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Research Article

CNS Bacterial Coinfections: An Uncommon Association of Tuberculous and Pyogenic Bacteria

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Abstract

Background: Pyogenic bacteria-tuberculosis coinfections in the CNS are uncommon, but some isolated cases have been reported. In contrast with other coinfections, they also can be observed in non-immunosuppressed patients.

Tuberculosis is still a major global health problem. CNS tuberculosis is the most severe form of extrapulmonary tuberculosis, and when associated with pyogenic bacterial infections it shows atypical clinical and radiological characteristics that make an accurate diagnosis difficult.

Methods: A case series of tuberculosis-pyogenic bacterial CNS coinfection in patients attended at two referral centers in Mexico City during the last 5 years.

Results: Evident immunosuppressive factors were observed in two of them. Specific antituberculous treatment was delayed in all three cases due to their atypical clinical and radiological characteristics. One patient died.

Conclusion: Since pyogenic bacterial-tuberculosis associationis uncommon; a high suspicion level and complementary paraclinical evaluations are required for an accurate diagnosis and an adequate clinical outcome.

Keywords: Tuberculous; Pyogenic; Coinfection; Central nervous system

Introduction

CNS coinfections by pyogenic and tuberculosis bacteria are uncommon infectious processes, with few cases reported to date [1-8]. These superadded bacterial infections during CNS tuberculosis present usually atypical clinical manifestations, which contributes to a delayed diagnosis, and inadequate treatment.

Tuberculosis (TB) is still a major global health problem. During 2014, it caused 1.5 million deaths [9]. CNS TB constitutes the most threatening form of the disease. It accounts for 5-10% of all extrapulmonary TB cases [10].

Concurrent CNS coinfections with TB constitute a major diagnostic challenge, but it should be suspected in cases with atypical clinical manifestations or in the presence of extraneural TB. An extensive approach is mandatory in order to administer an adequate antituberculous treatment (ATT) and to improve the clinical outcome.

In this report, we present the cases of four patients with CNS-TB that concurrently developed other CNS bacterial infections. They were attended at two referral centers during the last 5-years in Mexico City. One patient died due to complicated TB meningitis.

Methods and Patients

During the last five years (2011-2016) four-cases of CNS tuberculosis and pyogenic bacterial coinfection were retrieved. Here each case is presented.

Case 1

A 32-year-old previously healthy woman presented with a four days history of headache, fever, nausea, vomiting and circumoral vesicular eruption (oral herpes), she visited a clinic and was diagnosed with left acute otitis media and ceftriaxone and dexamethasone were prescribed, on the next day by the appearance of drowsiness and persistent vomiting she was brought to our institution. On hospital admission, she was found inattentive, disoriented prone to sleepiness with an extensive perioral rash with blisters and scabs. Neurologic examination revealed papilledema, upgaze paralysis, bilateral sixth nerve paresis and mild right hemiparesis with a right extensor plantar response. Neck stiffness was present. She was employee housework, had three children no known allergies or surgery and no past history of tuberculosis or contact with persons with tuberculosis. The hemoglobin was 12.9 g/dL, hematocrit 37.8%, leukocyte count 30,800 mm^3 with 94% polymorphonuclear (PMN) cells and platelet count 275,000 mm^3. Glucose 151 mg/dL, BUN 11 mg/dL creatinine 0.5mg/dL, albumin 3.4g/dL. An HIV serum test was negative. A CT-scan of the brain showed a hypodense lesion in the left internal capsule, with moderate ventricular dilatation, sulci effacement and contrast enhancement of the basal meninges (Figure 1A). Intravenous ceftriaxone, vancomycin, and dexamethasone were administered. CSF showed 4608 cells/mm3, protein level of 698 mg/dl and glucose of 5 mg/dL with serum glucose of 151 mg/dL. *Streptococcus pneumoniae* grew in culture; it was resistant to oxacillin and sensitive to ceftriaxone and vancomycin. The neurosurgery service recommended a ventriculostomy placement. A right ventriculostomy was placed and *Streptococcus pneumoniae* grew in ventricular fluid. Alertness of the patient improved with intermittent periods of agitation, four days after surgery she pulled out the ventricular catheter, a new CT-scan of the brain did not show an urgent need for repositioning. On the fifth hospital day, a

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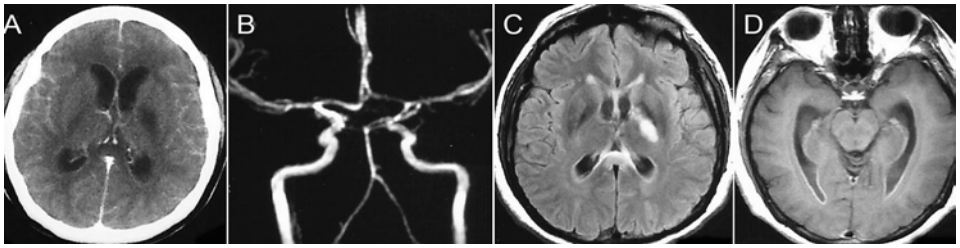

Figure 1A: Contrasted CT scan on admission shows hydrocephalus, a left capsular infarction and abnormal insular gyral enhancement.
Figure 1B: MRI angiography performed 18-days after admission revealed arteritis involving both proximal MCAs and at vertebrobasilar system.
Figure 1C: Axial FLAIR MRI shows hyperintensity at the left posterior limb of the internal capsule (ischemic infarction).
Figure 1D: Axial T1 gadolinium-enhanced MRI disclosed dilatation and abnormal ependymal enhancement.

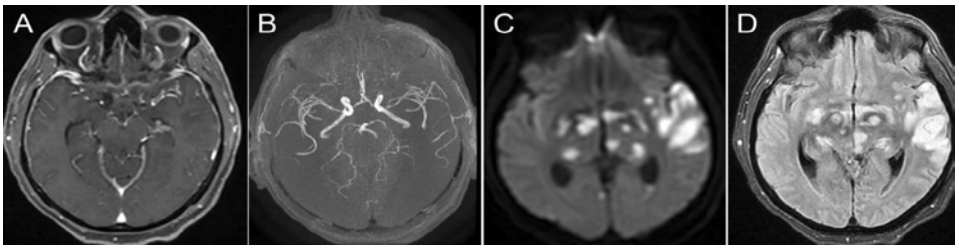

Figure 2A: MRI performed 10-days after admission. Axial T1 weighted contrast-enhancement shows basal cisterns and frontotemporal leptomeningeal enhancement.
Figure 2B: MRI angiography shows irregular arterial narrowing of anterior and posterior circulations.
Figure 2C: Axial diffusion image shows restriction in multiple areas on basal ganglia, left insula and left temporal lobe (Ischemic infarctions corroborated by ADC sequence. Not shown).
Figure 2D: Axial T1 FLAIR show hyperintensities on basal ganglia, left insular and temporal regions as well as perilesional edema and liquid-liquid interphase in the occipital horns.

new lumbar puncture reported 1536 cells/mm3, a protein level of 211 mg/dL and glucose level of 2 mg/dL, the differential count was 12% lymphocytes and 88% PMN cells, bacterial culture was negative. At that point considering early hydrocephalus, the left capsular infarction and persistent hypoglycorrhachia a transcranial Doppler (TCD) was requested it showed an increase in blood flow velocities in the right middle cerebral artery MCA and the proximal portion of the left MCA. On tenth hospital day adenosine deaminase in CSF was reported with 30 U/L, the cut-off point for tuberculous meningitis is 7U/L at our center. These data suggested the clinical possibility of concomitant tuberculous meningitis and ATT with rifampicin, isoniazid, pyrazinamide, ethambutol, and pyridoxine was added to vancomycin and ceftriaxone. A subsequent report confirmed a positive test in CSF for an IS6110 polymerase chain reaction (PCR) test for DNA of the *M. tuberculosis* complex. On the eighteenth hospital day, a brain MRI and MRI angiography (Figure 1B, 1C, 1D) disclosed secondary vasculitis in both MCA and vertebrobasilar system and an area of infarction in the left posterior limb of the internal capsule, as well as ventricular dilation and abnormal ependymal enhancement, was observed. The patient persisted with mild right hemiparesis and recovered a normal mental status; she was discharged after 22-days in the hospital with ATT and prednisone. As outpatient TCD, studies showed a slow normalization of cerebral blood flow velocities for the next ten months. With rehabilitation one year later, the patient was reinstated to their normal work without restrictions. She completed 18-months of ATT and was followed for 29 months without evidence of new symptoms relapse.

Case 2

A 49-year-old male with diabetes was diagnosed with chronic granulocytic leukemia six years before, initially treated with imatinib. Three years later allogeneic hematopoietic cell transplantation (HST) from an identical HLA donor was performed. He developed graft-versus-host disease (GVHD) five months after engraftment, treated initially with corticosteroid and tacrolimus, and 9 months with ponatinib that was withheld because he devolved pancreatitis. He continued with tacrolimus and imatinib. Functional asplenia was diagnosed. Three years and a half after allogenic HCT he consulted with 48 hours of fever, asthenia, headache, and progressive nuchal rigidity. The patient was admitted and started on vancomycin, ceftriaxone, and dexamethasone. Lumbar puncture was deferred because of thrombocytopenia and later performed after apheresis transfusion. The CSF showed glucose level of 15 mg/dL, 388 mg/dL, proteins and uncountable white cells, 66% PMN Gram, and Ziehl-Neelsen stains were negative. Two days later, *Streptococcus pneumoniae* susceptible to oxacillin was isolated in blood culture. Headache and meningeal signs improved, but five days later the patient's clinical condition worsened, he developed again fever neurological deterioration and mechanical ventilation was required. A second CSF showed glucose 8 mg/dL, proteins 318 mg/dL, and uncountable leucocytes. *Streptococcus pneumoniae* agglutination test was positive. Gram and Ziehl-Neelsen stains were negative. CSF culture was negative after 5 days. The GeneXpert MTB/RIF test was negative. Ceftriaxone dose was increased to 6 g/day, dexamethasone was reinitiated and the patient was transferred to ICU. A third CSF performed 10 days after admission showed Glucose 72 mg/dL,

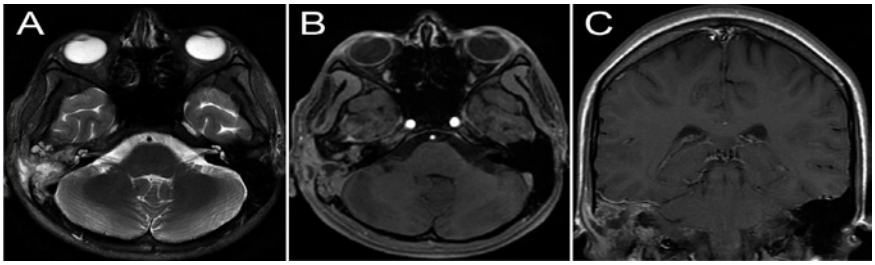

Figure 3A: Axial T2-weighted MRI shows a hyperintensity at the mastoid process of the right temporal bone.
Figure 3B: Axial gadolinium-enhanced MRI shows otomastoiditis and a subperiostic abscess on the right temporal bone.
Figure 3C: Coronal gadolinium-enhanced MRI shows abnormal enhancement of temporal meninges, otomastoiditis and a subperiostic abscess at the right temporal bone.

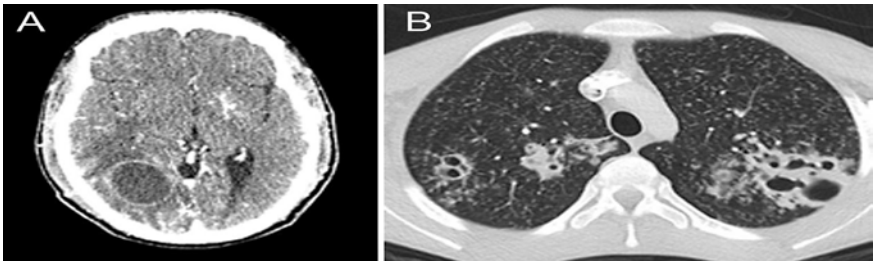

Figure 4A: Axial CT scan of the lung shows a miliar nodular infiltrate and multiple cavities in both pulmonary lobes.
Figure 4B: Contrasted CT scan on admission shows right temporo-occipital abscess with contrast ring enhancement and severe perilesional edema.

proteins 331 mg/dL, peripheral glucose 85 mg/dL and pleocytosis. The patient developed marked hyponatremia and lymphopenia.

At 10-days of admission clinical deterioration progressed and the brain MRI showed diffuse and multiple hyperintense parenchymal areas suggesting brain infarctions as well as pachymeningitis and bilateral otomastoiditis. A fourth CSF was performed glucose 34 mg/dL, 365 protein mg/dL and pleocytosis. Ziehl-Neelsen stain, as well as a new GeneXpert MTB test was positives. The patient was started on ATT, but patient condition worsened and died 25-days after admission.

Case 3

A previously healthy 15-year-old male began 3 months before admission with weight loss, night fevers and sweating associated with diarrhea. Two months later, he developed nausea and vomiting. Symptomatic treatment was given without amelioration, and the patient referred right otalgia and a purulent otorrhea. Upon evaluation by an otorhinolaryngologic at a general hospital, a tympanostomy tube was placed, and the patient was started on intravenous ceftriaxone and metronidazole. Purulent otorrhea continued, and a performed brain CT-scan showed right otomastoiditis. Patient was referred to our hospital, upon admission besides right purulent otorrhea cervical adenomegaly and hepatosplenomegaly were observed. Hematic cytometry showed 7790 leucocytes/μL, hemoglobin 11.8 g/dL, 467 000 platelets/μL, and 6670 neutrophils/μL. Due to the clinical and the MRI neuroimaging findings (Figure 3A, 3B and 3C) patient was started on ATT and a transmastoid biopsy was done. Histopathological analysis revealed acute and chronic inflammation with abundant alcohol-acid bacilli on Ziehl-Neelsen staining. Bacterial cultures of transchirurgical pus demonstrated *Staphylococcus coagulase-negative* resistant to oxacillin and vancomycin infusion was added. Three weeks later, the patient was discharged and clinical follow-up was continued at a general hospital.

Case 4

A previously healthy 33-year-old male was referred to our institution with a history of moderate to severe headache during the last 6-weeks, associated with generalized seizures. On neurological examination, slight memory alteration and generalized hyporeflexia were observed. Contrast-enhanced CT showed a right temporo-occipital abscess with perilesional edema (Figure 4A). The patient was started on ceftriaxone, metronidazole, and dexamethasone and later underwent surgical excision. Histopathological analysis revealed vascular granulation tissue containing acute and chronic inflammatory cells, and pus formation rich in acid-fast bacilli. In the bacterial culture grew gram-negative bacilli (*Enterobacter sp.*). ATT was added to empirical antibiotic treatment. TCD showed secondary vasculitis at the right MCA, and dexamethasone was continued for 2 weeks. ELISA-HIV test was positive. Plasmatic HIV load was 181, 754 copies/mL, with a CD4+lymphocyte count of 128 cells. Although patient did not complain of previous cough, hemoptysis or fever a performed thoracic CT-scan, showed micronodular infiltrates suggestive of miliary tuberculosis, apical cavities (Figure 4B). No other opportunistic infections were detected. After four weeks of ATT, antiretroviral treatment with FTC/TDF/EFV was added. Clinical follow-up was continued at a general hospital.

Literature Review

A total of 8 articles (9 patients) were retrieved from the literature (Table 1) six men and 3 women. Age was 35.6±18.43. Two patients were pediatrics, one newborn and one of 5-year-old. Only five presented fever or meningeal signs. Tuberculous bacterial isolation was initially detected only in 3 cases thus clinical diagnosis

Table 1: Cases of CNS bacteria- tuberculous coinfections.

Reference	Age/Sex	Risk predisposing factor	Clinical manifestation	Cerebrospinal fluid			First bacteria identified (by PCR, culture or CSF stain)	Second bacteria identified (by PCR, culture or CSF stain)	Clinical outcome
				Glucose mg/dL	Proteins mg/dL	Cells/mm^3			
Levinsky et al., 1974	Newborn/W	Low birth weight	Apneic attack meningitis	ND	ND	Purulent	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	Survived severe neurologic sequelae
Fu et al., 1998	52/W	None	Radicular syndrome at C3-C4	ND	ND	ND	*Staphylococcus aureus*	*Mycobacterium tuberculosis*	Survived without neurologic sequelae
Mousa et al., 2003	52/M	ND	Backache, fever	ND	ND	ND	*Nocardia/Moraxella*	*Mycobacterium tuberculosis*	survived
Garg et al., 2008	38/M	Sickle cell disease	Meningitis	43	115	4800	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	survived
Crisan et al., 2008	17/M	ND	Fever, headache, meningitis	48	520	120	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	survived
Siddiqui et al., 2008	55/M	Diabetes mellitus	Headache, vomiting, altered conscious	ND	ND	ND	*Streptococcus pneumoniae and Mycobacterium tuberculosis*		Survived
	42/W	ND	Headache, vomiting, hemiparesis	ND	ND	ND	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	Survived without neurologic sequelae
Ramesh et al., 2008	24/M	Pulmonary tubeculosis	Headache, neck pain, gait ataxia	ND	ND	ND	*Staphylococcus aureus and Mycobacterium tuberculosis*		Survived without neurologic sequelae
Manigandan et al., 2013	5/M	None	Fever and otorrhea	ND	ND	ND	*Mycobacterium tuberculosis*	*Staphylococcus aureus*	Survived without sequelae
Current case series	32/W	None	Fever vomiting and circumoral herpes	151	698	4608	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	Survived without sequelae
	49/M	Diabetes mellitus Myelodysplastic syndrome	Fever, headache and meningeal signs	15	388	uncountable	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*	Died
	15/M	None	Weight loss diaphoresis and otorrhea	ND	ND	ND	*Mycobacterium tuberculosis*	*Staphylococcus aureus*	Survived
	33/M	HIV	Headache, generalized seizures	ND	ND	ND	*Mycobacterium tuberculosis and Enterobacter sp*		Survived

Woman (W), Man (M), no data available (ND)

of coinfection was delayed despite of this no fatal cases were reported. The most common bacterial coinfection was *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*.

Discussion

Concurrent tuberculous and bacterial infection has been described in several anatomical locations, namely lung [11,12], liver [13], retropharinx [14], bone [15], and CNS [1-8].

In previously reported cases, the concurrent CNS infection of pyogenic and tuberculosis bacteria was mainly associated with *Streptococcus pneumoniae* and some factors of immunosuppression such as diabetes, sickle cell disease and prematurity. Remarkably no typical clinical manifestations for tuberculosis were reported for those patients, except a torpid clinical evolution and development of hydrocephalus in some cases, that forces to considerer other etiology than pyogenic bacterial meningitis. Several bacteria such as *Streptococcus pneumoniae, Listeria monocytogenes* etc. can induce acute meningitis and also hydrocephalus, this latter condition is much more common related to CNS tuberculosis.

Other pyogenic bacteria coinfections have been related with *Staphylococcus aureus, Nocardia sp.* and *Moraxella sp.* In our review all subjects survived, some of them with severe neurological sequelae. In most of the cases the diagnosis of tuberculosis was delayed without apparent increase of risk for a fatal outcome (Table 1).

Herein, we describe a series of 4 patients; two of them showed immunosuppressive factors such as HIV, type 2 diabetes, and myelodysplastic syndrome. One of them developed a torpid clinical and evolution and finally died.

CNS tuberculosis is the most severe form of tuberculous disease. In a large series of CNS TB cases in Atlanta, USA, including 212 patients with extrapulmonary tuberculosis, 47% (100) had HIV and 49% (103) concomitant pulmonary tuberculosis. In a multivariate analysis, CNS TB was a factor independently associated with an increased risk of death and disseminated disease [16]. More recently, Lui, et al. [17] reported the clinical outcome of adults hospitalized for tuberculosis with low HIV prevalence in an acute-care hospital in Hong Kong. In total, 349 patients were included in this retrospective

cohort; 84 patients died most of them before diagnosis (96.4%) or before ATT completion (69%). Another important factor that increases mortality in tuberculous patients is type 2 diabetes mellitus; in fact, Magee, et al. [18] studied 1325 tuberculosis patients, and type 2 diabetes was detected in 158 (11.9%). The risk of death for patients with extrapulmonary tuberculosis and diabetes was 23.8%, while it was significantly lower for non-diabetic subjects (9.8%, $P<$ 0.01). In our report, the patient who died had type 2 diabetes along with myelodysplastic syndrome. Coinfection of TB and HIV/AIDS is another important risk factor for death. Javalkar, et al. [19] made an estimation of mortality risk among patients infected with HIV in a retrospective study including 55,801 subjects cared for between 2006 and 2011; about 9% of the included patients died (4903) in the period under study. Both TB coinfection and older age increase mortality rate. In contrast, adherence to antiretroviral treatment significantly reduced death rate [19].

Coinfection of pyogenic bacteria and CNS tuberculosis does not seem to increase the risk of death. In fact, no death was reported in previous cases, and the patient who died at our Institution had several comorbidities, alcoholism, type 2 diabetes and myelodysplastic syndrome; additionally, TB diagnosis was delayed, another aggravating risk factor for death.

Although several factors can increase the risk of death in tuberculosis, the most determinant include extrapulmonary tuberculosis, particularly CNS involvement, coinfection with HIV and other immunosuppressive factors, such as type 2 diabetes.

While CNS coinfection of pyogenic and tuberculosis bacteria although is an uncommon association, it should be considered in patients with immunosuppressive factors and atypical clinical manifestations. A high degree of suspicion is mandatory in order to prevent a delayed diagnosis, which increases the risk of death.

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