CASE REPORT

Acute Disseminated Encephalomyelitis Associated with *Pasteurella multocida* Meningitis

Normand L. Proulx, Mark S. Freedman, James W. Chan, Baldwin Toye, Cathy C. Code

ABSTRACT: ***Objective:*** To describe a case of *Pasteurella multocida* meningitis associated with acute disseminated encephalomyelitis (ADEM). ***Case report:*** A 33-year-old woman employed in a dog pound presented herself to hospital with fever and meningismus and was found to have culture positive *Pasteurella multocida* meningitis. Despite appropriate antibiotic treatment her clinical course was characterized by a persistent fever and worsening encephalopathy, which prompted further neurological investigation. Spinal fluid exam and serial MRI scans as well as her one-year clinical course were found to be compatible with ADEM. ***Conclusion:*** Persistent fever and worsening encephalopathy in meningitis may indicate a para-infectious immune process such as ADEM, and may serve as indications for further neurological investigation.

RÉSUMÉ: Encéphalomyélite disséminée aiguë associée à une méningite à Pasteurella multocida. ***Objectif***: Décrire le premier cas connu de méningite à Pasteurella multocida associée à une encéphalomyélite disséminée aiguë (EMDA). ***Histoire de cas***: Une femme âgée de 33 ans, travaillant dans une fourrière, s'est présentée à l'hôpital à cause d'une hyperthermie et de méningisme. La culture a montré qu'il s'agissait d'une méningite à Pasteurella multocida. Malgré une antibiothérapie appropriée, la fièvre a persisté et l'encéphalopathie s'est aggravée, ce qui a motivé une investigation neurologique plus poussée. L'examen du liquide céphalo-rachidien et l'IRM ainsi que son évolution clinique sur un an se sont avérés compatibles avec une EMDA. ***Conclusion***: Une fièvre persistante et une encéphalopathie qui s'aggrave peuvent être des manifestations d'un processus immunitaire para-infectieux, l'EMDA, compliquant la méningite à Pasteurella multocida. Ce tableau clinique suggère qu'il y a indication de procéder à une investigation neurologique plus poussée.

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Case report

A 33-year-old woman, employed in a dog pound, presented herself to the emergency department complaining of worsening headache, photophobia, and neck pain. One week prior to her presentation she developed a dry cough, sore throat and nasal discharge and was treated with amoxicillin for an upper respiratory tract infection. There was no history of recent vaccination. She remembered having recently been scratched on the hand by a newly encountered dog. Her past medical history included recurrent sinusitis. She also had chronic neck pain which she related to a motor vehicle accident three years previously.

On initial examination the patient looked ill, her temperature was 39°C, her blood pressure was 130/80 mmHg, her pulse was 110 beats per minute, and her respiratory rate was 16 breaths per minute. A general examination did not reveal a rash, peripheral lymphadenopathy or break in the integument despite the history of a dog scratch on the hand. Ear, nose and throat examinations were unremarkable. Neurologically, she was fully oriented and the only finding was meningismus.

Admission laboratory investigations revealed the following: white blood cell count 14.6 X 10^9/L with neutrophil count 13.4 X 10^9/L, hemoglobin 129 g/L and platelet count 192 X 10^9/L. Her electrolytes, urea, and creatinine were within normal limits. Urine and microscopy were unremarkable. The chest roentgenogram and electrocardiogram were normal. A lumbar puncture yielded cloudy cerebrospinal fluid (CSF) containing 680 X 10^6/L leukocytes (78 % neutrophils, 1 % lymphocytes and 21 % monocytes), an elevated protein level of 0.93 g/L and a glucose level of 3.9 mmol/L. Serum glucose was 7.5 mmol/L.

From the Department of Medicine, Division of Internal Medicine (NLP, JWC, BT, CCC), and Neurology (MSF), The Ottawa Hospital - General Campus, Ottawa, Ontario, Canada

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Reprint requests to: Normand L Proulx, 110 Blv des Grives # 3, Hull, QC J9A 3E4 Canada.

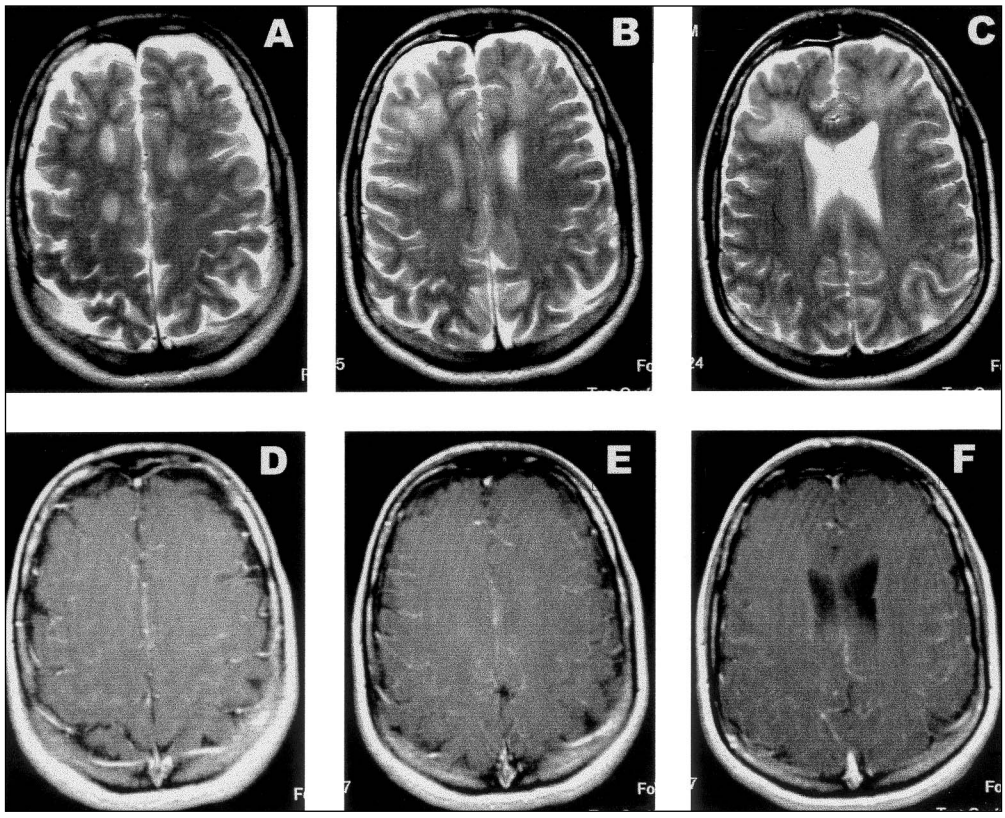

Figure 1: *Axial T2 MRI sequences of the brain highlight multiple confluent and oval shaped hyperintensities in both frontal lobe and periventricular white matter areas (Panels A, B, C). Corresponding axial post gadolinium T1 weighted MRI sequences of the brain do not demonstrate abnormal parenchymal, leptomeningeal or dural enhancement (Panels D, E, F).*

Intravenous cefotaxime and vancomycin were immediately initiated as empirical treatment for meningitis.

Microscopic examination of the CSF indicated the presence of rare gram-negative bacilli and rare gram-positive cocci. Subsequently, blood cultures and CSF cultures all grew *Pasteurella multocida*. The organism had the typical gram morphology and was identified using a commercially available bacterial identification system (API 20E) and confirmed by conventional biochemical tests.[1] The *Pasteurella multocida* isolate did not produce beta-lactamase and had a penicillin minimal inhibitory concentration of 0.125 mg/L by the E-test method. The CSF also grew coagulase-negative staphylococcus, which was considered a contaminant. The antibiotic regimen was changed to two weeks of high dose intravenous penicillin G, 4 million units every four hours.

Fever persisted despite 78 hours of antibiotic treatment - 36 hours with intravenous penicillin G and 42 hours with intravenous cefotaxime. She complained of a sustained headache, the new onset of both a bilateral earache and of mental lethargy suggesting the development of an encephalopathy. Examination at this time demonstrated a noticeable delay in her ability to answer questions appropriately, despite remaining fully oriented. Mild hyperemia of the left tympanic membrane was noted and her neck was no longer stiff or tender. No clinical evidence of phlebitis was found. Repeated urine and blood cultures as well as a chest roentgenogram were negative and there was no rash to suggest a drug reaction. Given the persistent fever, change in her neurological status and her history of sinusitis, an MRI study of the brain and spine was initiated to explore the possibility of a parameningeal abscess. There was no sign of a meningeal or parameningeal process but instead, the MRI revealed multiple confluent and oval shaped increased signal intensities in both frontal lobes and periventricular white matter regions. There were no detectible epidural or subdural fluid collections suggesting abscess formation (Figure 1; Panels A to F). The spine MRI studies were unremarkable.

At this point in time, acute disseminated encephalomyelitis (ADEM) or a CNS vasculitis were felt to be the two diagnostic possibilities most compatible with the above findings. Her erythrocyte sedimentary rate was 60 mm/hr (normal; 0 to 10 mm/hr) and her C reactive protein was 21.6 mg/L (normal; < 8 mg/L), thus further supporting the diagnoses. In addition surrogate markers including antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, complement 3, complement 4 were negative or within normal limits. Finally, a four vessel cerebral arteriogram was performed and the study was normal. We administered empiric treatment with intravenous methylprednisolone, 500mg twice a day for two days, followed by a tapering dose of oral prednisone. Shortly after corticosteroid treatment, her fever resolved as did both her headache and earache.

On follow-up nine weeks later, the neurological evaluation was normal but complaints remained of mental lethargy and poor

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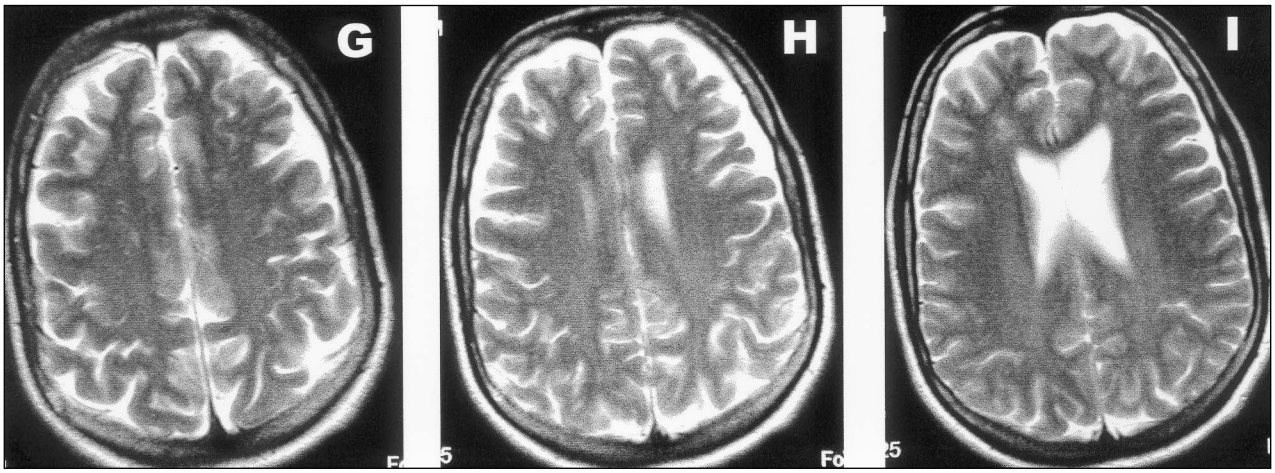

Figure 2: *Corresponding axial T2 weighted images performed nine weeks following the initial MRI studies. There is near complete resolution of the previously observed hyperintensities (Panels G, H, I).*

concentration. The erythrocyte sedimentary rate and CRP values fell to within normal limits. A repeat MRI study showed near complete resolution of the abnormalities previously observed in the white matter (Figure 2; panels G to I). A follow-up EEG performed due to continued cognitive complaints was normal. Sixteen months later the patient was no longer complaining of the aforementioned cognitive deficits, though there were minor lingering complaints of premature fatigue.

Discussion

Pasteurella multocida is a small, gram-negative coccobacillus. It is a commensal in the nasopharynx and gastrointestinal tract of many mammals with cats and dogs having higher carriage rates. In humans, manifestations of *Pasteurella multocida* infection most commonly involve local wound infections from animal bites. A major recent review on adult *Pasteurella multocida* meningitis reported only 29 such cases in the English language literature. This review outlined licking of mucosal surfaces as a more common form of animal exposure in meningitis patients.[2] Of the 29 cases, five (17%) manifested with neurological complications including seizures (two patients), facial palsy (two patients) and abducens palsy (one patient).[3] Penicillin is the antibiotic of choice for the treatment of *Pasteurella multocida* meningitis although rare cases of resistance have been reported. An alternative to penicillin is a third generation cephalosporin as supported by its minimal inhibitory concentration data, excellent CSF penetration and efficacy in other bacterial meningitides.[3-5]

Acute disseminated encephalomyelitis is presumed to be an immune-mediated inflammatory demyelinating disease of the central nervous system.[6] Its challenging diagnosis relies on a combination of clinical and CSF findings, MRI studies and, when indicated, brain biopsy. Clinically it is more typical in children, where it will present usually following vaccination, a viral illness from measles, varicella, rubella, or alternatively after a bacterial infection from *Mycoplasma, Legionella*, or *Streptococci*.[6-9] There are two reported cases of ADEM associated with *Cryptococcus neoformans* meningitis.[10,11] The presentation is characterized by an exanthem, headache, myalgias[7] and fever being especially common in the pediatric population[9,12] but less so in adults.[9,13] Following a delay ranging from 1 to 20 days,[7] monophasic neurological findings including encephalopathy (headache, disturbed consciousness), seizure, ataxia, cranial nerve abnormalities, and dysphasia may develop. Magnetic resonance imaging findings characteristic of ADEM are essential in confirming the diagnosis. Multiple, symmetrical, subcortical, confluent white matter patchy areas of increased signal intensity on conventional T2-weighted and proton density-weighted images are characteristic, but do have a broad differential including multiple sclerosis (MS), vasculitis, HIV encephalitis and subacute sclerosing panencephalitis. In order to qualify for ADEM, most authors will agree that lesions on the MRI scan should be of the same age, with lack of gadolinium enhancement, and no new lesions should appear on imaging studies done after the initial attack.[7,12-15] The presence of T1-weighted non-enhancing hypointensities (i.e. “black holes”) on the first scan can suggest the presence of prior disease and would be more typical of a demyelinating process such as MS.[13] Treatment of ADEM commonly involves high dose intravenous corticosteroids[7,8] and, alternatively, intravenous gammaglobulins or plasmapheresis have been used.[7]

This is the first case that we are aware of that describes *Pasteurella multocida* meningitis associated with ADEM. The organism was appropriately identified in the patient’s CSF and blood, and a close temporal relationship of 10 days exists between the onset of infectious symptoms and the development of worsening encephalopathic features (headache and mental lethargy), and the detection of the MRI lesions. Although headache and lethargy are not atypical findings in acute meningitis they are also key encephalopathic features of ADEM. The MRI lesions (Figure 1; Panels A to F) are characterized by their indiscrete borders, symmetrical appearance, subcortical distribution and lack of T1 hypointensities or enhancement. These MRI findings are atypical for MS and are more suggestive of either ADEM or vasculitis. Also, the near complete resolution of the MRI lesions within nine weeks would be more atypical for

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MS (Figure 2; Panels G to I). The clinical picture is also not typical of the first presentation of MS with the presence of fever, encephalopathy, a very high CSF white blood cell count and protein, which together with the aforementioned MRI studies would be more compatible with ADEM or a vasculitis. The patient has failed to develop any other symptoms or signs compatible with MS even more than a year after her initial presentation. In addition, CSF analysis for the presence of a raised IgG index and oligoclonal banding was negative ten months after the initial admission. Oligoclonal banding is usually absent in ADEM, but might be detected in the acute phase, whereas the opposite is true with regards to MS; i.e. possibly absent early on but usually positive later. The lack of oligoclonal banding in this follow-up CSF further supports a diagnosis of ADEM. Although the diagnosis of CNS vasculitis is not entirely excluded by the lack of serological markers and a normal cerebral arteriogram, it would have been unlikely for such lesions to resolve almost completely after only a single course of steroids. In addition such lesions tend to be more discrete and often enhance on MRI, which was not the case here. Overall, this case report presents convincing evidence for an association between *Pasteurella multocida* meningitis and ADEM.

We propose ADEM as an explanation for this patient's persistent isolated fever. We were initially concerned in this case because in our experience, fever should not persist beyond 48 hours in uncomplicated, adequately-treated bacterial meningitis. This finding is alarming to the clinician as it raises the possibility of treatment failure, incorrect diagnosis, or an unidentified nidus of infection. We conducted a MEDLINE search using the terms meningitis, antibiotics and fever duration in an attempt to identify the mean duration needed to reach defervescence. Three related articles, mainly addressing the pediatric population, were identified.[16,17,18] In summary, the combined results of all three studies showed that 50 % of patients with meningitis reached their first afebrile day after three to six days. Commonly identified causes of persistent fever included drug reaction, phlebitis, intercurrent infection and unknown cause. No case of resistance to antibiotics or relapse of meningitis were reported. Our patient's fever persisted despite over three days of antibiotic therapy. No evidence of phlebitis or intercurrent infection was found. A drug reaction to one of the antibiotics remains a possibility even though no rash was identified. We propose that when a persistent isolated fever complicates adequately-treated meningitis and an encephalopathic picture arises, this suggests the need for further neurological evaluation possibly with MRI scanning. Acute disseminated encephalomyelitis would be a rare diagnosis that should be considered in this context.

Conclusion

This case highlights the unusual scenario of a CNS infection with a relatively rare organism which, in addition, may have been responsible for a similarly rare para-infectious CNS immune process. Physicians need to be aware of *Pasteurella multocida* as a cause of meningitis especially in appropriate populations, as well as the possibility of ADEM complicating this type of infection. Cases such as this one with typical clinical features of meningitis would not have gone to MRI had concern over a persistent fever and worsening encephalopathic picture not been raised. The question arises as to whether radiological ADEM might be more common if MRI studies were done routinely for CNS infectious processes. Within the context of limited access to, and considerable expense of such studies, validating potential clinical indications of ADEM such as persistent fever and encephalopathy becomes important.

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