

Nontyphoidal Salmonellosis, Human Immunodeficiency Virus Infection, and Ischemic Stroke

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Nontyphoidal *Salmonella* infection and stroke are major causes of morbidity and mortality worldwide, with increased risk in the human immunodeficiency virus (HIV)-infected population. We report a rare case of ischemic stroke associated with *Salmonella enteritidis* subdural empyema in an older HIV-infected patient with multimorbidity, despite surgery and treatment with susceptible antimicrobial drugs.

Keywords. HIV; ischemic stroke; nontyphoidal salmonellosis; *Salmonella enteritidis*; subdural empyema.

History

Three months before hospital admission, a 69-year-old black male with untreated human immunodeficiency virus (HIV) infection suffered a mechanical fall with 10 minutes loss of consciousness. He presented to the emergency department. With no noted neurologic deficits, no neuroimaging was performed. During the month before hospitalization, he developed a progressively worsening headache. Two weeks before admission, he developed progressive somnolence, malaise, anorexia, and decreased physical activity. One week before hospitalization, he reported abdominal pain, fever, and drenching night sweats.

His history was otherwise notable for hypertension, obstructive sleep apnea (OSA), stage 3 chronic kidney disease, gout, and remotely treated syphilis. He was maintained on dapsone, nifedipine, furosemide, and metoprolol but was on no antiretroviral therapy (ART) due to medication nonadherence.

He immigrated to the United States from Jamaica 3 decades prior, with travel only to that country 4 months before admission. His meat consumption consisted solely of poultry, with no known ingestion of undercooked meat. He had no animal

contacts. He did consume undercooked eggs on 3 occasions over the 2 weeks before onset of his constitutional symptoms.

Major Findings and Vitals and Physical Exam

On admission his temperature was 39.4°C, pulse was 93 beats/minute, and blood pressure was 118/57 mm Hg. He was somnolent but arousable. He had oral thrush. He was oriented to person and place but not to year. Cranial nerves II–XII were intact. His motor strength and sensation were intact and his reflexes were 2+ and symmetric. He had no meningismus and his abdomen was benign. There were no other notable clinical examination findings.

Initial Laboratory and Imaging Data

His white blood cell (WBC) count was 10 400/mm³, hemoglobin was 12.8 g/dL, and platelet count was 366 000/mm³. CD4 count was 159 (6%) and HIV viral load was 24 851 copies/mL. Serum creatinine was 2.0 mg/dL (estimated glomerular filtration rate, 38). Electrolytes and liver function tests were otherwise normal. Computerized tomography of the head demonstrated a 1.7-cm hypodense right frontotemporoparietal subdural fluid collection with 5 mm right to left midline shift (Figure 1A). Lumbar puncture revealed a cerebrospinal fluid (CSF) glucose of 53 mg/dL and protein of 62 mg/dL. Cerebrospinal fluid WBC count was 46/mm³ (100% mononuclear cells). Cerebrospinal fluid Venereal Disease Research Laboratory test (VDRL), herpes simplex virus polymerase chain reaction (PCR), cryptococcal antigen, and bacterial and fungal cultures were all negative.

Hospital Course and Management

Therapy with vancomycin, ciprofloxacin, and metronidazole was initiated. Persistent fevers, mental status deterioration, urinary incontinence, and Gram-negative bacteremia identified on day 2 prompted a craniotomy on day 4. Purulent and hemorrhagic material was encountered, consistent with a subdural empyema (Figure 1B and 1C). He underwent drainage and copious wound irrigation, but residual fibrinous material remained adherent to cortical vessel structures. Admission blood cultures and intraoperative subdural cultures yielded *Salmonella enterica* serovar Enteritidis. Both isolates demonstrated susceptibility to ampicillin, ceftriaxone (minimum inhibitory concentration [MIC], ≤2 mcg/mL), aztreonam, meropenem, trimethoprim-sulfamethoxazole, and ciprofloxacin (MIC, ≤0.5 mcg/mL). Repeat blood cultures remained negative.

He defervesced and was transitioned to intravenous ceftriaxone. One week postoperatively, he developed dysarthria with left-sided ptosis, facial droop, and motor weakness. His hemiparesis progressed, and serial magnetic resonance imaging demonstrated acute and progressive right frontal, temporal,

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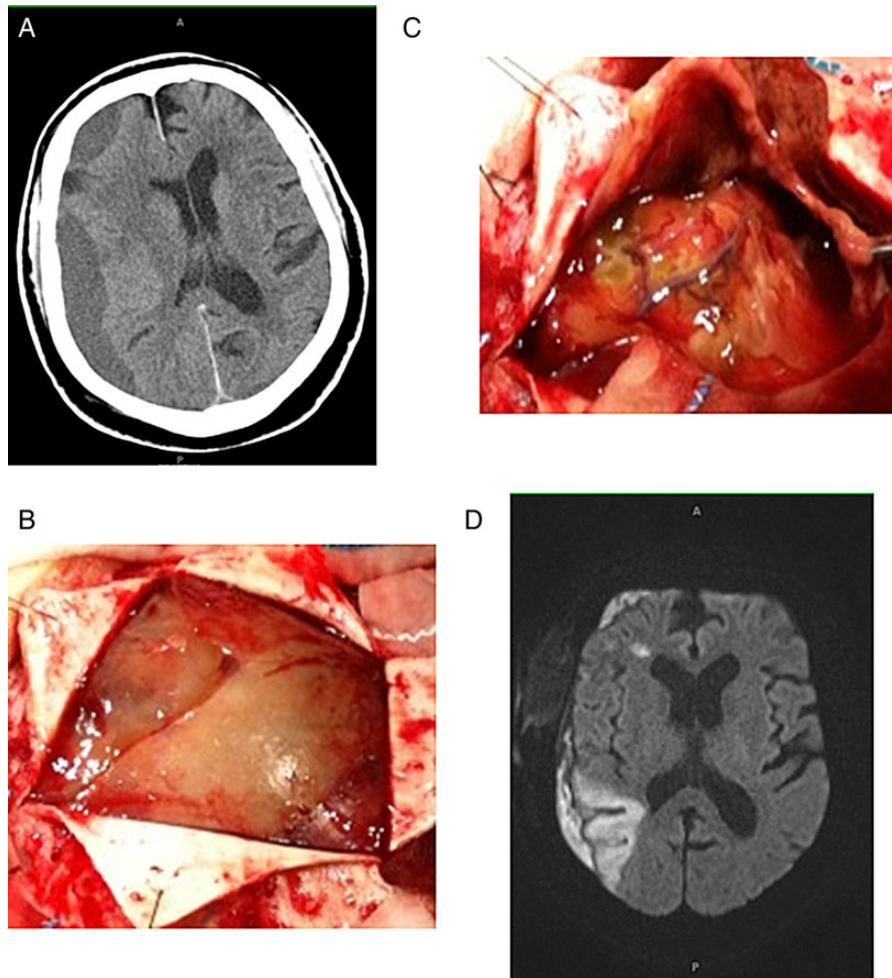


Figure 1. (A) Computerized tomography scan of the head without contrast. Hypodense fluid collection observed along the right frontotemporoparietal convexity with mass effect. (B) Intraoperative subdural space prior to debridement. Wall of abscess in the subdural space without visualization of brain cortical tissue on initial dissection of the dura. (C) Intraoperative subdural space post debridement. Brain cortical tissue post debridement with residual fibrinous material adherent to cortical structures. (D) Diffusion-weighted magnetic resonance image of the brain with contrast. Acute cerebral infarcts in the frontal and temporoparietal regions of the brain.

and parietal cerebral infarcts adjacent to his right frontotemporoparietal subdural empyema (Figure 1D), as well as chronic small vessel periventricular and subcortical ischemic disease. Magnetic resonance angiography demonstrated focal narrowings within the left middle cerebral and left carotid arteries consistent with atherosclerotic disease. Atorvastatin and aspirin were added. His left-sided motor strength improved to 4/5, and he was discharged to a rehabilitation facility 2 weeks after initial presentation.

He was readmitted 1 day later with fever, left-sided neglect, and flaccid paralysis of the left arm and leg. Magnetic resonance imaging demonstrated extension of his infarcts. Lumbar puncture revealed a CSF glucose and protein of 47 mg/dL. Cerebrospinal fluid WBC count was $158/\text{mm}^3$ (100% mononuclear cells). Cerebrospinal fluid VDRL, viral PCRs (including those for herpes simplex, varicella zoster, Epstein-Barr, cytomegalovirus, and JC virus), cryptococcal antigen, and bacterial,

mycobacterial, and fungal cultures were all negative. He suffered further mental status deterioration and underwent an electroencephalogram, which demonstrated intermittent seizure activity. Antiepileptic medication was initiated. His mental status improved, and he was discharged 7 weeks after initial hospital presentation. Upon discharge, he had completed a 4-week course of intravenous antimicrobial therapy and had been transitioned to oral ciprofloxacin. He had persistent left-sided neglect, left facial droop, 4/5 left lower extremity strength, and 0/5 left upper extremity strength. After completion of 10 weeks of antimicrobial therapy, he was reinitiated on combination ART (cART). Two years later, he had improved speech and decreased neglect, but his motor deficits persisted.

REVIEW AND DISCUSSION

Nontyphoidal salmonellosis remains a major cause of morbidity and mortality worldwide. Although introduction of cART

has brought declines in nontyphoidal *Salmonella* (NTS) incidence, HIV-infected persons remain at elevated risk for invasive NTS disease [1]. We provide a rare report of acute progressive ischemic stroke associated with a *Salmonella enterica* serovar Enteritidis subdural empyema in an older HIV-infected patient, with permanent neurologic sequelae despite surgical drainage and antimicrobial therapy.

Nontyphoidal *Salmonella* species have not been among the pathogens traditionally associated with stroke [2]. The few reported associations of NTS central nervous system (CNS) infection with stroke have been (1) primarily among neonates and infants and (2) predominantly associated with meningitis, in which delayed response to therapy and permanent neurologic sequelae have been observed [3, 4]. We identified in the research literature a single reported case of stroke associated with presumptive focal intracranial NTS infection in an adult patient, although without intracranial culture confirmation [5].

This case is more broadly illustrative of the evolving interaction between HIV and aging-associated factors in predisposing to stroke and other nonacquired immune deficiency syndrome disease. Higher rates of stroke have been observed in HIV-infected individuals relative to their HIV-uninfected counterparts in the cART era [6]. Both adverse cART effects and a greater prevalence of some traditional vascular risk factors have been considered contributors to this increased risk [6]. However, excess risk has been observed independent of these factors, supporting a direct role for HIV itself in stroke pathogenesis. Cerebral inflammation has been associated with promotion of atherosclerosis, and HIV-induced inflammation has been one proposed mechanism by which HIV may promote progression to stroke [2, 6]. Recent studies have supported such a role for HIV in directly promoting formation of atherosclerotic plaques [7]. *Salmonella* species have a known proclivity to attack atherosclerotic plaques [1, 8]. The clinical course here suggests an initial subdural hematoma hematogenously seeded by domestically acquired invasive NTS infection with cerebrovascular complication. Although without pathologic confirmation, *Salmonella*'s proclivity for atherosclerotic plaques may have contributed to these acute cerebral events.

This case further illustrates the adverse cumulative impact of the increasing burden of multimorbid disease on the aging HIV-infected population. Apart from HIV itself, several aging-associated conditions—hypertension, OSA, chronic renal failure, and a fall with presumptive structural brain injury—and race likely also predisposed this elderly HIV-infected patient to an acute ischemic stroke [6, 9, 10].

The limited data on effective management of focal intracranial *Salmonella* infections support the need for surgical drainage combined with appropriate antimicrobial therapy [3, 11]. However, despite surgical treatment and the prolonged use of appropriate antimicrobial drugs, this patient still suffered severe, residual, persistent disability. The optimal timing for

ART initiation in the concomitant management of intracranial NTS infection and HIV is not known. Studies support delayed ART initiation to reduce morbidity or mortality associated with CNS cryptococcosis or tuberculosis in individuals infected with HIV [12]. In this case, ART was initiated more than 2 months subsequent to initial *Salmonella* infection without death, worsening of neurologic or other clinical status, and without relapse of NTS infection. However, significant residual functional impairment remained.

Ultimately, there remains a substantial and overlapping burden of NTS disease and HIV infection worldwide [1, 13]. This case highlights the need for clinical awareness of stroke as a potential complication of NTS infection in the adult HIV-infected population. Such awareness may be most critical in resource-limited settings where the majority of strokes now occur and where the burden of HIV infection and invasive NTS disease is highest [1, 13]. Although focal intracranial NTS infection with ischemic stroke may be uncommon, the true burden of intracranial NTS infection in HIV-infected populations may be difficult to ascertain in settings with limited access to CNS imaging and microbiologic diagnostics. Dedicated studies in these settings may be valuable to establish incidence rates, associated morbidity and mortality, and the impact of early diagnosis and intervention in limiting severe neurologic sequelae of such infections. As our case illustrates, close monitoring for neurologic complications is necessary even after initiation of appropriate surgical and antimicrobial therapy, particularly for those HIV-infected persons with premorbid atherosclerotic risk factors.

CONCLUSIONS

This case also highlights the increasing clinical and public health relevance of stroke risk among the aging HIV-infected population. Critical attention to stroke prevention through adequate HIV control and effective, tailored management of both traditional and nontraditional risk factors will be needed to promote healthy aging outcomes for the HIV-infected population.

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