Primary HIV Infection

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Introduction

- A 56 year old man presented to the clinic complaining of 10 days of fevers, profuse sweating and fatigue. He had been given cephalexin by his doctor five days before and had developed an erythematous rash on the face and trunk and diarrhea. He denied sore throat, cough, headache, or myalgias or arthralgias. His health had been good except for mild hypertension and mild diabetes controlled with diet alone. He denied contact with others complaining of similar symptoms, exposure to children or animals, or recent travel. His physical revealed generalized lymphadenopathy and mild hepatomegaly. His initial laboratory studies were normal except for a white blood cell count of 3,800 (differential: PMNs – 75%, mononuclear cells – 10%, lymphocytes – 15%) and mild elevation of the AST and ALT.

- A 24 year old single mother came to the emergency room with severe global headache, sore throat, chills and fevers days duration. She had a monogamous relationship with her boyfriend of > 6 months, denied travel, animal exposure, or drug use. Her past medical history was negative. Except for a stiff neck, her physical examination was unremarkable. Analysis of her spinal fluid showed: WBCs 6ml, 100% mononuclear cells; glucose 56g/dl; protein 32g/dl; cryptococcal antigen negative; smears and cultures, negative. Her CBC showed a WBC of 5300/ml, 76% PMNs, 15% lymphocytes and 9% mononuclear cells. Three days later her WBC was 1700/ml with 63% PMNs, 2 % bands and 35% lymphs. She was discharged home with a diagnosis of aseptic meningitis. She returned two days later with continued fever and headache. A repeat CSF examination was unchanged.

- A 26 year old woman was referred from Panama for further evaluation of a pelvic mass and possible viral infection. Three weeks earlier she had given birth to a healthy term infant, but during delivery ruptured her uterus with extensive bleeding requiring 5 units of transfusion. She had a large retro-uterine hematoma and post-op fever but finally had done well. Three weeks later she developed fevers as high as 103.4° F although she did not feel very ill. Her evaluation showed a pelvic mass and she was advised to have an emergent total hysterectomy. Because of thrombocytopenia and a normal WBC a hematologist suggested that she might have a viral infection. She then came to Miami for a second opinion.
- **Question: which of these patients has acute or primary retroviral syndrome?**

An estimated 70% or more of patients acquiring HIV infection will develop a constellation of symptoms which are referred to as the primary HIV infection or Acute Retroviral Syndrome (ARS). The manifestations vary widely, with fever being the most frequently mentioned complaint. Although initially described as a mononucleosis–like illness with

generalized lymphadenopathy, the spectrum includes such manifestations as pharyngitis, aseptic meningitis, URT, gastroenteritis, diarrhea, pancreatitis, febrile dermatitis (see table). Oral ulcerations, present in ~30 %, are highly suggestive, as these are less likely to occur with other infections in the differential. The dermatitis is an erythematous process which usually involves the upper chest and shoulders.

Frequency & duration of signs & symptoms of ARS (adapted from Vanhems et al)

Sign or Symptom	No. (%) of patients	Avr. Duration in d [range] (no. pts)
Fever	168 (77)	16.9 [3 – 184] (162)
Lethargy	143 (66)	23.7 [1 – 184] (139)
Cutaneous rash	123 (56)	15.0 [1 – 73] (117)
Myalgia	119 (55)	17.7 [2 – 184] (112)
Headache	111 (51)	25.8 [2 – cont.] (108)
Pharyngitis or sore throat	96 (44)	12.2 [1 – 51] (90)
Cervical adenopathy	85 (39)	15.1 [3 – 32] (8)
Arthralgia	67 (31)	22.6 [3 – 184] (64)
Oral ulcer	63 (29)	13.4 [1 – 85] (63)
Odynophagia	61 (28)	16.3 [2 – 48] (58)
Nausea	52 (24)	17.8 [2 – 109] (50)
Diarrhea	50 (23)	12.5 [1 – 39] (47)
Abdominal pain	42 (19)	15.1 [1 – 73] (40)
Oral candidiasis	37 (17)	10.4 [1 – 34] (34)

Primary care givers must keep ARS in mind whenever presented with an acute febrile illness in an adult without an obvious alternative diagnosis, especially if the white blood cell count shows a leukopenia with lymphopenia. Although the clinic manifestations are protean and overlap with many other acute infections which collectively will outnumber ARS, to miss a diagnosis may be missing a chance to prevent further transmission. During the early weeks of HIV infection there is a veritable explosion of virus with plasma viral counts of millions with presumed corresponding increase in HIV in body fluids and increased chance of transmission to sexual or needle sharing partners.

Pathogenesis

The pathogenesis of initial stages of HIV infection has been of interest to investigators seeking to understand not only the way in which the infection unfolds but also to learn how intervention might prevent the destruction of the immune system and control the infection. As mentioned, during the initial stage of infection the viremia reaches extremely high levels. The HIV-1 specific response which normally develops with a viral infection is markedly impaired, although the CD8 cells are activated and are thought to be the host response that controls the viremia. A humoral response also develops, but the neutralizing

antibodies develop after the initial burst of viremia has resolved and are not thought to be of secondary importance to the control of the infection.

Diagnosis

There are no firm criteria for ARS. Most investigators would accept any illness associated with laboratory substantiation of recent HIV infection. The diagnosis of ARS is based not on the standard antibody assays such as EIA and Western Blot, but on antigen detection methods. The P-24 antigen assay is usually positive, but the more sensitive assay is a qualitative HIV-1 RNA or DNA PCR. These tests invariably will be positive with ARS. If the qualitative assay is not available, one of the quantitative HIV-1 RNA assays will be positive. The EIA and Western Blot are also obtained: the combination of a positive antigen assay with a negative antibody screen (occasionally equivocal) is considered diagnostic. The negative antibody screens confirm that the infection is new; if both antigen and antibody tests are positive, the patient is more likely to have a well established infection.

Pros and Cons for Treatment

There is no consensus on the value of ARS. As a clinical entity, it is self-limited and resolves without treatment. Although treatment probably curtails the symptoms, the importance of the underlying immunopathology overshadows early clinical considerations. What we ultimately decide is the best management of early HIV infection will likely depend upon what effect treatment has on the longterm course of the infection, the impact of adverse effects and the risk for selecting resistant mutants.

Arguments for early treatment may be summarized as follows: 1) during the initial stages of infection the HIV is homogeneous with less likelihood of encountering resistant strains; 2) permanent damage to the immune system can be avoided; 3) establishment of HIV in sanctuaries can be prevented, and 4) the possibility of eradication exists. There is data to show that early treatment allows a CD4 HIV-specific immune response to develop, that viral replication to below the level of detection is quickly achieved and that establishment of latent infection of CD4 cells and macrophages (sanctuaries) is limited albeit not fully prevented. The hope for eradication, however, does not seem realistic given the therapy now available.

Arguments against early treatment include: 1) absence of any pressing medical need to treat at this stage - the acute symptoms resolve spontaneously and severe immunodeficiency develops years later; 2) duration of therapy will be decades rather than years; 3) the risk for serious adverse effects is great and long term toxicity is not yet fully defined; 4) it is unrealistic to expect patients to adhere to the treatment during years of asymptomatic of infection; 5) the risk for emergence of resistant mutant strains is increased because of lapses in adherence and even for the adherent patient, the long duration of treatment may lead to

resistance; and 6) further advances in antiretrovirals are to be expected and treatment may be safer and more effective in the future.

It is conceivable that HAART administered for a defined period of time, say six to tweleve months, may alter the subsequent course of the infection. By stopping viral replication and allowing a stronger immune response to develop, the balance between the host and the pathogen can be reset in favor of the host – converting the patient into a slow progressor. This is a concept not yet proven.

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