# Case Files
## of Wake Forest Baptist Medical Center

# Things Deteriorated Quickly

Will McKay, C. Alston James
Participants: William Applegate, MD, Joel Bruggen, MD, Vera Luther, MD, K. Patrick Ober, MD, Wesley G. Willeford, MD
Moderator: Leslie Ellis, MD

In **Case Files of Wake Forest Baptist Medical Center**, the clinical presentation of a real patient is described to a panel of experts in stages (bold type) in front of an audience of residents and students. The panel discusses the differential diagnosis, asks relevant questions, explains their clinical thought process, and answers audience questions.

## Case Presentation

Wesley G. Willeford, MD.

**The patient is a 48-year-old gentleman who presents in late July with fever, fatigue, and shortness of breath. He has a chief complaint of fatigue for the past five days. He saw his primary care physician on the first day and was told that he had a low blood count. Five days later he presented to an outside hospital with complaints of dizziness, shortness of breath, and chest tightness. His temperature on the day of admission to the outside hospital was 103° F. He had a tonic-clonic seizure, which was treated with administration of 2 mg of lorazepam. He had no history of respiratory symptoms prior to his presentation to the hospital, and he did not have a history of recent travel, chest pain, or cardiac disease. He did report some diarrhea.**

**Dr. Luther**
Infectious Diseases

The chronicity of his presentation suggests that this is a relatively acute disease progression. You want to consider the organ systems affected, as manifested by fever, fatigue, shortness of breath, and seizure in the process of developing a differential diagnosis. Shortness of breath may indicate pneumonia and the various bacterial etiologies that cause it. With the presence of central nervous system symptoms, meningitis and encephalitis should be considered as well. Endocarditis and blood stream infections, among other disorders, can cause the constitutional symptoms seen in this patient. At this stage, it is important to keep a broad differential and not narrow too quickly on infection, despite the presence of a high fever. Diseases such as vasculitis need to be in the differential diagnosis, as well as malignancy and rheumatologic disorders.

**Dr. Applegate**
Gerontology and Geriatrics

An early finding of fatigue and low blood count before the onset of fever suggests that there may be an underlying condition predisposing him to infection.

**Dr. Bruggen**
Gastroenterology

HIV, for example, can predispose a patient to infection due to low counts of CD4-positive T-cells. We were not told which blood count was low.

**The patient has no diseases for which he is receiving treatment. Family history is unremarkable. His left forearm was amputated after a motor vehicle collision many years ago. He is a non-smoker, and he reports a significant amount of alcohol consumption. His alcohol use has increased lately to 6-12 beers a day. He denies illicit drug use. He is currently unemployed, and he lives at home with his father on their family farm.**

**Physical examination showed a temperature of 100.2$^0$ F. His heart rate was 144 bpm. Respiratory rate was 28/min. Blood pressure ranged from 83/53 to 100/57 mmHg over two hours. His mean arterial pressure was 60-73. He was initially given 4L of $O_2$, saturated at 98%. On examination he was responsive and conversed fluently, but he was oriented only to himself. He was not oriented to location, month or year. His eyes, nose, and mouth were unremarkable on exam, which the exception of scattered petechiae in his oropharynx. His neck was supple. He had no jugular venous distention. Lymphadenopathy was not present on palpation. Cardiovascular and respiratory findings were unremarkable. Gastrointestinal examination revealed hyperactive bowel sounds, but the abdomen was non-tender, non-distended, and without hepatosplenomegaly. The extremities were normal except for the amputated left forearm. Examination of the skin revealed erythematous, fine petechiae scattered on the trunk, arms, and legs, including the palms and soles (see Image 1).**

Image 1: Wake Forest Baptist Medical Center / Wesley G. Willeford

**Dr. Bruggen** Are we worried about Waterhouse-Friderichsen disease in this patient?

**Dr. Ober**
Endocrinology & Metabolism

Waterhouse-Friderichsen is a disease with the presence of petechiae and hemorrhagic bleeding into the adrenal glands. Patients present with fever, petechiae, and a low platelet count, which leads many to recognize the underlying infection. Despite antibiotic therapy, patients can die unless they also receive therapy for the concomitant adrenal insufficiency.

**Dr. Luther** He lives on a farm; what animals are on the farm?

**They used to have farm animals. They currently only have dogs**.

**Dr. Ellis**
Hematology-Oncology

And how would that change your diagnosis? What animals are you looking for, and why?

**Dr. Luther** We were not given a history that included bites, but with outdoor dogs potential tick exposure is a concern. Brucellosis is common in households with cats, particularly if the cats have just given birth. The differential diagnosis of fever and rash is broad, but important. There are both non-infectious and infectious causes to consider. Vasculitis, for example, is still in the differential diagnosis as a non-infectious cause. Then there are also some important infectious causes to think about. Acute HIV is one. Disseminated gonococcal infection is another. Meningococcemia is important, particularly with his central nervous system involvement. Rocky Mountain Spotted Fever (RMSF), Ehrlichiosis, and rat-bite fever are important to consider. Drug reactions can also cause fever and a rash.

**The only drug he has taken recently is ibuprofen, and only occasionally.**

**Dr. Luther** An early finding of fatigue and low blood count before the onset of fever suggests that there may be an underlying condition predisposing him to infection.

**Dr. Bruggen** HIV, for example, can predispose a patient to infection due to low counts of CD4-positive T-cells. We were not told which blood count was low.

**He was admitted to the medical intensive care unit, and he soon experienced another tonic-clonic seizure. After this episode he was much less responsive. He was electively intubated to protect his airway. As the night progressed, he developed shock. The initial labs after his admission were notable for a sodium level of 132 mmol/L, and a low potassium level of 3.1 mmol/L. Chloride was 104 mmol/L. $CO_2$ was 15 mmol/L. The creatinine was elevated at 1.7 mg/dL. As far as we know this gentleman had no history of chronic kidney disease, and his baseline creatinine was not known at that time. The albumin was 2.3 g/dL, and the protein was 4.2g/dL. The alkaline phosphatase was mildly elevated at 195 IU/L. Aspartate transaminase (AST) and alanine transaminase (ALT) were both elevated at 242 IU/L and 108 IU/L respectively. The anion gap was 13. The estimated glomerular function was 40 ml/min. His complete blood count indicated some leucopenia, with a white blood cell count (WBC) of 4,000. The hemoglobin (Hb) was 8.3, which is fairly anemic for a young man, and he was somewhat thrombocytopenic with a platelet count of 19,000. Blood sugar and bilirubin were in the normal ranges. The EKG showed sinus tachycardia.**

**Dr. Ober** He has low calcium, which could be the cause of his seizures. Most of the apparent hypocalcemia is corrected by taking into account the low albumin, however. The corrected serum calcium is about 8.1 (normal range is 8.5-10.5 mg/dL), which is still a little low. Given his presentation, though, infection is the primary consideration, and the hypocalcemia is of secondary importance. Thrombocytopenia alone would be concerning for RMSF, but this is more of a pancytopenia.

**Dr. Applegate** This kind of course strongly suggests RMSF or meningococcemia. In the setting of HIV there can be lymphopenia in addition to thrombocytopenia, which could also be relevant to this case.

**Dr. Bruggen** This presentation could also be concerning for disseminated intravascular coagulation (DIC).

**Dr. Ellis** Why are you worrying about DIC?

**Dr. Bruggen** It's in the differential for thrombocytopenia. In this situation it is necessary to take measures to stabilize his condition with intravenous fluids and pressors, and think about starting steroids.

**Dr. Ober** The question about steroids is a good one, and in an acute situation they may have benefit. A cortisol level should be obtained first, though.

**Dr. Luther** Antibiotics should be given as well, especially if corticosteroids are being administered. Broad-spectrum antibiotics should be started while blood cultures and other tests are in process. I agree with Dr. Applegate; the biggest concern at this moment would be for RMSF or meningococcus. Therapies should be targeted to ensure coverage of those organisms.

**Dr. Ober** There is a tendency to worry that giving a large dose of steroids in the setting of possible infection could cause harm, because they are immunosuppressive. It is important to note that steroid-induced immunosuppression is a chronic phenomenon. A patient with bacteremia, hypotension, or shock will have a high cortisol (as much as they can possibly make at that time), and giving them a bolus of steroids is generally warranted. If the patient has a deficiency, it might save his or her life. Chronic steroids present a different situation, but one time use acutely is safe.

**Student** Dr. Ober, how much would you give?

**Dr. Ober** In adrenal insufficiency, the textbooks say 300 mg hydrocortisone for 24 hrs is as much as any human being can make under maximal stress. So generally they get dosed at 100 mg intravenously every eight hours.

**After the initial evaluation, further lab tests were ordered. The IgG for hepatitis A came back positive, but hepatitis A IgM was not reactive, ruling out an active infection. Hepatitis B surface Ag and Core Ab were negative. Hepatitis C Ab was also negative. The HIV test was nonreactive, which was confirmed by a negative viral load. The RMSF assay was negative. Lactate dehydrogenase (LDH) was elevated at 1138 U/L. The haptoglobin was <30 mg/dL, and on peripheral smear there were a few schistocytes. His urine drug screen was negative.**

**Dr. Luther** The concern for DIC, especially with the presence of schistocytes, has been raised. Both could be present in association with some of the infections mentioned, including RMSF. Was that the latex antibody that was negative?

**Yes, the latex antibody was negative.**

**Dr. Luther** A negative latex antibody doesn't rule out the diagnosis. It is very rapid, and is helpful if it is positive, but it is not as sensitive as the send-out test. If there a high clinical suspicion, an ELISA test should be done. It takes longer to obtain a result, but is more accurate.

**Dr. Bruggen** Given the evidence of a hemolytic anemia, and with this clinical course, this could be microangiopathic hemolytic anemia. If so, we could consider hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.

**Dr. Luther** Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP) can present with diarrhea and fever.

**Dr. Ellis** Students will remember the pentad associated with TTP. Along with low ADAMSTS13 activity, TTP patients have fever, microangiopathic hemolytic anemia, renal failure, neurological symptoms, and thrombocytopenia. There is typically a pentad, but there are only two symptoms that are necessary for the diagnosis: thrombocytopenia and microangiopathic hemolytic anemia.

**The next morning, the lab ran the ADAMSTS13 assay, and the activity was 37%.**

**Dr. Ellis** For TTP, activity must be less than 5% for a definitive diagnosis. Although the activity is low, it is not low enough to qualify for TTP.

**Neurology was consulted and an MRI of the brain was requested. Image 2 is a T2-weighted**

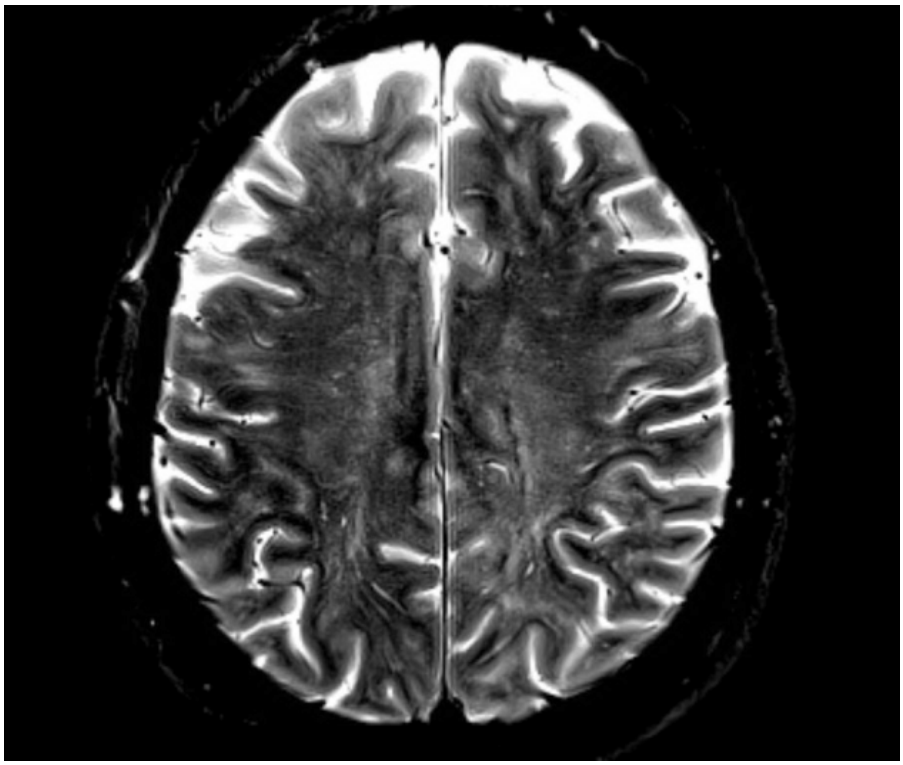

Image 2: Wake Forest Baptist Medical Center / Wesley G. Willeford

**MRI image, with an excerpt of the final interpretation by the radiologist.**
**The distinct diffuse linear T2 signal abnormalities suggest a process involving the perivenous spaces (perivascular spaces) of the brain, which may be secondary to cerebrospinal fluid dissemination of an infectious agent with encephalitis. The numerous small diffusion signal abnormalities are most consistent with punctate infarcts, possibly from vasculitis or a thromboembolic process.**
**A spinal tap was performed, and platelets were transfused to ensure patient safety. Cerebrospinal fluid (CSF) protein was 180, and glucose was 45. PCR studies were negative for herpes simplex virus 1 and 2. CSF cultures showed no growth of bacterial or fungal isolates. Enterovirus PCR culture was also negative. Studies to evaluate possible rheumatologic diseases were negative, including ANCA (anti-neutrophil cytoplasmic antibody) studies. ANA (anti-neutrophil antibody) was also negative. The RMSF serology was rechecked, and was noted to be positive at 1:128.**

## COMMENTARY

**Dr. Willeford**
Internal Medicine

The MRI findings, physical exam, and positive RMSF serology confirmed the diagnosis. The patient was started on empiric doxycycline therapy. One of the complications of this therapy was status epilepticus, which continued for 4 days. The patient had been on a benzodiazepine drip, and ultimately was placed on a three-drug regimen of levetiracetam, lacosamide and phenytoin that controlled his seizures. He was transferred to the neurology service for management, and regained much of his functional and mental status.

This case elucidates the point that in patients presenting with RMSF, empiric treatment must be initiated based on high clinical suspicion, as serologies may not accurately reflect disease etiology. This was a late-presenting case. When he presented to his primary care physician, he did not have a rash, and showed marked CNS deficiency, so RMSF was not an immediate concern. Perhaps if he had been given empiric therapy earlier, much of his clinical course could have been avoided. There are reports in the literature demonstrating RMSF involvement in the central and peripheral nervous system, but this is not common as patients often receive treatment before the disease can progress to that point.

**Dr. Luther**

This case is valuable in highlighting the importance of having a high clinical suspicion. RMSF has a high prevalence in North Carolina. It is found throughout the United States, but is most common in the central southeast region. North Carolina, Tennessee, and Missouri have the highest incidence of RMSF infections in the United States, which elucidates the need for a high clinical suspicion. Patients present in myriad ways, but typically fever and headache are prominent. On initial presentation, about 15% of patients have a rash. If they go untreated, within about three days 90% will develop a rash and progress to capillary leak syndrome and DIC.[1] Doxycycline is the treament of choice. Often a shorter course of 5 days is warranted, but therapy should be continued for three days after the fever abates.[6]

### Authors

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**Address correspondence to:**
Will McKay
Wake Forest School of Medicine
Winston-Salem, NC 27157
Email: wmckay@wakehealth.edu

### References

1. Gathwala G; Goel M; Singh J; Mittal K. Intravenous diazepam, midazolam and lorazepam in acute seizure control. Indian J Pediatr. 2012 Mar; 79(3): 327-32 doi: 10.1007/s12098-011-0505-y.
2. Tormos LM1, S. C.. The significance of adrenal hemorrhage: undiagnosed Waterhouse-Friderichsen syndrome, a case series. J Forensic Sci, 2013 Jun, 58(4), 1071-4. doi:10.1111/1556-4029.
3. Mathiesen O, et al. Adverse effects of perioperative paracetamol, NSAIDS, glucocorticoids, gabapentinoids, and their combinations: a topical review. Acta Anaesthesiol Scand, 2014 Nov; 58(10):1182-98 doi: 10.1111/aas.12380.
4. Kaplan, JE; Schonberger, LB. The sensitivity of various serologic tests in the diagnosis of Rocky Mountain spotted fever. Am J Trop Med Hyg, 1986 Jul; 35(4): 840-844.
5. Bell W. E.; Lascari A. D. Rocky Mountain spotted fever: Neurological symptoms in the acute phase. Neurology. 1970 Sep; 20(9): 841-847.
6. Dantas-Torres F. Rocky Mountain spotted fever. Lancet Infect Dis. 2007 Nov; 7(11): 724-32.