HIV Lymphadenopathy: Differential Diagnosis and Important Imaging Features

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OBJECTIVE. The purpose of this article is to review important imaging and clinical features to help elucidate causes of lymphadenopathy in patients with HIV infection.

CONCLUSION. HIV lymphadenopathy has various causes generally categorized as inflammatory or reactive, such as immune reconstitution syndrome; infectious, such as tuberculous and nontuberculous mycobacterial infections and HIV infection itself; and neoplastic, such as lymphoma, Kaposi sarcoma, and Castleman disease. It is important to consider patients' demographic characteristics, clinical presentations, CD4 lymphocyte counts, and radiologic features to identify likely causes of lymphadenopathy.

Lymphadenopathy in a patient with HIV infection is a diagnostic challenge for radiologists and clinicians because a myriad of conditions present with enlarged lymph nodes. Lymphadenopathy is extremely frequent and is more commonly localized than generalized [1]. Possible causes include the HIV infection itself presenting with enlarged lymph nodes at any disease stage, opportunistic infections, inflammatory conditions, and neoplastic processes. Knowledge of the imaging and clinical features of different causes of HIV-associated lymphadenopathy can narrow the differential diagnosis and aid in correct diagnosis. The goal of this article is to provide an overview of important predictors and summarize the imaging features of the most common causes of lymphadenopathy in patients with HIV infection. To achieve this purpose, we completed a PubMed open-source search using the key terms "HIV lymphadenopathy," "cause," and "imaging" and including retrospective and prospective research papers, meta-analyses, and reviews reflecting the differential features.

Demographic, Clinical, and Laboratory Predictors of HIV Lymphadenopathy

Geographic Predictors

Reactive lymphadenopathy (corresponding to the clinical diagnosis of persistent generalized lymphadenopathy and spectrum of cytologic changes from follicular hyperplasia to lymphocyte depletion) and inflammatory lymphadenopathy (presence of polymorphic lymphocytes and macrophages and no specific organisms) lymphadenopathy is the most common cause of enlarged lymph nodes in patients with HIV infection across countries with varying resource levels, being found in 40–50% of fine-needle aspirations (FNAs) [2, 3]. Additionally, in countries where tuberculosis is endemic, such as India, Pakistan, Bangladesh, China, Indonesia, the Philippines, Nigeria, and South Africa, this infection has been reported as a predominant cause of lymphadenopathy in patients with HIV infection and is found in 30% of FNAs performed to identify a cause of lymphadenopathy [4–6]. In countries where tuberculosis is not endemic, including the United States, nontuberculous mycobacterial infection and neoplastic processes such as lymphoma are the main causes of lymphadenopathy [7, 8]. Possible explanations for the low frequency of nontuberculous mycobacterial infection in some countries include difficulties in microbiologic diagnosis and early death from more virulent agents [8].

In areas with access to highly active antiretroviral therapy (HAART), there has been a shift in neoplastic causes of lymphadenopathy from HIV-related to non–HIV-related neoplasms, such as bronchogenic carcinoma, which may also present from metastatic lymphadenopathy [9]. Immune reconstitution inflammatory syndrome (IRIS) should also be considered as

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a potential cause of lymphadenopathy or lymphadenopathy progression in patients with recent initiation of HAART.

Lymph Node Distribution

Most patients with HIV infection have generalized lymphadenopathy with enlarged or abnormal lymph nodes in two or more noncontiguous areas. The most common locations are cervical and axillary nodes. Most localized lymph nodes are seen in the head and neck region and less commonly in the inguinal region [10]. Reactive lymphadenopathy is more common in superficial locations (subcutaneous tissues); deep lymph nodes are more likely to be affected by infectious or malignant entities [2].

Immune Status

CD4 lymphocyte count is one of the most important predictors of development of a specific disease. In patients with a CD4 count greater than cells/μL, bacterial and viral infections, particularly pneumonia, are the most common cause of lymphadenopathy. If the CD4 count decreases to less than 200 cells/μL, opportunistic infections, such as fungal infections and *Pneumocystis carinii* pneumonia, and Kaposi sarcoma (KS) are more likely. Lymphoma and tuberculous infection are added to the differential diagnosis when the lymphocyte count decreases to less than 50 cells/μL. In general, patients with neoplastic causes of lymphadenopathy have higher CD4 cell counts than patients with infections ($p < 0.01$) [11].

Indications for and Value of Lymph Node Biopsy

After consideration of the demographic information, anatomic location, and CD4 lymphocyte count, lymph node biopsy may be indicated for a definitive diagnosis of HIV lymphadenopathy in following clinical contexts of disproportionately larger lymph nodes in one site and enlarging generalized lymphadenopathy.

FNA of lymph nodes leads to an adequate diagnosis in 76% of cases and is a useful initial test that may guide management [5, 6]. However, FNA is not a final diagnostic tool when the results are negative or inconclusive. In those cases, core or excisional biopsy should be performed for final diagnosis.

FNA cytologic analysis may elucidate different cytomorphologic types of HIV lymphadenopathy, including reactive hyperplasia, caseating necrosis, ill-defined granuloma with caseation necrosis, well-formed granuloma alone, and lymphoma. In one study [10], a positive acid-fast bacillus test result was most consistently identified in patients whose FNA analysis showed ill-formed granulomas with caseating necrosis (100%) followed by caseation necrosis alone (80%). Reactive hyperplasia was associated with a positive acid-fast bacillus result in only 5% of cases. There was also a strong association between positive acid-fast bacillus result and low CD4 lymphocyte count: 70% of patients with a CD4 count greater than 350 cells/μL had reactive hyperplasia, and 71% of patients with a CD4 count less than 50 cells/μL had caseation necrosis with positive culture results in all cases.

Differential Diagnosis of HIV Lymphadenopathy

Persistent Generalized Lymphadenopathy

Persistent generalized lymphadenopathy is defined as palpable lymphadenopathy larger than 1 cm, involving two or more noncontiguous lymph node groups, and lasting longer than 3 months in the absence of concurrent disease other than HIV infection. Lymphoid hyperplasia is the most common cause of generalized lymphadenopathy in patients with HIV infection and is found in approximately 50% of lymph node aspirates [7].

HIV is a lymphotropic virus that causes remodeling of lymph nodes on a pathologic level that clinically manifests as persistent lymphadenopathy in three distinct phases: stage I, explosive follicular hyperplasia with large germinal centers; stage II, germinal center involution and lymphocytes depletion; stage III, proliferation of blood vessels inside the lymph nodes [12].

Low CD4 lymphocyte counts correlate with increased incidence of lymphadenopathy. A decreasing CD4 count is associated with a progressive increase in lymph nodes size. Therefore, patients with severe lymphopenia are more likely to have larger lymph nodes [13]. Decreasing lymphadenopathy may be seen with profound lymphocyte depletion and is associated with increased risk of transformation to AIDS [14]. The stages of lymph node remodeling may also be altered as the result of antiretroviral therapy–related immune reconstitution [12].

The most common site of persistent generalized lymphadenopathy is the head and neck region; it is commonly accompanied by nasopharyngeal lymphatic tissue hypertrophy and parotid gland changes [13, 15] (Figs. 1 and 2). Cystic parotid lesions are caused by lymphoproliferation in the intraglandular lymphoid tissue that obstructs epithelium and results in cystic enlargement [16].

Fig. 1—47-year-old man with HIV infection (CD4 lymphocyte count, 300 cells/μL). Axial CT image of chest shows multiple enlarged mediastinal lymph nodes due to generalized lymphoid hyperplasia.

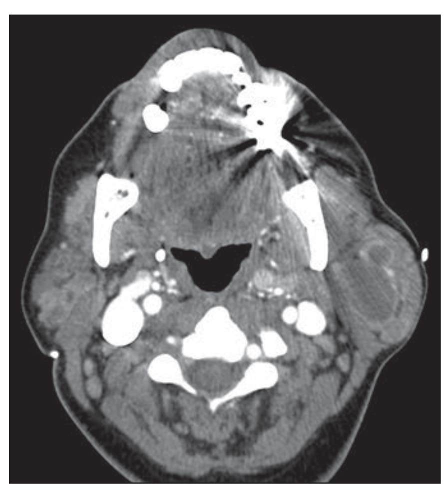


Fig. 2—53-year-old woman with HIV infection (CD4 lymphocyte count, 13 cells/μL). Axial CT image of neck shows bilateral lymphoepithelial cysts in parotid glands.

TABLE 1: Comparison of Mycobacterial Tuberculosis and Nontuberculous Mycobacterial Infections in Patients With HIV Infection

Feature	Mycobacterial Tuberculosis	Nontuberculous Mycobacterial Infection
Transmission	Person to person	Environment to person
Lymph node attenuation	Central or diffuse hypoattenuation (93% of cases)	Central or diffuse hypoattenuation (14% of cases); clustered lymph nodes typical
Presence of visceral lesions	More common (73% of cases)	Less common (20% of cases)
Individual node size	Typical mean, 4 cm	Typical mean, 2 cm

Tuberculous Mycobacteria Versus Nontuberculous Mycobacteria

After persistent generalized lymphadenopathy, infection is the second most frequent cause of HIV lymphadenopathy, particularly in countries where tuberculosis is endemic. *Mycobacterium tuberculosis* (MTB) is the most common agent and requires person-to-person transmission. Nontuberculous mycobacteria, such as *Mycobacterium avium* complex (MAC), are abundant in the environment—found in water, soil, and dust—and are a frequent cause of HIV lymphadenopathy in countries where tuberculosis is not endemic. Nontuberculous mycobacteria enter the body through the gut or lung and can then disseminate in immunocompromised people. Unlike tuberculosis, nontuberculous mycobacterial infections are not spread by person-to-person transmission. Overall in industrialized countries, the incidence of MAC infection in the general and HIV populations is increasing while the incidence of tuberculosis continues to decrease [17].

In immunocompetent hosts, MAC infection is is a disease limited to the lungs, often with solid patchy nodular opacities, which can occur in a tree-in-bud configuration or as discrete nodules and cavitating nodules. MAC infection is a more disseminated disease in immunocompromised patients, with lung involvement occurring in only 19% of cases [18].

On CT, mycobacterial lymphadenopathy due to either MTB or nontuberculous mycobacteria characteristically has low attenuation because of the presence of caseating necrosis. However, this finding is more frequently seen with MTB (93%) and less frequently with MAC (14%) infections, probably because of induction of a more severe immune response by MTB that leads to caseation [19, 20].

A few imaging features may favor MTB over nontuberculous mycobacterial infection. For example, uniform low-attenuation mesenteric or retroperitoneal lymph nodes are suggestive of MAC rather than MTB infection [21]. Mesenteric lymphadenopathy in MAC infection can result in masslike conglomerations [22]. Other findings suggestive of MAC infection include hepatomegaly, defined as craniocaudal dimension greater than 21 cm (20%); splenomegaly, defined as larger than 16 cm (14%); and diffuse jejunal thickening (18%) [19]. Solid organ granulomas are seen more commonly with MTB (73%) than with MAC (20%) infections [23] (Table 1 and Figs. 3 and 4).

Immune Reconstitution Inflammatory Syndrome

IRIS is worsening of symptoms of previously controlled disease or unmasking of unsuspected disease after initiation of HAART. IRIS occurs in as many as 25% of patients with HIV infection who start HAART [24]. Some subsets of patients at risk of development of IRIS are drug-naïve patients with a recent opportunistic infection, those with a CD4 lymphocyte count less than 50 cells/μL, and those with a high viral load (> 100,00 copies/mL) before initiation of treatment [25]. Immune restoration after HAART with increased CD4 lymphocyte counts leads to an excessive immune response to infectious or noninfectious agents and various manifestations of IRIS, depending on the pathogen. The key clinical feature is an interval decrease in viral load, increase in CD4 count, or both within 8–12 weeks of initiation of HAART [24]. Infectious and neoplastic and noninfectious inflammatory conditions associated with IRIS are highlighted in

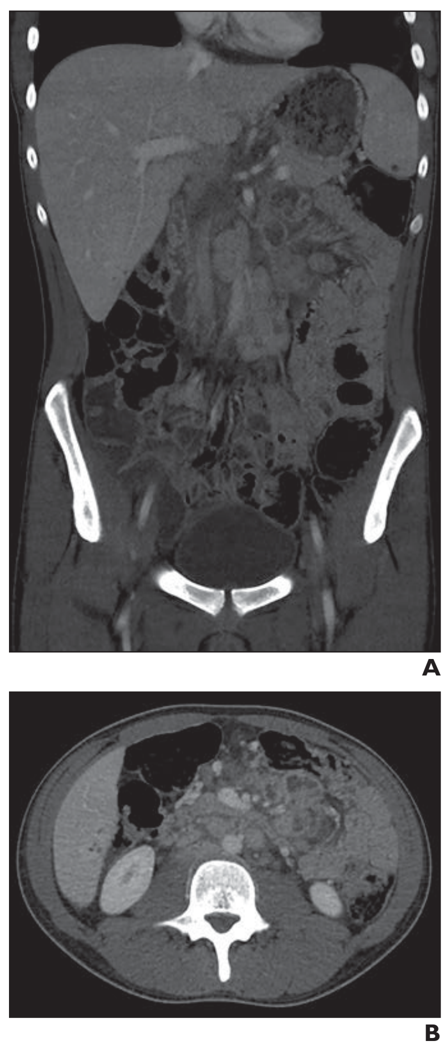


Fig. 3—37-year-old woman with HIV infection and *Mycobacterium tuberculosis* lymphadenopathy (CD4 lymphocyte count, 29 cells/μL). **A** and **B,** Coronal (**A**) and axial (**B**) CT images of abdomen show enlarged mesenteric lymph nodes with central hypoattenuation and rim of enhancement. Liver and spleen lesions also are present.

Fig. 4—34-year-old woman with HIV infection and intraabdominal lymphadenopathy caused by nontuberculous mycobacterial infection (CD4 lymphocyte count, 3 cells/μL). Coronal CT image of abdomen shows multiple clustered mesenteric lymph nodes.

Table 2 [26]. A systematic review and meta-analysis on the incidence of IRIS [27] showed that among patients with previously diagnosed AIDS-defining conditions, cytomegalovirus retinitis had the highest incidence (38%), followed by cryptococcal meningitis (20%), progressive multifocal leukoencephalopathy (17%), and tuberculosis (16%). Lymphadenopathy is a common imaging feature of IRIS, commonly with central low-attenuation centers due to necrosis or suppuration [28, 29].

Mycobacterium avium Complex Infection in Immune Reconstitution Syndrome

MAC infection is the most common infectious complication of IRIS, especially in countries in which MTB is not endemic [26]. There are three major clinical and radiologic forms of MAC infection in IRIS: peripheral lymphadenopathy (33%), a pulmonary-thoracic form (29%), and an intraabdominal form (25%) [30]. The most common imaging finding of MAC IRIS is lymphadenopathy. The involved lymph nodes are typically isoattenuating (50%) or hypoattenuating (50%) on CT [26, 31] (Fig. 5). Patients typically present with fever and painful suppurative lymphadenitis commonly in the neck and thoracic or intraabdominal distribution. Peripheral lymphadenitis spontaneously forms a draining sinus to the skin surface in 59% of patients [30].

The pulmonary form of IRIS presents with airspace consolidation, sometimes masslike, or pulmonary nodules with or without cavitation. Endobronchial lesions, either polypoid or sessile and sometimes necrotic, causing bronchial obstruction may also be seen [30]. Unlike MAC IRIS, MTB IRIS is not accompanied by endobronchial lesions [28].

The intraabdominal form of IRIS manifests as mesenteric lymphadenopathy; ascites, peritonitis, or both; splenomegaly; low-attenuation splenic lesions; bowel obstruction; and an intraabdominal mass. This form of MAC IRIS is associated with high morbidity [30]. Aside from the three major forms of MAC during IRIS, MAC may also present with musculoskeletal and CNS involvement, such as vertebral osteomyelitis, septic arthritis, and brain abscesses [28, 31]. MAC prophylaxis does not prevent the development of IRIS attributed to this infection [30].

Lymphoma

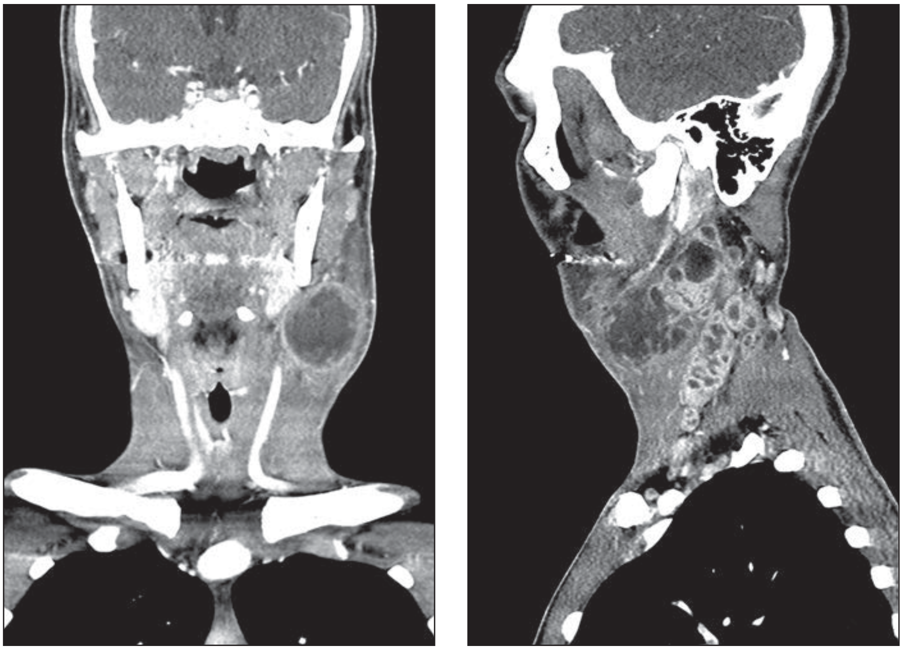
The incidence of lymphoma among patients with HIV infection is significantly higher that in the general population. In particular, the risk of non-Hodgkin lymphoma in patients with HIV infection is 60–200 times that of the general population [32–34]. This increased risk is the result of immunosuppression caused by HIV, which facilitates virus-induced carcinogenesis. Since the introduction of HAART, non-Hodgkin lymphoma has become less common. Estimates in the literature indicate that approximately 5–20% of patients with HIV infection undergoing HAART will eventually have lymphoma [35]. Lymphomas in the population with HIV infection develop in a younger age group (mean age, 37 years) than in the general population (mean age, 65 years).

Non-Hodgkin lymphoma in patients with HIV infection usually presents as disseminated disease with generalized lymphadenopathy and therefore is difficult to discern from generalized HIV lymphadenopathy. Clues that may suggest the presence of lymphoma include disproportionately larger or enlarging lymph nodes and the presence of extranodal involvement, which is seen in most patients (84–90%) [36–38] (Fig. 6).

The most frequent location of lymphoma-related lymphadenopathy in patients with HIV infection is the neck (50%) [39]. The most common locations of extranodal involvement are the CNS, gastrointestinal tract, and bone marrow [38]. Extranodal disease

TABLE 2: Diseases Associated With Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy

Type of Condition	Disease
Infectious	
Mycobacterial	Mycobacterial tuberculosis, nontuberculous mycobacterial infections
Fungal	Cryptococcal infections, *Pneumocystis carinii* pneumonia, histoplasmosis
Viral	Cytomegalovirus infection, hepatitis B or C, herpes simplex infection, progressive multifocal leukoencephalopathy
Neoplastic	Kaposi sarcoma, lymphoma
Inflammatory	Sarcoidosis
Autoimmune	Polymyositis, lupus erythematosus, rheumatoid arthritis, Graves disease



A B

Fig. 5—40-year-old woman with HIV infection, nontuberculous mycobacterial infection after highly active antiretroviral therapy (CD 4 lymphocyte count improved from 22 to 166 cells/μL), and worsening generalized lymphadenopathy.
A and **B,** Coronal (**A**) and sagittal (**B**) CT images of neck show enlarged low-attenuation cervical lymphadenopathy.

involving the lung, rectum, anus, heart, adrenal glands, oral mucosa, and muscles has also been well described in patients with AIDS-related lymphoma [38].

Castleman Disease

Castleman disease is characterized by excessive B-lymphocyte and plasma cell proliferation in lymphatic tissue. Lymphadenopathy in Castleman disease may be generalized, multicentric, or unicentric. Castleman disease in patients with HIV infection is typically multicentric and exclusively associated with human herpesvirus 8 (HHV-8) infection. An imaging hallmark of this disorder is the presence of avid enhancement of enlarged lymph nodes due to increased production of vascular endothelial growth factor by excess plasma cells and resultant angiogenesis within the lymphatic tissue [40]. HHV-8–associated Castleman disease manifests as less avidly enhancing lymphadenopathy.

Castleman disease in patients with HIV infection often presents with concomitant systemic features, such as diffuse pulmonary infiltrates, pleural or pericardial effusions, hepatomegaly, splenomegaly, and ascites [41–43] (Fig. 7). Most cases of HHV-8–associated Castleman disease coexist with KS. Additionally, the risk of non-Hodgkin lymphomas among patients with HIV infection and Castleman disease is 15 times that of patients with HIV infection without Castleman disease [44]. It may be difficult to differentiate Castleman disease from lymphoma in patients with HIV infection given the presence of systemic manifestations and coexistence of both conditions. The survival time of HHV-8–associated Castleman disease is generally on the order of months [45].

Kaposi Sarcoma

KS is a tumor that originates in the vascular endothelium. It is composed of spindle cells with cleftlike spaces filled with extravasated erythrocytes. As in Castleman disease, the causative agent of KS is HHV-8. As a result, the two conditions commonly coexist [46].

KS commonly affects mucocutaneous sites and less frequently viscera [37]. The most common site of visceral involvement is lymph nodes (72%), followed by the lungs and gastrointestinal tract (50%) [47]. A distinctive feature of KS lymphadenopathy is avid contrast enhancement due to robust vascularity [48] (Fig. 8). This can also be seen with multicentric Castleman disease, making radiographic distinction based on lymphadenopathy alone impossible. Unlike KS, HHV-8–associated Castleman

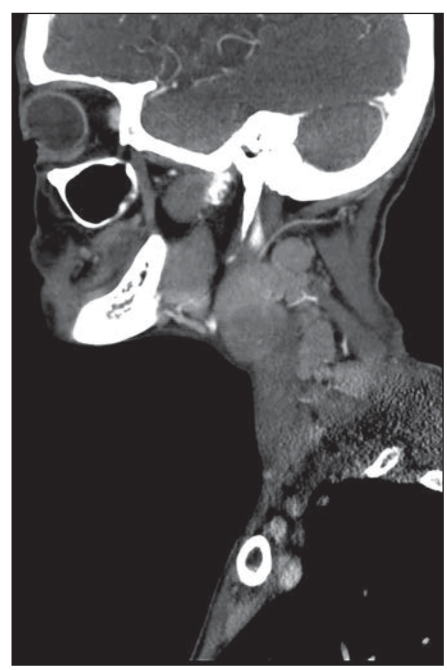


Fig. 6—56-year-old woman with HIV infection and non-Hodgkin lymphoma (CD4 lymphocyte count, 50 cells/μL). Sagittal CT image of neck shows multiple enlarged cervical lymph nodes disproportionally larger than other lymph nodes.

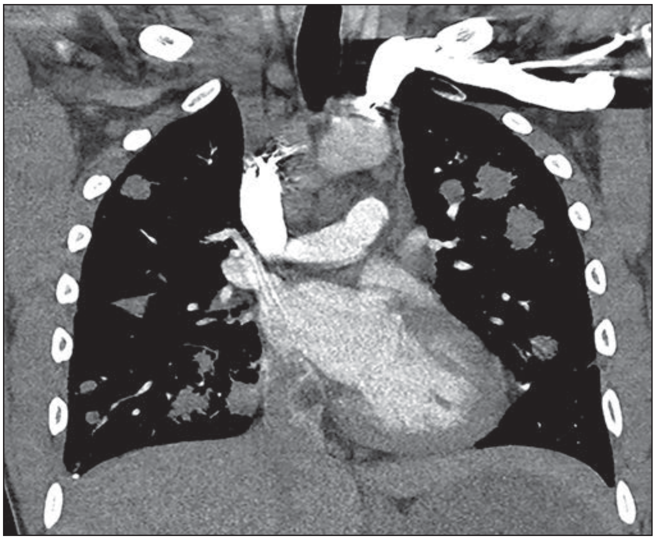


Fig. 7—49-year-old woman with HIV-associated Castleman disease. Coronal CT image of chest shows multiple diffuse nodular opacities and mediastinal lymphadenopathy. Absence of avid contrast enhancement of lymph nodes makes it difficult to differentiate Castleman disease from lymphoma.

disease is independent of CD4 lymphocyte count or the use of HAART [49].

Craniofacial and oral involvement is one of the most common manifestations of AIDS KS (60%) [48]. Patients present with purple polypoid lesions commonly on the skin or oral cavity. On CT and MRI, KS lesions appear as cutaneous enhancing soft-tissue masses. Ultrasound may aid in differentiating AIDS-associated KS from classic KS by showing hypervascularity of the AIDS KS lesions on color Doppler ultrasound, which is found in 75% of AIDS-associated KS cases versus 15% of cases in the classic form. In addition, ultrasound can be used to assess the clinical activity of the disease by showing vascular activity and help in ultrasound-guided biopsy of the involved lymph nodes [50].

Gastrointestinal involvement in KS is usually clinically silent but may present as gastrointestinal bleeding, perforation, intussusception, or obstruction. The most common findings in the lungs are irregular solid nodules (85%) and peribronchovascular consolidation with a characteristic flame shape (81%) [26].

Diffuse Infiltrative Lymphocytosis Syndrome

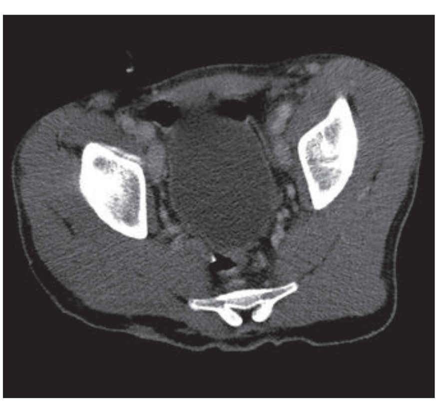
Diffuse infiltrative lymphocytosis syndrome (DILS) is a rare manifestation of HIV infection characterized by infiltration of the solid organs by $CD8^+$ lymphocytes. DILS is caused by a host's response to HIV infection consisting of expansion of the $CD8^+$ lymphocyte population. It is more common in black (60%) than white (26%) Americans [51, 52].

Clinically DILS resembles Sjögren disease because it presents with sicca symptoms (dry mouth and eyes) and salivary gland enlargement. The parotid glands often contain multiple lymphoepithelial cysts (88–100%) [53]. Ultrasound of the parotid glands is an important diagnostic tool to confirm involvement of the glands, particularly in pediatric patients. The ultrasound evaluation may reveal parotid gland heterogeneity due to the presence of lymphocytic aggregations, lymphoepithelial cysts, and intraparotid lymphadenopathy [54]. Salivary gland involvement is usually associated with neck lymphadenopathy or generalized lymphadenopathy. The lungs are the second most commonly involved organ, and DILS presents as lymphocytic interstitial pneumonia manifesting as ground-glass opacities, centrilobular nodules, and cysts (31%) [52, 53]. Other imaging manifestations of DILS include myositis (26%), peripheral neuropathy (25%), and hepatitis (23%) [52, 55, 56]. The diagnosis is confirmed by an elevated serum $CD8^+$ lymphocyte count and salivary gland biopsy showing $CD8^+$-predominant focal lymphocytic infiltrate.

Patients with DILS typically have higher CD4 levels, longer survival, and fewer opportunistic infections than patients with typical HIV infection [57]. Neoplastic conversion of DILS to non-Hodgkin lymphoma has been described in patients with HIV infection [53] (Fig. 9).

Conclusion

Lymphadenopathy in patients with HIV infection is a diagnostic challenge for both radiologists and clinicians. Familiarity with the distribution, attenuation, and enhancement of lymphadenopathy in a patient with HIV infection will help narrow the differential diagnosis. In addition to the characteristic imaging findings, awareness of the patient's demographic, clinical, and immune factors plays a crucial role in diagnosis because imaging features can overlap. CD4 lymphocyte count is one of the most important predictors of the likelihood of development of a specific disease.



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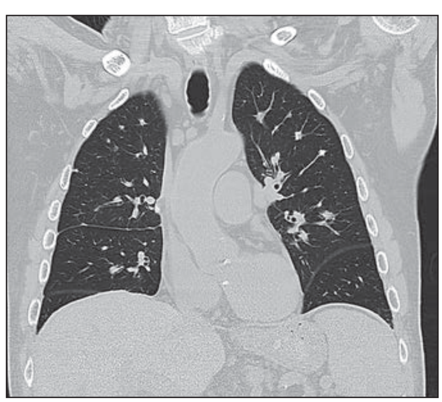

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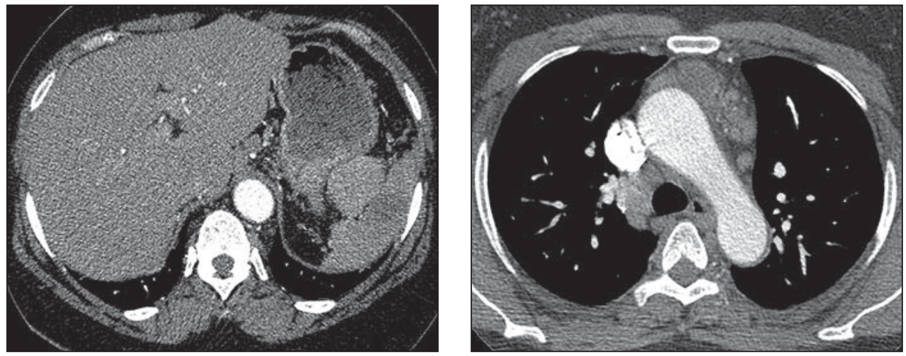
Fig. 8—39-year-old man with AIDS Kaposi sarcoma. **A** and **B,** Axial CT image of pelvis (**A**) and coronal CT image of chest (**B**) show enhancing inguinal and pelvic lymphadenopathy and peribronchovascular opacities.

Fig. 9—50-year-old woman with HIV infection and long history of diffuse infiltrative lymphocytosis syndrome that converted to lymphoma.
A, Coronal CT image of neck shows bilateral enlargement of parotid glands with lymphoepithelial cysts.
B and **C,** Axial CT images of upper abdomen (**B**) and chest (**C**) show enlarged cervical and mediastinal lymph nodes and splenic lesion.



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