Clinical Aspect and Application of Laboratory Test in Herpes Virus Infection

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- Cytomegalovirus (CMV), Epstein Barr Virus(EBV), Herpes Virus(HSV) are double-stranded DNA virus and is a member of the Herpesviridae family.
- At least 60% of the population has been exposed to them, with a more prevalence in high-risk groups (eg , unborn babies whose mothers become infected with CMV during the pregnancy) or people with HIV.

- CMV usually causes an asymptomatic infection or produces mild flulike symptoms; afterward, it remains latent throughout life and may reactivate
- Most patients with CMV infection exhibit few clinical findings on physical examination.
- Primary CMV infection may be a cause of fever of unknown origin. Symptoms, when apparent, develop 9-60 days after primary infection. Pharyngitis may be present and examination of the lungs may reveal fine crackles.

Lymphadenopathy & Splenomegaly

- The lymph nodes and spleen may be enlarged, so CMV, EBV and HSV should be included in the differential diagnoses of infections that produce lymphadenopathy.

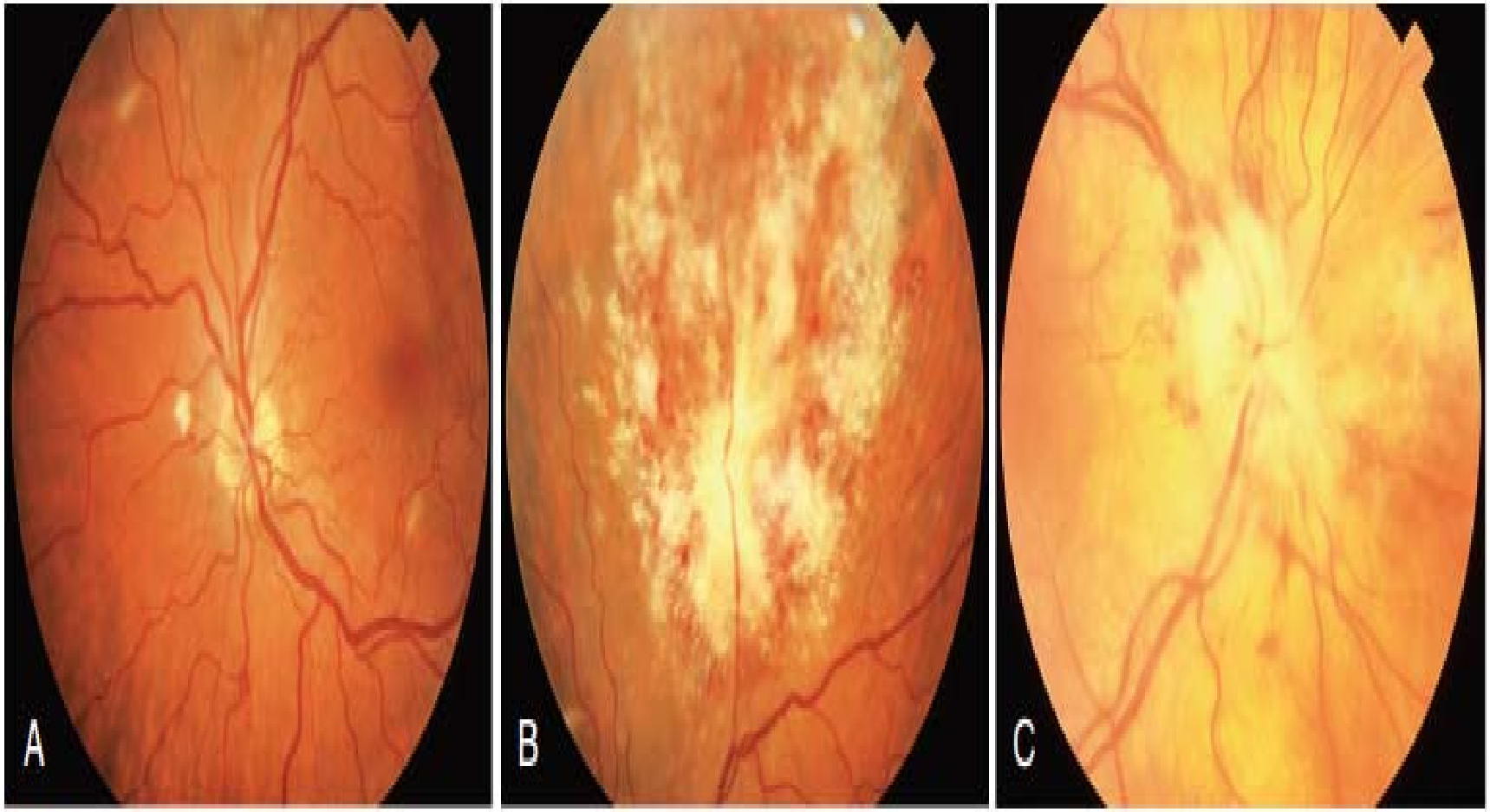
- Adult cytomegalovirus infection in the Immunocompromised host
- CMV infection in transplant recipients may be primary or recurrent.
- Again, the former refers to CMV detection in an individual who was previously seronegative, while recurrent infection includes both reinfection and reactivation.

- CMV infection may cause direct or indirect effects.
- Direct effects include bone marrow suppression, pneumonia, myocarditis, GI disease, hepatitis, pancreatitis, nephritis, retinitis, and encephalitis.

The main indirect effects include acute and chronic graft rejection, accelerated atherosclerosis (heart transplants), secondary bacterial or fungal infections, EBV-associated posttransplant lymphoproliferative disease (PTLD), and decreased graft and patient survival.

CMV in HIV infection

- CMV infection may affect the same organ systems in HIV-positive patients with low CD4 counts as those in organ transplant recipients.
- Retinitis has been the major reported CMV disease in patients with HIV infection, followed by CNS involvement.



GURE 140-2 Cytomegalovirus (CMV) retinitis. A, Early disease with retinal involvement along blood vessels. **B,** Extensive retinal damage and tinal hemorrhages. **C,** CMV retinitis with papillitis.

Organ transplantation and cytomegalovirus

- CMV disease occurs with the highest frequency in donor-positive/recipient-negative transplant recipients.
- This relationship is true for all organ transplant recipients except those who receive bone marrow, in whom the highest incidence of CMV disease is in donor-negative/recipient-positive individuals.
- The reason for this is unknown but may be related to the level of immunosuppression observed in patients who have received marrow transplants compared with those who have received other transplants.

Life-threatening CMV pneumonia

- Life-threatening CMV pneumonia may develop in immunocompromised patients, with the incidence varying based on the type of transplant received.
- Patients who receive marrow, lung, heart, heart-lung, liver, pancreas-kidney, and kidney transplants have different levels of immunosuppression.
- Those most at risk include bone-marrow transplant recipients and recipients of lung transplants.

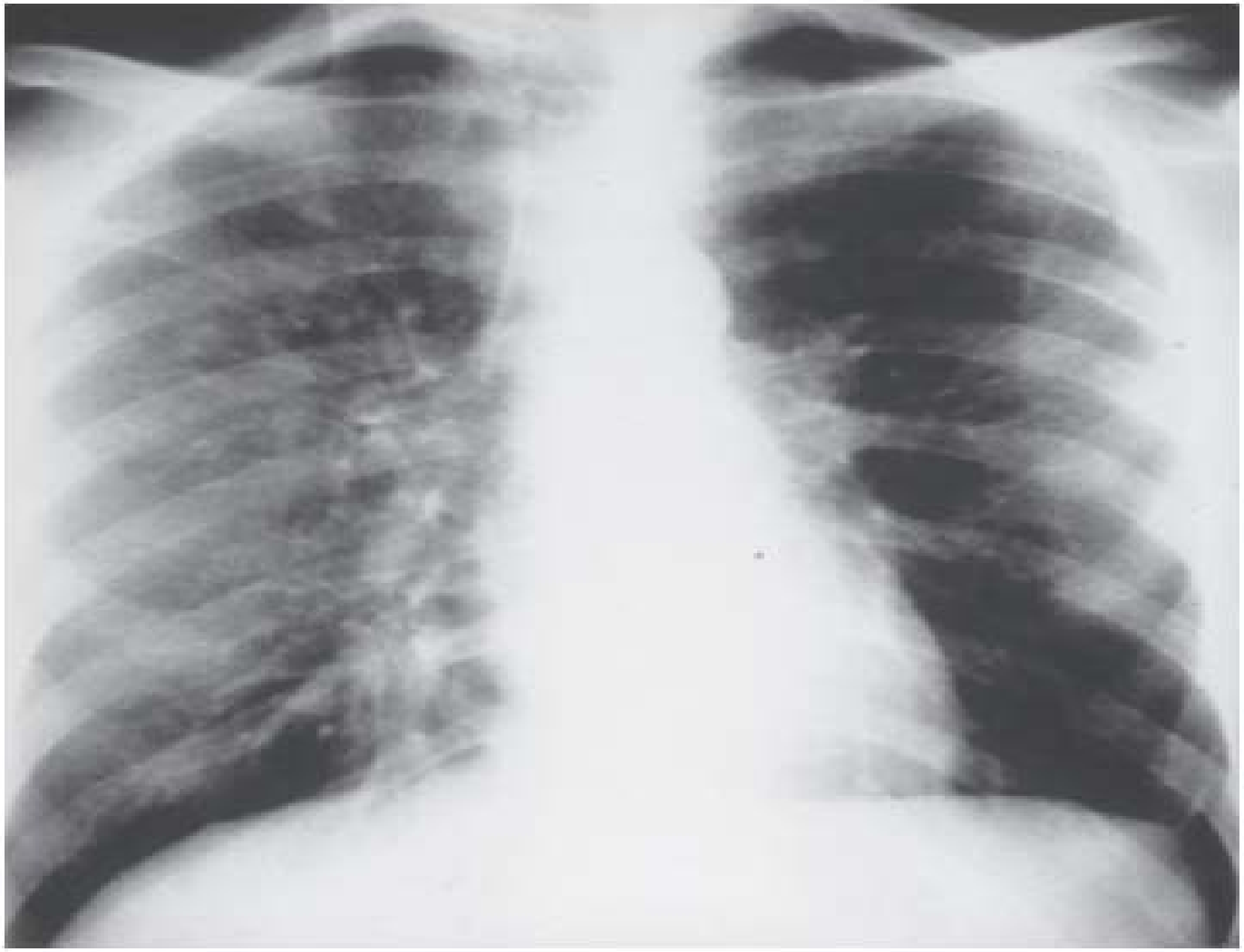


FIGURE 140-1 Bilateral interstitial pneumonitis caused by cytomegalovirus in bone marrow transplant recipient.

- In patients who have received marrow transplants, CMV disease is most likely 30-60 days after transplant.
- Fatal CMV pneumonia is much less common in patients who have received solid organ transplants than in those who have received marrow transplants.
- Patients may initially present with an asymptomatic infiltrate on chest radiograph.

- The most common clinical presentation of CMV pneumonia is fever and shortness of breath, accompanied by an interstitial infiltrate.
- The differential diagnoses of CMV pneumonia in immunocompromised patients include : Pneumocystis pneumonia, viral respiratory Infections, pulmonary hemorrhage, drug toxicity, recurrent lymphoma, and other infections.

Treatment of CMV pneumonia

- CMV pneumonia is difficult to treat, even with the antivirals now available. The mortality rate among bone marrow transplant recipients with CMV pneumonia was approximately 85% prior to the introduction of ganciclovir and CMV-specific immune globulin.
- The addition of these drugs has decreased the CMV pneumonia mortality rate to 15%-75%. The mortality rate of CMV pneumonia in marrow transplants that requires mechanical ventilation is high, despite treatment with ganciclovir and immune globulin.

- CMV has been detected via culture (human fibroblast), serologies, antigen assays, polymerase chain reaction (PCR), and cytopathology.
- In the transplant population, antigen assays or PCR is used (sometimes in conjunction with cytopathology) for diagnosis and treatment.

Antigen testing

- Antigenemia is defined as the detection of the CMV pp65 antigen in leukocytes.

- The pp65 assay is used to detect messenger matrix proteins on the CMV virus, with either immunofluorescence assay or messenger RNA amplification. These proteins are typically expressed only during viral replication.
- Antigen tests are often the basis for institution of antiviral therapy in transplant recipients and may allow for the detection of subclinical disease in high-risk patients. The assay is sensitive and specific yields results quickly.

- Antigen assays **cannot** be used in patients with leukopenia, as these tests detect antigen within neutrophils.
- In immunocompromised patients, low or moderate CMV antigenemia may indicate reactivation or infection.
- It has been reported that the pp65 antigen assay and quantitative CMV PCR yield similar effectiveness in diagnosing and monitoring patients with active CMV infection.

Qualitative polymerase chain reaction

- Qualitative PCR is used to detect CMV in **blood** and **tissue** samples.
- PCR depends on the multiplication of primers specific for a portion of a CMV gene. The primers usually bind to the area of virus that codes for early antigen.
- Qualitative PCR is extremely **sensitive**, but, because CMV DNA can be detected in patients with or without active disease, the clinical utility of qualitative PCR is limited.
- Serial PCR may be more helpful clinically.It yields a positive result before the antigenemia test in transplant recipients with viremia.

Quantitative polymerase chain reaction

- Quantitative PCR has been used to detect plasma CMV.
- The advantage of quantitative PCR over regular PCR is unknown. Ideally, quantitative PCR is as sensitive as qualitative PCR and provides an estimate of the number of CMV genomes present in plasma.

Use of Viral Load

- In theory, the CMV viral load would indicate whether therapy is necessary because patients whose viral load is below a certain cutoff would not develop CMV disease.
- However, the level of viremia necessary for CMV disease to occur may vary depending on host factors and the type of organ transplant, and this may need to be determined empirically.
- For example, in CMV retinitis, the viral load has a poor positive predictive value, meaning its clinical utility is limited.

- Some tests are sensitive enough to detect anti-CMV IgM antibody early in the course of the illness (CMV early [nuclear] antigen, CMV viral capsid antigen) and during CMV reactivation.
- As with EBV infection, observing reactivation of the virus with a positive IgM result in the presence of IgG antibody is not uncommon. This is most commonly observed during intercurrent infection in immunocompromised patients.

Epstein-Barr virus (EBV)

- Epstein-Barr virus (EBV), or human herpesvirus 4, is a gammaherpesvirus that infects more than 95% of the world's population.
- The most common manifestation of primary infection with this organism is acute infectious mononucleosis, a self-limited clinical syndrome that most frequently affects adolescents and young adults. Classic symptoms include sore throat, fever, and Lymphadenopathy.

- Infection with Epstein-Barr virus in younger children is usually asymptomatic or mild. However, Epstein-Barr virus is also a human tumor virus, the first virus associated with human malignancy.
- Infection with Epstein-Barr virus is associated with lymphoproliferative disorders, especially in immunocompromised hosts, and is associated with various tumors, including nasopharyngeal carcinoma and Burkitt lymphoma.

Posttransplant lymphoproliferative disease (PTLD)

- Posttransplant lymphoproliferative disease (PTLD) is a well-recognized complication of both solid organ transplantation (SOT) and allogeneic hematopoietic stem cell transplantation (HSCT).
- It is one of the most common posttransplant malignancies. In most cases, PTLD is associated with Epstein-Barr virus (EBV) infection of B cells, either as a consequence of reactivation of the virus posttransplantation or from primary EBV infection.

- PTLD is identified by having a high index of suspicion in the appropriate clinical setting. The diagnosis is made by histopathological evidence of lymphoproliferation, commonly with the presence of EBV DNA, RNA, or protein detected in tissue.
- Most cases of PTLD occur within the first posttransplant year. The more intense the immunosuppression used, the greater the risk of PTLD and the earlier it tends to occur.

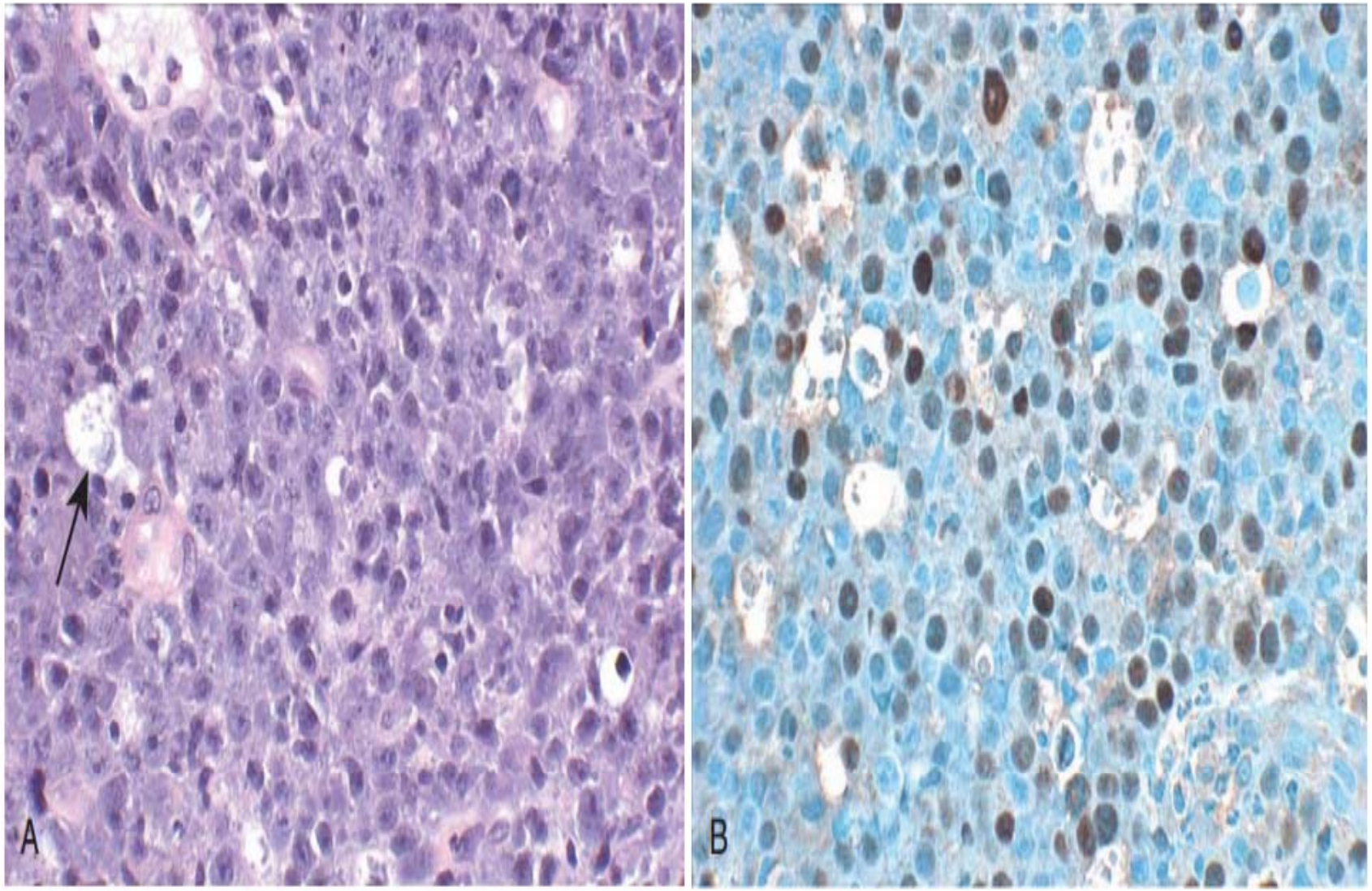


FIGURE 141-2 Post-transplant lymphoproliferative disease involving the colon. A, Tumor is composed of large, atypical lymphoid cells (hematoxylin and eosin). Scattered macrophages *(arrow)* are seen, producing "starry-sky" appearance. **B,** In situ hybridization for Epstein-Barr virus (EBV)–encoded RNA (EBER; *brown*) shows variably intense nuclear staining in most tumor cells, indicating EBV infection. (Original magnification, ×400.) *(Courtesy Dr. Jeffery Kutok.)*

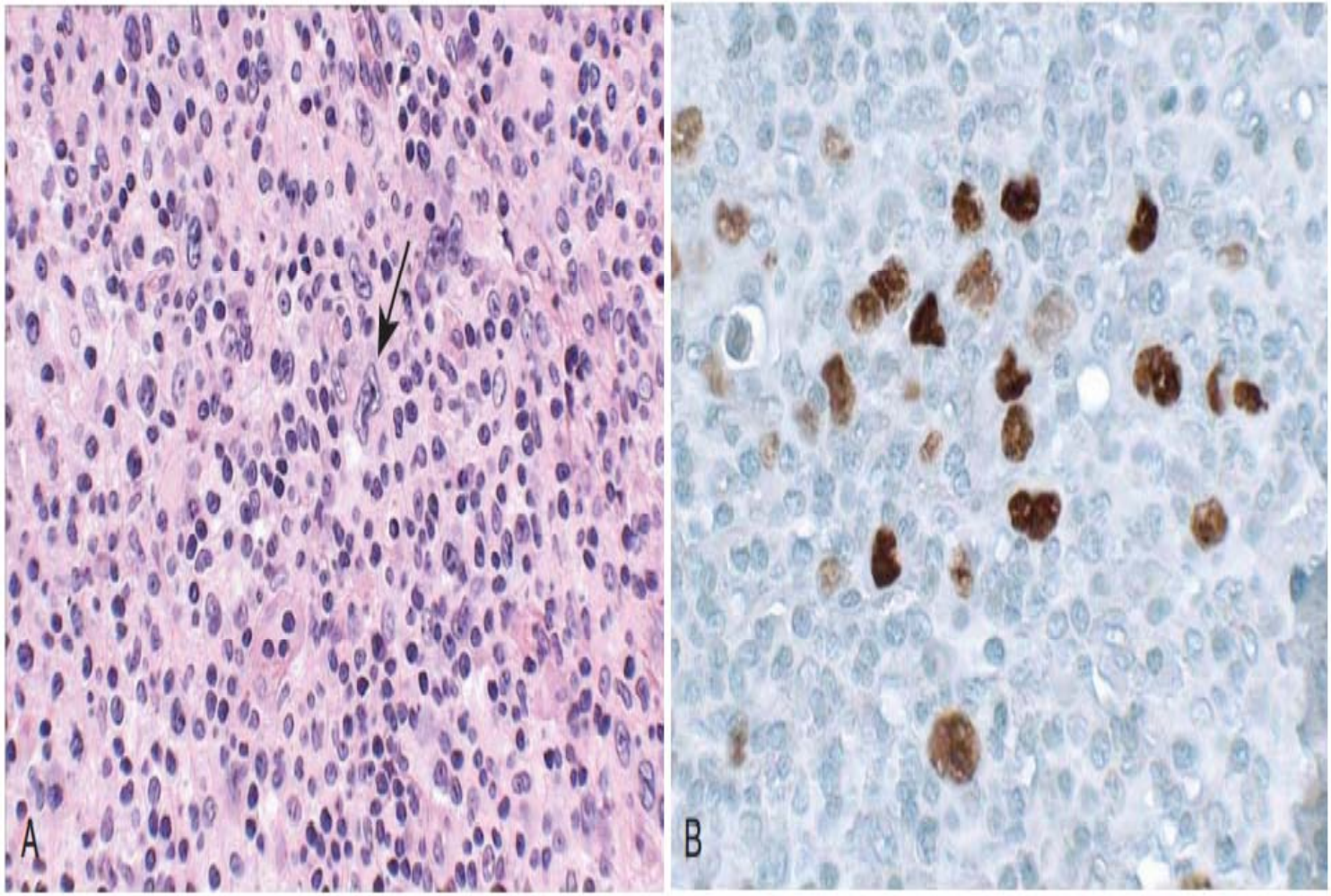


FIGURE 141-3 **Mixed cellularity classic Hodgkin's lymphoma. A,** Lymph node architecture is effaced by infiltrate composed of small lymphocytes, epithelioid histiocytes, plasma cells, eosinophils, and Hodgkin and Reed-Sternberg cells (*arrow;* hematoxylin and eosin). **B,** In situ hybridization for Epstein-Barr virus (EBV)–encoded RNA (EBER; *brown*) shows EBV infection in malignant Hodgkin and Reed-Sternberg cells. (Original magnification, ×400.) *(Courtesy Dr. Jeffery Kutok.)*

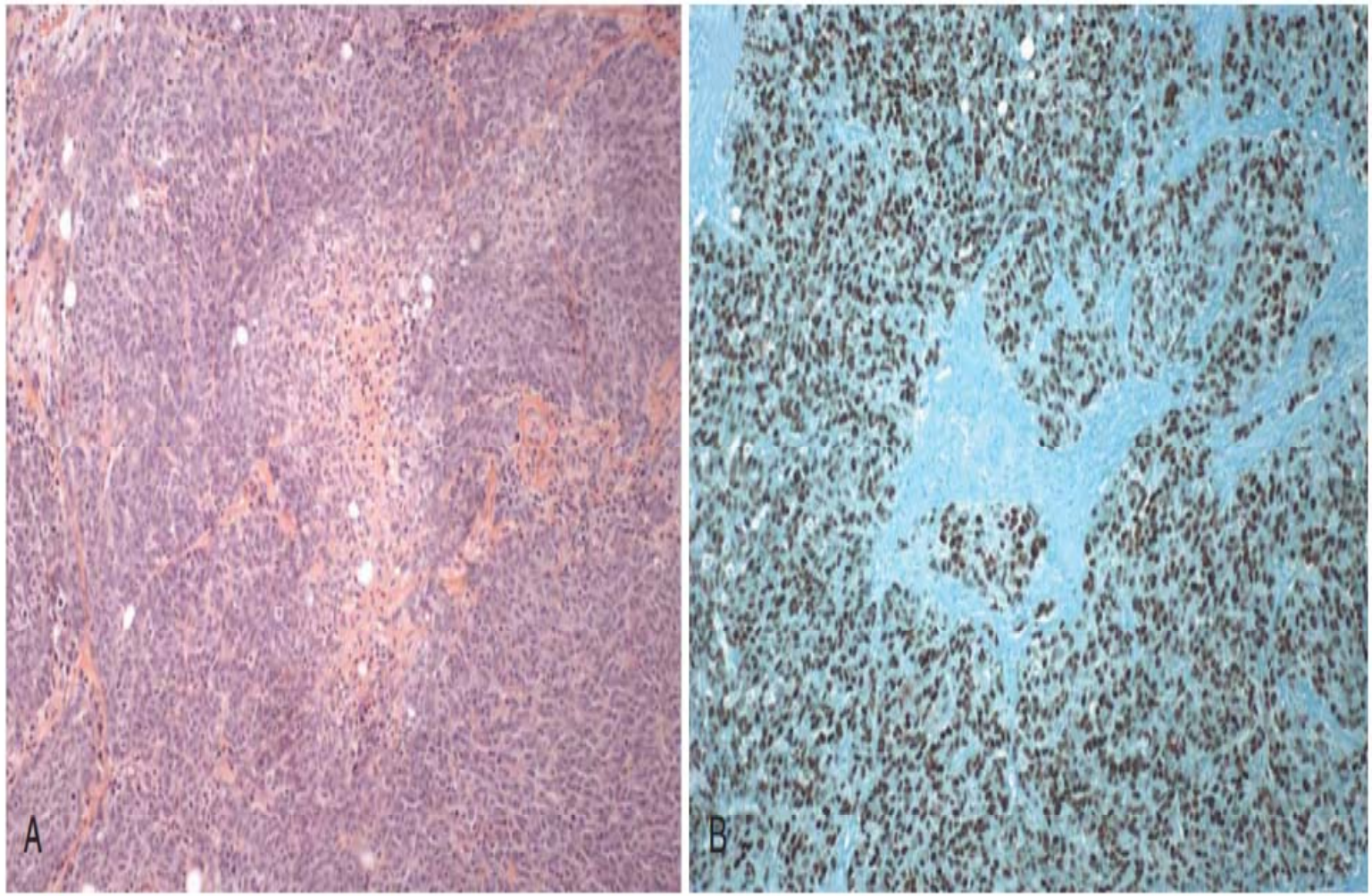


FIGURE 141-4 Nasopharyngeal carcinoma. A, Nests of metastatic undifferentiated nasopharyngeal carcinoma in a fibrous stroma in lymph node (hematoxylin and eosin). Metastases often lack infiltrating lymphocytes. **B,** In situ hybridization for Epstein-Barr virus (EBV)–encoded RNA (EBER; *brown*) shows EBV infection in most cells in the same area of tissue. (Magnification, ×100.) *(Courtesy Dr. Miguel Rivera.)*

- In cases of primary infection, EBV may be acquired from the donor graft or, less commonly, from environmental exposure. While T-cell lymphoproliferative disorders that are not typically associated with EBV infection also occur after SOT and HSCT, the vast majority are B-cell proliferations.

- The cornerstone of initial management of PTLD is reduction or withdrawal of immunosuppression, which in some situations may reverse the lymphoproliferative process.
- This potential for reversibility with reduction of immunosuppression distinguishes PTLD from neoplastic lymphoproliferative disorders that occur in immunocompetent patients.
- Other potential treatments include surgical excision of the lesion, localized radiation therapy, antiviral therapy, immunoglobulin therapy, combination chemotherapy, monoclonal antibodies, and the use of cytotoxic T lymphocytes.

HSV

- Herpes simplex viruses are ubiquitous, host-adapted pathogens that cause a wide variety of disease states. Two types exist:

herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2).

- Both are closely related but differ in epidemiology. HSV-1 is traditionally associated with orofacial disease ,while HSV-2 is traditionally associated with genital disease; however, lesion location is not necessarily indicative of viral type.

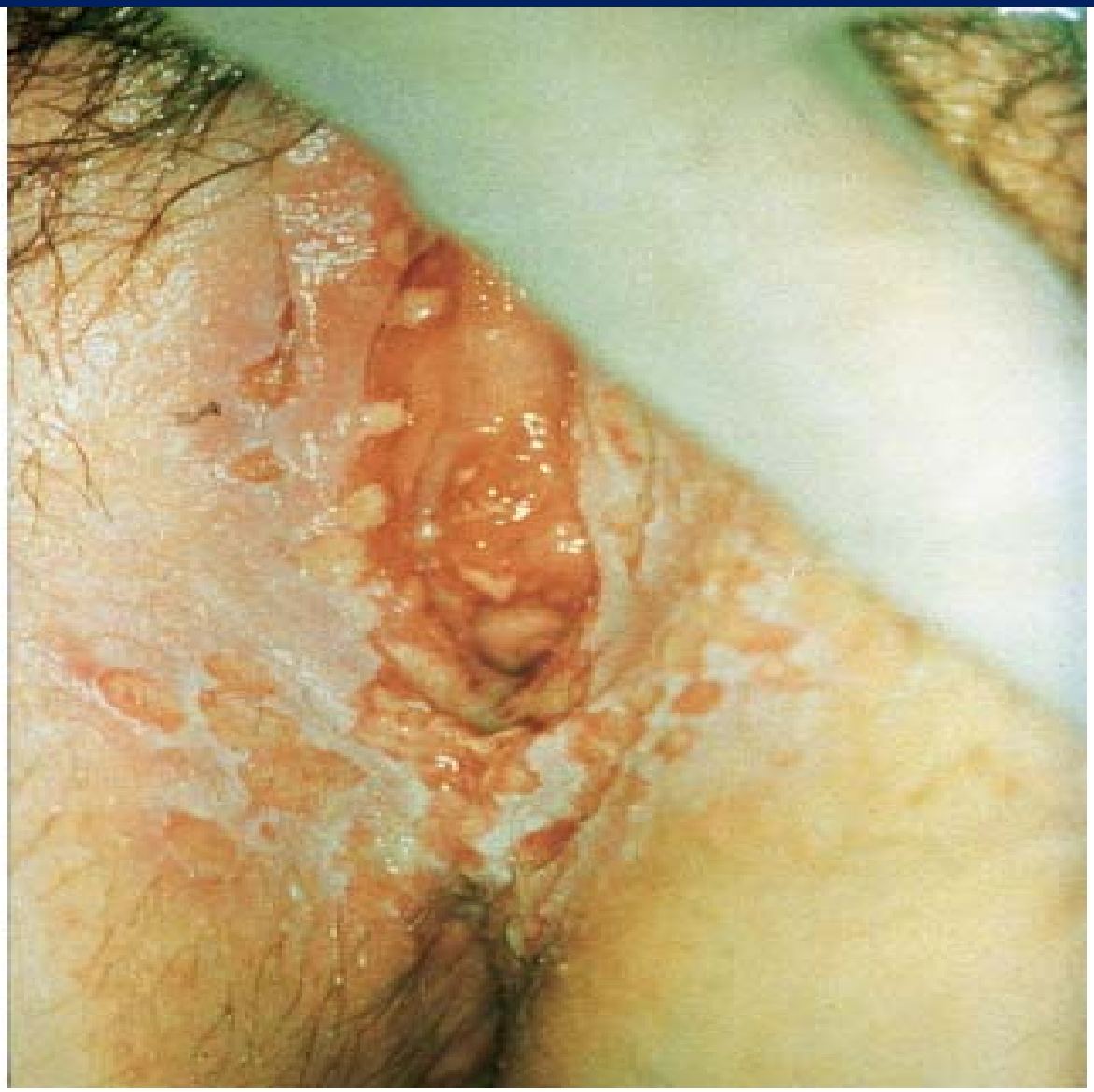


FIGURE 108-3 Primary herpes simplex infection. Severe primary herpes simplex virus infection.

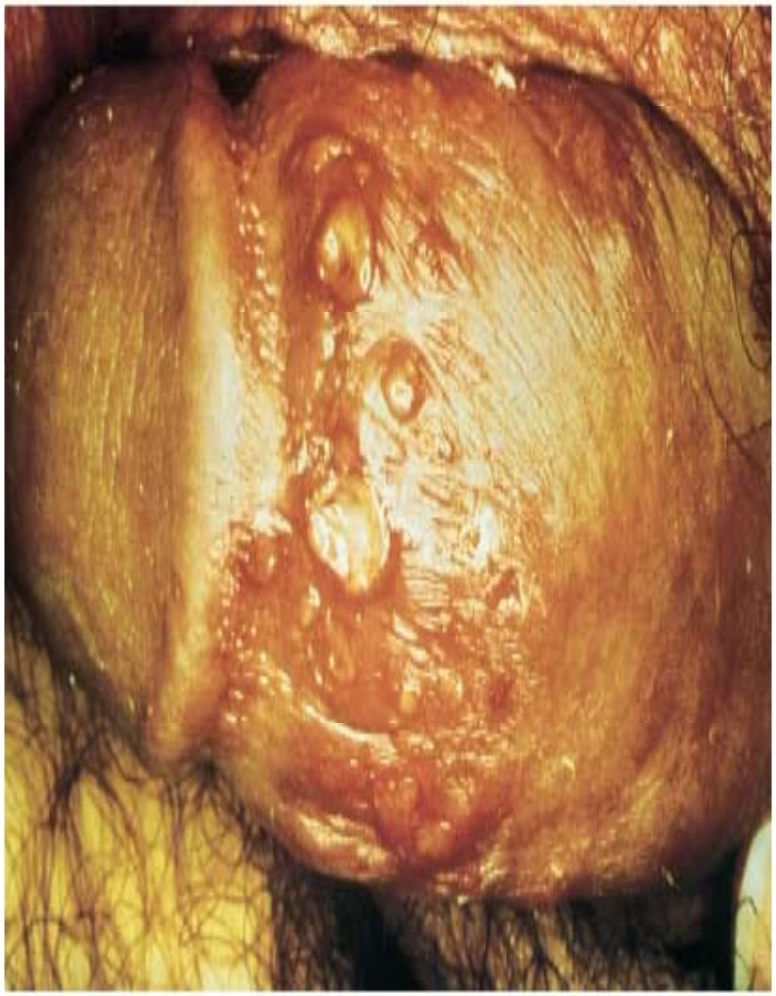


FIGURE 108-1 Herpes simplex virus infection. Genital infection with herpes simplex virus.

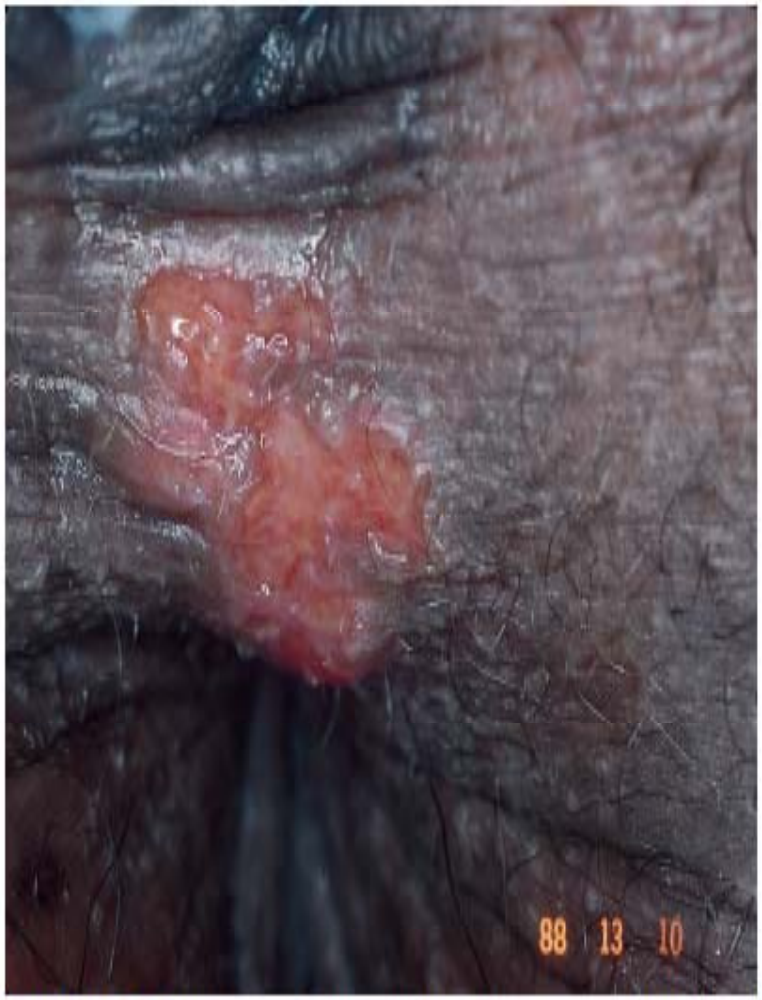


FIGURE 108-2 Herpes simplex virus ulcer. An irregularly shaped herpes simplex virus ulcer.

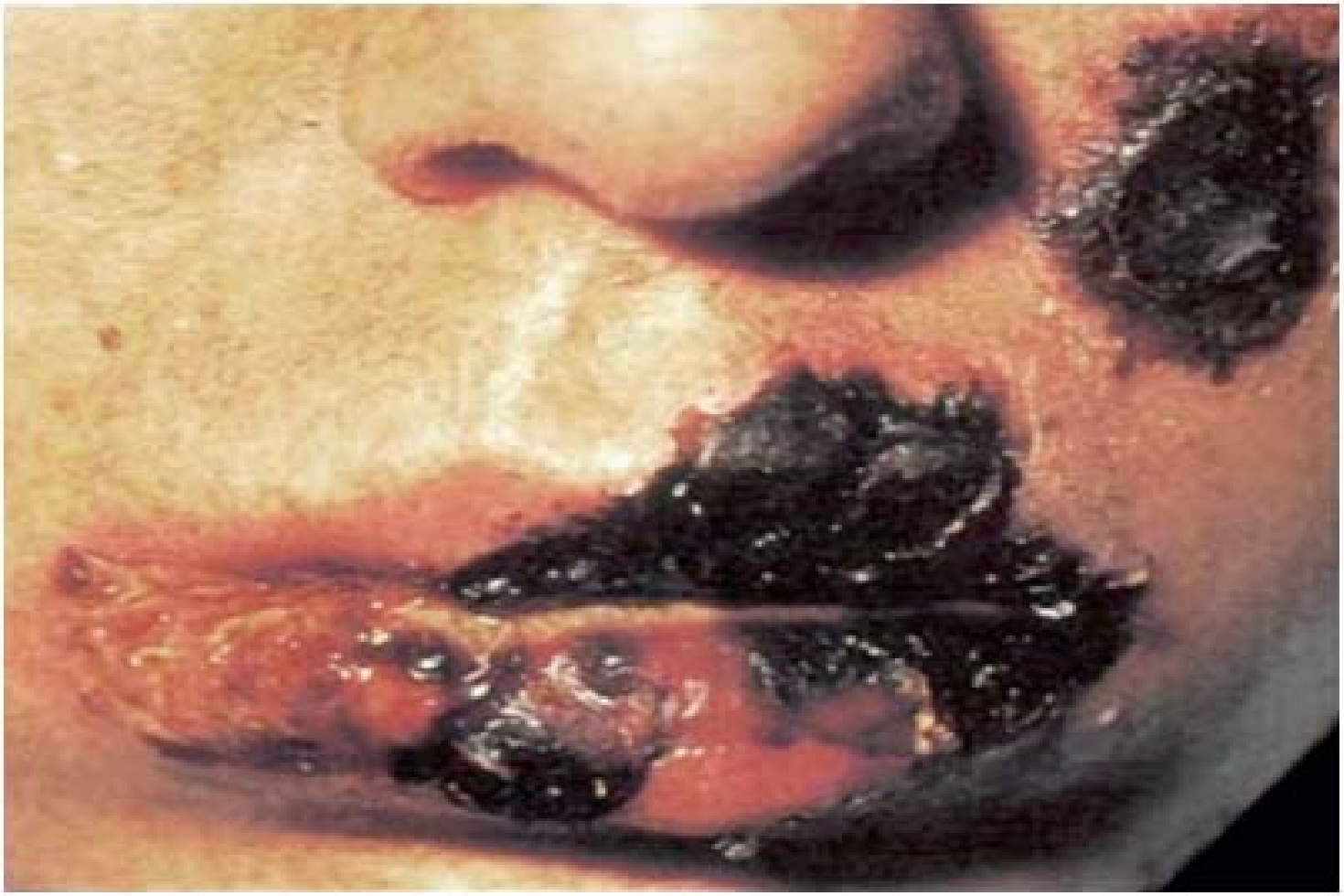


FIGURE 138-9 Severe mucocutaneous herpes simplex virus type 1 infection in a bone marrow transplant patient. *(From Corey L. Herpes simplex virus infections. In: Mandell GL, series ed; Rein MF, ed.* Atlas of Infectious Diseases, vol. V, Sexually Transmitted Diseases. *Philadelphia: Churchill Livingstone; 1996.)*

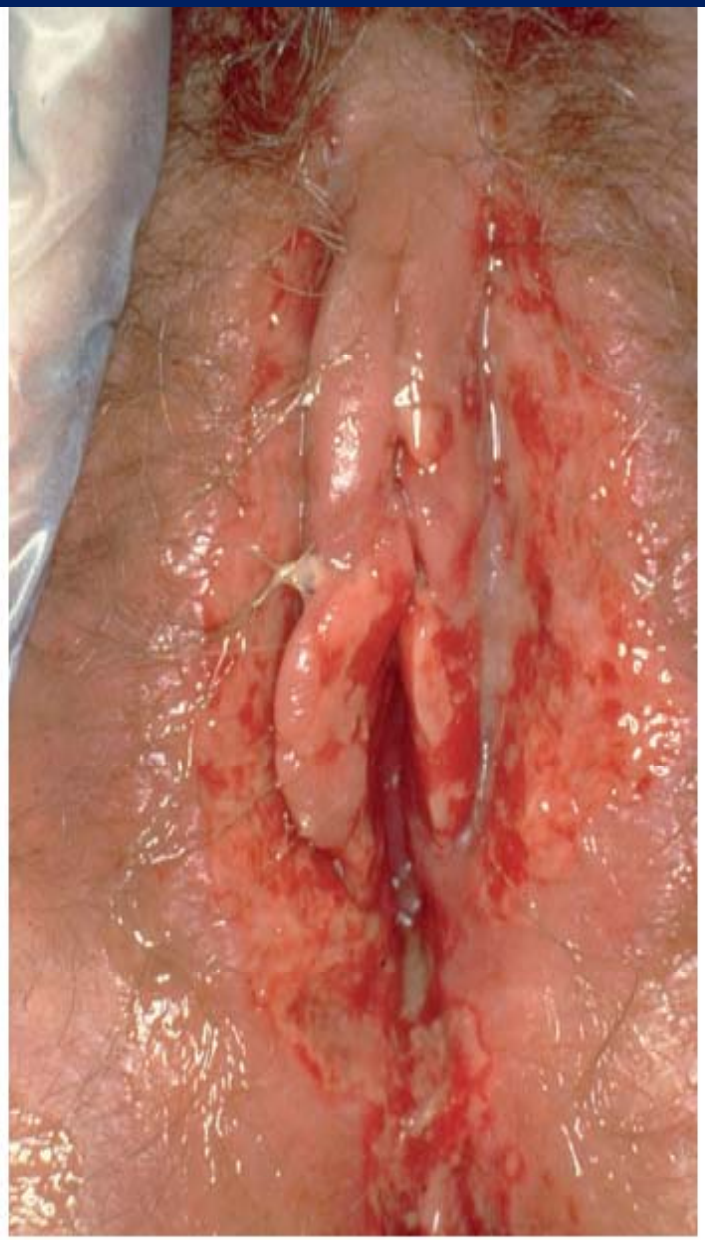


FIGURE 138-5 Primary genital herpes simplex virus type 2 infection of the vulva.

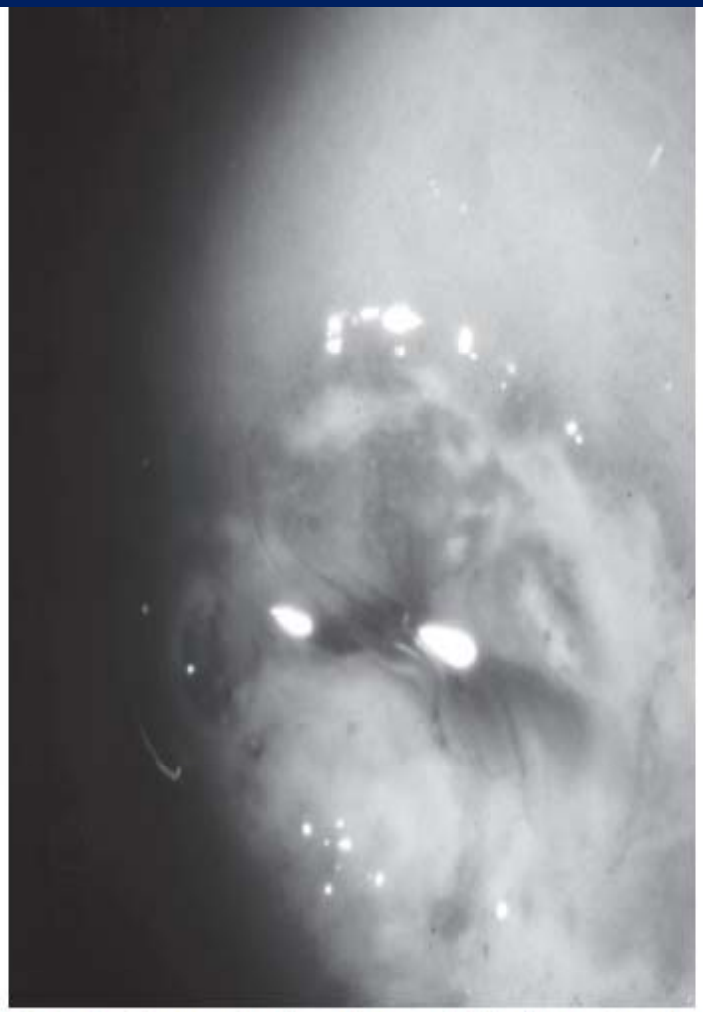


FIGURE 138-7 **Herpes simplex virus cervicitis.** *(From Corey L. Herpes simplex virus infections. In: Mandell GL, series ed; Rein MF, ed.* Atlas of Infectious Diseases, vol. V, Sexually Transmitted Diseases. *Philadelphia: Churchill Livingstone; 1996.)*

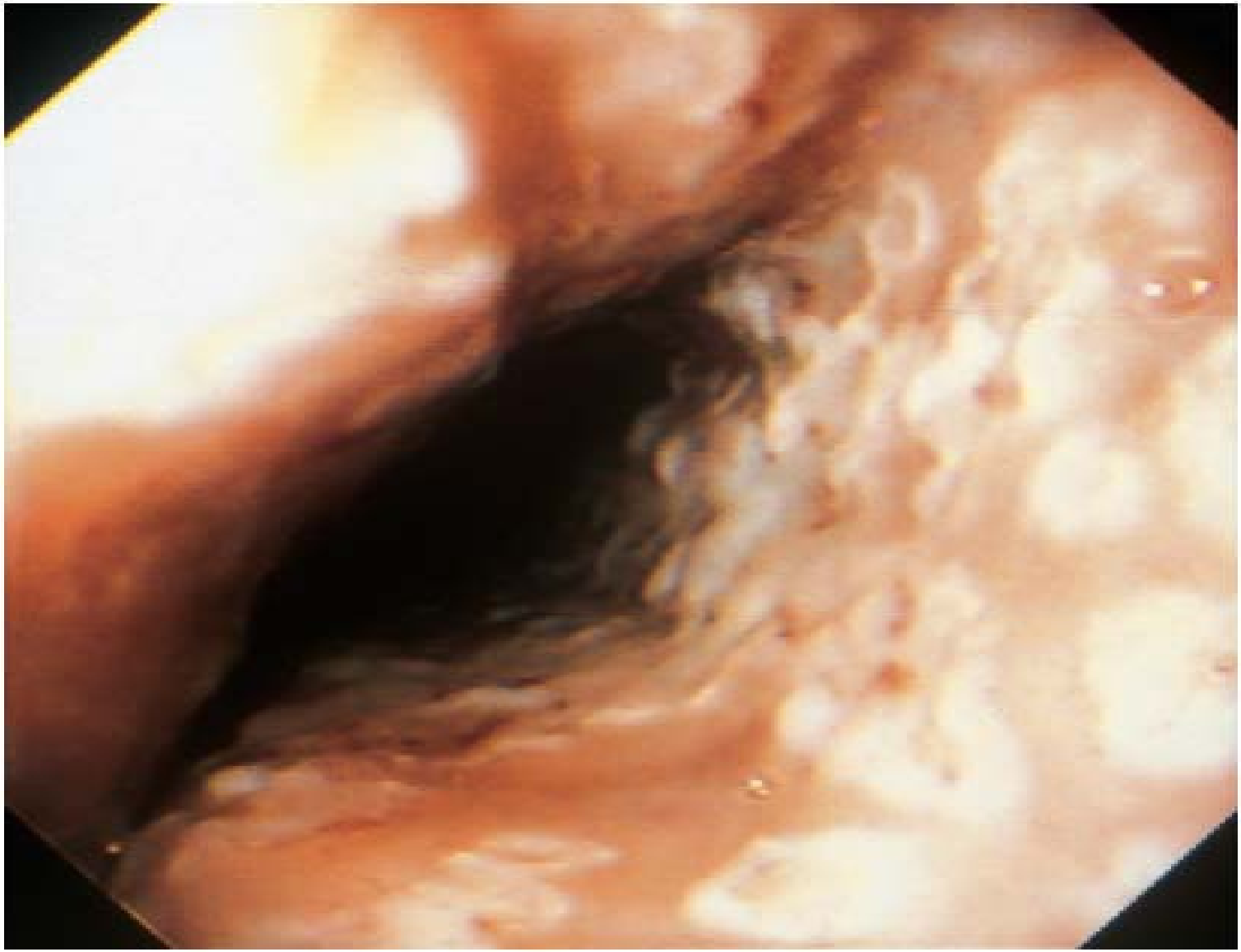


FIGURE 99-3 **Herpes simplex esophagitis, characterized by numerous small ulcerations, in an immunocompetent adult with fever and odynophagia.** *(Courtesy Dr. Charles Michalko, Rochester, NY.)*

- Up to 80% of herpes simplex infections are asymptomatic. Symptomatic infections can be characterized by significant morbidity and recurrence. In immunocompromised hosts, infections can cause life-threatening complications.
- The prevalence of HSV infection worldwide has increased over the last several decades, making it a major public health concern. Prompt recognition of herpes simplex infection and early initiation of therapy are of utmost importance in the management of the disease.

HSV in IMMUNCOMPROMISED host

- Although recurrent HSV infections may last much longer (>30 d) in immunocompromised hosts, such as individuals with AIDS, frequent recurrences are **not** necessarily a sign of an altered immune system.

Medical Care

- Overall, medical treatment of herpes simplex virus (HSV) infection is centered around specific antiviral treatment. **While** the same medications are active against HSV-1 and HSV-2, the location of the lesions and the chronicity (primary or reactivation) of the infection dictate the dosage and frequency of medication.
- It **is important** to note that life-threatening HSV infections in immunocompromised patients and HSV encephalitis require high-dose intravenous acyclovir, often started empirically.
- When constitutional effects such as fever occur, symptomatic treatment can be used.

Thanks for your patience