The Pathology of AIDS

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Synopsis

The acquired immunodeficiency syndrome (AIDS) is a devastating new disease caused by the human immunodeficiency virus (HIV). This retrovirus causes profound immunoincompetence in its infected hosts, who are thereafter susceptible to develop myriad severe and relapsing protozoal, fungal, bacterial, viral, and arthropodal opportunistic infections, as well as unusual malignancies. The more than 50,000 patients who have developed AIDS in the United States have produced a sudden unexpected deluge of diagnostic dilemmas that are stressing laboratories of pathology everywhere.

This paper describes the gross and microscopic pathology of the numerous complications in patients infected by HIV: (a) *the prodromal AIDS-related complex with persistent generalized lymphadenopathy,* (b) *lymphoid infiltration of salivary gland and lung, including the complex of lymphoid interstitial pneumonitis-pulmonary lymphoid hyperplasia,* (c) *extranodal non-Hodgkin's lymphomas,* (d) *multifocal mucocutaneous and visceral Kaposi's sarcoma,* (e) *small cell undifferentiated (oat cell) carcinomas,* (f) *protozoal infections caused by* Pneumocystis carinii, Toxoplasma gondii, Acanthamoeba, Cryptosporidium *species (sp.), and* Isospora belli, (g) *the causes of chronic enteritis,* (h) *mycotic infections caused by* Candida *sp.,* Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, *and* Sporothrix schenckii, (i) *bacterial infections caused by* Mycobacterium avium-intracellulare, M. tuberculosis, M. kansasii, Nocardia *sp.,* Listeria monocytogenes, Legionella *sp.,* Treponema pallidum, *and others,* (j) *viral infections caused by cytomegalovirus, herpes simplex and zoster, polyomavirus (progressive multifocal leukoencephalopathy), hepatitis B, molluscum contagiosum, and papillomavirus,* (k) *oral hairy leukoplakia,* (l) *subacute encephalopathy, and* (m) *Norwegian scabies.*

INFECTION by the human immunodeficiency virus (HIV) is a dynamic process with pathological features that vary with the chronology of the disease. Thus, hyperplastic reactive lymph nodes biopsied during the prodromal AIDS-related complex (ARC) phase of the illness bear little resemblance to the burned out, depleted lymph nodes seen terminally, and the sometimes subtle angiomatous lesions of Kaposi's sarcoma (KS) are at one end of a histological spectrum that also encompasses lesions that may be frankly sarcomatous. An understanding of the various pathological findings in patients infected by HIV is fundamental to an appreciation of the diverse clinical manifestations of this syndrome. Because of the multiplicity of infectious and neoplastic processes encountered in patients with AIDS (acquired immunodeficiency syndrome), and because of the potential hazards of the various therapeutic agents involved, specific pathological diagnoses are essential for a rational approach to therapy.

To collate, organize, and study clinical data and pathological material from patients with AIDS, on October 1, 1985, the Collaborative Center for the Investigation of AIDS was established at the Armed Forces Institute of Pathology by Public Health Service Surgeon General Vice Admiral C. Everett Koop and Army Surgeon General Lieutenant General Quinn Becker. The Collaborative Center created the Registry of AIDS Pathology in the American Registry of Pathology. This international Registry has been soliciting all AIDS-related surgical and postmortem pathological materials from domestic and foreign, civilian and military hospitals, including all cases from the Veterans Administration and Armed Forces, the National Institutes of Health, and the Centers for Disease Control. The mission of the Collaborative Center

and the Registry is to define the pathology of AIDS.

AIDS-Related Complex

Persistent generalized lymphadenopathy occurs in patients infected with HIV. This chronic lymphadenopathy syndrome, or ARC, represents a prodromal phase of AIDS and occurs prior to the development of opportunistic infections, Kaposi's sarcoma, and non-Hodgkin's lymphomas. Patients may be otherwise asymptomatic, or they may suffer from a variety of constitutional symptoms such as fever, weight loss, malaise, diarrhea, and oral candidiasis. Some may also present with autoimmune phenomena, including thrombocytopenic purpura and hemolytic anemia.

The hyperplastic lymph nodes are grossly enlarged—up to 6 centimeters in greatest dimension—and are mobile, discrete, and soft. Microscopic sections of biopsied lymph nodes stained with hematoxylin and eosin (H/E) reveal reactive, sometimes florid, follicular hyperplasia with prominent, irregularly shaped, mitotically active germinal centers with tingible body histiocytes; occasional large lymphocytes with vesicular nuclei (immunoblasts) within the interfollicular areas; clusters of perivascular neutrophils and plasma cells; and rare multinucleated giant cells.

Lymphoid Infiltration of Salivary Gland, Lung

Lymphoid aggregates may occur in other tissues, particularly salivary gland and lung. We have studied the cases of a number of HIV seropositive patients who presented with unilateral or bilateral parotid enlargement. Microscopic sections of salivary gland revealed marked lymphoid infiltration with florid follicular hyperplasia. Pediatric patients have a propensity to develop pulmonary infiltrates and pulmonary insufficiency caused by the complex of pulmonary lymphoid hyperplasia/lymphoid interstitial pneumonitis (PLH/LIP). In these cases, there are prominent nodular peribronchiolar and perivascular lymphoid aggregates, often with germinal centers, and mild to moderately severe lymphocytic infiltration of alveolar septae.

Non-Hodgkin's Lymphomas

Patients with AIDS have an increased incidence of non-Hodgkin's lymphomas. They frequently present in extranodal locations, a feature also seen in Burkitt's lymphomas and lymphomas in immunosuppressed (for example, post transplant) persons. Notably, like Burkitt's lymphoma in Africa but unlike the nonendemic form, these neoplasms are frequently EBNA-positive (Epstein-Barr nuclear antigen-positive). Cytogenetic analyses of several undifferentiated lymphomas in patients with AIDS have revealed chromosomal translocations typical of Burkitt's lymphoma involving the long arm of chromosome 8 and one of the chromosomes containing immunoglobulin genes, namely 14 (heavy chains) or 22 (lambda light chains).

These extranodal lymphomas may present in the central nervous system, orbit, pharynx and jaw, intestine, liver, kidney, bone marrow, and muscle. Tumors may remain localized or they may disseminate widely. Systemic sites of involvement include spleen, pleura, and peripheral blood. These lymphomas are often architecturally diffuse and of the undifferentiated small noncleaved (Burkitt's and non-Burkitt's) or of the large cell (histiocytic) subtypes. The undifferentiated lymphocytes possess noncleaved nuclei that approximate the nuclear size of macrophages, multiple small nucleoli, and scanty cytoplasm; a starry-sky (composed of tingible body macrophages) architectural pattern is often present, indicative of a high rate of cellular turnover. Large cell lymphomas most commonly belong to the high grade, immunoblastic or to the intermediate grade, diffuse large cell categories. Plasmacytomas have also been reported (*1*). When immunohistochemistry has been performed in cases of AIDS-related lymphomas, these tumors have been determined to be of B-cell lineage, with expression of either kappa or lambda light chain and a heavy chain, most commonly IgM (immunoglobulin M) (*2*).

Although these lymphomas may be the initial manifestation of AIDS, they may also follow the diagnosis of Kaposi's sarcoma, or they may develop subsequent to the emergence of the unusual opportunistic infections that characterize AIDS. Occasionally, they are first discovered at autopsy.

Persistent generalized lymphadenopathy, lymphoid infiltration of salivary glands, PLH/LIP, and B-cell lymphomas may represent a continuum or spectrum of lymphoid lesions that probably represent host responses to viral infections—for example, HIV, EBV (Epstein-Barr virus).

Kaposi's Sarcoma

Before Kaposi's sarcoma (KS) appeared in patients with AIDS, most cases of this relatively rare cutaneous neoplasm were localized to the lower

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extremities of older men of Mediterranean descent. KS was also reported in iatrogenically immunosuppressed organ transplant recipients and among young blacks in regions of equatorial Africa, where it is endemic. KS is considered to be an angioproliferative disorder and differs from other neoplasms in that its pattern of dissemination suggests multicentric origin rather than hematogenous metastatic spread from a single primary site. It is not known whether under certain conditions HIV is capable of inducing KS, or if, as is thought more likely, KS has a different etiologic basis that is permitted expression in immunosuppressed patients.

In patients with AIDS, KS most frequently presents in one or more mucocutaneous sites. Within the oral cavity, lesions may appear on the lips, gingiva, buccal mucosa, palate, tonsils, tongue, oropharynx, and epiglottis. Depending on the time course of the disease process, the erythematous to violaceous mucocutaneous lesions, which range from several millimeters to several centimeters across, may appear as macules, infiltrative plaques, or nodules. Lymph node involvement by KS is common. Although nodal disease usually accompanies mucocutaneous lesions, occasionally only lymph nodes are involved. Grossly and microscopically, lymph nodes involved by KS exhibit hemorrhagic lesions in capsular, subcapsular, sinusoidal, and hilar locations. Lesions may be subtle, and small foci may be missed unless serial tissue sections are obtained.

Visceral lesions almost always appear in association with generalized mucocutaneous disease, although exceptions have been reported (*3*). On gross examination of visceral lesions, the tumors appear as areas of petechiae or hemorrhage, usually first appearing in connective tissue surrounding blood vessels. This perivascular predilection is well demonstrated in the heart, where KS is often confined to the distribution of the epicardial coronary arteries, and in the liver, where the tumor exhibits a striking predilection for portal tracts. In the lungs, KS grossly appears as erythematous plaques and nodules, localized to the pleura, to perivascular sites along bronchi and interlobular septae, and to the submucosa of the tracheobronchial tree. Serosanguinous pleural effusions may accompany pleural involvement by KS. Diffuse pulmonary KS may result in massive intra-alveolar hemorrhage and death. Lesions of KS in the gastrointestinal tract may appear in the esophagus, stomach, small and large intestines, appendix, and rectum and appear as flat to nodular vascular lesions, characteristically originating within the submucosa. Lesions frequently extend into the lamina propria and may produce mucosal ulcerations. Other sites of involvement by KS include spleen, gallbladder, pancreas, kidney, adrenal, testis, epididymis, palpebral conjunctivae, adventitia of aorta and large vessels, and perineural connective tissue.

The typical pattern of organ and tissue involvement by KS may reflect the disparate ability of the etiologic agent of KS to permeate certain vascular barriers or to stimulate angiogenesis within selected tissue sites. Although we have not seen KS in bone marrow or the brain, involvement at these sites has been referred to in case reports by others (*4*).

The Registry has studied more than 600 cases of KS. Histopathologically, there is no difference between KS of patients with AIDS and lesions from older, presumably heterosexual men with classic KS; nor are there differences between the lesions of black Africans and whites. The histological spectrum of the lesions of KS may progress from angiomatous (early) to sarcomatous (late) forms. Histological features of KS include (*a*) proliferation of bland-appearing spindle cells, (*b*) arrangements of some of the neoplastic cells into small slit-like vascular spaces, (*c*) scattering of erythrocytes and variable hemosiderin deposition in and around the lesions, (*d*) the presence of intracellular, periodic acid-Schiff (PAS) positive, diastase resistant, hyaline globules in many of the specimens, and (*e*) a variable accompaniment of plasma cells and lymphocytes. Mitotic figures, which may be present, are few, and there may be mild nuclear atypia. Early lesions are frequently angiomatous (telangiectatic), consisting of haphazardly arranged vascular channels with lumina that are either empty (lympathic channel-like appearance) or contain erythrocytes.

In sections of biopsied cutaneous lesions, KS dissects through the collagen of the mid-dermis and exhibits a predilection for perivascular areas

and the loose connective tissue surrounding adnexal structures. The overlying epidermis may become attenuated in nodular lesions. Nodular lesions are typically more cellular, with spindle cells arranged in interweaving fascicles. As indicated above, there is a histological spectrum of KS lesions, and on occasion we and others (*5*) have seen lesions that are frankly sarcomatous, possessing a higher degree of cellularity, increased mitotic activity, and greater nuclear atypia than angiomatous forms. We have also studied specimens of skin that simultaneously showed angiomatous, intermediate, and sarcomatous stages of KS.

Other Malignancies

The male homosexual population is at increased risk for the development of squamous cell carcinoma of the oropharynx and cloacogenic carcinoma of the anorectum. Several cases of small cell undifferentiated (oat cell) carcinomas involving the rectosigmoid, pancreas, and lung have been reported in patients with AIDS.

Infections

Profoundly immunoincompetent patients with AIDS are vulnerable to myriad opportunistic pathogens. Opportunistic infections in patients with AIDS are often severe, persistent, and relapsing despite appropriate therapy. Some infections are virtually untreatable.

Protozoa.

Pneumocystis carinii. Pneumonia caused by *P. carinii* is the most common life-threatening opportunistic infection in patients with AIDS. Grossly infected lungs are heavy and increasingly resistant to cutting. Early involvement is characteristically patchy, although at postmortem lungs may be diffusely consolidated. *P. carinii* cannot be readily cultured; hence, diagnosis is dependent upon direct visualization of the protozoan. The diagnosis may be established with smears of induced sputa, centrifuged bronchial lavages and washings, frozen sections and touch imprints of unfixed transbronchial and open lung biopsies, and formalin-fixed paraffin-embedded transbronchial and open lung biopsy specimens. Histopathologically, in sections stained by H/E, cysts of *P. carinii* are most likely to be found within eosinophilic foamy exudates that distend alveoli and terminal bronchioles. Rapid diagnoses may be accompanied using Giemsa and Gram's staining techniques, which demonstrate up to eight internal sporozoites per cyst. Toluidine blue O and methenamine silver techniques demonstrate the cyst walls as oval or round collapsed structures 3–7 micrometers (μm) across. Because *P. carinii* pneumonia may present with other concomitant opportunistic pulmonary infections, additional pathogens should always be ruled out in every case.

We have studied a number of patients with AIDS who had pulmonary and disseminated extrapulmonary infections caused by *P. carinii.* One patient had *P. carinii* in the spleen, lymph nodes, liver, kidneys, adrenals, ureter, jejunum, omentum, mesentery, appendices epiploicae, pancreas, heart, thyroid, bone marrow, choroid of both eyes, and lungs. Splenomegaly and lymphadenopathy, not infrequent findings in patients with AIDS, may be caused by disseminated extrapulmonary *P. carinii* infections.

Toxoplasma gondii. In patients with AIDS, toxoplasmosis may present as an acute, subacute, or chronic meningoencephalitis. Patients with AIDS who develop neurological deficits and single or multiple contrast-enhancing intracerebral lesions on computed tomographic (CT) scans frequently have toxoplasmal encephalitis, although lesions caused by *Cryptococcus neoformans*, *Mycobacterium* species (sp.), *Nocardia* sp., cytomegalovirus, non-Hodgkin's lymphoma, and other processes must also be considered in the differential diagnosis. Definitive diagnosis requires visualization of cysts or tachyzoites on smears stained with Wright-Giemsa, or tissue sections stained with H/E. The crescentic (Greek "toxon" = arc) or round basophilic tachyzoites are 2–6 μm across. The large spherical cyst forms contain punctate bradyzoites. In tissue sections stained by H/E, the basophilic cysts and extracellular tachyzoites are found within a background of acute and chronic inflammation with vasculitis and necrosis. In our experience at the Armed Forces Institute of Pathology, AIDS patients with toxoplasmal encephalitis may also have disseminated toxoplasmosis with involvement of meninges, heart, lung, adrenal, pancreas, and testis. As in the brain, *T. gondii* may also cause extensive necrosis in these organs.

Acanthamoeba. The free-living amoebas of the Hartmannella-Acanthamoeba group may infect immunosuppressed persons and cause a meningoencephalitis. We studied the case of a patient with AIDS who presented with numerous contrast-

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enhancing intracerebral lesions that were clinically thought to represent toxoplasmal encephalitis. Histopathological examination of sections of brain stained by H/E revealed multiple areas of acute and chronic inflammation with vasculitis and necrosis suggestive of toxoplasmosis. However, we did not find cysts nor tachyzoites of *T. gondii.* Instead, there were numerous oval and round trophozoites, 10–25 μm across, each with a sharply outlined nucleus and a dense nucleolus. Sections stained by methenamine silver revealed cyst forms as well. These findings are characteristic of amoebic encephalitis caused by the Hartmannella-Acanthamoeba group.

Cryptosporidium. In patients with AIDS, *Cryptosporidium* may cause chronic, profuse, watery diarrhea. Infection begins when cryptosporidia attach to the surface of mucosal epithelial cells lining the small and large intestines. Diagnosis is confirmed by identifying oocysts in specimens of stool. The 2–6 μm cysts are refractile, are acid-fast with the use of a modified Ziehl-Neelsen technique, and fluoresce with the use of an auramine stain. Histopathologically, sections of stomach, small intestine, large intestine, and appendix stained by H/E demonstrate rows of basophilic spherical cryptosporidia attached to the surface of mucosal epithelial cells. Cryptosporidia may lie free in the crypts. Cryptosporidia may also attach to respiratory epithelium.

Cryptosporidium may infect the gallbladder, as well as extrahepatic and intrahepatic bile ducts of patients with AIDS. We studied the cases of two AIDS patients who presented with right upper quadrant abdominal pain caused by cryptosporidial cholecystitis and cryptosporidial sclerosing cholangitis. Histopathologically, numerous basophilic cryptosporidia were attached to the mucosal surface epithelium of the gallbladder and intrahepatic bile ducts.

Isospora belli. Isospora belli causes chronic diarrhea in patients with AIDS. In cases of human isosporiasis in non-AIDS patients, these protozoa have been demonstrated as intracellular parasites of intestinal epithelium. In patients with AIDS, however, enteric infections with *I. belli* may disseminate beyond the intestinal wall. In a case we studied, intracellular and extracellular crescentic merozoites of *I. belli* were in the mucosa and lamina propria of the small and large intestines, as well as in mesenteric and tracheobronchial lymph nodes. Lymphadenopathy, not an infrequent finding in patients with AIDS, may be caused by disseminated extraintestinal lymphadenopathic isosporiasis.

Other enteric pathogens. Chronic diarrhea in patients with AIDS may be caused by a variety of microorganisms, ranging from bacteria such as *Salmonella* sp. *Shigella* sp., and *Campylobacter* sp., to protozoans like *Entamoeba histolytica* and *Giardia lamblia.* Furthermore, patients with AIDS and chronic diarrhea may present with recurrent bacteremias caused by *Salmonella* sp., *Shigella* sp., and *Campylobacter* sp. Finally, chronic diarrhea in patients with AIDS may also be caused by fungi, cytomegalovirus, Kaposi's sarcoma, non-Hodgkin's lymphoma, and *Strongyloides stercoralis.*

Fungi.

Candida sp. Oral candidiasis (thrush), manifested by cheesy-white intraoral mucosal patches, frequently occurs in patients who are seropositive for HIV. The diagnosis is established by examination of unstained wet-mounted, or Gram-stained mucosal scrapings that reveal budding yeasts and pseudohyphae characteristic of *Candida* sp. Patients with *Candida* esophagitis frequently complain of odynophagia, and mucosal ulcerations may be demonstrated by esophagoscopy or barium swallow esophagrams. Sections of esophagus reveal budding yeasts and pseudohyphae attached to and invading the mucosal epithelium. Candidiasis of the trachea, bronchi, and lungs also occurs, particularly among pediatric patients with AIDS.

Cryptococcus neoformans. Cryptococcus neoformans is a common cause of meningitis and disseminated disease in patients with AIDS. Analysis of cerebrospinal fluid (CSF) usually reveals a mild pleocytosis, hypoglycorrhachia, and elevated protein; however, any or all of these parameters may be normal. The India ink test, cryptococcal anti-

gen, and fungal cultures are almost always positive. Patients with AIDS may also present with localized or disseminated extrameningeal disease, with or without an accompanying meningitis. Pneumonitis, lymphadenitis, peritonitis, thyroiditis, and chorioretinitis may also be caused by *C. neoformans*. Blood cultures in these patients are often positive for *C. neoformans*. In postmorten examinations, we have demonstrated disseminated infections in the brain, eye, lung, lymph node, bone marrow, liver, spleen, heart, adrenal, kidney, prostate, thyroid, intestine, pancreas, skin, and ovary.

Encapsulated narrow-pored budding yeasts within the CSF may be detected by India ink wet mount preparations. Microscopic examination of biopsied tissue sections stained by mucicarmine demonstrate carminophilic yeasts, which distinguishes *C. neoformans* from yeasts of *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Sporothrix schenckii*.

Histoplasma capsulatum. Disseminated histoplasmosis occurs in patients with AIDS. These patients may present with pneumonia, hepatosplenomegaly, abnormal liver function tests, lymphadenopathy, pancytopenia, chorioretinitis, meningitis, and endocarditis. Most of these patients are fungemic and both intracellular and extracellular narrow-pored budding yeasts may be seen on Wright-Giemsa stained smears of their peripheral blood. In postmortem examinations, we have demonstrated *H. capsulatum* in sections of brain, eye, lung, liver, spleen, lymph node, adrenal, kidney, heart, intestine, appendix, pancreas, testis, prostate, bone marrow, and thyroid.

In sections of tissue stained by H/E, PAS, and methenamine silver, characteristic oval, 2–4 μm, narrow-pored budding yeasts of *H. capsulatum* are typically found to be expanding the cytoplasm of histiocytes. In some cases, there may be foci of caseation necrosis, and staining with PAS and methenamine silver techniques demonstrate the yeasts. The areas of caseation necrosis are surrounded by minimal to absent granulomatous inflammation; multinucleated giant cells are infrequently seen. The histiocytic infiltrates, as well as the nongranulomatous areas of caseation necrosis, represent "anergic" host responses to their histoplasmal infections. Such anergic histopathological reactions are also seen in the tissues of AIDS patients with disseminated infections caused by *Mycobacterium tuberculosis* (nongranulomatous caseation necrosis) and *Mycobacterium avium-intracellulare* (histiocytic inflammation).

Coccidioides immitis. *Coccidioides immitis* is endemic in the southwestern United States and is frequently found as a disseminated opportunistic infection in patients with AIDS living in this area. Patients may present with pneumonia, meningoencephalitis, hepatosplenomegaly, lymphadenopathy, arthritis, osteomyelitis, and cutaneous lesions. In postmortem examinations we have seen disseminated infections in the brain, lung, lymph node, liver, spleen, skin, bone, adrenal, kidney, prostate, and thyroid. Sections of tissue stained with H/E and PAS reveal thick-walled spherules containing internal endospores; the spherules may be found within foci of caseation necrosis surrounded by minimal granulomatous inflammation.

Sporothrix schenckii. Disseminated sporotrichosis also occurs in patients with AIDS. Patients may present with cutaneous lesions, tenosynovitis, arthritis, and pneumonia. Postmortem examinations have revealed disseminated infections in lung, liver, spleen, skin, and bone. Sections stained with PAS and methenamine silver reveal elongated (cigar-shaped) budding yeasts characteristic of *S. schenckii*.

Bacteria.

Mycobacterium avium-intracellulare (*MAI*), *M. tuberculosis*, *M. kansasii*. Prior to the AIDS pandemic, the ubiquitous atypical acid-fast bacillus of MAI was an infrequent cause of disseminated disease in immunosuppressed patients. Now patients with AIDS frequently develop disseminated MAI infections and may present with lymphadenopathy, hepatosplenomegaly, pancytopenia, pneumonia, diarrhea, and mycobacteremia. Postmortem examinations have revealed MAI in the brain, eye, lung, heart, lymph node, liver, spleen, bone marrow, intestine, pancreas, skin, adrenal, kidney, prostate, and thyroid. In contrast to the caseating granulomas and giant cell reactions that are classically observed in mycobacterial infections, histological sections of MAI-infected tissues of patients with AIDS typically reveal sheets of foamy histiocytes and poorly formed or absent granulomas. For this reason, overwhelming MAI infections may go undetected unless special stains are performed. Acid-fast staining of affected tissues frequently reveals surprisingly large numbers of mycobacteria within the cytoplasm of histi-

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ocytes, reminiscent of the "globi" seen in patients with lepromatous leprosy. Involvement of the small intestine may mimic Whipple's disease. Disseminated infections by *M. tuberculosis* and *M. kansasii* also occur in patients with AIDS.

Nocardia sp. Patients with AIDS may develop disseminated nocardiosis presenting as pneumonia, pleural effusion (empyema), purulent pericarditis, cervical osteomyelitis, retropharyngeal abscess, subcutaneous abscess, draining sinus tract, and brain abscess. Unlike pneumonia caused by *P. carinii*, pulmonary nocardiosis often presents with a productive cough. The initial illness may resemble a bacterial pneumonia, but slow radiological progression continues despite antibiotic therapy, often with cavitation of radiodense central areas. Contiguous spread causes pleural, pericardial, osseous, and subcutaneous lesions. Lymphohematogenous dissemination to the brain and subcutaneous tissue is frequent in nocardiosis.

Sputum, pus, or bronchial lavage and washing specimens should be examined by Gram and modified acid-fast stains. The organisms appear as Gram-variable, weakly acid-fast, filamentous, beaded, branching bacilli. Conventional acid-fast staining procedures such as Ziehl-Neelsen or a fluorochrome do not stain *Nocardia.* In sections of tissue, *Nocardia* bacilli are found within foci of suppurative necrosis.

Other bacteria. In patients with AIDS, *Listeria monocytogenes* may cause meningitis and bacteremia. *Legionella* sp. may cause pneumonia and disseminated infections. *Treponema pallidum* may cause dermatitis, lymphadenitis, orchitis, and relapsing seronegative neurosyphilis; histopathological examination of sections of lymph node and testis may reveal unusually large numbers (dense masses) of spirochetes. Cat scratch disease (CSD) may appear as lymphadenitis or dermatitis or both; histopathological examination of tissue sections may reveal unusually dense masses of CSD bacilli within blood vessels and areas of suppurative necrosis. This anergic nongranulomatous form of CSD with prominent vascular proliferation may be misinterpreted as KS. Other bacteria (for example, *Streptococcus* sp., *Hemophilus* sp.) may also cause serious infections (pneumonia, meningitis, bacteremia), particularly in children with AIDS.

Viruses.

Cytomegalovirus (CMV). Many patients with AIDS have persistent cytomegaloviremia, and CMV is a major cause of dysfunction in a variety of organs. Patients may present with pneumonia, blinding chorioretinitis, esophagitis, colitis with extensive ulcerations and perforation, meningoencephalitis, radiculitis with polyneuropathies, and hepatitis. Diagnosis may be established by typical cytopathic changes observed in viral tissue cultures, or by direct histological detection of the characteristic viral inclusion cells in specimens. The virus induces cellular gigantism (cytomegaly) with characteristic intranuclear and intracytoplasmic inclusions. In sections stained with H/E, the enlarged nucleus of an infected cell possesses a large eosinophilic inclusion with a peripheral clear halo; within the cytoplasm of an infected cell are numerous punctate inclusions which are also stained by PAS and methenamine silver techniques.

Cytomegaloviral infection of lung results in focal and diffuse hemorrhagic interstitial pneumonitis. Sections of adrenal gland infected by CMV may reveal massive bilateral hemorrhagic necrosis. Many male homosexuals shed CMV in their semen and urine, and it may be detected histologically within the male genitourinary system, especially in seminal vesicles and epididymis. Gastrointestinal involvement by CMV is characterized by ulceration in sites ranging from the esophagus to the rectum, and these ulcers may provide a portal of entry into the bloodstream for a variety of enteric organisms. In CMV retinitis, affected retinas show varying degrees of perivascular exudative hemorrhagic lesions, and histological sections reveal foci of necrosis and characteristic viral inclusions within retinal, choroidal, and optic nerve tissues. In the central nervous system, CMV may produce a destructive meningoencephalitis, or a subacute encephalitis

with microglial nodules. In patients with polyneuropathies and abnormal cerebrospinal fluids, histopathological sections of spinal nerve roots may reveal necrotizing cytomegaloviral radiculitis.

Herpes simplex and zoster virus. In patients with AIDS, herpes simplex may produce ulcerative mucocutaneous lesions, esophagitis, bronchitis, pneumonitis, and encephalitis. Herpes zoster may present as multiple dermatomal (shingles) lesions. Histopathologically, the mucocutaneous herpetic lesion consists of an intraepidermal vesicle produced by marked acantholysis and ballooning degeneration of epithelial cells. Eosinophilic viral inclusion bodies may be detected in enlarged nuclei of balloon cells. Infected cells may coalesce to form syncytial multinucleated inclusion cells.

Polyomavirus. Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder of the central nervous system caused by polyomaviruses of the papova family. Infections develop in adults who are immunologically suppressed, and PML occurs in patients with AIDS. Computed tomographic scans of the brain usually show hypodense white matter lesions without contrast enhancement or mass effect. Gross pathological examination reveals a granular softening of white matter. Histopathologically, there are patchy areas (plaques) of demyelination, necrosis, and gliosis. In sections stained with H/E, within these areas are scattered oligodendroglia with intranuclear amphophilic inclusions, large bizarre astrocytes, and numerous foamy macrophages. Presence of polyomavirus can be demonstrated by immunohistochemical staining and electron microscopy.

Hepatitis B. In addition to being at risk for the development of AIDS, male homosexuals and intravenous drug abusers are also at risk for acquiring hepatitis B infections. We have studied a number of hepatic tissue specimens from patients with AIDS who are antigenemic for hepatitis B. Although immunohistochemical staining for hepatitis B core antigen reveals numerous infected hepatocytes, there is usually minimal to absent associated inflammation. Perhaps patients with AIDS lack the effector cells responsible for the damaging sequelae of hepatitis B infection.

Molluscum contagiosum. Molluscum contagiosum is a DNA virus of the poxvirus group. Infections in patients with AIDS typically appear as multiple 2- to 4-millimeter shiny, pearly-whitish, dome-shaped, umbilicated cutaneous papules distributed over the face and chest. Over a period of several months, the papules characteristically increase dramatically in number and size and spread to the scalp, forehead, and nose. Histopathologically, the lesions exhibit the following features: (*a*) downward proliferation of the epidermis in a lobular configuration, (*b*) numerous intracytoplasmic eosinophilic inclusions (molluscum bodies) in the epidermal cells, (*c*) expansion of the epidermal cell with compression of the nucleus by proliferating viral particles, and (*d*) release of molluscum bodies into the central crater.

Condyloma acuminatum. Common warts occur frequently in patients seropositive for HIV. Lesions often occur on the face, hands, and feet. Homosexuals with AIDS are prone to develop large perianal condylomata acuminata. Histopathologically, the lesions exhibit papillomatosis and acanthosis. The diagnostic feature is the presence of vacuolated epithelial cells with hyperchromatic, basophilic intranuclear inclusions, which may be shown to contain the papillomavirus by immunohistochemical stains.

Oral hairy leukoplakia (OHL). The lesion of OHL is a slightly raised, poorly demarcated, asymptomatic glossal plaque that has a corrugated or "hairy" surface. Although most OHL lesions are localized to the lateral border of the tongue, they may also occur on the ventral surface of the tongue, the buccal mucosa, floor of the mouth, palate, and dorsal tongue. Histopathologically, there is acanthosis, koilocytosis, and marked hyperkeratosis with projections of keratin.

Subacute encephalopathy. Patients with AIDS may also develop idiopathic subacute encephalitis, aseptic meningitis, vacuolar myelopathy, and peripheral neuropathies. Neuropathological findings in cases of subacute encephalopathy include microglial nodules with or without foci of demyelination. The microglial nodules may also contain multinucleated giant cells.

Arthropods. Homosexual men are at increased risk of acquiring sexually transmitted diseases, including scabies (*Sarcoptes scabiei*). Norwegian scabies is an uncommon, more virulent form of scabies that may occur in patients with AIDS. Instead of the usual infestation with 10 to 20 mites, hundreds to thousands of adult *Sarcoptes* mites infest the

body. To diagnose scabies, skin scrapings are treated with 10 percent potassium hydroxide and examined microscopically to reveal mites and eggs. Histopathological examination of a biopsy specimen reveals mites and eggs within tunnels in acanthotic epidermis.

Postscript

The Collaborative Center for the Investigation of AIDS has now studied more than 1,000 cases. As a consultative service, the Center has provided diagnoses on numerous previously undiagnosed surgical (and postmortem) specimens. In addition, the Center has reported a number of new entities in patients with AIDS (for example, extraintestinal disseminated lymphadenopathic isosporiasis, bilateral choroiditis caused by *Pneumocystis carinii*). As more cases are collected and studied from worldwide sources, the pathology of AIDS will undoubtedly expand as additional opportunistic infections, neoplasms, and unusual entities are discovered.

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