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COVID 19 Presenting as Acute Rhombencephalitis.

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Abstract

Rhombencephalitis is an acute inflammation of the brainstem and cerebellum. It has been associated with Listeria monocytogenes. Nevertheless, its association with Sars-Cov-2 (COVID 19) infection is rare. We present the case of a migrant worker from Chihuahua Mexico, infected with COVID 19 with Acute Hypoxic Respiratory Failure that developed Listeria Monocytogenes rhombencephalitis. MRI showed evidence of brainstem inflammation. Blood culture was consistent with Listeria. Despite aggressive mechanical ventilator support and antibiotics, he passed away. The case demonstrated a unique presentation of a common disease which is rare considering COVID 19.

Patient: Male, 57-year-old Male

Final Diagnoses: Rhombencephalitis, COVID 19, Sars-Cov-2, Acute Hypoxic Respiratory Failure, Sepsis, Pneumonia.

Specialty: Pulmonology, Critical Care, Neurology

MeSH: Keywords: COVID 19, Rhombencephalitis, Inflammation, Brainstem and Cerebellum Infarct.

Objective: Unusual clinical course

Background

Rhombencephalitis is an acute inflammation of the brainstem and cerebellum. It can present as encephalopathy, cranial neuropathies, cerebellar dysfunction. It has high morbidity and mortality. There have been several cases due to infections, inflammatory disorders, autoimmune encephalitis and paraneoplastic syndrome. The etiology of this patient was the possible consumption of infected cheese with listeria monocytopenia. With the Covid 19 pandemic and millions of infections we are seeing in the world, this remains a very rare cause of brainstem dysfunction and infarction. Most of these cases will present with the classic respiratory symptoms, anosmia, fever and the most severe ones with hypoxic respiratory failure. Nevertheless, a few rare cases like this have presented as a late complication with a very poor prognosis.

Case

57-year-old male, unvaccinated, with a history of hypertension and obesity. Presents with increased dyspnea, fever and shortness of breath. The patient's COVID PCR was positive. The patient had bilateral infiltrates on chest x-ray, he required supplemental oxygen 3 liters to start on the day of admission. Overall, his condition deteriorated and he required mechanical ventilation. During his course of treatment, he received Remdesivir, Decadron and broad-spectrum antibiotics. The patient had a decrease of sedation on day 5 and was noticed to have a poor neurological exam, not following commands, the patient was not waking up after sedation was discontinued. Neurology was consulted and lumbar puncture was performed that showed lymphocytic pleocytosis, White Blood Cell per lumbar puncture, 140/ mm^3 (95% lymphocytes and 5 % neutrophils), a protein concentration of 47 mg/dl and a glucose of 65. The Gram stain of the cerebrospinal fluid was negative for fungi and bacteria. The patient had been on penicillin for antibiotics, acyclovir was added, and ampicillin for presumed central nervous system infection. His White Blood Cells are 12 x 10^9 /l (85% Neutrophils). Liver function test and renal function were normal. His MRI showed gross brainstem inflammatory changes. The patient was not able to wean from the ventilator despite the fact his oxygenation and ventilator mechanics

improved. On day 5 his blood cultures were positive for listeria. The family in light of the presence of brainstem infarction and the fact the patient did not want long-term care decided to proceed with comfort care. The patient was extubated and passed away under hospice care.

Discussion

Listeria Monoyctognesis is a common cause of central nervous system infection. It has been reported to cause rhombencephalitis. This has very high mortality with prolonged neurologic sequelae. Studies have reported up to 11 % to be related to listeriosis in brainstem infarction. Nerveless, its incidence in COVID is very rare **(**13**)**. The patient was a Hispanic male with a family that came to visit from Mexico. He ate cheese and fruits from his hometown. Review of symptoms, he did have a fever, Upper Respiratory Infection and headaches in his prodromal phase. He was diagnosed with COVID and subsequently develop respiratory failure. His blood cultures returned as positive on day 5 and listeria and Lumbar Puncture confirmed the lymphocytic pleocytosis consistent with the MRI history and culture. This patient was non vaccinated but also had a BMI of 30, making him obese and pre-diabetic. His CRP was elevated, and other inflammatory markers were consistent with COVID 19 respiratory failure. Liver function test, creatine, urine, West Nile, HIV 1 and 2, and RPR were negative.

Listeria monocytogenes in their non-invasive form is usually a self-limiting illness. This means that a majority of infected individuals will improve without the need for medical care. The elderly, pregnant women and anyone immunocompromised is most at risk for contracting the more severe foodborne disease called Listeriosis. The pathogen received its name from British surgeon Joseph Lister, Listeria can be found living unsuspectingly in soil, water, and vegetation which often leads to food contamination. L. monocytogenes is contracted by eating food contaminated with the bacteria. **(**1**)** This specific pathogen is very hardy and can grow in a wide range of environments and temperatures from 39°F (4°C) (the temperature of your refrigerator) to 98.6°F (37°C) (your body internal temperature). It can even be found in wet damp areas such as drains, and it has an incubation period that can vary from three to 70 days. It is often isolated in cattle, sheep, fowl and can be found in dairy products, fruits and vegetables. **(**3**)**

Listeria monocytogenes is a Gram-positive bacterium, in the division Firmicutes, it is a facultative anaerobic bacterium, capable of surviving in the presence or absence of oxygen. It can grow at varying temperatures, as low as 0 °C permits multiplication at typical refrigeration temperatures, greatly increasing its ability to evade control in foods **(**5**)**. It is motile via flagella at 30 °C and below, but usually not at 37 °C. Listeria monocytogenes can instead move within eukaryotic cells by explosive polymerization of actin filaments known as comet tails or actin rockets. Because of its frequent pathogenicity to pregnant mothers, they are often advised not to consume unpasteurized dairy products, especially soft cheeses because it can cause meningitis in a newborn. The soft cheeses to avoid are the

mold-ripened soft cheese, such as brie, camembert and chevre (a type of goat's cheese) and others with a similar rind. **(**4**)** Other cheeses recommended avoiding are soft, blue-veined cheeses such as Danish blue or gorgonzola, because they are also made with a mold and they can contain listeria. Due to the long incubation period and how it acts at different temperatures, it is difficult to investigate and determine where the contaminated food originated. For this reason, Listeria statistically is one of the most fatal bacteria, with death rates near 25%, this in comparison to Salmonella which has mortality rates of less than 1%. In the US it is estimated 1,600 people are infected each year. **(**2**)** Epidemiological data has revealed that Listeria is at least in 37 mammalian species and in several species of birds. The route of infections is the gastrointestinal tract through foods such as raw milk, eggs, ice cream, raw fruits and vegetables, fermented raw-meat sausages, cooked poultry and meats of all types. **(**7**)**

The CDC's Listeria Initiative has categorized the genus Listeria as follows, it contains seven species (monocytogenes, ivanovii, seeligeri, innocua, welshimeri, martii, and grayi), two of which are pathogenic. L. monocytogenes is pathogenic to humans and animals; L. ivanovii (previously L. monocytogenes serotype 5) primarily infects animals and very rarely causes disease in humans. Serotyping differentiates isolates of Listeria below the species level. Serotypes are designated based on the immunoreactivity of two cell surface structures, the O and H antigens. Twelve serotypes of L. monocytogenes (1/2a, 1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, and 7) are recognized, three of which (1/2a, 1/2b, and 4b) cause most (95%) human illness; serotype 4b is the one most associated with outbreaks.

The pathogenesis of L. monocytogenes centers on its ability to survive and multiply in phagocytic host cells. It seems that Listeria originally evolved to invade membranes of the intestines, as an intracellular infection, and developed a chemical mechanism to do so. This involves a bacterial protein called internalin (InlA/InlB), which attaches to a protein on the intestinal cell membrane "cadherin" and allows the bacteria to invade the cells through a zipper mechanism. These adhesion molecules can also be found in two other unusually tough barriers in humans, the blood-brain barrier and the fetal–placental barrier. This may explain the apparent affinity that L. monocytogenes has for causing meningitis and affecting babies in utero. Once inside the cell, L. monocytogenes rapidly acidify the lumen of the vacuole formed around it during cell entry to activate listeriolysin O, a cholesterol-dependent cytolysin capable of disrupting the vacuolar membrane. This frees the pathogen and gives it access to the cytosol of the cell, where it continues its pathogenesis. **(**6**)** Motility in the intracellular space is provided by actin assembly-inducing protein, which allows the bacteria to use the host cell's actin polymerization machinery to polymerize the cytoskeleton to give a "boost" to the bacterial cell so it can move in the cell. The same mechanism also allows the bacteria to travel from cell to cell.

Those persons who suffer a Listeria infection that does not resolve on its own, can have numerous complications and possibly severe ones. The most common complication is septicemia, with meningitis being the second most common. Other complications can include encephalitis, brain abscess, endocarditis, septic arthritis, osteomyelitis, and localized infection, either internally or of the skin. Death

is the most severe consequence of listeriosis, and it is tragically common. The CDC has estimated that Listeria monocytogenes is the third leading cause of death from foodborne illness. Based on 2018 FoodNet surveillance data, 96% of 126 Listeria cases ended up in the hospital, the highest hospitalization rate for pathogenic bacterial infection. This data showed a fatality rate of 21%. According to the FDA, case-fatality rate increases substantially based on complications, possibly reaching rates of 70% in cases with listerial meningitis, 50% in septicemia cases, and over 80% for perinatal/neonatal infections. Johns Hopkins cites the following about the outcomes with invasive disease: in pregnancy: ~20-25% have fetal loss (especially before 29 weeks), with a CNS infection: ~30% mortality and with bloodstream infection: ~45% mortality.

Listeria is anaerobic and facultatively anaerobic, motile, beta-hemolytic, non–spore-forming, a short, gram-positive rod that exhibits characteristic tumbling motility by light microscopy. Listeria produces a characteristic appearance on blood agar with small zones of clear beta-hemolysis around each colony. Listeria grows well at refrigeration temperatures (4° to 10°C). To review, the primary habitat of Listeria is the soil and decaying vegetable matter. Most Listeria infections in adults are thought to result from oral ingestion and subsequent intestinal mucosal penetration and systemic infection. The binding of listerial internals (Inl) to E-cadherin, a host cell adhesion factor, or Met (c-Met), hepatocyte growth factor. This binding activates certain Rho-GTPases, which subsequently bind and stabilize the Wiskott Aldrich syndrome protein (WAsp). WAsp can then bind the Arp2/3 complex and serve as an actin nucleation point. Subsequent actin polymerization creates a "phagocytic cup", an actin-based structure normally formed around foreign materials by phagocytes before endocytosis. The net effect of internalin binding is to exploit the junction-forming apparatus of the host into internalizing the bacterium. L. monocytogenes can also invade phagocytic cells (e.g., macrophages), but requires only internalin for invasion of nonphagocytic cells. Following internalization, the bacterium must escape from the vacuole/phagosome before fusion with a lysosome can occur. Three main virulence factors that allow the bacterium to escape are listeriolysin O (LLO-encoded by hly) phospholipase A (encoded by plcA) and phospholipase B (plcB). **(**5,6**)** Secretion of LLO and PlcA disrupts the vacuolar membrane and allows the bacterium to escape into the cytoplasm, where it then proliferates. Once in the cytoplasm, L. monocytogenes exploits host actin for the second time. ActA proteins associated with the old bacterial cell pole (being a bacillus, L. monocytogenes septates in the middle of the cell, thus has one new pole and one old pole) are capable of binding the Arp2/3 complex, thereby inducing actin nucleation at a specific area of the bacterial cell surface. Actin polymerization then propels the bacterium unidirectionally into the host cell membrane. The protrusion formed may then be internalized by a neighboring cell, forming a double-membrane vacuole from which the bacterium must escape using LLO and PlcB. This mode of direct cell-to-cell spread involves a cellular mechanism known as paracytophagy. **(**5**)**

The empiric treatment **(**12**)** for listeriosis is through IV medication and with the patient hospitalized under close observation. Patients with meningitis are treated with Ampicillin 2gm IV q4-6h (or penicillin G 4 MU IV q4h) + gentamicin 1.7mg/kg IV q8h x ≥ 3wks. For bacteremia (without meningitis): use meningitis options x 2wks, unless immunocompromised, in which case longer therapy may be necessary. For brain abscess, rhombencephalitis or cerebritis: use meningitis options x 4-6 wks or longer.

Conclusion

The Novel SARS-CoV-2, COVID 19 infection has caused over 5 million deaths worldwide and many millions of infected patients per day in the world. This case is an example of a rare presentation of a common bacterium that causes food-borne illness. This patient had an increased BMI> 30, and we suspect possible diabetes. His origin from Mexico and his predilection for cheeses and fruits from the region and lack of vaccine put him at a higher probability of developing listeriosis. Unfortunately, his presentation with acute COVID hypoxic respiratory failure mimics many other symptoms that may have been caused by listeria. His lumbar puncture, MRI and positive blood culture were the keys to making the diagnosis.

Treatment of secondary infection and a high level of suspicion for concomitant diseases and infection is warranted. No practical guideline exists to prevent this patient from getting listeriosis. We have discussed some of the Guidelines for listeriosis prevention. But further studies are warranted to prevent further demise from this rare complication.

COVID -19 can cause a significant amount of inflammation and compromise the immune system. This case is an example of a rare presentation of a food disease that already has high mortality without COVID. The MRI showed a significant brainstem infarct. The patient was a Hispanic male with a family that came to visit from Mexico. He ate cheeses and fruits from his hometown. Reviewed symptoms he did have a fever, upper respiratory infection and headaches in his prodromal phase. He was diagnosed with COVID and subsequently developed respiratory failure. His blood cultures returned as positive on day 5 of hospitalization. Listeria and lumbar puncture confirmed the lymphocytic pleocytosis consistent with the MRI, history and culture. This patient was non vaccinated but also had a BMI of 30, making him obese and pre-diabetic. His CRP was elevated, and other inflammatory markers were consistent with COVID 19 respiratory failure. Liver function test, rnal function and urinalyses were normal. Serologies for West Nile, HIV 1 and 2, and RPR were negative.

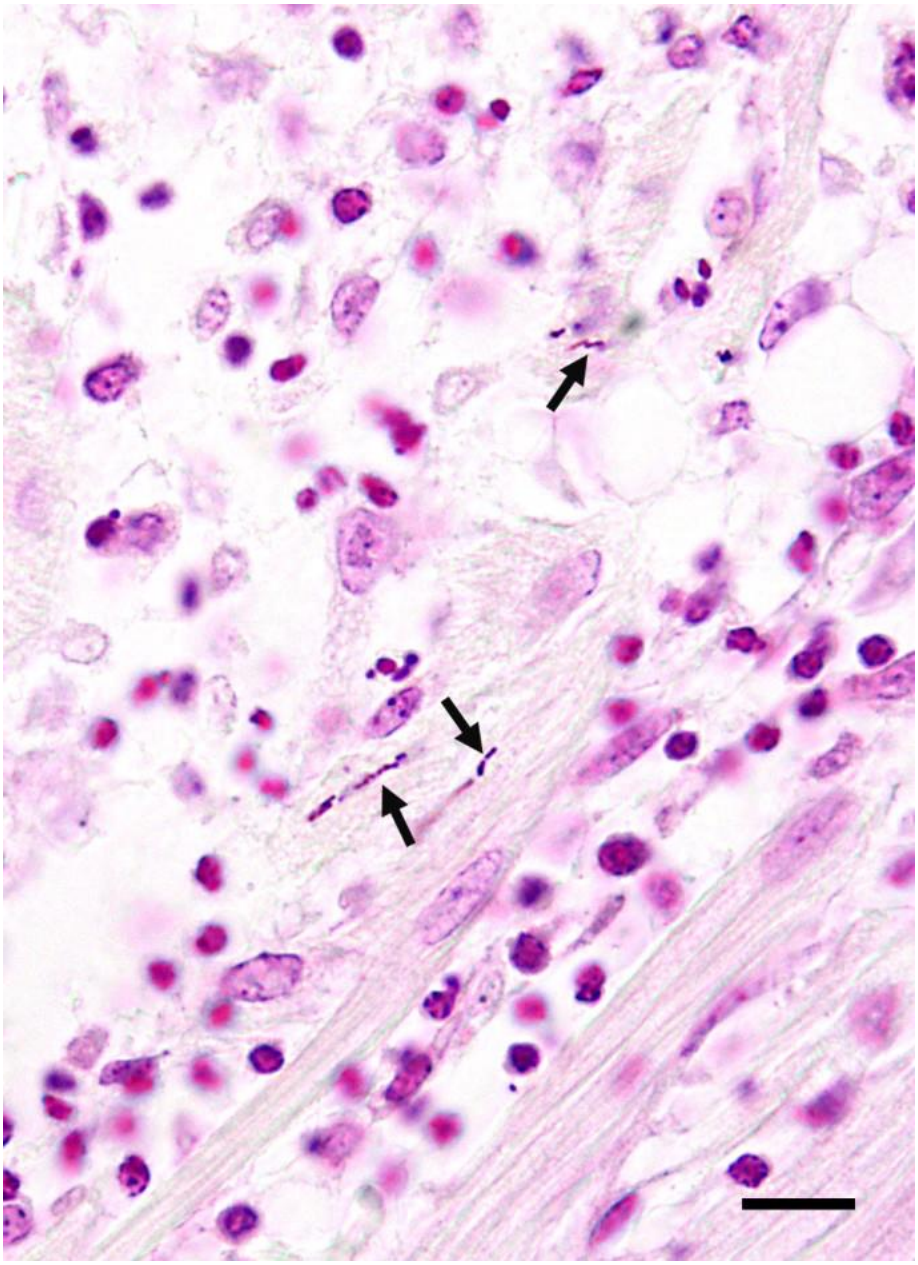

Figure 1: Grams Stain showing a gram-positive non-Spore Forming Road in a Lung Sample.

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