Virology

Lec (12)
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Teaching Objectives:

1. Know different methods for escape from immune system.
2. Recognize the mechanism of diagnosis.
3. List methods of treatment and prevention.

Explain why infection with HIV leading to the death of helper T cells.

- The first mechanism, the virus bind with CD4 receptor and leading to death of cell
- The second mechanism, HIV acts as a "super antigen" which indiscriminately activates many helper T cells and leads to their demise.

Why some person has protection against HIV?

- In 1995, it was reported that a group of HIV-infected individuals has lived for many years without opportunistic infections and without a reduction in the number of their helper T (CD4) cells. The strain of HIV isolated from these individuals has mutations in the nef gene, indicating the importance of this gene in pathogenesis. The Nef protein decreases class I MHC protein synthesis, and the inability of the mutant virus to produce functional Nef protein allows the cytotoxic T cells to retain their activity.
- Another explanation why some HIV-infected individuals are long-term "non progressors" may lie in their ability to produce large amounts of alph-defensins. alph-Defensins are a family of positively charged peptides with antibacterial activity. In 2002, they were shown to also have antiviral activity. They interfere with HIV binding to the CXCR4 receptor and block entry of the virus into the cell.
In addition to the detrimental effects on T cells, abnormalities of B cells occur. Polyclonal activation of B cells is seen, with resultant high immunoglobulin levels. Autoimmune diseases, such as thrombocytopenia, occur.

**HIV has three main mechanisms by which it evades the immune system:**

1. Integration of viral DNA into host cell DNA, resulting in a persistent infection.
2. High rate of mutation of the env gene
3. The production of the Tat and Nef proteins that downregulate class I MHC proteins required for cytotoxic T cells to recognize and kill HIV-infected cells.

The ability of HIV to infect and kill CD4-positive helper T cells further enhances its capacity to avoid destruction by the immune system.

**Clinical Findings**

The clinical picture of HIV infection can be divided into three stages:

1. Early, acute stage
2. Middle stage (Latent stage)
3. Late or immunodeficiency stage

- In the acute stage, which usually begins 2-4 weeks after infection, a mononucleosis-like picture of fever, lethargy, sore throat, and generalized lymphadenopathy occurs. A maculopapular rash on the trunk, arms, and legs (but sparing the palms and soles) is also seen. Leukopenia occurs, but the number of CD4 cells is usually normal. A high-level viremia typically occurs, and the infection is readily transmissible during this acute stage. This acute stage typically resolves spontaneously in about 2 weeks. Resolution of the acute stage is usually accompanied by a lower level of viremia and a rise in the number of CD8-positive (cytotoxic) T cells directed against HIV.
Antibodies to HIV typically appear 10–14 days after infection.

2- In the middle stage, a long latent period, measured in years, usually ensues. In untreated patients, the latent period usually lasts for 7–11 years. The patient is asymptomatic during this period. Although the patient is asymptomatic and viremia is low or absent, a large amount of HIV is being produced by lymph node cells but remains sequestered within the lymph nodes. This indicates that during this period of clinical latency, the virus itself does not enter a latent state.

3- Late stage or called AIDS-related complex (ARC) can occur during the latent period. The most frequent manifestations are persistent fevers, fatigue, weight loss, and lymphadenopathy. ARC often progresses to AIDS. The late stage of HIV infection is AIDS, manifested by a decline in the number of CD4 cells to below 400/μL and an increase in the frequency and severity of opportunistic infections.
<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Disease or Symptom</th>
<th>Causative Organism</th>
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<tbody>
<tr>
<td>Lung</td>
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<tr>
<td></td>
<td>1. Pneumonia</td>
<td><em>Pneumocystis carinii</em>, cytomegalovirus</td>
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<td>2. Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td>Mouth</td>
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<td></td>
<td>1. Thrush</td>
<td><em>Candida albicans</em></td>
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<td></td>
<td>2. Hairy leukoplakia</td>
<td>Epstein-Barr virus</td>
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<td></td>
<td>3. Ulcerations</td>
<td>Herpes simplex virus-1, <em>Histoplasma capsulatum</em></td>
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<tr>
<td>Esophagus</td>
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<tr>
<td></td>
<td>1. Thrush</td>
<td><em>Candida albicans</em></td>
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<td></td>
<td>2. Esophagitis</td>
<td>Cytomegalovirus, herpes simplex virus-1</td>
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<tr>
<td>Intestinal tract</td>
<td>Diarrhea</td>
<td><em>Salmonella sp.</em>, <em>Shigella sp.</em>, cytomegalovirus, <em>Cryptosporidium parvum</em>, <em>Giardia lamblia</em></td>
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<tr>
<td>Central nervous system</td>
<td>1. Meningitis</td>
<td><em>Cryptococcus neoformans</em></td>
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<td></td>
<td>2. Brain abscess</td>
<td><em>Toxoplasma gondii</em></td>
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<td>3. Progressive multifocal leukoencephalopathy</td>
<td><em>JC virus</em></td>
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<tr>
<td>Eye</td>
<td>Retinitis</td>
<td>Cytomegalovirus</td>
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<tr>
<td>Skin</td>
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<td></td>
<td>1. Kaposi's sarcoma</td>
<td>Human herpesvirus 8</td>
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<td></td>
<td>2. Zoster</td>
<td>Varicella-zoster virus</td>
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<td></td>
<td>3. Subcutaneous nodules</td>
<td><em>Cryptococcus neoformans</em></td>
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<tr>
<td>Reticuloendothelial system</td>
<td>Lymphadenopathy or splenomegaly</td>
<td><em>Mycobacterium avium</em> complex, Epstein-Barr virus</td>
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**Laboratory Diagnosis**

2- The presumptive diagnosis of HIV infection is made by the Detection of antibodies by ELISA. Because there are some false-positive results with this test. The definitive diagnosis is made by Western blot analysis, in which the viral proteins are displayed by acrylamide gel electrophoresis, transferred to nitrocellulose paper (the blot), and reacted with the patient's serum. If antibodies are present, they will bind to the viral proteins (predominantly to the gp41 or p24 protein). Enzymatically labeled antibody to human IgG is then added. A color reaction reveals the presence of the HIV antibody in the infected patient's serum.

3- The polymerase chain reaction (PCR) is a very sensitive and specific technique that can be used to detect HIV DNA within infected cells.

4- The amount of viral RNA in the plasma (i.e., the viral load) can also be determined using PCR-based assays.

**Ora- Quick** is a rapid screening immunoassay for HIV antibody that uses a blood sample obtained by fingerprick. Results require confirmation by a western blot test.

**Treatment**

- The current treatment of choice for advanced disease is a regimen consisting of two nucleoside inhibitors (zidovudine and lamivudine) and a protease inhibitor (indinavir). This combination is known as **HAART**, which is an acronym for "highly active antiretroviral therapy." It is very effective in prolonging life.

- Zidovudine (ZDV, azidothymidine, AZT, Retrovir) inhibits HIV replication by interfering with proviral DNA synthesis.

- Didanosine (dideoxyinosine, ddI, Videx) is recommended for patients who are intolerant of ZDV or whose disease has progressed while they were taking ZDV.
**Vaccination:**
- Whole virus vaccines: Attenuated, killed, defective.
- Subunit vaccines: monovalent or multivalent.
- Target cell protection: e.g. Abs to viral attachment route in or to CD4 receptor.
- Antigen presentation options: e.g. nonspecific immunostimulation.

**Control measures:**
- Eliminate the high risk factors.
- Screening of blood.

**Health education through:**
- Avoid illegal sex.
- Avoid sharing needles or syringes.
- HIV infected mother should avoid breast-feeding.

**Laboratory diagnosis:**
- Virus isolation.
- Serology
  - **ELISA techniques** (sensitivity and specificity exceeding 98%). If the ELSA tests are used for screening of low risk population (Blood donors), a twice-positive sera must be confirmed by repeated test. If it is also positive, Confirmatory test should be performed. Western blot technique is widely used, in which Abs to HIV proteins of specific M.Ws could be detected. To be considered positive, at least two bands including p 24, gp 41, gp 120/160 should be present. Other band pattern are interpreted as indeterminate. The majority of HIV infected persons are seroconvert after 2 ms of exposure.

**Detection of viral Nu.acid & Ags: Viral infection is quantified by**
1- Reverse transcriptase assay, which measure the enzyme activity of released HIV particles.
2- Indirect immunofluorescence, which measured the percentage of infected cells.
3- RT- polymerase chain reaction (RT-PCR) or Branched chain DNA amplification assay, which measure HIV nucleic acid.

- The amount of HIV I the blood (viral load) is of significant prognostic value. It is the best predictor of long-term clinical outcome & in assessing the effectiveness of antiviral therapy.
- Estimation of peripheral CD4 and CD8 T cells is also of value in this regard. It is the best predictor of short-term risk of developing OPIs.
Treatment:
- Classes of drugs include both nucleoside and nucleotide inhibitors of RT & protease enzymes of HIV.
- The current recommendation is to treat HIV infected persons with combination of antiviral drugs including protease inhibitor, since monotherapy usually result in the rapid emergence of resistant mutants.
- Zidovudin (AZT) treatment during pregnancy and after delivery reduces the perinatal transmission by 65-75%.
- Gene therapy to achieve intracellular immunization.

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