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Benign and Malignant Lymphoproliferative Disorders in HIV/AIDS

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1. Introduction

Owing to the striking lymphotropism exhibited by the human immunodeficiency virus, HIV/AIDS patients demonstrate a wide breadth of both benign and malignant lymphoproliferative disorders. These disorders span the spectrum from viral lymphadenopathy to lymphocentric opportunistic infections to proliferations of uncertain and frankly malignant potential. This chapter explores a number of the many possible HIV/AIDS associated disorders from the perspective of the lymphoid system. Notably, some of these disorders are themselves AIDS defining illnesses while others are entities known to occur frequently in the HIV/AIDS population but not directly influenced by HIV infection. In most cases, HIV-associated lymphoproliferative disorders are thought to result from an aberrant host immune response in the context of chronic inflammatory stimulation rather than as a direct consequence of HIV infection.

1.1 Pathogenesis

The human immunodeficiency virus is a member of the lentivirus genus (*lenti-*, *latin* “slow”), a group of viruses in the retrovirus family characterized by tropism for immune cells (Norkin, 2010). HIV demonstrates strong affinity for a specific cohort of human T-cells, the CD4 “Helper” T-cell; this is accomplished by means of the viral gp120 protein’s strong affinity for the CD4 molecule (Wain-Hobson, 1996). HIV infects cells with CD4 cell-surface receptor molecules, using them to gain entry into the cell (Verani, et al., 2005). In early infection, HIV is widely disseminated by way of its interaction with antigen presenting cells (e.g. Langerhans and dendritic cells) which direct antigen obtained from mucous membranes toward the tissues of the adaptive immune system (namely the lymph nodes); HIV can accomplish this both by means of CD4 receptor binding but also by exploiting the immune response itself by allowing phagocytosis into these antigen presenting cells through either interactions with complement or Fc receptors (Verani, et al., 2005). The result is a systemic dissemination of HIV infection to lymphoid tissues (Pantaleo, et al., 1993). Once gained access to the lymphoid tissues of the body, HIV may engage in a latent infection of T-cells by way of viral integration into resting or memory T-cells; these cells may then serve another reservoir of infection (Sierra, et al., 2005).

A number of studies have explored the biological influences that HIV may have on lymphomagenesis. The primary role of the CD4 T-cell is played out in the adaptive immune

response. More specifically, non-infected CD4 T-cells function as immune system modulators through interactions with a multitude of other cells of both the adaptive immune system (i.e. B-cells) as well as the innate immune system (e.g. macrophages and monocytes)(Robbins, et al., 2010). HIV infected CD4 cells cannot execute these normal immunomodulatory functions: HIV replication within CD4 cells is directly cytopathic (Hazenbergh, et al., 2000); non-infected CD4 cells will be reduced in number due to activation-induced cell death under the influence of both HIV infection as well as other concomitant infections (McCune, 2001); HIV tropism for CD4 cells will result in colonization and persistent immunostimulation in lymphoid tissues; HIV will also infect immature CD4 positive precursor T-cells thereby further reducing the effective CD4 T-cell pool (Robbins, et al., 2010).

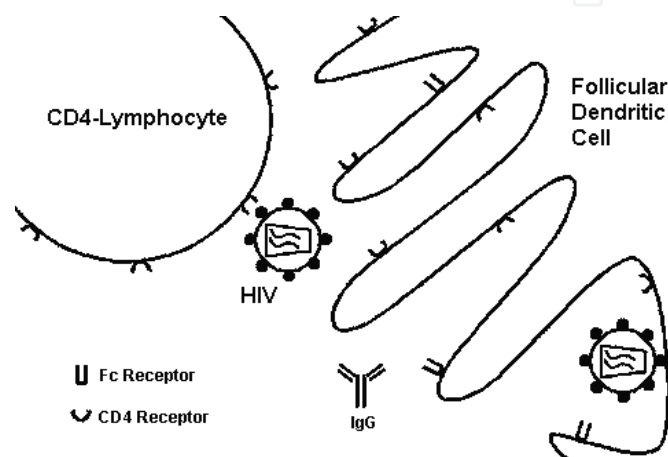


Fig. 1. HIV receptor-specific pathogenesis

In contrast to other viruses associated with neoplasms, HIV is not regarded as a directly transforming virus (i.e. its effect on the host cell genome does not directly initiate neoplastic transformation). This is evidenced by a number of observations regarding HIV-associated lymphomas: there is a wide etiologic range of possible HIV-associated lymphomas; there is frequent association of HIV-associated lymphomas with “super-infecting” known oncogenic pathogens (e.g. Kaposi-sarcoma virus and Epstein-Barr virus); and most HIV-associated lymphomas are lymphomas of B-cells (and not of T-cells, which one would expect if HIV were a uniformly transformative virus). Molecular studies have also noted a propensity for viral genomic integration at random active gene sites; while this may theoretically lead to an insertion at a transformative locus, HIV does not show consistent insertion at a transformative site (Mitchell, et al., 2004).

EBV has been shown to contribute to lymphomagenesis in a number of ways; the latent membrane proteins, in particular, have garnered much research interest in this vein. In the 1980s it was recognized that EBV latent membrane protein-1 gene was able to transform mouse cell models (Wang, et al., 1985). EBV-LMP has also been shown to activate the tumor necrosis factor and p38 mitogenic pathways (Mosialos, et al., 1995; Eliopoulos, et al., 1999); activation of these pathways may contribute to the ability of EBV-infected (and potentially transformed) cells to evade host defense mechanisms. Another EBV encoded protein, latent membrane protein A2 has been shown to stimulate lymphocyte development and proliferation in mouse models outside of the normal immunologic milieu (Caldwell, et al., 1998). Finally, Vockerodt and colleague recently demonstrated that latent membrane

protein-1 was capable of inducing a Hodgkin-like state in non-previously transformed germinal centre B-cells (Vockerodt, et al., 2008).

Less commonly, HIV-associated lymphomas demonstrate co-infection with the Kaposi sarcoma herpes virus, HHV-8. A number of HHV-8 viral proteins have been implicated in lymphomagenesis: the HHV-8 latency-associated nuclear antigen has been shown to interfere with normal p53 and Rb gene protein functions; the K13 viral protein interferes with host cell Fas-mediated apoptosis pathways; and the Kaposin B viral protein has been shown to prevent the normal degeneration of stimulatory cytokines (Wen & Damania, 2010). The combined influence of these and other HHV-8 encoded proteins, especially within the context of an already abnormal immunomodulation from HIV infection, places infected B-cells at high risk of malignant transformation.

2. Non-neoplastic lymphoid disorders in HIV/AIDS

2.1 HIV-associated lymphadenopathy

Lymphadenopathy is a characteristic (though certainly not specific) finding in HIV/AIDS patients. Variable definitions of lymphadenopathy exist in the medical literature, typically making reference to enlarged, swollen or painful lymph nodes as definitive. Size cut-offs have been proposed in some definitions and many clinicians will investigate lymph nodes exceeding 1 cm in size. Ioachim notes that lymph nodes larger than 3 cm should raise suspicion of neoplasia (Ioachim & Medeiros, 2009b). Often lymphadenopathy will come to clinical attention as rapidly enlarging lymph nodes; unfortunately, there is little data to suggest how the rapidity of lymph node enlargement pertains to the presence or absence of a neoplastic proliferation. Other features of clinical concern include matting or adherence of multiple nodes to one another, as well as enlargement of several nodes in a given nodal chain (Ioachim & Medeiros, 2009b). Most frequently, due to the frequent clinical concern that an enlarged lymph node may admonish, biopsy and pathological examination of lymph nodes is necessary, especially in the at risk HIV/AIDS community. For our purposes, HIV-associated lymphadenopathy refers to enlarged lymph nodes attributable strictly to a non-neoplastic viral process excluding other opportunistic pathogens (discussed later).

Lymphadenopathy was identified as one of the earliest clinical signs in early epidemiologic studies of patients with AIDS; the closely studied 1982 Vancouver cohort of at risk homosexual men demonstrated a prevalence of 50% of post-seroconversion lymphadenopathy (Boyko, et al., 1987). Similar values were noted in other cohorts, including heterosexual males and females, such as the Zimbabwean cohort of Latif, et al. (Latif, et al., 1989). Lymphadenopathy is also more commonly identified in HIV positive children than in non-HIV infected children (Bakaki, et al., 2001; Nielsen, et al., 1997). HIV-associated lymphadenopathy demonstrates preponderance for the head and neck area, often presenting as cervical lymphadenopathy (Prasad, et al., 2006). Other radiologic studies have also demonstrated frequent (typically occult) intra-abdominal lymphadenopathy in HIV positive patients, most commonly as a result of opportunistic infection but also due to lymphomas (Jasmer, et al., 2002). Concern over the latter not infrequently results in invasive abdominal lymph node biopsies for diagnostic purposes.

HIV-associated lymphadenopathy follows a consistent histological pattern of progression (see Figure 2). Lymphadenopathy typically begins with the onset of HIV viremia; this acute phase of HIV infection (the acute retroviral syndrome) is typically described as a

mononucleosis-like cluster of symptoms. Acute retroviral syndrome typically begins 2-6 weeks post-infection and may last for several weeks. Typical symptoms include fever, headache, malaise, pharyngitis and lymphadenopathy (Carpenter, et al., 2004). The lymphadenopathy, however, often persists beyond this acute phase. The histological features of early HIV-associated lymphadenopathy typically demonstrate exuberant hyperplastic changes: large lymphoid follicles with irregular serpiginous shapes are characteristic; irregular enlargement of germinal centres is noted; these large germinal centres typically demonstrate prominent apoptotic bodies and tingible body macrophages; and there may be expansion of the interfollicular zones by numerous transformed B lymphocytes (these have a monocytoid appearance and correspond to antigenically stimulated B-cells). These features are typical of the so-called Grade 1 HIV-associated lymphadenopathy.

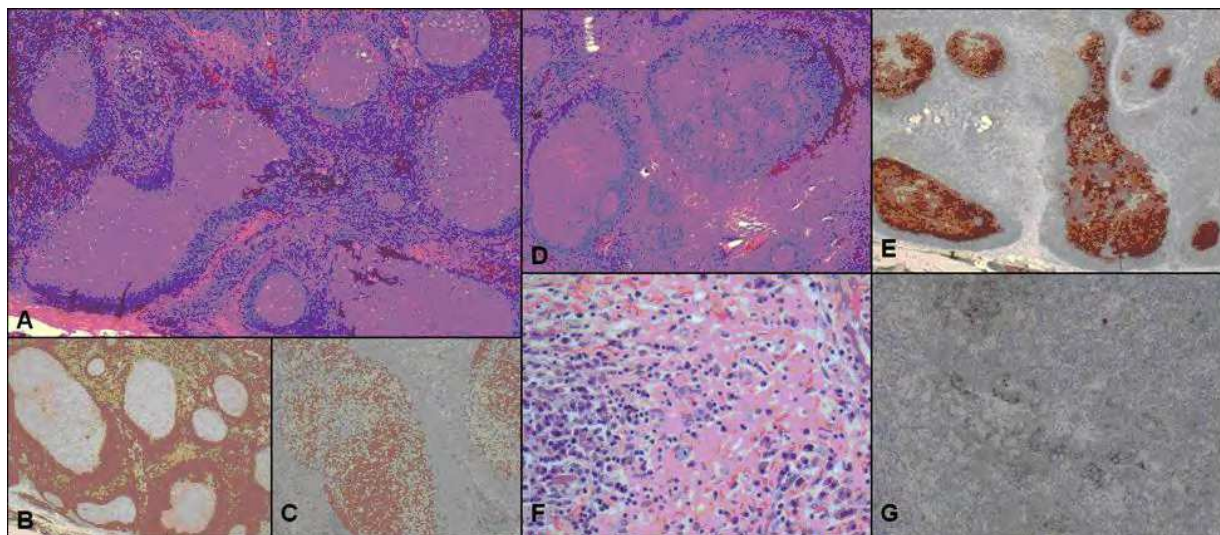


Fig. 2. HIV Lymphadenopathy: A: Early HIV Lymphadenopathy (Grade 1); B: BCL2 stain demonstrating benign follicle staining pattern (negative in follicles and positive in interfollicular zones); C: Ki67 demonstrating benign follicle staining pattern (high index nuclear staining in follicles with low index in interfollicular zones); D: Grade 2 HIV Lymphadenopathy demonstrating early follicular-lysis; E: Corresponding CD21 stain demonstrating hyperplastic moth-eaten follicular dendritic cell meshwork (replaced by fibrosis); F: Grade 3 HIV Lymphadenopathy demonstrating marked fibrosis and loss of follicles; G: Corresponding CD21 stain demonstrating near absence of follicular dendritic meshwork

As HIV infection progresses, the antigenic stimulation within the lymph node begins to wane. This leads to a Grade 2 pattern of HIV-associated lymphadenopathy characterized by a reduction in the number of lymphoid follicles, an increase in the number of plasma cells and a proliferation of perifollicular blood vessels. At the extreme of HIV-associated lymphadenopathy is the Grade 3 pattern in which the residual follicles begin to display sclerosis of their germinal centres.

Although consistent, none of the histologic features noted above are specific to HIV. The Grade 1 pattern, for example, is frequently observed in non-HIV viral lymphadenitides. The Grade 2 and 3 patterns show a significant overlap with those of Castleman's disease (see later). In such cases, a clinical history of known or suspected HIV infection is essential in

order that the correct diagnosis be made and that the correct treatment regimen be instituted. The vascular proliferation noted in Grade 2 and 3 may also be misconstrued for Kaposi's sarcoma (see later for the lymph node features of Kaposi's sarcoma); immunohistochemistry for the Kaposi's sarcoma virus is now a commonplace tool to avoid this diagnostic confusion. Other more aggressive lymphoproliferative disorders need to be ruled out in lymph nodes sampled in the context of HIV; the key feature in HIV-associated lymphadenopathy of any Grade is the relative preservation of lymph node architecture which is often lost in lymphoid malignancies.

EBV seropositivity is widespread in HIV positive patients and in the context of lymphadenopathy EBV infection can confuse the histopathologic diagnosis (see Figure 3). More specifically, EBV infection may produce reactive cells demonstrating a striking resemblance to the Reed-Sternberg cells of Hodgkin's lymphoma. In such cases, immunohistochemistry is essential. In order to rule out Hodgkin's lymphoma, the atypical Reed-Sternberg like cells seen in lymphadenitis will typically stain positive for CD20, CD45, and may stain positive for CD30 (an activation marker); these cells, unlike true Reed-Sternberg cells, should not stain for CD15.

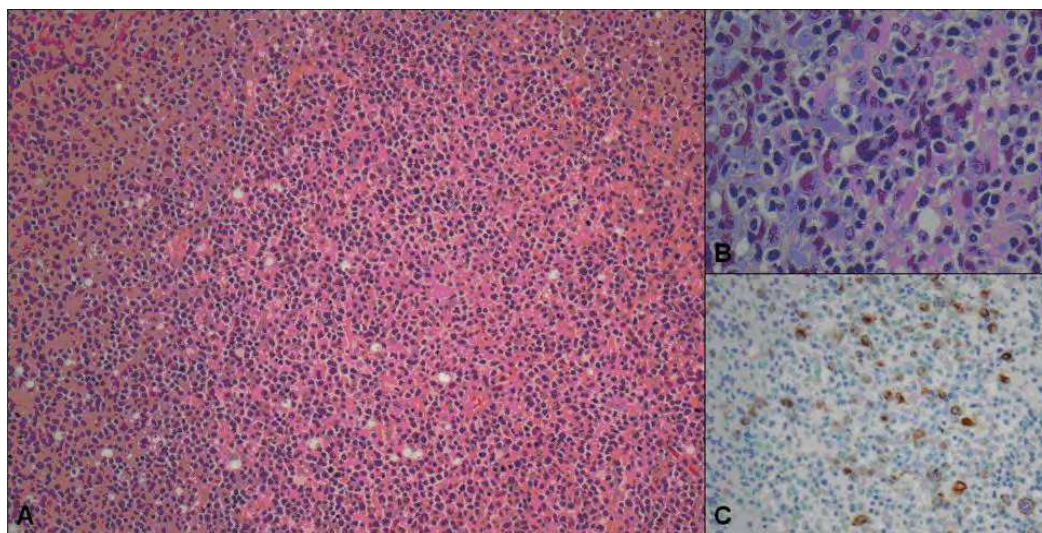


Fig. 3. HIV Lymphadenopathy with EBV related changes: A: Loss of normal lymph node architecture; B: Reed-sternberg-like cells present in EBV-related HIV Lymphadenopathy; C: Corresponding EBV Stain

Treatment for HIV-associated lymphadenopathy is focused around optimizing antiretroviral therapy, treated other concomitant infections as needed and clinical follow-up. The latter point is emphasized in order that lymphoid neoplasia not be missed. Studies have explored the outcomes of patients diagnosed with HIV-associated lymphadenopathy and graded according to the above scheme. In their cohort of HIV patients with lymphadenopathy, Ioachim and colleagues noted that most cases of HIV-associated lymphadenopathy began as Grade 1; many cases subsequently progressed from Grade 1 to 2 and from Grade 2 to 3; most cases with Grade 3 lymphadenopathy subsequently developed AIDS defining illnesses (Ioachim & Medeiros, 2009; Ioachim, et al., 1990). Ioachim et al also noted a distinct survival difference between the various grades of HIV-associated lymphadenopathy (Ioachim & Medeiros, 2009; Ioachim, et al., 1990). Grade 3 HIV-associated lymphadenopathy is also strongly associated with development of Kaposi's sarcoma (Ioachim & Medeiros, 2009c).

2.2 Bacillary angiomatosis

Bacillary Angiomatosis is a lesion of proliferating endothelial cells caused by *Bartonella* species occurring in immunocompromised patients, almost exclusively in patients with AIDS. The first documented case of HIV/AIDS associated bacillary angiomatosis was reported by Stoler and colleagues in 1983 (Cotell & Noskin, 1994; Stoler, et al., 1983); they reported a peculiar case of a young AIDS patient with multiple cutaneous nodules found to consist of proliferating endothelial cells forming lobular networks of small caliber blood vessels. Interspersed within this network were small gram-negative bacillary forms visible only on Warthin-Starry staining. For many years, efforts to speciate the organism observed histologically were unsuccessful; initial attempts at culturing the organism with a range of media produced no results (Cotell & Noskin, 1994; Stoler, et al., 1983). Finally, with the dawning of PCR based techniques, the organism believed to be the causal agent in bacillary angiomatosis was found to be genomically comparable to the species known to cause Cat Scratch Disease, the organism known today as *Bartonella henselae* (Relman, et al., 1990).

It is now known that bacillary angiomatosis may be associated with a number of *Bartonella* species, most common *B. henselae* and *B. quintana* (Maguina, et al., 2009). Interestingly, studies have shown high seroprevalence for *Bartonella* species in the population overall (Lamas, et al., 2010). Furthermore, clinically silent *Bartonella* seroprevalence has been observed in the HIV population, rarely with very high titres (Pape, et al., 2005; Yousif, et al., 1996). These laboratory data mirror the clinically evident divergence of *Bartonella* infection observed in the immunocompromised and immunocompetent populations. In immunocompetent individuals, *Bartonella* infection, if clinically evident, typically manifests as the so-called “cat-scratch disease,” characterized by lymphadenopathy demonstrating caseating granuloma formation. In immunocompromised patients, on the other hand, the infection manifests as vascular lesions, sometimes progressing to a potentially fatal systemic infection. This stark contrast has spawned a number of studies demonstrating the importance of an intact adaptive immune system.

Bartonella infection is transmitted either by means of an insect vector (e.g. mites, lice) or by means of trauma by an animal vector (the namesake “cat-scratch” is evident) (Minnick, et al., 2003; Ioachim & Medeiros, 2009a; Wolff, et al., 2005). Studies exploring the comparative genomics of *Bartonella* infections in HIV patients and their pet cats have confirmed this long suspected epidemiologic link (Chang, et al., 2002). After inoculation, *Bartonella* species home to erythrocytes and endothelial cells, thereby allowing it access to multiple sites in the body (Minnick, et al., 2003). *Bartonella* then exploits a number of molecular pathways to evade its host’s immune system (Minnick, et al., 2003); this evasion may explain the clinically observed propensity of *Bartonella* to produce granulomatous lymphadenitis. In immunocompromised patients, exploiting an already weakened immune system, *Bartonella* stimulates angiogenesis; *Bartonella* infection stimulates the production of hypoxia-induced factor and other cytokines, thereby upregulating angiogenesis (Minnick, et al., 2003).

Bacillary angiomatosis typically occurs in AIDS patients with low CD4 counts (typically less than 100/mm³) (Maguina, et al., 2009). Most patients present with skin lesions, characteristically as multiple violaceous or red papules; these lesions may be painful, typically progress over days to weeks and may resemble cherry hemangiomas or pyogenic granulomas (Wolff, 2005). In most cases a combination of clinical history, known HIV/AIDS status and clinical assessment will result in the correct diagnosis; the differential diagnosis, however, may include Kaposi’s sarcoma thereby mandating histopathological assessment

(Maguina, et al., 2009). In a notable number of cases of BA, lymphadenopathy may be identified as the inciting event (Gasquet, et al., 1998). *B. henselae* BA, in particular, tends to demonstrate lymphadenopathy, both with and without skin lesions (Ioachim & Medeiros, 2009a). Aggressive cases of bacillary angiomatosis may demonstrate splenic or hepatic involvement as bacillary peliosis, often with fatal outcomes.

The histologic features of bacillary angiomatosis in lymph nodes are similar to those seen in skin lesions and elsewhere (see Figure 4). Bacillary angiomatosis typically forms richly vascular nodules. Proliferating endothelial cells are evident, forming variably sized blood-filled vascular spaces into which their nuclei protrude. There may be notable anisonucleosis, multiple nucleoli and numerous mitoses; these features may suggest a malignant entity. Ancillary staining with Warthin-Starry silver stain invariably demonstrates numerous bacilli, 0.2-0.3 μm in size, often noted in clumps (Maguina, et al., 2009; Ioachim & Medeiros, 2009a). Electron microscopy will demonstrate a trilaminar bacillus in association with an obvious proliferation of endothelial cells with characteristic Weibel-Palade bodies (Kostianovsky & Greco, 1994). Modern attempts at developing reliable immunohistochemical markers to aid in the diagnosis of bacillary angiomatosis have been as yet unsuccessful; PCR techniques may be relied upon to confirm the presence of *Bartonella* infection in cases that may be diagnostically equivocal (Caponetti, et al., 2009).

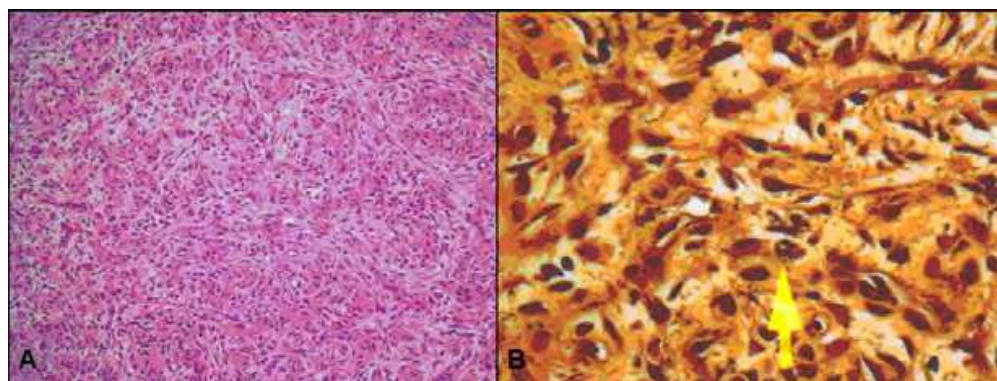


Fig. 4. Bacillary Angiomatosis: A: Low-power view demonstrating proliferating venules; B: Warthin-starry stain demonstrating extracellular clump of bacteria (arrow)

The differential diagnosis of bacillary angiomatosis may include a number of entities, especially if the HIV/AIDS status of the patient is unknown. On hematoxylin & eosin staining alone, bacillary angiomatosis may resemble a hemangioma. Gram staining may help distinguish bacillary angiomatosis from pyogenic granuloma (the former being invariably negative). Bacillary angiomatosis may sometimes be difficult to discern from Kaposi's sarcoma. Histologically, Kaposi's cells are more characteristically spindled and there is a predominance of slit-like vascular spaces. Nonetheless, most authorities recommend using an immunohistochemical stain against HHV-8, the causal virus of Kaposi's sarcoma, in order to rule out this more serious condition. Another malignant condition that may be mimicked by bacillary angiomatosis is typical angiosarcoma; this entity is highly aggressive and demonstrates an infiltrative architecture.

Although the clinical course of bacillary angiomatosis is variable, the treatment of choice is antibiotics (typically a course of erythromycin or doxycycline); some cases may also resolve spontaneously even without treatment, however (Wolff, et al., 2005). Care should be taken in HIV/AIDS patients with very low CD4 counts; these patients not only require quick accurate diagnosis to define the appropriate treatment regimen, but further preventative action may also be beneficial, such as prevention of exposure to animals.

2.3 Other common infectious lymphadenitides in HIV/AIDS

While a complete review of the opportunistic and co-infectious agents encountered in HIV/AIDS is beyond the scope of this book, any discussion of the lymph node based disease entities encountered in HIV/AIDS would be remiss if not for a discussion of the commonest node-based co-infections. The following is a brief discussion of the most common opportunistic infections encountered in HIV/AIDS patients from the perspective of lymph node disease.

2.3.1 Pneumocystis

Pneumocystis jiroveci is a ubiquitous organism in nature manifesting as a disease-causing organism only in the immunocompromised. This fungus first came to broad clinical attention in the early 1980s when it was noted in 70-80% of AIDS patients, most commonly manifest as pneumonia. Rarely, however, pneumocystosis does involve the lymph nodes. Anderson and Barrie were probably the first to report pneumocystis in a lymph node, two decades prior to the first identified cases of HIV/AIDS (ANDERSON & BARRIE, 1960). Of the reported extra-pulmonary cases of pneumocystis, the lymphoreticular system is probably the most common (Grimes, et al., 1987; Ioachim & Medeiros, 2009d). When involving lymph nodes, pneumocystis most commonly involves the mediastinum and retroperitoneal lymph nodes (Ioachim & Medeiros, 2009d). The gross features typically reflect the presence of necrotizing granuloma: lymph nodes are typically enlarged with central areas of purulent material. Microscopically, granulomata with central necrotic eosinophilic material will be noted (see Figure 5). The causal microorganisms are generally not overtly evident on routine histologic stains but can be readily identified on fungal silver stains as helmet-shaped organisms within the necrotic foci. Immunohistochemical stains for *Pneumocystis jiroveci* are available, though a combination of clinical history of HIV infection and morphologic features identified on silver staining are often sufficient. The current treatment of choice is trimethoprim-sulfamethoxazole antibiotics; the US centres for disease control also recommend that all HIV-positive patients diagnosed with pneumocystosis be maintained on indefinite prophylactic anti-fungal agents provided that CD4 count remains below 200 cells/ μ L (Kaplan, et al., 2009).

2.3.2 Mycobacteria

Globally the risk of co-infection with *Mycobacteria tuberculosis* is 20-37 times higher in patients with HIV than those without (WHO Department of HIV/AIDS Stop TB Department, 2010). The WHO also estimates that 25% of HIV-positive patients will die due to concomitant tuberculosis (WHO Department of HIV/AIDS Stop TB Department, 2010). Other non-tuberculous infections are also frequent in (and many are characteristic of) HIV infection. In addition to their primary involvement of the lungs, mycobacteria are also frequently encountered in lymph nodes, especially in the context of HIV infection. Mycobacterial lymphadenitis, regardless of the underlying species, will characteristically produce lymph node enlargement with foci of necrosis. The histologic features are often characteristic, namely central eosinophilic necrosis surrounded by a rim of palisading histiocytes and giant cells (see Figure 5). In this peripheral rim of histiocytes, mycobacteria may be identified, often few and far between, on acid fast staining (pathologists often use a Ziehl-Neelsen stain for this purpose). Positivity on acid-fast staining does not equate to tuberculosis, however, and in many cases distinguishing between *Mycobacteria tuberculosis*,

atypical mycobacteria or the *Mycobacterium avium complex* can be challenging, often requiring molecular testing for speciation (which can fortunately be performed off formalin-fixed and paraffin-embedded tissues). The presence of the so-called Langhans giant cells (with peripherally rimmed nuclei) may hint at the presence of *Mycobacteria tuberculosis* but is by no means specific. Another advantage to molecular testing when acid-fast bacteria are encountered is the ability to test for antimicrobial resistant strains by PCR; this may be an invaluable aid given the burgeoning cohort of multidrug resistant TB cases encountered in HIV/AIDS.

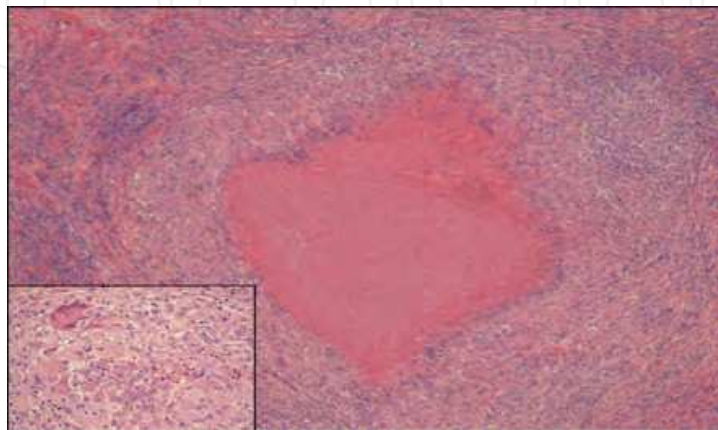


Fig. 5. Tuberculous Lymphadenitis: Granuloma with eosinophilic necrotic centre; inset: characteristics Langhans giant cell (top left) with adjacent necrosis (bottom right)

2.3.3 Toxoplasmosis

Toxoplasma gondii is the causative agent of toxoplasmosis, a parasitic infection believed to be one of the world's most prevalent. *Toxoplasma gondii* seropositivity in the at-large population has previously been reported as high as 70-90%, though modern estimates in the range of 10-40% seem reasonable (Shin, et al., 2009; Kamani, et al., 2009; Fromont, et al., 2009). Not unexpectedly, the overall seroprevalence of *Toxoplasma gondii* is also high; while the estimates may be lower in North American and Europe, one recent Nigerian cohort demonstrated a seroprevalence of over 50% with active parasitism in the blood detected in over 20% (Lindstrom, et al., 2006). *Toxoplasma gondii* demonstrates parasitism of a number of animal hosts, most commonly of felines (the definitive host). Humans are typically infected by way of consumption of contaminated foods or exposure to contaminated soil or animal droppings. Vertical transmission is also possible, producing a dangerous congenital toxoplasmosis. One of the most frequent presentations of toxoplasmosis in the HIV population is toxoplasma encephalitis (Ioachim & Medeiros, 2009e); a histologically characteristic infection of lymph nodes is also common, however. Toxoplasmosis lymphadenopathy typically affects the lymph nodes of the head and neck; these are typically slightly enlarged and tender to palpation. The most frequently encountered histologic features are nodal follicular hyperplasia with interspersed aggregates and sheets of monocytoïd lymphocytes and scattered clusters of epithelioid cells (see Figure 6). The monocytoïd cells are immunoglobulin producing B-cells (which will stain positive for B-cell markers) and can most typically be found in the subcapsular and paratrabeular locations while the epithelioid cells are histiocytes and are characteristically seen to encroach upon follicles but do not form true granulomas. Many HIV positive cases of toxoplasma

lymphadenopathy will demonstrate free or engulfed trophozoites (which may be seen staining hook-like organisms H&E, either free floating or within macrophages); they are rarely observed in immunocompetent patients, however. The giemsa special stain can be used to highlight the organisms and some labs use immunohistochemistry with *Toxoplasma gondii* antibodies; PCR testing is the gold-standard, however. The histologic differential diagnosis is long—as would be expected in most cases with prominent collections of histiocytes. For this reason, it is advisable to use ancillary testing or special stains when examining lymph nodes with prominent collections of histiocytes. In addition to antibiotics for treatment of acute toxoplasmosis (such as pyrimethamine, sulfadiazine or clindamycin), the centres for disease control and prevention also currently recommend antibiotic prophylaxis for HIV patients with low CD4 counts (less than 200 cells/ μ L) (Kaplan, et al., 2009). Routine serologic testing of HIV positive patients is also recommended (Kaplan, et al., 2009).

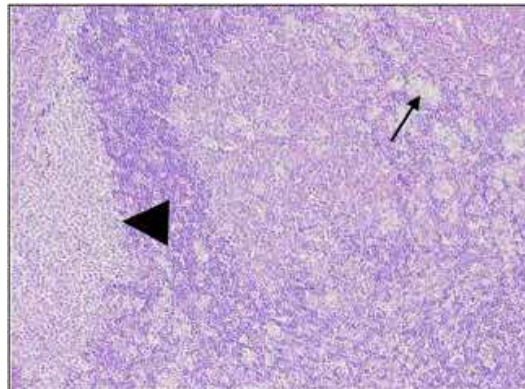


Fig. 6. Toxoplasma Lymphadenitis: Hyperplastic follicle with moth-eaten appearance infiltrated by epithelioid histiocytes (arrow) with adjacent collection of monocytoid B-cells (arrowhead)

2.4 Castleman's disease

Castleman's disease, also known as angiofollicular lymphadenopathy, was first described by Castleman and colleagues in the 1950's. The first studies of Castleman's disease predated the recognition of HIV and it was not until decades later that its connection to HIV and HHV-8 was recognized. We now recognize two distinct histological forms, the hyaline-vascular and plasma variants. The plasma cell variant may further be categorized into unicentric and multicentric forms, the latter characteristically HIV-associated and of poorer prognosis.

The pathogenetic mechanisms leading to the development of Castleman's disease remain debated. Evidence supports HHV-8 as the etiologic agent in at least some cases; in one study, 50% of the unicentric plasma cell variant cases and nearly all cases of the multicentric form were noted to be positive for HHV-8 (Soulier, et al., 1995). Further evidence in support of HIV and HHV-8 viral pathogens as etiologic agents stems from studies indicating a response of HIV associated multicentric Castleman's disease to antiviral agents (Casper, et al., 2004). Other studies have identified the lymphokine interleukin-6 (IL-6) as a potential contributor to the development of the plasma cell variant (Oksenhendler, et al., 2002). Interleukin-6 is a chemokine with a number of roles: it acts as an activator of T and B-cells; it also acts to downregulate pro-inflammatory cytokines by inhibiting interleukin-1 and

tumour necrosis factor α (Jones, et al., 2001). Another study demonstrated that HHV-8 produces an interleukin-6 homologue (Osborne, et al., 1999). These factors together may account for the pathogenesis of the plasma cell variant, especially the multicentric form. The hyaline vascular variant, however, does not demonstrate as strong an association with HHV-8 and is most common in non-HIV patients, some with no evident immune dysregulation; in these cases, the pathogenesis has yet to be elucidated.

The hyaline vascular variant is the most common variant of the unicentric form, representing 80-90% of cases (Ioachim & Medeiros, 2009f). This variant typically presents as enlargement of a lymph node or lymph node group, often in the mediastinal region. This variant is also more common than the plasma cell variant to affect younger patients. Few systemic symptoms are present in the hyaline vascular variant and most symptoms are related to mass effect. The classical histological features demonstrate preservation of overall lymph node architecture with an abundance of follicles (see Figure 7). In these follicles are one or two (sometime conjoined) germinal centres demonstrating prominent sclerosis and paucicellularity. The mantle/marginal cells of these follicles can be seen to form concentric layers (termed “onion-skinning”) around the sclerosed germinal centres. The classic form also demonstrates a hyalinized penetrating vessel passing into the sclerotic germinal centre from the exterior of the follicle (forming so called “lollipop” lesions). Other interfollicular zone changes may be noted including extensive proliferation of small vascular channels (termed “high endothelial venules”). Sclerosis of the lymph node capsule is also a common finding. As noted previously, similar features may also be noted in cases of high-grade HIV-associated lymphadenopathy. The latter usually lack the classical lollipop lesions and the mantle/marginal zone onion-skinning is usually far less prominent. Ancillary tests for HHV-8 may be helpful but typically the diagnosis is made histologically.

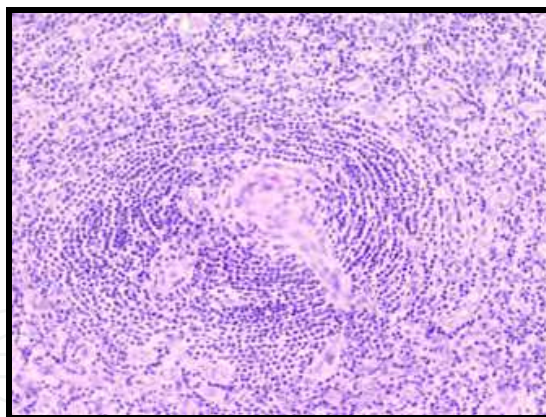


Fig. 7. Hyaline Vascular Variant of Castleman's Disease

The plasma cell variant is the less common of the unicentric forms (Ioachim & Medeiros, 2009f). As in the hyaline vascular variant, the unicentric plasma cell variant may present as an enlarging mass. Patients with this histological variant, however, are more prone to systemic clinical symptoms than those patients with the hyaline vascular variant. Typical symptoms include fevers, night sweats, malaise, and weight loss (these symptoms, in conjunction with enlarged lymph nodes often arouse suspicions of a lymphoproliferative disorder; biopsy for diagnosis is generally recommended). The plasma cell variant demonstrates the similar features of onion skinning and lollipop lesions, though the degree of hyalinization of the germinal centres is markedly reduced relative to the hyaline vascular

variant; this may sometimes make the recognition of the lollipop lesions difficult (see Figure 8). Examination of the interfollicular zones is generally very helpful since it demonstrates numerous sheets of mature plasma cells (these generally stand out prominently since prominent plasma cells are rare in lymph nodes). The prominent vascularity noted in the interfollicular zones of the hyaline vascular variant is typically absent. Some cases may have foci demonstrating features of the hyaline vascular variant; when the histologic features of the plasma cell variant dominate, however, the latter diagnosis is appropriate. A number of studies have demonstrated a histological difference between plasma cell variant affected lymph nodes positive and negative for HHV-8 infection. In HHV-8 negative cases, residual hyperplastic follicles are usually notable; in contrast in HHV-8 positive cases, fewer residual follicles are noted and a more prominent interfollicular space vascular proliferation is present. Also, HHV-8 positive immunoblastic cells are also more prominent in the HHV-8 positive cases.

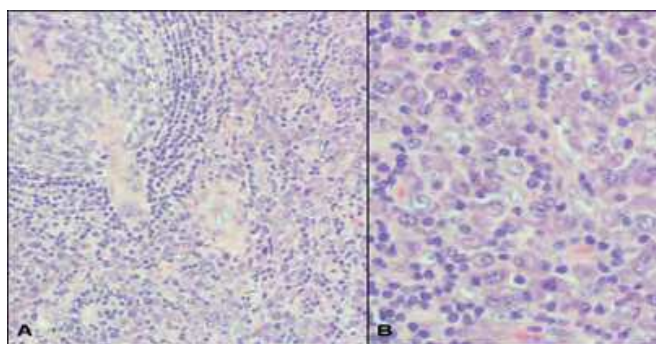


Fig. 8. Plasma Cell Variant of Castleman's Disease: A: Non-hyalinized "lollipop" lesion; B: High-power view demonstrating prominent interfollicular plasma cell infiltrates

Multicentric castleman's disease almost invariably involves multiple lymph nodes most typically demonstrating the histology seen in the unicentric plasma cell variant. The multicentric form has been traditionally under-recognized since its diagnosis requires positive detection of Castleman's disease in multiple locations. This form is also most often present in the context of HIV infection. Patients are nearly always symptomatic, usually presenting with fever, malaise, night sweats and weight loss (the so called B-symptoms) and may also present with hepatosplenomegaly, skin rash, edema and neurologic changes (Ioachim & Medeiros, 2009f). Other laboratory findings include cytopenias, elevated erythrocyte sedimentation rate and elevated C-reactive protein (Ioachim & Medeiros, 2009f). Diagnosis may be confused when a number of the latter clinical signs and symptoms are present, since these are suggestive of the so-called POEMS syndrome (this is a syndrome characterized by the presence of peripheral neuropathy, organomegaly, edema, monoclonal serum paraprotein, and skin changes). POEMS syndrome demonstrates significant diagnostic overlap Castleman's disease, especially the multicentric form. It is felt to be a para-neoplastic syndrome resulting from plasma cell disorders and is felt to have a common pathogenetic link with the plasma cell variant of Castleman's disease via interleukin-6 (Dispenzieri, 2007). The differential diagnosis can be further confused when HIV is considered; the latter, or rather the anti-retroviral drugs used to treat it, can cause peripheral neuropathies, skin changes, edema and other symptoms. In order to avoid diagnostic confusion, specific POEMS criteria have been set forth (Dispenzieri, 2007) and lymphadenopathy should be investigated histopathologically for features of Castleman's disease.

The treatment and prognosis of Castleman's disease depends greatly on both the histologic type as well as the presence or absence of multicentric disease. The hyaline vascular variant is often treated only with excision but adjuvant radiation therapy has been used in cases not amenable to complete resection (Roca, 2009). Some cases of both the hyaline vascular and plasma cell variants may be complicated by recurrence (chiefly the latter more than the former) (Roca, 2009). Cases of unicentric disease with persistent symptoms may also require steroids or chemotherapy (Roca, 2009). The multicentric form often requires aggressive treatment, frequently with chemotherapy (using regimens similar to those used in aggressive lymphomas, often combined with the anti-CD20 antibody rituximab) (Mylona, et al., 2008). There is controversy as to the actual benefit of anti-retroviral therapy; in their systematic review of Multicentric Castleman's disease in HIV, Mylona and colleagues determined that the survival outcomes from Multicentric Castleman's disease with and without antiretroviral therapies were comparable (Mylona, et al., 2008). The caveat to this latter observation is the reduction in incidence of Kaposi's sarcoma in patients on antiretrovirals (Mylona, et al., 2008).

2.5 Polymorphous post-transplant lymphoproliferative disease-like B-cell lymphoproliferative disorder

With the development of immunosuppressive medications permitting greatly improved successes of allogeneic transplant, it was noted that chronically immunosuppressed patients had a uniquely increased risk of a variety of lymphoproliferative disorders. These proliferations, 80% of B-cell lineage (Jacobson & LaCasce, 2010), were termed post-transplant lymphoproliferative disorders to reflect their unique clinicopathologic characteristics. For our purposes, it is interesting to note that, many decades after the concept of iatrogenic immunosuppression was introduced for the purposes of ameliorating transplant outcomes, the HIV/AIDS epidemic revealed an equally dangerous wave of immunosuppression in which many other cases clinically and histologically similar to post-transplant lymphoproliferative disorder were encountered.

The first series of HIV-associated post-transplant lymphoproliferative disorders was reported in 1987. Four infant autopsy cases from patients with HIV (at that time, the human T-lymphotropic virus-III) and a clinical picture compatible with AIDS were included in the report. At autopsy, splenic and liver infiltrates were noted. These infiltrates, as well as other microscopic infiltrates in the lungs, were noted to consist of a polymorphous collection of inflammatory cells with a preponderance of lymphocytes. These lymphocytes were noted to be polyclonal by kappa and lambda immunohistochemistry. Currently, this entity is known as HIV-associated polymorphous lymphoproliferative disorder (Raphaël, et al., 2008).

Though few cases have been reported, some small series have explored the clinical and pathologic characteristics of this entity. HIV-associated polymorphous lymphoproliferative disorder typically presents in adults with low CD4 counts (typically less than 200 cells/ μ L) (Nador, et al., 2003). This entity is identified both within and without lymph nodes and tends most often to present unifocally. In contrast to most HIV-associated lymphomas, HIV-associated polymorphous lymphoproliferative disorder tends to lack a monotonous morphology, often demonstrating a mixture of lymphocytes, plasma cells, immunoblasts and histiocytes (see Figure 9). Of particular interest is the tendency for the majority of cells to bear plasmacytoid morphology. A variable degree of cytologic atypia and even necrosis may also be observed.

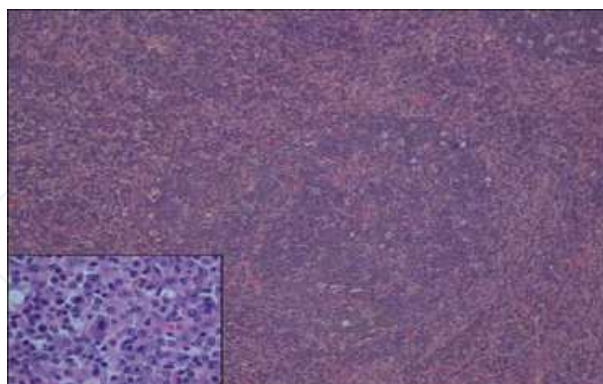


Fig. 9. HIV-associated Polymorphous post-transplant lymphoproliferative disease-like B-cell lymphoproliferative disorder: low-power view demonstrating follicular-lysis; inset: high-power view demonstrating polymorphous infiltrate

The immunophenotypic features of HIV-associated polymorphous lymphoproliferative disorder are also unique. Most cases will demonstrate some form of B-cell phenotype, either in the form of CD20 expression or by presence of immunoglobulin expression (Nador, et al., 2003). Most, but certainly not all, will demonstrate kappa or lambda light-chain restriction and molecular evidence of clonal immunoglobulin gene rearrangement (Nador, et al., 2003). Some will even demonstrate co-expression of CD20 and CD43, considered an aberrant quality most often observed in B-cell lymphomas (Nador, et al., 2003). The largest series to our knowledge failed to demonstrate any cases demonstrating non-germline T-cell receptor rearrangements (Nador, et al., 2003). Most cases also demonstrate EBV co-infection with few also demonstrating HHV-8 co-infection (Nador, et al., 2003).

HIV-associated polymorphous lymphoproliferative disorders also tend to have a relatively better prognosis than other HIV-associated lymphomas, further reinforcing the debatable malignancy of this entity. As noted by Nador and colleagues, many patients will do well, even in the absence of chemotherapy (Nador, et al., 2003). This observation was echoed in one such patient from our institution who responded well by way of optimization of his anti-retroviral therapy. Minimal data is available for the development of optimal treatment regimens, however.

3. HIV-associated lymphomas

HIV patients have a 60-110 fold increased risk of developing a lymphoma relative to the HIV negative population at large (Raphaël, et al., 2008; Lewden, et al., 2005; Whelan & Scadden, 2006). The incidence of HIV-associated lymphomas also increases with duration of disease (Besson, et al., 2001); this is a notable concern in the modern era of antiretrovirals in which the latency period from HIV infection to the development of AIDS is increasing. In recent studies exploring causes of death among HIV/AIDS patients treated with potent antiviral medications, lymphomas were reported as the most common malignancy (Lewden,

et al., 2005; Besson, et al., 2001); this is in contrast to the evident predominance of Kaposi's sarcoma in the pre-anti-retroviral era (Carpenter, et al., 2004). Lymphomas in HIV also demonstrate unique preponderances for extra-nodal sites. Characteristic sites of extra-nodal primary involvement include the gastrointestinal tract and the central nervous system (Thirlwell, et al., 2003).

Epidemiological data suggests that the overall incidence of many lymphomas has fallen since the introduction of anti-retroviral treatment. In particular, Besson et al noted a significant reduction in AIDS-related lymphomas in a retrospective review of lymphoma rates before and after the introduction of anti-retroviral treatment (Besson, et al., 2001). The particularly devastating primary central nervous system lymphoma characteristic of AIDS in the pre-antiretroviral era was found to virtually disappear in Besson et al.'s post-antiretroviral cohort (Besson, et al., 2001). Similar observations were made in other studies, noting both improved survival for HIV-associated lymphoma patients and also an overall decrease in incidence (Wolf, et al., 2005; Biggar, et al., 2005; Sacktor, et al., 2001). (One notable exception is Hodgkin's lymphoma in HIV/AIDS patients which, in pre- and post-antiretroviral cohorts has shown an increased incidence; this phenomenon will be explored in the later section "Hodgkin's Lymphoma.")

3.1 Burkitt's lymphoma

Burkitt's lymphoma is a highly aggressive lymphoma eponimized for Denis Burkitt, a British surgeon working in Africa in the 1950s. In his seminal paper, Burkitt described a peculiar "sarcoma" demonstrating a predilection for the jaws of African children. This lesion, Burkitt noted, was first described in 1938 by Christiansen; it was Burkitt's attention to the geographic preponderance of this lesion in Africa, in addition to his detailed clinicopathologic description of 38 cases, which led the disease to be named after him however (BURKITT, 1958). In the 1960s, by way of the work of O'Connor and Wright, the pathologic nature of Burkitt's lymphoma was further detailed: in particular, O'Connor identified the lesion as a lymphoma and Wright demonstrated that the lesion could be accurately histologically distinguished from other lymphomas (O'CONOR & DAVIES, 1960; WRIGHT, 1963). Later, in the 1970s, the association of EBV infection and Burkitt's lymphoma was elucidated with the first publication of EBV viral culture from lymphoblasts obtained from Burkitt's lymphoma samples (EPSTEIN, et al., 1964).

The WHO currently acknowledges three major classes of Burkitt's lymphoma: the endemic form (referring to the entity described by Burkitt with a predilection for the jaws of African children); the sporadic form (more common to adults than children and without a specific geographical or anatomical predilection); and Burkitt's lymphoma arising in the context of immunocompromise (Leoncini, et al., 2008). The latter category was only recently added in order to highlight the unique clinical and pathogenetic features of this entity relative to the other two. Of note, all three entities share the common morphologic, immunophenotypic and molecular features which have come to define Burkitt's lymphoma; they are chiefly distinguished from one another, therefore, on the basis of clinical features.

The first few cases of HIV/AIDS associated Burkitt's lymphoma were reported in the early 1980s; likely the first case was reported by Doll and List (Doll & List, 1982) with a subsequent small case series reported by Ziegler and colleagues (Ziegler, et al., 1982). These cases all presented in homosexual men with AIDS-like clinical features (though these cases

were documented prior to the definition of AIDS and before the discovery of HIV) and involved both nodal and extra-nodal sites. Interestingly, these cases were etiologically associated with immunosuppression, despite a lack of awareness of HIV; the immunocompromised in these cases was originally thought to be associated with CMV infection or drug use.

More than two decades later, Burkitt's lymphoma has become one of the most common malignancies in patients with HIV/AIDS. According to the WHO, Burkitt's lymphoma accounts for 30% of all HIV-associated lymphomas (Raphaël, et al., 2008); this number has been noted to reach as high as 40% in some series (Spina, et al., 1998). The WHO also notes that in patients with HIV, Burkitt's lymphoma is 1000 times more likely than in patients without concomitant HIV infection (Raphaël, et al., 2008). An HIV positive patient can furthermore expect a 10-20% lifetime risk of Burkitt's lymphoma (Noy, 2010). In contrast to other HIV/AIDS associated lymphomas, Burkitt's lymphoma often presents relatively early on in the course of infection, often before the severe immunocompromise that precedes most HIV-associated lymphomas (Gaidano, et al., 1998). A recent large study also noted an intriguing decrease in the incidence of Burkitt's lymphoma in cases of profoundly low CD4 counts relative to less immunocompromised AIDS patients (Guech-Ongey, et al., 2010). Despite the distinct classification status afforded to HIV-associated Burkitt's lymphoma relative to other non-immunocompromised Burkitt's cases, controversies persist regarding the need for the distinction. In their cohort of African children with Burkitt's lymphoma, Orem and colleagues noted more similarity than difference between HIV positive and negative patients, with the caveat that HIV-positive Burkitt's patients tended to present with less lymphadenopathy and at higher stage than the others (Orem, et al., 2009). This was in keeping with the previous observations of Spina and colleagues noting similar clinicopathologic features amongst their cohort of HIV-positive and negative Burkitt's patients, including comparable disease free survival rates in HIV patients receiving antiretroviral therapy (Spina, et al., 1998). In contrast, epidemiologic data have suggested that Burkitt's lymphoma age-adjusted incidence may be influenced by HIV status (Mbulaiteye, et al., 2010).

HIV-associated Burkitt's lymphoma demonstrates identical classic histologic features to the other classes of Burkitt's lymphomas (see Figure 10). Whether nodal or extra-nodal, the classic Burkitt's histomorphology is a diffuse effacement of normal tissue architecture by sheets of cohesive intermediately sized ($\sim 12 \mu\text{m}$) cells with minimal basophilic cytoplasm and central round to oval nuclei usually with multiple distinct nucleoli. These cells are interspersed by larger macrophages (bearing characteristic reniform or kidney-bean shaped nuclei) with enlarged pale cytoplasm often containing engulfed cellular debris; these interspersed "tangible-body" macrophages produced the characteristic "starry-sky" appearance. The macroscopic corollary to this histomorphology is the typical fish-flesh tan white irregular tumour mass. As in most lymphomas, however, there are no macroscopic features characteristic of given specific entity. One unique histopathological feature observed more frequently in HIV-associated Burkitt's lymphomas is Burkitt's lymphoma with a lymphoblastic morphology. In these cases, the tumour cells are notable for their eccentric nuclei, prominent central large nucleoli, and often contain cytoplasmic eosinophilic globules representing immunoglobulin deposits (Leoncini, et al., 2008). These features are observed in up to two-thirds of cases according to the WHO (Leoncini, et al., 2008).

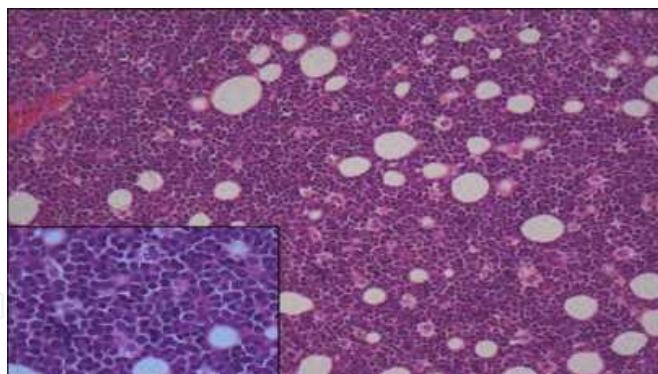


Fig. 10. HIV-associated Burkitt's lymphoma: diffuse "starry-sky" appearance of intermediate-sized cells; inset: high-power of Burkitt cells with scattered macrophages (containing tingible bodies or engulfed debris). The optically clear spaces are fat droplets (this biopsy was taken from a mesenteric lymph node).

Similar immunophenotypic features to the endemic and sporadic Burkitt's forms are observed in HIV-associated Burkitt's lymphoma. The tumour cells are B-cells, demonstrating a variety of possible B-cell antigens including CD19, CD20 and CD22. Burkitt's lymphomas of all types demonstrate characteristic positivity for BCL-6 and CD10 (both immunomarkers of germinal centre phenotype). Unlike diffuse large B-cell lymphomas of germinal centre origin, furthermore, Burkitt's cells are only weakly positive (and often completely negative) for BCL2-. The Ki-67 proliferation immunostain is also characteristically positive nearly in 100% of Burkitt's cells (indicating an extremely high cell proliferation index). To aid in distinguishing Burkitt's lymphomas from precursor B-cell neoplasms (such as pre-B ALL and others, which may have overlapping morphologic features with Burkitt's lymphoma), the TdT stain (a stain indicating a primitive phenotype) is characteristically negative in Burkitt's lymphoma.

The molecular and cytogenetic features in Burkitt's lymphomas (while not entirely specific) are also characteristic. Translocation of the proto-oncogenic MYC region (which encodes a highly conserved cellular transcription factor) to the transcriptionally active IG heavy chain gene, t(8:14), is the most frequently encountered cytogenetic mutation in Burkitt's lymphoma. As previously noted, this translocation is not specific; MYC:IGH translocations have been observed in many diffuse large B-cell lymphomas (often themselves demonstrating high cellular proliferation indices) as well as other malignancies. Using sensitive molecular techniques, EBV virus sequences are observed in 50-70% of HIV-associated Burkitt's lymphomas. This is in contrast to the endemic form, which are virtually all found to contain EBV sequences, as well as the sporadic form which only rarely are found to harbor EBV co-infection.

Chemotherapy for HIV-associated Burkitt's lymphoma has evolved as the HIV/AIDS epidemic has progressed. Early on, when most HIV-associated Burkitt's patients presented having previously been diagnosed with AIDS, the chemotherapy treatment regimen applied to Burkitt's lymphomas focused on minimizing iatrogenic immunodeficiency. In these cases, the rapid progression characteristic of Burkitt's lymphoma was unfortunately allowed to sway the balance in favor of early mortality from lymphoma (Levine, et al., 2000). Later, with the introduction of anti-retrovirals and the accompanying benefit of improved immunostatus, chemotherapy has evolved toward similar regimens used in the endemic and sporadic Burkitt's lymphomas. Modern HIV-associated Burkitt's lymphomas seem to be

treated most commonly with combinations of cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate with or without rituximab. Use of the latter anti-CD20 antibody (used frequently to augment the chemotherapeutic response in numerous B-cell lymphomas) remains controversial, in particular relative to the potential immunocompromise that the latter may induce (Levine, et al., 2000); studies exploring optimal treatment regimens in HIV-associated Burkitt's lymphoma are limited given the relative rarity of cases (Noy, 2010).

3.2 Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma is a heterogeneous category of lymphomas typified by an aggressive clinical aspect, a large cell histomorphology (i.e. neoplastic cells greater than two-times the normal lymphocyte) and B-cell immunophenotype. This category has been the subject of a multitude of classifications over the course of the previous half-century. Currently, the most commonly used WHO classification acknowledges a number of possible "large B-cell" entities, of which diffuse large B-cell lymphoma not otherwise specified is probably the most common. Other diffuse large B-cell lymphoma subtypes (other than the NOS subtype) include rare entities such as primary diffuse large B-cell lymphoma of the central nervous system (an entity characteristically found in HIV/AIDS patients). The current WHO classification schema also allows for molecular and immunohistochemical subgroups in addition to morphologic classes; some of these subgroups have gained notoriety for their distinct therapeutic responses. While a complete description of diffuse large B-cell lymphoma is beyond the scope of this chapter, we will focus heretofore on the specific distinguishing features of HIV/AIDS related diffuse large B-cell lymphomas.

While the most recent edition of the WHO Classification of Hematolymphoid tumours suggests that diffuse large B-cell lymphoma in HIV is second to Burkitt's lymphoma as the most common lymphoma encountered in HIV/AIDS, newer studies have suggested that diffuse large B-cell lymphoma may in fact be more common (Raphaël, et al., 2008; Mantina, et al., 2010; Gucalp & Noy, 2010). There also appear to have been changes in the incidence of diffuse large B-cell lymphoma over the course of the HIV/AIDS epidemic: at the outset in the early to mid 1980s, diffuse large cell lymphoma was very infrequently diagnosed; a marked increase in this diagnosis was seen toward the mid to late 1990s, however (Levine, et al., 2000). These latter results may relate to the observation that diffuse large B-cell lymphoma in HIV/AIDS appears to afflict patients in the setting of long-standing infection with concomitantly low CD4 counts, in contrast to other HIV-associated lymphomas (Raphaël, et al., 2008). As with most HIV-associated lymphomas, diffuse large B-cell lymphoma can often be found in extra-nodal sites; this entity, furthermore, is commonly associated with central nervous system involvement (Agarwal, et al., 2009); furthermore, while overall numbers of central nervous system lymphomas in HIV/AIDS have dropped since the onset of the antiretroviral era, diffuse large-B-cell lymphoma currently seems to be the most frequent offender in the central nervous system (Agarwal, et al., 2009). Important clinical prognostic factors have been noted as pertaining to HIV-associated diffuse large B-cell lymphoma: Vaccher and colleagues noted the importance of CD4 counts, in addition to the other factors incorporated into the international prognostic index (namely age, advanced stage disease, elevated levels of serum lactate dehydrogenase as an indicator of rapid neoplastic cell turnover, extranodal spread and functional performance status) (Vaccher, et al., 1996).

The macroscopic and microscopic features of diffuse large B-cell lymphoma in HIV/AIDS are comparable to those seen in the non-HIV population. Diffuse large B-cell lymphoma generally causes uniform enlargement of a node or group of nodes, often with a characteristic “fish flesh” macroscopic cut surface. On microscopic exam, sheets of large cells typically efface the normal lymph node architecture (these cells are often greater than 12 μm in maximal dimension) (see Figure 11). These neoplastic cells will demonstrate variable cytoplasm, variably sized nuclei, often with clumping or vesiculated chromatin and variable nucleoli. Areas of necrosis may be present, either as individual cells or clusters of cells. Mitotic figures are common and markedly atypical mitoses may be frequent. Often, however, it is difficult to ascribe any specific morphologic features other than diffuse architecture and large cell size to diffuse large B-cell lymphomas. When involving extra-nodal sites, the same diffuse pattern of effaced normal tissue architecture can also be seen, sometimes producing an obvious mass suspicious for a metastatic lesion. The predominant cell type will be the large neoplastic B-cell with variable numbers of intervening fibroblasts and inflammatory cells, sometimes producing a desmoplastic response. In these circumstances, it may be necessary to exclude a malignancy of origin other than the hematolymphoid system such as a carcinoma; these differential diagnoses are usually quickly excluded using a panel of immunohistochemical stains.

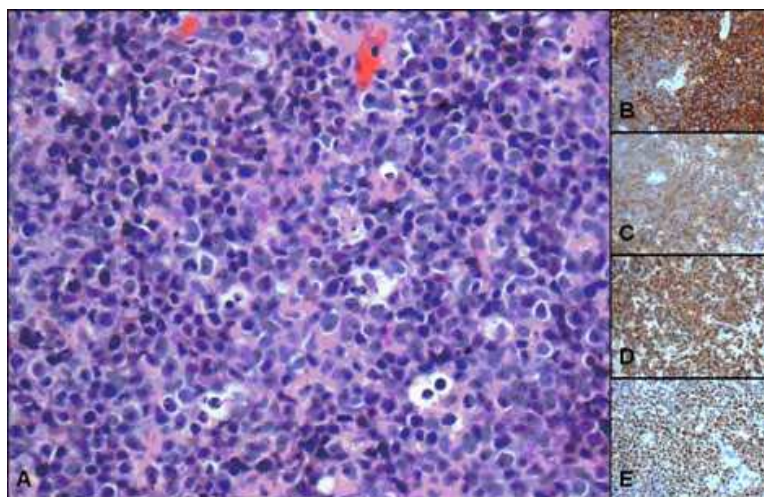


Fig. 11. Diffuse Large B-cell Lymphoma: A: Diffuse pattern of infiltration by pleomorphic large cells; B: CD20 immunostain confirming B-cell lineage; C: CD10 immunostain suggesting germinal centre phenotype; D: BCL2 immunostain strongly and diffusely positive, as is consistent with a B-cell neoplasm; E: BCL6 immunostain suggesting germinal centre phenotype

Immunophenotyping, either by immunohistochemistry or flow cytometry (or ideally both) is required. Diffuse large B-cell lymphomas must, by definition, express one or more of the B-cell markers (e.g. CD19, CD20, CD79a, PAX5, etc.). Diffuse large B-cell lymphomas will frequently be positive for BCL2, though poorly differentiated forms may show only focal or patchy staining. Subsequent stratification of the lesion into “germinal centre” or “non-germinal centre” types is then recommended; the former will generally demonstrate expression of either BCL6 or CD10 (both germinal centre markers) whereas the latter are typically both BCL6 and CD10 negative and may also be MUM-1 positive. This form of stratification can be helpful in directing treatment. More specifically, it has been

demonstrated by means of both gene expression profiling (and the surrogate use of immunophenotyping) that diffuse large B-cell lymphomas with a germinal centre phenotype/gene expression profile have a better prognosis (Chang, et al., 2004). Additional staining with Ki67 to demonstrate neoplastic cell proliferation index is also recommended. Diffuse large B-cell lymphomas typically demonstrate a Ki67 proliferation index less than 60-70%; higher indices may suggest a more aggressive entity. High Ki67 index in combination with BCL6 positivity and weak BCL2 staining raises the possibility of a lymphoma intermediate between a diffuse large B-cell and Burkitt's lymphoma. Staining with CD38 or CD138 is also helpful in ruling out a potentially highly aggressive plasmablastic phenotype. Studies have also demonstrated a negative association between HIV-associated diffuse large B-cell lymphoma progression free-survival as well as overall survival and co-infection with EBV (Park, et al., 2007). In our experience however studies exploring the contribution of EBV to the specific pathogenesis of HIV-associated diffuse large B-cell lymphoma are lacking.

The treatment of HIV-associated diffuse large B-cell lymphoma has traditionally been the same as those cases in the HIV-negative population, namely with a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. This approach has been met with controversy however as a variety of studies using more traditionally "aggressive" chemotherapy regimens, regimens with concomitant rituximab therapy and even regimens incorporating a reduction in antiretroviral therapy have shown promising results in their own rights. Navaro and colleagues demonstrated that patients with HIV-associated diffuse large B-cell lymphoma treated with routine chemotherapy but with additional antiretrovirals demonstrated no significant differences in clinical and laboratory parameters relative to HIV-negative cases of diffuse large B-cell lymphoma (with the caveat that HIV cases were more likely to present with B-symptoms) (Navarro, et al., 2005). Ezzat and colleagues recently indicated that a combination of rituximab with standard chemotherapy and antiretrovirals improved the survival of HIV patients with diffuse large B-cell lymphoma; this study also incorporated epidemiologic data from before and after the antiretroviral era to elucidate a difference in survivability (Ezzat, et al., 2007). In a recent study, Dunleavy and colleagues performed a trial of chemotherapy using short-course etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab after having halted antiretroviral therapy for the duration of the chemotherapy (with subsequent restart after completion) (Dunleavy, et al., 2010). In their cohort of 33 authors reported a progression free survival and overall survival of 84% and 68% respectively after a median follow-up of 5 years; 10 deaths were reported with 5 attributed to HIV (3 due to purported previous persistent mycobacterial infection) (Dunleavy, et al., 2010). Head-to-head outcome comparisons, with and without antiretroviral therapy (with particular attention to the long-term effects of short-term iatrogenic HIV-related immunosuppression) have yet to be reported.

3.3 Hodgkin's lymphoma

Thomas Hodgkin, a British physician, first described this strange disease in 1832. Over the course of his work as a pathologist working in Guy's Hospital's anatomical library in London, he noted a number of patients at autopsy with bizarre lymphadenopathy (Mukherhee, 2010). These patients were frequently young and male and died rapidly after a brief fever-stricken illness (Mukherhee, 2010). Having received a less than stellar response to

his newly reported disease, he abandoned any further academic exploration of this peculiar lymphadenopathy (and, furthermore, abandoned his life's work soon after) (Mukherjee, 2010). The disease was later further characterized by Samuel Wilks, who coined the eponym "Hodgkin disease" (Stone, 2010). It was not until decades after the first descriptions of Hodgkin's lymphoma that the microscopic feature of the disease – the Reed-Sternberg cell – was discovered by Carl Sternberg of Germany (followed by Dorothy Reed Mendenhall) (Mukherjee, 2010). The current state of the art suggests that the Reed-Sternberg cell is a germinal centre B-cells, as evidenced by the detection of immunoglobulin gene rearrangements; these cells, it is thought, demonstrate abortive differentiation and therefore do not proceed to produce immunoglobulin (Ioachim & Medeiros, 2009g). Reed-Sternberg cells have also been found to produce a number of pro-inflammatory cytokines; these, it is believed, contribute to the spectrum of "by-stander" non-neoplastic inflammatory cells which make up the majority of the cellular constituents in Hodgkin's lymphomas (Ioachim & Medeiros, 2009g).

One of the earliest series of Hodgkin's lymphomas in a cohort of probable AIDS patients was reported by Ioachim and colleagues (Ioachim, et al., 1985). In this series, only 3 of 21 patients in this study were diagnosed with Hodgkin's lymphoma (Ioachim, et al., 1985). Since these first cases were diagnosed, many more cases of Hodgkin's lymphoma in HIV/AIDS patients have been identified and modern epidemiologic data suggests that HIV-positive patients have at least a 2-10-fold increased risk of developing Hodgkin's lymphoma relative to the HIV-negative population (Carbone, et al., 2009; Sissolak, et al., 2010). Despite this increase, Hodgkin's lymphoma is infrequent relative to diffuse large B-cell lymphoma and Burkitt's lymphoma (the latter two accounting for at least 60% of HIV-associated lymphomas) (Raphaël, et al., 2008).

The pathobiology of HIV-associated Hodgkin's lymphoma serves to demonstrate the unique environment of immunocompromise that HIV infection causes, even in patients with relatively high CD4 counts or on antiretroviral regimens. More specifically, epidemiologists have observed not only an increased incidence of Hodgkin's lymphoma with severe AIDS related immunocompromise but also a paradoxical increased incidence of Hodgkin's lymphoma in HIV-positive patients without AIDS after the introduction of antiretrovirals. In their large cohort study for instance, Biggar and colleagues noted that there was an increased risk of development of Hodgkin's lymphoma in HIV-positive patients with only moderate immunosuppression (Biggar, et al., 2006). Experts have offered hypotheses to explain these unique observations. It is thought that the Reed-Sternberg cell of Hodgkin's lymphoma relies upon intact immunomodulatory signals from T-cells. With T-cell numbers sufficiently stabilized in HIV-infection treated with antiretrovirals—but in an immunologically active environment caused by chronic HIV infection with upregulated inflammatory cytokine production—Reed-Sternberg cells may be inadvertently stimulated and Hodgkin's lymphoma may develop (Sissolak, et al., 2010). Despite the relatively low risk of Hodgkin's lymphoma in HIV-infection, therefore, it is incumbent that HIV patients on anti-retroviral therapy be carefully surveilled for the development of potential Hodgkin's lymphoma.

As noted previously, HIV/AIDS patients are at extremely high risk for lymphadenopathy; when these patients present with symptoms of fever, chills, night sweats and weight loss, furthermore, a long differential must be considered—with lymphomas high on the list. Most HIV-associated Hodgkin's cases will present with lymphadenopathy, typically in a cervical

distribution (Sissolak, et al., 2010). Perhaps due to the unique pathobiology of HIV-associated Hodgkin's lymphomas, many HIV-associated Hodgkin patients present at a relatively young age (in addition to possibly presenting earlier on in the course of infection). Many of these patients will also present with advanced stage disease relative to the HIV-negative population (Sissolak, et al., 2010). High clinical suspicion warrants lymph node biopsy, which is required for accurate diagnosis. Most authorities also recommend an initial staging bone marrow biopsy given that 40-60% of cases present with bone marrow involvement (Sissolak, et al., 2010).

While a complete discussion of the possible histological subtypes of Hodgkin's lymphoma is beyond the scope of this chapter, it is warranted to discuss the histopathologic features of the most common form, namely the mixed cellularity subtype of classical Hodgkin's lymphoma. As in all the classical Hodgkin lymphoma subtypes, mixed cellularity subtype is characterized by the presence of scattered Reed-Sternberg cells (see Figure 12). These have a characteristic morphology: the cells are large (~15-40 μm) with abundant lightly basophilic cytoplasm and they have a central bilobed nucleus, each lobe having a central large inclusion-like eosinophilic nucleolus. More importantly relative to the other forms of Hodgkin's lymphoma, the mixed cellularity subtype demonstrates a diffuse effacement of normal lymph node architecture by a mixed population of inflammatory cells consisting of variable number of eosinophils, small lymphocytes, histiocytes, plasma cells and neutrophils. Also, this subtype lacks the characteristic fibrous bands of sclerosis that typify the nodular sclerosing subtype.

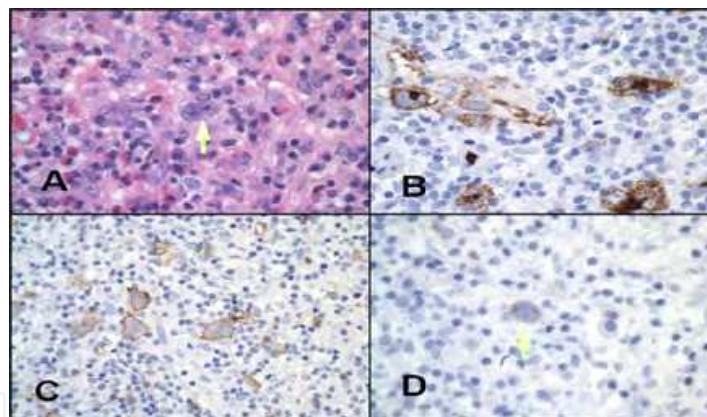


Fig. 12. Hodgkin's lymphoma: A: High-power view demonstrating Reed-Sternberg cell (arrow); B & C: CD15 and CD30 immunostains, respectively; D: EBV stain positive in Reed-Sternberg cell (arrow)

The immunophenotype is also characteristic of mixed cellularity Hodgkin's lymphoma. In particular, the Reed-Sternberg cell is characteristically positive for CD15 (a membrane protein involved in cell adhesion present on a number of hematolymphoid lineage cells) and CD30 (a marker of cell activation). Reed-Sternberg cells seen in Classical Hodgkin's lymphoma are also characteristically negative for the standard B-cell markers CD19 and CD20. Proof of the B-cell nature of Reed-Sternberg cells, however, may be derived from their frequent positive staining for PAX5, a B-cell transcription factor. Most cases of HIV-associated Hodgkin's lymphoma are also positive for EBV co-infection, often identifiable using the immunostain for the EBV-latent membrane protein antigen. This is in contrast to notably fewer cases of EBV positivity outside of HIV-infection (Carbone, et al., 2009).

Treatment approaches for HIV-associated Hodgkin's lymphomas are often similar to those used in non-HIV patients. Limited disease may be treated by a combination of adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy, often with adjuvant radiation therapy to the involved area (if restricted to an amenable nodal region). Advanced cases are not typically amenable to radiation therapy (Sissolak, et al., 2010). Advanced cases may also be considered for bone marrow transplant. The use of rituximab as an adjuvant biological agent may also be considered; those cases demonstrating a large complement of CD20 cells (whether Reed-Sternberg or not) may respond (Sissolak, et al., 2010). Notably, studies looking at the appropriateness of traditional treatments for Hodgkin's disease in the context of HIV-positivity remain ongoing and optimal regimens may yet be discovered. Despite the potential etiologic impact of antiretroviral therapy in cases of HIV-associated Hodgkin's lymphoma, its use is still warranted given the reduction in risk of opportunistic infection (and other HIV-associated malignancies) in order that optimal chemotherapeutic regimens be instituted (Carbone, et al., 2009).

3.4 Plasmablastic lymphoma

Plasmablastic lymphoma is a highly aggressive B-cell lymphoma characterized histologically by a diffuse proliferation of large cells with plasmacytoid features. This entity was only recently recognized and has been shown to occur not only in HIV/AIDS patients but in other immunodeficient individuals, in particular in patients chronically immunosuppressed from solid organ transplants (Rafaniello Raviele, et al., 2009). In its most recent editions, probably owing to its unique clinicopathologic features, plasmablastic lymphoma was classified as an entity unto itself (Raphaël, et al., 2008). Many authors (and other previous classifications) consider plasmablastic lymphoma to be a variant of diffuse large B-cell lymphoma; Chang and colleagues, for example, demonstrated that plasmablastic lymphoma shows a number of overlapping genomic lesions with diffuse large B-cell lymphoma by comparative genomic hybridization techniques (Chang, et al., 2009). Nonetheless, from a treatment and prognostic perspective, plasmablastic lymphoma appears to differ from diffuse large B-cell lymphoma and its classification as a distinct entity is reasonable (Montes-Moreno, et al., 2010).

A number of reports have noted plasmablastic lymphoma arising from transformation from various low-grade lymphomas. Ouansafi and colleagues demonstrated evolution of a follicular lymphoma to plasmablastic lymphoma by means of sequence comparison of the immunoglobulin heavy chain gene rearrangements in both tumours (Ouansafi, et al., 2010). Another report of a plasmablastic lymphoma was described arising in concert with a monoclonal population of plasma cells suggesting potential transformation of the former from the latter (Qing, et al., 2011). Even more intriguing is the case report of concurrent plasmablastic lymphoma and classical Hodgkin's lymphoma arising in a patient with relative immunosuppression from history of chronic lymphocytic leukemia/lymphoma; this case was notably EBV positive (Foo, et al., 2010). The grand majority of cases, however, appear not to represent transformation from a lower grade lesion.

Estimates of the incidence of plasmablastic lymphoma are based on the few reported cases and small series; a recent review of the literature reported approximately 180 cases of plasmablastic lymphoma (Rafaniello Raviele, et al., 2009). While this number is undoubtedly an underestimate (since at least one other unreported case from our own institution in the previous 5 years was encountered), it speaks to the rarity of this entity. The majority of cases

are encountered in the HIV/AIDS setting and many, though not all, of the remaining cases are associated with transplant related immunosuppression (Rafaniello Raviele, et al., 2009). The majority of cases, furthermore, were found to be EBV positive (Rafaniello Raviele, et al., 2009). While most cases of plasmablastic lymphoma have demonstrated an odd predilection for the oral cavity, many reports have noted a number of broad ranging almost invariably extranodal sites. A number of reported cases have demonstrated involvement of the central nervous system (Ustun, et al., 2009); involvement of the gastrointestinal tract has also been reported (Rafaniello Raviele, et al., 2009); there are even unique reports of plasmablastic lymphoma involving the penis and vulva (Sun, et al., 2011; Chabay, et al., 2009). Studies have furthermore demonstrated some intriguing clinicopathological factors pertaining to the primary site of plasmablastic lymphomas. Hanra and colleagues for instance, in comparing oral and extraoral cases of plasmablastic lymphoma, demonstrated a distinct survival difference favouring the oral forms (Hansra, et al., 2010). Plasmablastic lymphoma has also demonstrated different clinicopathologic features in the HIV/AIDS population relative to other immunosuppressed populations. Castillo et al. demonstrated that HIV positive cases of plasmablastic lymphoma tend to occur in younger, typically male patients with a notable preponderance for the oral cavity (Castillo, et al., 2010). Castillo et al. also demonstrated a distinct survival difference between the HIV positive and negative cases of plasmablastic lymphoma, favouring those from HIV positive patients (Castillo, et al., 2010). Regardless of the primary site or of HIV status, plasmablastic lymphoma demonstrates consistent histological characteristics (see Figure 13). Plasmablastic lymphoma shows a monomorphic morphology comprised of large cells with abundant often-eosinophilic cytoplasm and eccentrically located hyperchromatic nucleus often containing one or more nucleoli. The tumoural cells demonstrate a uniformly diffuse architecture, often with a number of interspersed apoptotic bodies and mitotic figures. Intermingled macrophages or smaller plasma cells may be noted; in some cases in which the latter are particularly abundant, the plasmablastic lymphoma with “plasmacytic differentiation” may be applied.

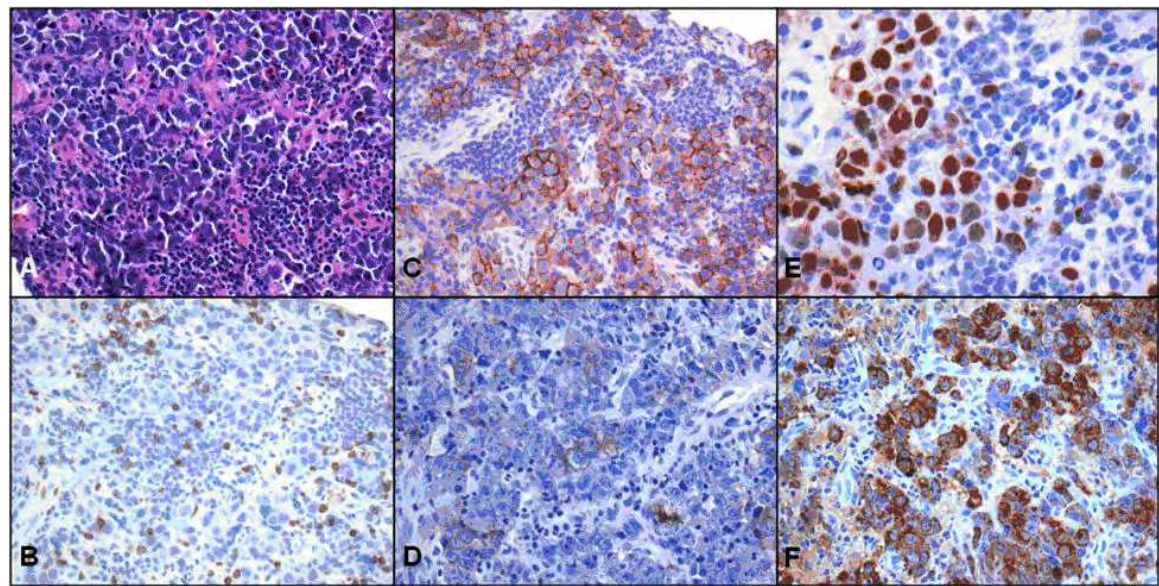


Fig. 13. A: Plasmablastic Lymphoma. B: LCA positive in reactive small T lymphocytes and negative in large neoplastic cells. C: CD138 positive in large neoplastic cells. D: EMA positive in large neoplastic cells. E: MUM-1 positive in large neoplastic cells. F: Lambda light chain positive in large neoplastic cells

In order to distinguish plasmablastic lymphoma from other diffuse lymphomas (and to rule out a simple but more common diffuse large B-cell lymphoma), immunophenotyping is crucial. In plasmablastic lymphoma, in addition to demonstrating minimal positivity for leukocyte common antigen (CD45), CD20 and CD79a, the tumoural cells are invariably positive for CD138; these features are of striking resemblance to the normal immunophenotype of plasma cells. Other post germinal centre markers such as MUM-1 and CD38 are also often positive. Some additional pathologic features that may potentially confuse the diagnosis include positivity for CD3, CD4 and CD56, all of which have been reported to be positive in some cases of plasmablastic lymphoma (Rafaniello Raviele, et al., 2009). Given the primary immunophenotypic differential diagnosis of a plasma cell malignancy (i.e. based on the combination of CD38, CD138, MUM-1 positivity with CD45, CD20 and CD79a negativity), the plasmablastic moniker is assigned given the histomorphology in combination with the absence of clinical features in support of a plasma cell dyscrasia. Plasma cell neoplasms also do not demonstrate positivity for EBV. Other possible differential diagnoses include carcinomas and melanomas, which can be ruled out by the way of an immunohistochemical panel of cytokeratins and melanoma markers. Goedhals et al. explored the electron microscopic features of ten plasmablastic lymphomas and found that 90% of cases demonstrated the consistent plasma cell features of eccentric nuclei with concentric perinuclear endoplasmic reticulum (Goedhals, et al., 2006).

The outcomes in cases of plasmablastic lymphoma are usually poor. In their in depth review, Raviele and colleagues noted disease related deaths in 59.6% of cases of oral-type plasmablastic lymphoma at an average of 10.4 months post-diagnosis as compared to 58.6% at an average of 6.2 months for the extra-oral type (Rafaniello Raviele, et al., 2009). Raviele and colleagues also noted a survival advantage to the use of highly active anti-retrovirals (Rafaniello Raviele, et al., 2009). Given the rarity of plasmablastic lymphoma, there are few studies addressing optimal chemotherapeutics; one large series of published cases noted that the most common chemotherapeutic regimen in plasmablastic lymphoma cases is CHOP (Castillo, et al., 2010). Other more intensive regimens have also been used (e.g. the CODOX-M, often used for HIV-associated Burkitt's lymphoma cases). Two case reports have noted responses to chemotherapy with bortezomib (Bibas, et al., 2010; Bose, et al., 2009); trials looking at optimal treatment regimens are lacking, however.

3.5 Primary effusion/body cavity lymphoma

Primary effusion/body cavity lymphoma is a rare aggressive lymphoma with a peculiar propensity for the serous cavities of the body, namely the peritoneum, pleura and pericardium. These lymphomas are also not primarily associated with a solid component though they may later develop nearby solid tumours and may extend to involve lymph nodes. Primary effusion lymphoma is characteristically a disease of HIV/AIDS patients, though rare cases have been reported in HIV negative patients. Primary effusion lymphomas are also almost invariably positive for HHV-8 and may show co-infection with EBV.

Knowles and colleagues diagnosed the first cases of primary effusion lymphoma in 1989. Three cases were originally reported, all occurring in homosexual HIV-positive males with clinical features of AIDS. Each case presented with a body cavity effusion containing cytologically malignant cells and quickly died. The effusions were all noted to contain populations of large cells with generous eosinophilic to amphophilic cytoplasm,

anisonucleosis and clumped chromatin. Several multinucleated giant cells and abnormal mitotic figures were also noted. The malignant effusion cells were positive for CD45, indicating a hematolymphoid origin, but were negative for B- and T-cell markers as well as a variety of myelomonocytic markers. Subsequent restriction fragment analysis of the DNA obtained from the neoplastic cells revealed immunoglobulin gene rearrangements, suggesting a B-cell origin. The three original cases were also found to be EBV positive; these cases were not tested for HHV-8 positivity in the original publication.

Since the first reported cases, several more have been reported; this entity is nonetheless very rare relative to the other HIV/AIDS-associated lymphomas and accounts for approximately 3% (Boulanger, et al., 2005). The WHO notes that this lymphoma is most commonly encountered in HIV patients, but that some cases have been encountered in HIV-seronegative patients and even within the context of immunocompetence (Raphaël, et al., 2008). Primary effusion/body cavity lymphoma cells are almost invariably HHV-8 positive. This is of particular interest in those cases encountered in immunocompetent patients since, as a result of the high prevalence of HHV-8 infection, there is a notably increased risk in peoples (especially males) of the Mediterranean (Said & Cesarman, 2008).

In one of the largest and more recent series of primary effusion/body cavity lymphomas, Boulanger and colleagues reported a wide age range (33-78 years) with only one female of 28 cases (Boulanger, et al., 2005). While the majority of cases were noted to originate in patients from populations with low HHV-8 seroprevalence, Boulanger et al. did note that a substantial number (38%) of patients originated from geographic areas with seroprevalence higher than 5% (Boulanger, et al., 2005). Most cases were noted to present with effusions, predominantly pleural (Boulanger, et al., 2005). Primary effusion/body cavity lymphoma typically remains restricted to the original presenting body cavity (Carbone, et al., 2010). Involved serosal surfaces are often diffusely thickened (Carbone, et al., 2010). Interestingly, 42% of Boulanger et al.'s cases presented with additional extra-cavitary lesions. It has also been documented that many primary effusion/body cavity lymphoma patients have preceding or complicating Kaposi's sarcoma (Boulanger, et al., 2005). Most patients are also profoundly immunosuppressed; in the HIV-positive cohort of Boulanger et al. for example, the average CD4 count was below 200 cells/ μ L (Boulanger, et al., 2005).

Diagnosis of primary effusion/body cavity lymphoma is typically made on cytologic examination of effusion contents (see Figure 14). As Carbone and colleagues note, the malignant cells of primary effusion/body cavity lymphoma have an appearance resembling a combination of immunoblastic and anaplastic features (Carbone, et al., 2010). A variable degree of plasma cell differentiation may also be noted; a background of pronounced cellular debris and numerous mitoses often accompanies these features. A mixture of reactive inflammatory cells as well as admixed mesothelial cells will also be noted. These morphological features result in a differential diagnosis that may include Burkitt's lymphoma (which may also involve body cavities); as with most lymphomas, however, the immunophenotype will typically indicate the diagnosis. The effusive nature of this lymphoma is highly conducive to flow cytometry. Primary effusion/body cavity lymphoma, as noted previously, demonstrates CD45, CD138 and MUM-1 positivity in the context of dim or negative immunostaining for B-cell markers. This immunohistochemical pattern reflects the plasmablastic phenotype of primary effusion/body cavity lymphoma. Interestingly, a few cases have noted aberrant T-cell antigen expression (Carbone, et al., 2010). The diagnostic clincher, however, is the demonstration of HHV-8 positivity in the

tumour cells; this can usually be accomplished reliably with immunohistochemical staining for the HHV-8 latency-associated nuclear antigen.

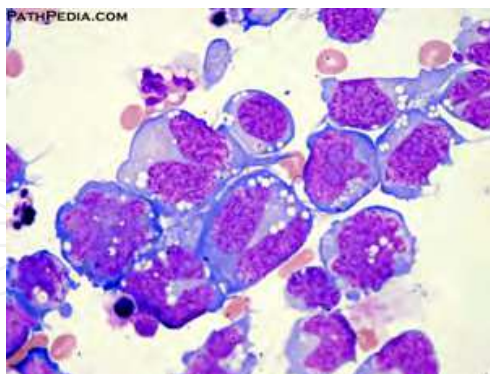


Fig. 14. Primary Effusion Lymphoma: Large cells with clear-coloured cytoplasmic bodies (vesicles containing immunoglobulin); note the eccentrically placed nuclei in a number of the cells, others with large atypical lobated nuclei and prominent nucleoli. Compare the size difference of the neoplastic cells with the small normally sized (dark stained) round lymphocyte nucleus at the bottom left.

Despite its rarity, a number of studies have explored the molecular pathogenesis of primary effusion/body cavity lymphoma. Gene expression profile studies in primary effusion/body cavity lymphoma have demonstrated a unique profile relative to other aggressive lymphomas; these results tend to substantiate the distinct clinicopathologic distinction of primary effusion/body cavity lymphomas from other lymphomas (Ueda, et al., 2010). Other studies have demonstrated a number of complex cytogenetic abnormalities as well as a reduction in tumour-suppressor gene expression in primary effusion/body cavity lymphoma (Luan, et al., 2010; O'Hara, et al., 2009); these features may further contribute to the aggressiveness of this lesion.

Most published cases appear to be treated with CHOP or derivations thereof. Fewer cases have been treated with a more "aggressive" approach in line with regimens such as doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone. Some reported cases were also tried on an antiviral regimen (e.g. interferon alpha and cidofovir); the efficacy of these drugs in this context is uncertain, however. Unfortunately, regardless of the chemotherapy regimen, outcomes are poor. In Boulanger and colleagues' cohort, for example, only 14 of 28 patients received clinical remission and only 32% were alive after a median follow-up of 3.2 years (Boulanger, et al., 2005). Most patients who relapse, furthermore, will die of disease (Boulanger, et al., 2005). As in other HIV-associated lymphomas, prognosis appears to be improved with the early incorporation of anti-retroviral medications (Boulanger, et al., 2005; Carbone, et al., 2010).

3.6 T-cell lymphomas

T-cell lymphomas occurring in HIV/AIDS are substantially rarer than B-cell lymphomas. In their large cohort study of 302,834 AIDS patients, Biggar and colleagues noted that only 1.4% of non-hodgkin's lymphomas were of T-cell phenotype (Biggar, et al., 2001). Nonetheless, considering the extreme rarity of T-cell lymphomas in general, Biggar and colleagues estimated a relative risk of 15 of a T-cell lymphoma in the HIV positive population relative to the HIV negative population (Biggar, et al., 2001).

The first documented HIV positive T-cell lymphoma was noted in 1988 by Nasr and colleagues (Nasr, et al., 1988). This case consisted of a large cell lymphoma demonstrating loss of CD3 but with preservation of CD2 and CD4 immunoreactivity. Although CD30 and ALK-1 immunoreactivity were not reported in this case, the reported morphologic features seem most in keeping with anaplastic large cell lymphoma. The earliest reported T-cell lymphoma in a patient with suspected AIDS, however, predated Nasr and colleagues' case by four years; this case was reported in Japan in a patient with AIDS-defining clinical characteristics but co-infected by human t-cell lymphoma/leukemia virus-1 (Kobayashi, et al., 1984).

The most common T-cell lymphoma encountered in HIV-positive patients appears to be peripheral T-cell lymphoma, unspecified (Biggar, et al., 2001; Arzoo, et al., 2004). Several cases of anaplastic large cell lymphoma, NK/T-cell lymphoma and angioimmunoblastic T-cell lymphoma have also been reported, however (Biggar, et al., 2001; Arzoo, et al., 2004; Perez, et al., 2010; Castillo, et al., 2011). A few cases of enteropathy-associated T-cell lymphoma as well as adult T-cell leukemia/lymphoma have also been reported, though little specific information pertaining to the role of HIV in these cases could be gleaned (Arzoo, et al., 2004; Castillo, et al., 2011).

In the largest case series to date, Castilo and colleagues noted that the bulk of HIV-associated T-cell lymphomas occurred in males, typically presenting at high stage (stage III-IV), and often accompanied by B-symptoms (fever, night sweats and weight loss) (Castillo, et al., 2011). Similar clinical characteristics were noted in other smaller cohorts (Arzoo, et al., 2004; Perez, et al., 2010). Many T-cell lymphomas in HIV patients will also present with skin findings, apparently in greater proportions than HIV-associated B-cell lymphomas (Arzoo, et al., 2004).

Peripheral T-cell lymphoma, unspecified, typically occurs in lymph nodes and consists of medium to large-sized lymphocytes with irregular nuclei. The neoplastic T-cells usually show a diffuse pattern of involvement, preferentially involving the paracortical zones, often sparing the lymphoid follicles (see Figure 16). HIV-associated anaplastic large cell lymphoma also demonstrates a range of histological features. A range of cell size may be noted from the typical large anaplastic cell to the so-called small cell variant (see Figure 17). These cells may form loosely cohesive clusters, diffuse sheets and, as is often seen in lymph nodes, may present as subtle subcapsular aggregates. Angioimmunoblastic lymphoma, in contrast, is most commonly described as a diffuse process often completely obliterating the lymph node architecture; most commonly the lymph node will be replaced by an arborizing network of proliferating endothelial cells interspersed by an infiltrate of atypical lymphocytes, often accompanied by various non-neoplastic inflammatory cells. Mycosis fungoides is characterized by band like superficial dermal infiltrates of atypical lymphocytes (often described as "cerebriform") (see Figure 18). When these atypical cerebriform lymphocytes are noted in the peripheral blood or in lymph nodes, the Sezary syndrome is suspected (sezary syndrome does not always demonstrate the same epidermotropism as mycosis fungoides, however, and the skin changes in this context may be non-specific). NK/T-cell lymphomas occur most often in the aerodigestive tract where they often manifest as mucosal ulceration by atypical lymphocytes. These atypical lymphocytes may have ample cytoplasm and irregular convoluted nuclear membranes. An angioinvasive pattern is also common to NK/T-cell lymphoma, typically with associated areas of necrosis.

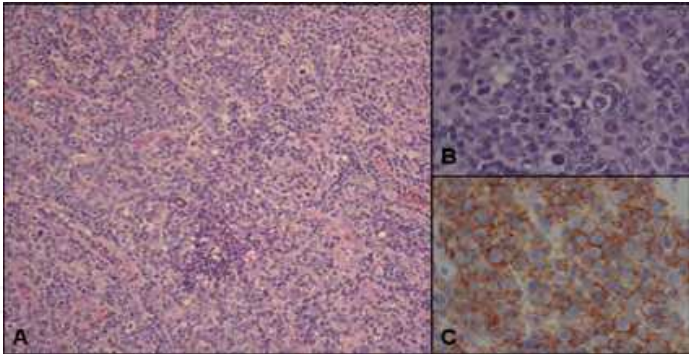


Fig. 15. Peripheral T-cell Lymphoma: A: Atypical cells expanding paracortical interfollicular regions; B: High-power demonstrating atypical cells (larger than normal interfollicular cells) with mitotic figures present; C: Diffuse CD3 positivity confirming T-cell lineage

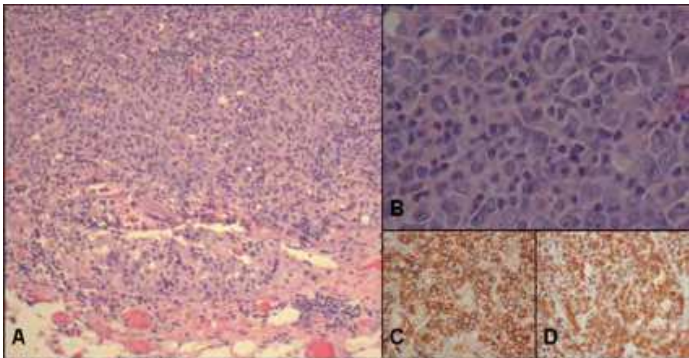


Fig. 16. Anaplastic Large Cell Lymphoma: A: Low-power view of lymph node involved by anaplastic large cell lymphoma showing subcapsular sinus involvement by tumour cells; B: High-power view of tumour cells demonstrating the characteristic hallmark cells (large nuclei with convoluted semi-lunar shapes); C: CD30 immunostain (diffuse positivity in tumour cells); D: ALK-1 immunostain (diffuse positivity in tumour cells)

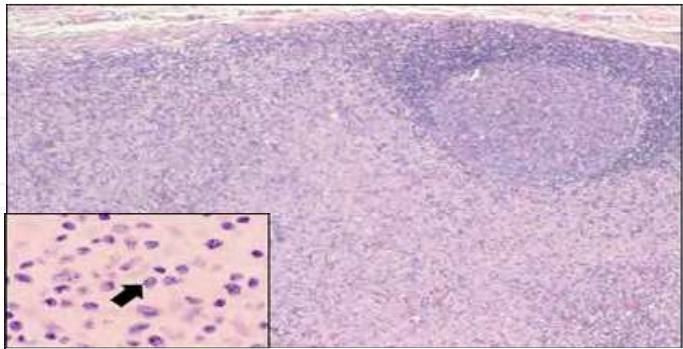


Fig. 17. Mycosis Fungoides: Lymph node demonstrating paracortical expansion by atypical lymphoid infiltrate; inset: large (cerebriform) sezary cells of mycosis fungoides

The typical T-cell lineage markers CD2, CD3, CD5, CD7, CD4, CD8 and CD43 are variably positive in T-cell lymphomas; these markers are useful at demonstrating aberrant phenotype (such as an aberrant CD4:CD8 ratio) or to hint at T-cell lineage neoplasm when the other T-cell markers are negative. The normal progression of T-cell marker ontogenesis

proceeds from CD7 to CD2, CD3 and CD5 (in immature T-cells) and then onto CD4 and CD8 (in mature T-cells); the loss of one of the so-called pan-T-Cell markers CD2, CD3, CD5 or CD7 is helpful in the identification of an aberrant (plausibly neoplastic) phenotype. In one of the largest series of HIV-associated anaplastic large cell lymphomas, Perez and colleagues noted that the majority of cases were positive for one or more of CD45, CD2, CD3, CD5, CD4 and CD43 (Perez, et al., 2010); the uniting feature in all cases of ALCL, however, is diffuse strong CD30 positivity. Although the CD30 stain is not entirely specific to anaplastic large cell lymphoma (since this stain is a marker of activated cells), its presence in a diffuse pattern in cells with typically anaplastic morphology is characteristic. Also commonly positive in anaplastic large cell lymphoma is CD45 (also known as leukocyte common antigen, a marker indicating hematolymphoid origin). Interestingly, ALK-1 was noted to be positive in only two of their cases; this is in stark contrast to the non HIV-associated anaplastic large cell lymphomas, which are typically ALK-1 positive (Perez, et al., 2010; Nava, et al., 2008). Although this lack of ALK-1 positivity may represent a distinct molecular feature of HIV-associated anaplastic large cell lymphoma, to our knowledge, no studies have explored this as yet. The neoplastic T-cells in angioimmunoblastic T-cell lymphoma, in addition to staining positive for a number of pan-T-cell markers, are typically positive for CD4 but negative for CD3. These cells also stain positive for a number of markers of follicular centre origin including CD10 and BCL-6. The lymphocytic infiltrates in mycosis fungoides syndrome will often demonstrate a lack of CD3 and CD8 staining often with pronounced CD4 positivity. NK/T-cell lymphoma also demonstrates positivity for one or more pan-T-cell markers, in addition to positivity for CD56 and (unlike most T-cell lymphomas) EBV. These features can easily be demonstrated efficiently, and with only minimal tissue, using flow cytometry.

Most patients with HIV-associated peripheral T-cell lymphomas are treated with a CHOP-based chemotherapy regimen, though a variety of other regimens have also been employed (Castillo, et al., 2011). While most patients seem to demonstrate a complete or partial response to initial therapy, the majority die of progressive disease (Castillo, et al., 2011). A statistically significant improvement in the survival curve of HIV-associated peripheral T-cell lymphomas was also noted in patients treated with anti-retrovirals (Castillo, et al., 2011).

3.7 Lymph node findings in HIV/AIDS related Kaposi's sarcoma

We will limit the discussion of Kaposi's sarcoma in HIV/AIDS to those aspects pertaining to lymph node disease. Whether due to its underlying viral etiology or to the endothelial differentiation of the malignant cell of interest, Kaposi sarcoma often manifests itself in lymph nodes. The disease was first described in 1872 by Moritz Kaposi as a pigmented sarcoma of skin (Mesri, et al., 2010), this form probably represented the modern sporadic subtype seen predominantly in the Mediterranean. In the 1950s, Kaposi's sarcoma was encountered in Africa (Mesri, et al., 2010); this may have represented the first discovery of Kaposi's sarcoma in association with the as yet unknown HIV. When the HIV outbreak was identified, Kaposi's sarcoma was observed to be the most frequent (and AIDS defining) malignancy in this immunocompromised population. It was not until 1996 that a viral pathogen was discovered in association with Kaposi's sarcoma, later named the Kaposi sarcoma herpes virus, or HHV-8 (Mesri, et al., 2010).

Ioachim and colleagues undertook an intriguing study of extra-cutaneous Kaposi's sarcoma in AIDS patients; they noted that lymph nodes were the third most common extra-

cutaneous sites of involvement by Kaposi's sarcoma in AIDS cases, next to the gastrointestinal tract and the lungs (Ioachim, et al., 1995). Cases demonstrating primarily nodal involvement may be entirely asymptomatic, with the exception of lymphadenopathy. In these cases the clinical differential diagnosis can be lengthy and histological diagnosis is required.

Lymph nodes involved by Kaposi's sarcoma are typically enlarged and demonstrate preserved architecture in areas not invaded by the tumour, often with follicular hyperplasia (see Figure 18). Involvement of lymph nodes by Kaposi's sarcoma typically begins in the form of triangular nodules with later encroachment into the cortex and medulla; these initial nodules may form wedges with bases parallel to the node capsule. Circular whorled-patterned nodules are also common and can be found throughout the nodal parenchyma. The cells within Kaposi's nodules are spindled with intervening slit-like vascular spaces. The neoplastic cells are usually fairly uniform with plump nuclei; mitoses may be present but are usually not numerous. Characteristic hyaline globules may be seen within Kaposi cells and in nearby histiocytes. Infiltration of tumour foci by lymphocytes, plasma cells and hemosiderin-laden macrophages is also frequent.

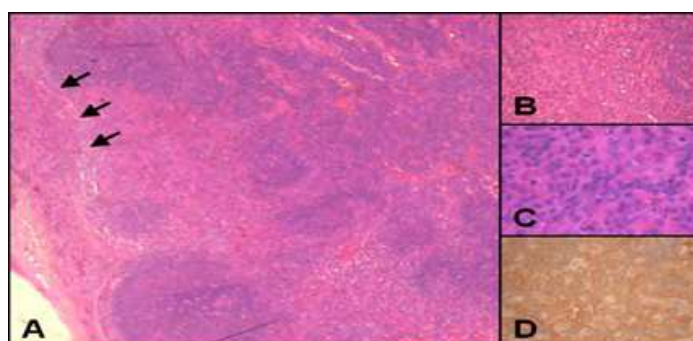


Fig. 18. Kaposi's Sarcoma: A: Low-power view of a lymph node involved by subcapsular nodules of Kaposi's sarcoma; B: Focus of neoplastic endothelial cells encroaching upon a follicle; C: High-power view of neoplastic endothelial cells with notable tumour cell cytoplasmic hyaline globules; D: HHV-8 immunostain demonstrating diffuse positivity

The morphologic differential diagnosis includes many vascular lesions, though the morphologic features are usually characteristic in Kaposi's sarcoma. Bacillary angiomatosis may show nodule formation but typically does not contain the uniformly plump monotonous spindle cells with intervening slit-like spaces seen in Kaposi's sarcoma. The vascular proliferation and hyalinization that may be seen in HIV-associated lymphadenopathy or Castleman's disease may be confused with Kaposi's sarcoma. Angiosarcomas should also be included in the differential diagnosis, though this typically demonstrates a much more sarcomatoid appearance with more marked atypia, necrosis and numerous mitoses. Confusion is avoided by using an immunohistochemical panel including markers for endothelial cells (such as CD31, CD34 or Factor VIII) in combination with a stain for HHV-8.

Antiretroviral therapy is used both to prevent Kaposi's sarcoma but also to treat it. Nonetheless, HIV patients with Kaposi's sarcoma may not respond curatively to antiretroviral optimization and some cases treated with antiretrovirals de novo have been known to develop more severe disease due to the so-called immune reconstitution inflammatory syndrome (in which the presumed increased inflammatory mediators

results in unintentional cytokinetic stimulation of the sarcoma) (Mesri, et al., 2010; Di Lorenzo, et al., 2007). Localized disease may respond to surgery or radiation therapy (though lymph node disease is frequently not localized) and more widespread disease is treated with chemotherapeutic regimens, typically including liposomal anthracyclines and taxanes (Di Lorenzo, et al., 2007). Newer biological therapies including the vascular endothelial growth factor receptor and tyrosine kinase inhibitors are currently being investigated (Di Lorenzo, et al., 2007). Some early studies exploring the use of antivirals (such as gancyclovir and foscarnet) have noted encouraging results though more definitive studies are ongoing (Di Lorenzo, et al., 2007).

4. Conclusion

In the three decades since the beginning of the modern HIV/AIDS epidemic, a great deal of advancement has been made in the understanding of retrovirology, immunology and hematolymphoid pathology. In these 30 years, the recognition of a unique and fastidious retrovirus causing AIDS has occurred, its biologic interaction with human cells has been detailed, and the variety of possible resulting illnesses following infection have been documented. In particular, the range of malignant disease that may occur in HIV/AIDS has been widely enumerated and, thankfully, has shown a distinct reduction in incidence and prevalence since the introduction of antiretroviral therapy, truly a modern medical elixir able to prolong life in a medical context once tantamount to a death sentence.

The above discussion should not only serve to highlight the unique clinical features of HIV-associated hematolymphoid disorders but also demonstrate the unique pathologic work-up necessary to ensure accurate classification and clinical follow-up. In particular, we emphasized the need to obtain tissue biopsies in any scenario in which a potential malignancy is considered. Furthermore, for the pathologist readership, it is imperative to properly handle and work-up a lymph node biopsy from any case in which there is a suspicion of lymphoma; we especially encourage the use of flow cytometry which is an invaluable tool in the diagnosis of lymphoid neoplasms and is extremely helpful in proper classification. Also, in addition to the standard H&E evaluation, a panel of immunohistochemical stains is usually needed to properly identify the lineage, malignant potential and classification of a lymphoid lesion. Many hematolymphoid malignancies require further molecular or cytogenetic work-up as well, the latter requiring fresh tissue.

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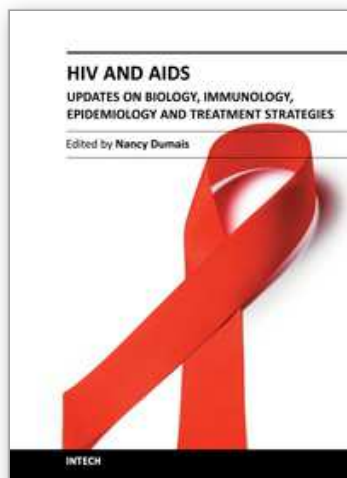
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