebowitz, 1998), where EBNA 2 and LMP-1 (latent membrane protein- 1) are the most important considereing their transforming capacity exert on B lymphocytes. According to the presence of protein EBNA-2, two types of EBV are identified with different transforming activity. The most active is type 1 (Anagnastopulos et al 1999). In lymphomas, there is only one variant of the EBV, usually type 1 in the diffuse large B cell lymphomas, and type 2 in Burkitt´s lymphoma (Ometto et al 1997). The finding of viral episomes of a single type or clones in a given lymphoma indicates that the virus was present in the tumor cells at the start, and that it is probable relevant in its pathogenesis (Lyons and Liebowitz, 1998).

Factors that contribute to the development of the NHL act in stages and successively. After the initial stage of increased B lymphocytes proliferation follows one of oligoclonal B expansions, genetic alteration are introduced that conclude in a lymphoma (Gaidano et al 1998). When expressed in B lymphocytes, LMP-1 aggregates to the cell membrane and, just like CD 40, reacts with TNF (tumor necrosis factor) associated factors (TRAF), which translate the signal and activate the NK-kb transcriptional factor (Rickinson 1998). Binding of protein LMP-1 with TRAF (TNF associated factors) is the major determinant of the

transforming activity of B lymphocytes and as substances implicated in tumor invasion and in metastases (ICAM-1-LFA-3, metalloproteinases, among others). EBV infection is only one step in NHL genesis in HIV patients. In Burkitt´s lymphoma, EBV is present in a third of cases it has a type 1 latency, rarely LMP-1 protein is positive, since activation of C-MYC usually suppresses this protein (Gaidano et al 1998, 1997). In diffuse large B cell lymphomas, EBV is present in 80% of tumors and generally EBNA-2 and LMP-1 are positive.

The human herpes virus type 8 (HHV-8) has received increasing attention in the last years, it was described in Kaposi´s sarcoma (KS), but it has been constantly found in a special type of B lymphoma, i.e., in the primary lymphoma of cavity, where it is thought to have a direct etiological role (Cesarman et al 1995). This virus induces latent infection in peripheral B lymphocytes, immortalizes these cells in vitro, and induces development of NHL in humans.

It is believe that their presence in KS and LPC is needed but not enough for the pathogenesis, and other factors associated to inflammation are needed to develop malignancy (Mesri, 1999).

The virus could adopt a latency stage in CD19+B lymphocytes, it has been identified in normal tissues such as the gastrointestinal mucosa, lymph nodes and spleen. Its presence has been described in multicentric Castleman´s disease, in angio-immunoblastic lymphadenopathy, and in plasmablastic lymphomas (Luppi et al 1999).

4.4 Genetic alterations

These occur as posterior events to the polyclonal proliferation of lymphocytes B, they affect most frequently: c-MYC (re-arrangement and translocation in 50-75% of occasions, and point mutatuions in the second exon), P53(non-sense point mutations or at 16-375 of lymphomas), RAS (variable incidence of point mutations), and BCL-6 (rearrangements).

Molecular alterations affect differently the diverse types of NHL, HIV-infected patients with neoplasms have higer frequency of unstability of DNA microsatellites, which indicates that they have defficient DNA repair mechanisms (Simonelli et al 2003).

Changes in the incidence of lymphomas have been observed and marked decrease in primary lymphomas of the central nervous system has been confirmed. Incidence of systemic lymphomas has also varied, although there is no consensus among the different research groups (Skies and Crosby 2003).

The most frequent NHL varieties are the diffuse large B cell lymphoma, the Burkitt lymphoma, the plasmablastic and the primary effusion lymphomas.

Morphologically lymphomas in HIV patients are similar to those described in patients without viral infection. Diffuse large B cell lymphoma, without further specification, is defined as a heterogeneous group of lymphoid neoplasms of B cells with a diffuse growth pattern. According to current WHO classification (Swerdlow et al 2008), it is classified by morphological appearance in the following varieties: centroblastic, immunoblastic and anaplastic. Immunoblastic variant is more common in patients with HIV and is characterized by large cells, abundant cytoplasm and evident nucleoli center, about 90% of the cells must have these features to be called immunoblastic (Fig 7).

They are classified by their expression to different immunohistochemical markers such as CD 5 positive, those originated from the germinal center when tumor cells express CD10 and/or bcl6, and in non-germinal center originated when they do not express CD 10 (Hans et al 2003). Characterstically, they always express B markers such as: CD 19, CD 20 and CD 79a
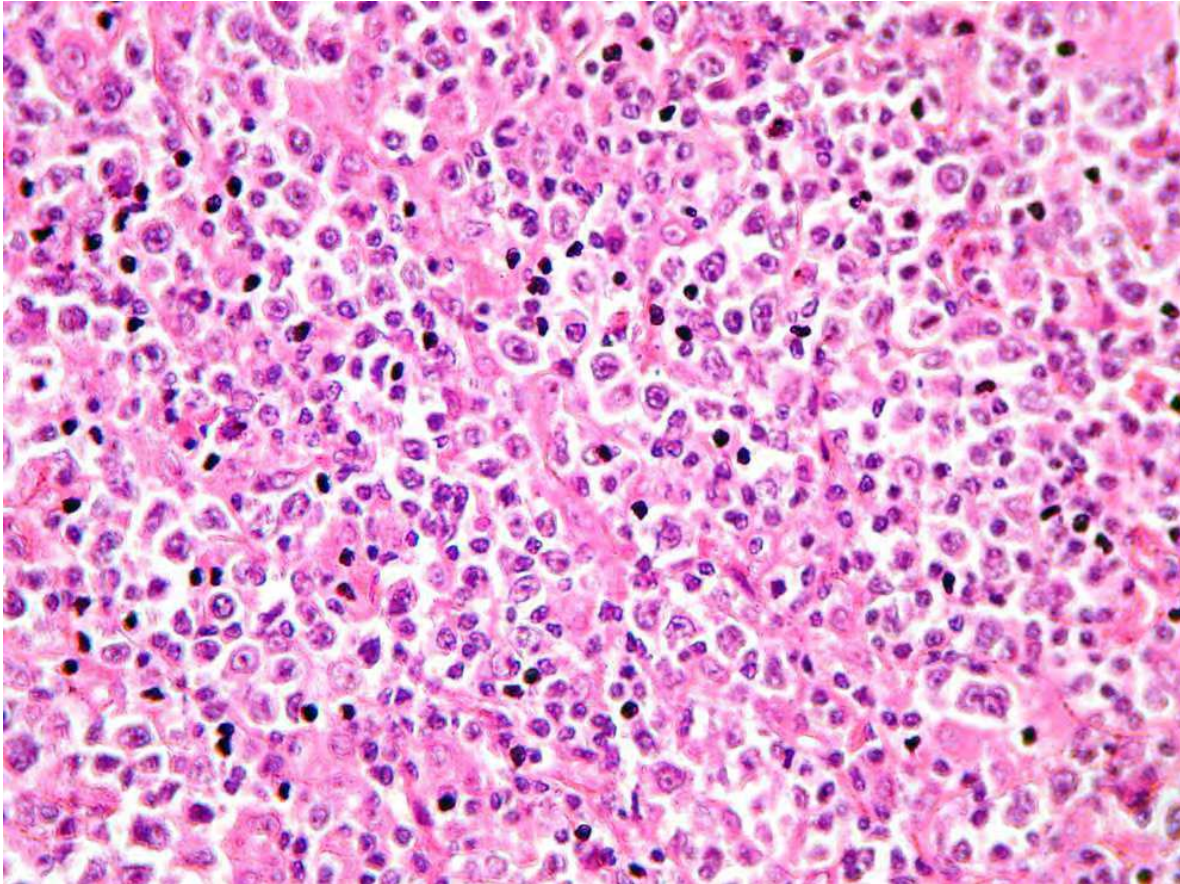
Fig. 7. Large B cell lymphoma (H-E 10X)

The plasmablastic lymphoma is characterized by diffuse proliferation o large cells that resemble immunoblasts, but the tumor cells have the immunophenotype of plasmatic cells. It was originally described in the oral cavity but can occur at any site. The express CD 138, CD 38, MUM-1 and Eber.

Primary effusion lymphoma is a large B cell neoplasm that occurs in the serose tissues without a palpable tumor mass. Co-infection with the EBV can be observed and it is the lymphoma most strongly associated with the HHV-8. The most affected sites are the pleural, pericardial and peritoneal cavities. According to phenotype, they express pan-B markers.

The Burkitt lymphoma associated to HIV generally occurs in lymph node and is characterized by the presence of monotonous o uniforme tumor cells with small nucleoli and fine and dispersed chromatine; cells are medium-sized and the classical "starry sky" pattern is observed quite frequently, characterized by the presence of abundant marcrophages with apoptotic cells. Through immunophenotype they are positive to pan B, CD 10, bcl 6, CD-38, and CD-43 markers. They depict a high cellular proliferation index (100%) and do not express TdT or bcl 2. (Swerdlow et al 2008).

Other lymphomas may also occur in patients with HIV, and one of the common extranodal sites is the gastrointestinal tract where the above mentioned types of lymphoma can occur, as well as small lymphocyte lymphomas such as the MALT-type B-cell lymphoma of the marginal zone (Ho- Yen et al 2007).

T lineage lymphomas are rare and have been, reported in isolated cases of patients with HIV. In a series of nose, palate and oropharynx lymphomas in a hospital in Mexico City,

two male homosexual patients 54 years of age were found with nasal typeT/NK lymphoma, as known this is a lymphoma with certain regional characteristics and widely associated with EBV. (Romero et al 2008)(Figs 8 and 9), other peripheral T lymphomas may be present in these patients, clinically they tend to infiltrate skin and bone marrow more frequently but there is little information on treatment outcomes in the era of HAART (Arzoo et al 2004).

4.5 Hodgkin lymphoma

The Hodgkin lymphoma (LH) in HIV-infected patients can be seven-times more frequent that in healthy individuals, particularly in Europeans and Northeamericans (Tirelli et al 1995; Knowles et al 1988). Diagnostic criteria for LH are the same for either HIV or healthy individuals. However the most frequent subytype in HIV patients comprises the most unfavorable variants such as mixed cellularity and depletion of lymphocytes of the clasical HL(p<0.01), other features published are the abundance of a proliferation of the fibrohistiocyte stroma and a higher perecentage of Reed-Sternberg cells (Ree et al 1991; Bellas et al 1996).
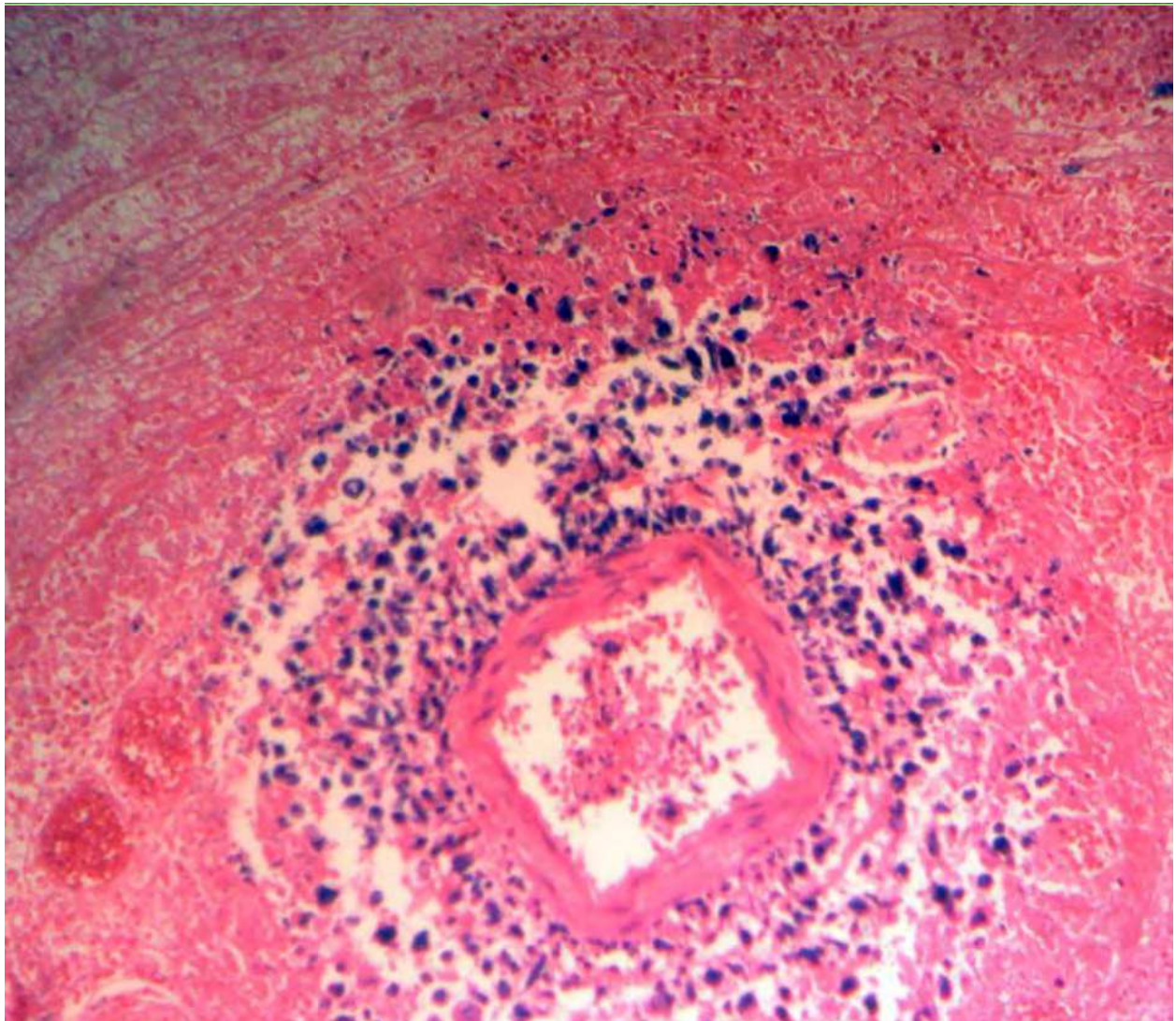

Fig. 8. Extranodal NK/T-cell lymphoma, nasal type. There is a lymphoid infiltrate, with angio-invasion and prominent coagulative necrosis (H-E 10X)
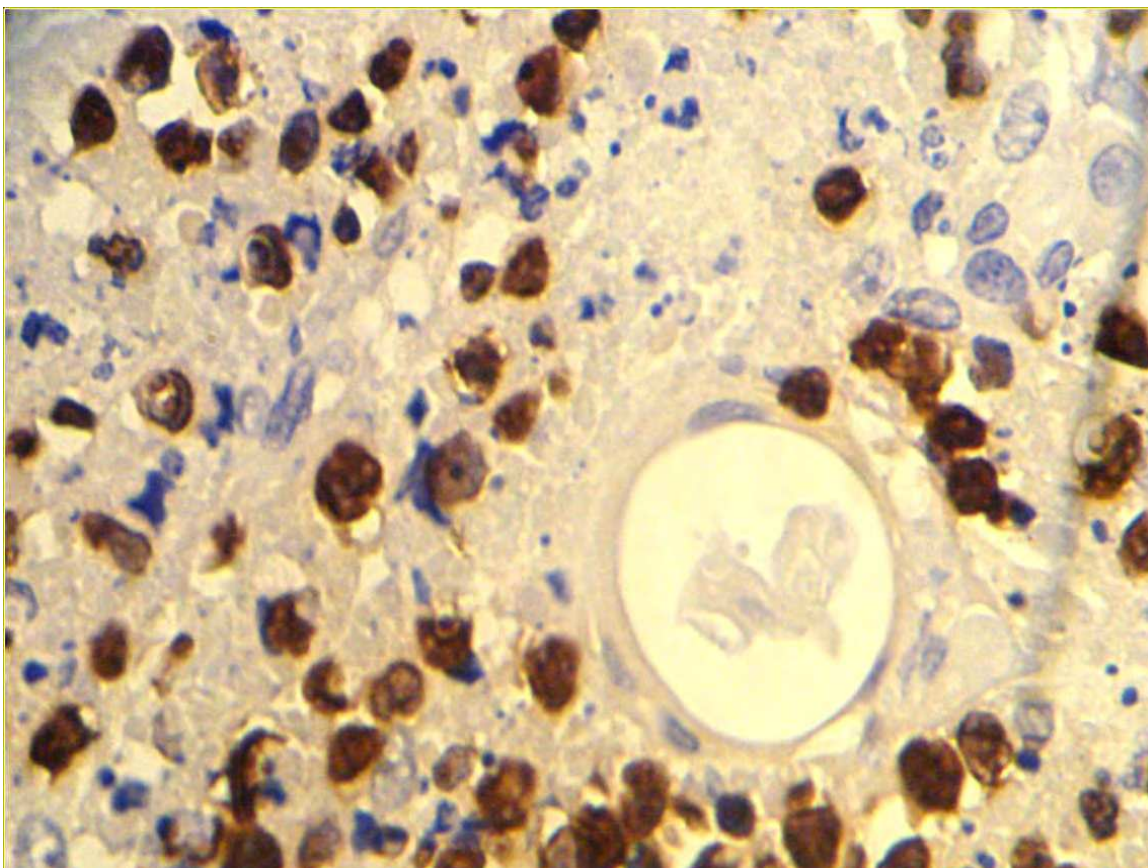
Fig. 9. *In situ* hybridization for EBV-encoded RNA (EBER), in this nasal tumor, practically all the neoplastic cells show nuclear labeling. (40X)

Relation between EBV infection and the origin of LH seems to be tighter in HIV infected patients than in the reamainder LH cases (Ree et al 1991). The combined use of in situ hybridation techniques, immunohistochemistry to determine the expression of LMP-1, indicative of latent EBV infection, and other molecular biology techniques have demonstrated that 78 to 100% of HIV+HL cases are associated to the EBV. On the other side, studies on the expression of bcl-6, generally expressed in centro-follicular lymphocytes, and of a proteglycan (CD138/Syndecan-1), characteristic of post-germinal differentiation have demonstrated the Reed-Sternberg cells of HL associated with HIV are post-germinal lymphocytes, in contrast to what occurs with the neoplastic cells of HL patients not HIV-infected (Carbone et al 1999). Incidence of HL in HIV patients has not increased (Seaberg et al 2010).

4.6 Other malignancies (Carcinoma)

Squamous cells carcinoma of different sites in HIV patients. Despite the association of infection with the human papiloma virus in HIV patients and cancer at different sites, such as anal, cervix, lip, conjunctiva, penis, vagina, and vulva, has increased the role of immunodepression in this type of epithelial cells is still unknown, nor do we know their incidence after antiretroviral drugs use. In a recently performed study by (Chaturvedi et al 2009), these authors found statistical significance between the number of CD4 lymphocytes and anal, vaginal, and vulva cancer, but not when dealing with cervical cancer.
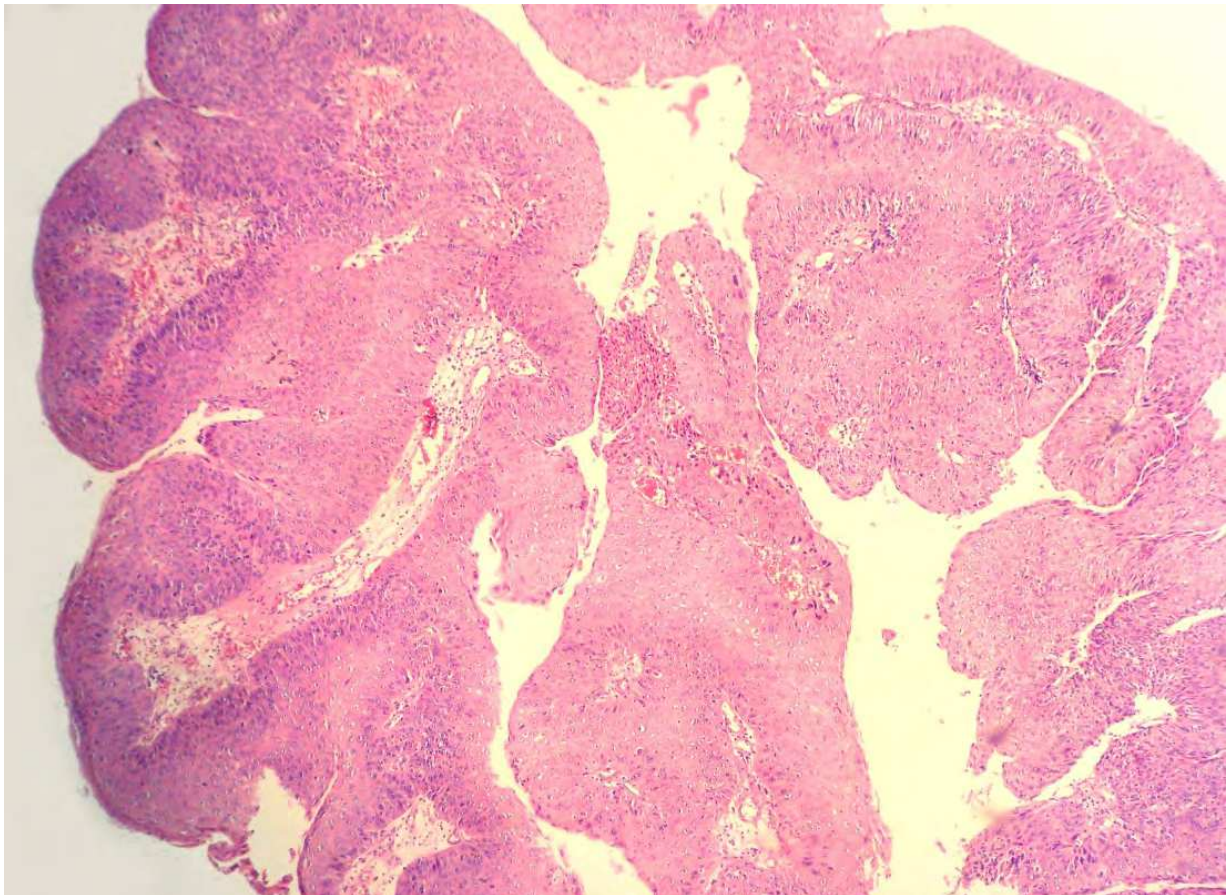
Fig. 10. Anal squamous cell carcinoma. (H-E 10X)

Anal cancer is a rare disease, it corresponds to only 4% of the malignant tumors of the gastrointestinal tract (Clark et al 2004).

Squamous cell carcinoma is by far the most common type of anal malignancy (Ryan and Mayer 2000). The incidence of anal carcinoma is higher in those who practise ano-receptive intercourse, those who are HIV-positive and in transplant recipients. Anal intraepithelial neoplasia is a premalignant lesion associated with human papilloma virus, thought to develop into invasive squamous cell carcinoma in a manner analogous to the progression of cervical intraepithelial neoplasia to cervical squamous cell carcinoma. Bleeding and pain are common in anal carcinoma. Anal carcinomas are dividided into keratinized and non keratinized tumors with subtypes of the non keratinized tumors referred to as clacogenic or basaloid. The behavior of these subtypes is similar. Irrespective of the anatomic and histologic classification, anal squamous cell carcinoma can be thought of as a tumor that may show squamous, basaloid, ductal or a mixed morphology. The type 16 is the most frequently isolated type with 40-75% of all HPV positive samples. Verrucous carcinoma is a low-grade well-differentiated squamous cell carcinoma characterized by papillomatosis, acnathosis and boroad down growths with keratin clefts. The incidence of this disease is increasing in the United States, Europe and South America, especially in the male population.

In Mexico, cervical-uterine cancer remains a public health problem and patients infected with HIV, are at high risk of being infected with HPV, particularly with high risk subtypes, and develop invasive cervical carcinoma (Volkow et al 2001), that occurs in young women

between the third and fourth decade of life and is clinically more aggressive. The most common morphological type is squamous cell carcinoma and there are no unique characteristics among carcinomas from patients without HIV.

Vulvar cancer is likely to be a multifactorial tumor in which recognized risk factors include advanced age, HPV infection, smoking habits, HIV infection, previous VIN (vulvar intraepithelial neoplasm) lesions, lichen sclerosus in the vulva and immunessupression. The expected proportion of vulvar cancers attributable to HPV lies within a range of 15-40% with a summary point estimate of 14%. Nevertheless, distinct subtypes of squamous cell carcinomas (SCCs) are recognized with different prevalence of HPV infection, but in HIV infection most patients are HPV positive. The warty and basaloid subtypes which account for 10-25% of all vulvar cancers have a range of HPV positivity of 59-90%, and the prevalence in the most common conventional squamous cell carcinoma the HPV prevalence is a low as 10-15% (Kurman et al 1993)

Recognized risk factor for vaginal cancer are HPV infection, exposure during pregnancy to diethylstilbestrol, previous history of cervical cancer and previous history or VAIN lesions. The most frequently isolated HPV types identified in cancers of the vagina are 16 and 18 (Srodon et al. 2006).

Other types of tumors have been reported in HIV patients, such as smooth muscle tumors (leiomyomas and leiomyosarcomas) related to EBV in children (Chadwick et al 1990)

5. Conclusions

In conclusion, despite the low morbidity and mortality of HIV infected patients due to opportunistic infections, such as atypical mycobacteral and some fungal infections, particularly in developed countries and thanks to the antiretroviral therapy, there is still much to learn, especially because of the resistant HIV strains and the resistance to antibiotic therapy of some opportunistic pathogens frequently occurring in this type of patients. It must also be taken into account that there are other infectious agents that may arise and it is necessary to know their clinical and diagnostic characteristics to be able to provide specific treatment. Neoplasms in HIV patients are well identified, however, with time and from future research, new types can up particularly in geographical regions were some oncogenic viruses are prevalent.

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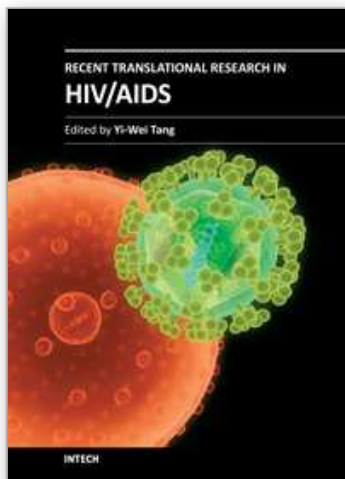
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