Herpes zoster occurs in 10% to 20% of the general population as a result of reactivation of the varicella-zoster virus (VZV) and is generally benign. It occurs more frequently in persons with cellular immunodeficiency and older age. The association between herpes zoster and HIV was confirmed early in the course of the HIV epidemic by numerous studies. Zoster was noted to precede AIDS in high-risk groups. Both the incidence and complication rate of herpes zoster are increased in HIV-infected patients.

CASE SUMMARY
A 59-year-old man with AIDS was admitted to the hospital with fever and headache. He reported several days of malaise and progressive weakness, with difficulty in ambulating. On the morning of admission, the patient was too weak to get out of bed. His roommate noted periods of confusion and disorientation.

The patient's medical history was significant for HIV-1 infection, which had been diagnosed several years earlier. He had been treated for Pneumocystis pneumonia and cerebral toxoplasmosis in 1999. He had HIV-associated cognitive impairment, normal-pressure hydrocephalus with baseline tremor, ataxia, and urinary incontinence, as well as peripheral sensory neuropathy due to HIV infection. He had a generalized seizure disorder, which was controlled with medication, and he had had no seizure activity in over 2 years. His most recent CD4+ cell count was 122/µL, and his HIV RNA level was less than 400 copies/mL. The patient's medication at admission included zidovudine, lamivudine, lopinavir/ritonavir, trimethoprim/sulfamethoxazole, levetiracetam, donepezil, haloperidol, and quetiapine. There was no history of tobacco, alcohol, or illicit substance use.

On arrival at the emergency department, the patient was febrile, with a temperature of 38.4°C (101.1°F). He was hemodynamically stable and had no meningismus. His general physical examination was unremarkable. On neurologic examination, however, he was confused and disoriented to time and had difficulty in answering questions and cooperating with the examiners. His speech was fluent, but his attention span and concentration were poor. His cranial nerves were intact, and he moved all 4 extremities symmetrically, with a mild, bilateral upper extremity tremor that was reportedly stable. He could not stand without assistance. He was uncooperative with sensory and mental status examinations.

Initial laboratory tests included a white blood cell count of 3.5 × 10^9/L, with a normal differential. Serum chemistry results, including renal and liver function, were within normal limits. Findings on chest radiograph were unremarkable, and a CT scan of the brain without contrast showed cortical atrophy, known/stable hydrocephalus, and diffuse white matter hypodensities (Figure 1). A lumbar puncture was performed (Table).

Treatment was begun with vancomycin, ceftriaxone, ampicillin, and acyclovir to provide broad coverage for bacterial meningitis and herpes simplex encephalitis. Antibacterial agents were discontinued on the second hospital day, when cerebrospinal fluid (CSF) bacterial cultures remained negative. Acyclovir alone was continued.

The patient was persistently febrile (temperature to 39.2°C [102.6°F]), and a second lumbar puncture was undertaken for additional CSF studies. On the fourth hospital day, the patient defervesced and his mental status began to improve. Results of the repeated lumbar puncture included negative polymerase chain reaction (PCR) analyses for herpes simplex virus (HSV), Epstein-Barr virus, JC virus, Cytomegalovirus, and Mycobacterium tuberculosis. A VDRL test was nonreactive in both serum and CSF. MRI of the brain revealed stable hydrocephalus and extensive,
Clinical Challenge

CONFLUENT T2 HYPERINTENSITIES THROUGHOUT BOTH CEREBRAL HEMISPHERES (FIGURE 2). THE PATIENT BEGAN TO IMPROVE BY THE FIFTH HOSPITAL DAY.

ON THE SIXTH DAY OF HOSPITALIZATION, VZV WAS DETECTABLE AT 1.83 X 10⁶ COPIES/mL BY CSF PCR, ALTHOUGH CSF CULTURES REMAINED NEGATIVE FOR VIRUSES. FEVER RESOLVED, AND THE PATIENT'S MENTAL STATUS RETURNED TO BASELINE IN THE FOLLOWING WEEK. THE PATIENT WAS ABLE TO RECALL A HISTORY OF DERMATOMAL HERPES ZOSTER (SHINGLES) MORE THAN 6 MONTHS BEFORE ADMISSION AND CHICKENPOX DURING CHILDHOOD. THERAPY WITH INTRAVENOUS ACYCLOVIR WAS CONTINUED FOR 14 DAYS, AND THE PATIENT WAS EVENTUALLY TRANSFERRED TO A NURSING FACILITY FOR PHYSICAL THERAPY.

DISCUSSION

VZV IS A HUMAN HERPESVIRUS THAT MAY COMPLICATE ANY STAGE OF HIV INFECTION. FOLLOWING PRIMARY VARICELLA (CHICKENPOX), VZV INFECTION SPREADS FROM THE SKIN VIA SENSORY NERVE FIBERS TO THE CRANIAL NERVE AND DORSAL ROOT GANGLIA. THERE, THE VIRUS PERSISTS IN LATENCY, FIFTH PRIMARY WITHIN NEURONS. VZV REACTIVATION IN THE FORM OF HERPES ZOSTER OCCURS IN 10% TO 20% OF THE GENERAL POPULATION. VZV TENDS TO REACTIVATE WITH INCREASING AGE AND IMMUNOSUPPRESSION.

DERMATOMAL ZOSTER IS OFTEN THE FIRST MANIFESTATION OF HIV/AIDS. THE INCIDENCE OF ZOSTER IS MARKEDLY INCREASED IN PERSONS LIVING WITH HIV/AIDS. IN A STUDY BY BUCHBINDER AND COLEAGUES, IN KAPLAN-MEIR ANALYSIS, THE CUMULATIVE PROPORTION OF A COHORT OF MEN IN WHOM ZOSTER DEVELOPED INCREASED IN A LINEAR FASHION FROM THE TIME OF SEROCONVERSION. BY 12 YEARS AFTER INFECTION, ZOSTER HAD DEVELOPED IN 30% OF THE MEN. HERPES ZOSTER IS USUALLY BENIGN, WITH THE EXCEPTION OF POSTHERPETIC NEURALGIA.

HOWEVER, HIV-SERPOTIVE PERSONS HAVE A HIGHER RISK OF RECURRENT ZOSTER, MULTIDERMATOMAL ZOSTER, AND ZOSTER INVOLVING CRANIAL DERMATOMES.

VZV IS ALSO ASSOCIATED WITH 2 TYPES OF RETINITIS IN HIV-POSITIVE PERSONS. THE FIRST TYPE IS ACUTE RETINAL NECROSIS (ARN), WHICH MAY ALSO AFFECT IMMUNOCOMPETENT HOSTS AS WELL AS PERSONS WITH HIV INFECTION AND MAY OCCUR AT ANY STAGE OF HIV INFECTION. ARN IS CHARACTERIZED BY FULL-THICKNESS RETINAL NECROSIS WITH LESIONS THAT BEGIN PERIPHERALLY AND EXTEND CIRCUMFERENTIALLY, VITRITIS, OCCLUSIVE RETINAL AND CHOROIDAL VASCULITIS, AS WELL AS RETINAL DETACHMENT IN TWO THIRDS OF PATIENTS.

THE SECOND TYPE OF VZV-ASSOCIATED RETINITIS IS PROGRESSIVE OUTER RETINAL NECROSIS (PORN); IT OCCURS ONLY IN PATIENTS WITH ADVANCED IMMUNOSUPPRESSION, USUALLY AT CD4+ CELL COUNTS BELOW 50/µL. PORN IS CHARACTERIZED BY MULTIFOCAL RETINAL LESIONS WITH MINIMAL OR NO INFLAMMATION. IT IS OFTEN BILATERAL AND PROGRESSES RAPIDLY WITH HIGH RATES OF RETINAL DETACHMENT AND VISUAL LOSS EVEN WITH APPROPRIATE ANTIVIRAL THERAPY.

VZV IS A NEUROTROPIC VIRUS, AND SUBCLINICAL EXTENSION TO THE CNS IS NOT UNCOMMON. SEVERE COMPLICATIONS OCCUR IN ONLY 0.1% TO 0.3% OF IMMUNOCOMPETENT PATIENTS BUT CAN DEVELOP IN UP TO 35% OF PATIENTS WITH CELLULAR IMMUNODEFICIENCIES SUCH AS HIV INFECTION. ALTHOUGH MORE FREQUENT THAN IN THE GENERAL POPULATION, CNS DISEASE DUE TO VZV STILL ACCOUNTS FOR ONLY A FEW (2.5% TO 7%) NEUROLOGIC COMPLICATIONS IN HIV-POSITIVE PATIENTS AND MAY POSE DIAGNOSTIC DIFFICULTIES.

CLINICIANS MUST BE FAMILIAR WITH THE PROTEIN SPECTRUM OF CNS MANIFESTATIONS THAT HAS BEEN DESCRIBED. SUCH MANIFESTATIONS INCLUDE NONFOCAL PRESENTATIONS (ENCEPHALITIS, MENINGITIS, MENINGOENCEPHALITIS, VENTRICULITIS) AS WELL AS FOCAL NEUROLOGIC SYNDROMES (MYELITIS, RADICULOMYELITIS, AND VASCULOPATHY). THERE ARE 2 DISTINCT FORMS OF CNS VASCULOPATHY: A NONINFLAMMATORY, LARGE-VESSEL GRANULOMATOUS ARTERITIS AND A SMALL-VESSEL VASCULITIS THAT IS FOUND ALMOST EXCLUSIVELY IN IMMUNODIFFICENT PATIENTS.

THE DIAGNOSIS OF CNS VZV INFECTION HAS CLASSICALLY BEEN SUGGESTED BY THE PRESENCE OF A CONCURRENT OR RECENT ZOSTER RASH. HOWEVER, THIS IS NOT A RELIABLE ASSOCIATION. IN A SERIES OF 84 HIV-POSITIVE PATIENTS, CUTANEOUS RASH PRECEDED THE ONSET OF NEUROLOGIC SYMPTOMS BY AS LONG AS 34 MONTHS, WHILE 9% OF PATIENTS HAD NO HISTORY OF HERPES ZOSTER. OTHERS HAVE ALSO REPORTED THE UNRELIABILITY OF THIS ASSOCIATION IN CLINICAL PRACTICE.

CNS COMPLICATIONS DO APPEAR TO BE ASSOCIATED WITH CD4+ CELL COUNTS BELOW 200/µL. FEVER COMMONLY ACCOMPANIES NEUROLOGIC SYMPTOMS; IN THE ABOVE SERIES OF 84 PATIENTS, FEVER WAS REPORTED IN 59% OF CASES. RETINITIS (ARN OR PORN) MAY ALSO BE PRESENT. NEUROIMAGING PROVIDES NONSPECIFIC CONTRIBUTIONS TO THE DIAGNOSIS. IN CASES OF ENCEPHALITIS, CT SCANS TYPICALLY SHOW SUBCORTICAL WHITE MATTER AND PERIVENTRICULAR HYPODENSITIES. TYPICAL MRI FINDINGS INCLUDE WHITE MATTER AREAS OF T2-WEIGHTED HYPERINTENSITY. INFARCTS MAY BE SEEN WITH BOTH MODALITIES IN CASES OF VASCULOPATHY.

CSF IS ABNORMAL, WITH LYMPHOCYTIC PLEOCYTOSIS AND/OR Elevated PROTEIN CONCENTRATION. ONLY 2 REPORTS DESCRIBE HYPOGLYCERORACHHIA. VZV IS NOT EASILY ISOLATED FROM THE CSF, AND VIRAL CULTURE IS NOT A SENSITIVE TOOL. AS IN THE CASE PRESENTED HERE, DIAGNOSIS HINGES ON PCR DETECTION OF VIRAL DNA.

THE TREATMENT OF CHOICE IS INTRAVENOUS ACYCLOVIR, 10 TO 15 MG/KG OF BODY WEIGHT. THE DURATION OF THERAPY IS UNCLEAR, WITH A RANGE OF 7 TO 15 DAYS IN MOST REPORTS. PATIENT OUTCOMES VARY FROM...
complete recovery to various degrees of neurologic sequelae (cognitive and/or motor) to death despite appropriate therapy.\textsuperscript{19,22,30} The most important predictor of a poor prognosis appears to be the severity of neurologic symptoms at presentation.\textsuperscript{19}

In the present case, global, acute, progressive neurologic decline developed in a patient with AIDS and a remote history of zoster. He had evidence of a meningoencephalitis with lymphocytic pleocytosis. He was treated successfully with acyclovir, initially for HSV, but the diagnosis of VZV infection was eventually made using PCR. Because VZV infection can cause a wide spectrum of focal and nonfocal neurologic manifestations, clinicians need a high index of suspicion to identify VZV among the many other, more frequent pathogens that affect the CNS in HIV/AIDS patients. PCR analysis can establish the diagnosis and allow such patients to benefit from appropriate therapy. No potential conflict of interest was reported by Dr Archuleta.

References:


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