Clinical Pathologic Case:

38 years old with Sjögren's syndrome and rheumatoid arthritis presents with acute onset of headaches

Francis Wadskier[1], Judith Berger[2], David Engelbrecht[3], Richard Hwang[4], and Victoria Bengualid[2]

[1]Department of Internal Medicine, SBH health care system, Bronx, NY

[2]Department of Infectious Disease, SBH health care system, Bronx, NY

[3]Department of Rheumatology, SBH health care system, Bronx, NY

[4]Department of Pathology, SBH health care system, Bronx, NY

Key Words: Rheumatoid arthritis, Sjögren's disease, Meningitis, Vasculitis

Chief Complaint: "I have a headache."

A 38-year-old female with a history of Sjögren's syndrome and rheumatoid arthritis came to the emergency room complaining of headaches. The headache started suddenly two hours earlier and was severe. It was located in the frontal and basilar area, non-radiating, constant, with no alleviating factors. She noted subjective fever, chills, nausea and one episode of non-bloody non bilious vomiting. The patient gave a history of a cold several days earlier. She denied photophobia, trauma, abdominal pain, diarrhea, cough, animal exposure, recent travel or any sick contacts.

Five years prior to admission, the patient complained of dry mouth and eyes, hair loss, pain and swelling of her shoulders, wrists and hands, and morning joint stiffness that lasted for about one hour. Serologies were notable for a positive Sjögren SSA, negative SSB, positive CCP antibodies, normal ESR and negative RF and DNA antibodies. X-rays of her shoulder and wrists showed joint space narrowing. She was treated for rheumatoid arthritis and Sjögren's syndrome with a combination of medication to decrease her pain and inflammation. Two months prior to admission on routine clinic visit, she noted increase dryness of her mouth and severe joint pain which became manageable on medications. Her knees and ankles remained swollen and painful. She also noted difficulty sleeping.

Review of systems was notable for multiple joint pains, including knees, all fingers and the entire spine including the neck.

Her past medical history was otherwise notable for a history of bulimia.

She denied any tobacco drug or alcohol use.

Home medications: hydroxycloroquine 200mg twice a day, sulfasalazine 500mg twice a day, prednisone 10mg daily, chlorzoxazone 500mg three times a day, artificial tears, diclofenac 75mg twice a day, senna and pepcid.

Physical Exam: temperature (T) 100.4^{o}F, heart rate (HR) of 104 beats per minute (bpm), blood pressure (BP) 99/52 mm hg, respiratory rate (RR):18, O2 saturation: 98% on room air. Patient was alert, able to give a history, but visibly uncomfortable, restless, complaining of joint pain and headache. Her physical exam was notable for conjunctival injection, a positive Kernig's and Brudzinski's sign. Laboratory results are shown in table 1.

Table 1. **Results of Analysis of Blood of the Patient from Hospital Admission**

Variable	Result	Normal Range
Complete blood count		
WBC (10^3/uL)	4.5	4.0-10.0
RBC (10^3/uL)	4.21	3.93-5.22
Hgb (gm/dl)	11.9	11.2-15.7
Hct (%)	37.4	34.1-44.9
MCV (fl)	88.8	79.4-94.8
RDW (%)	12.8	11.7-14.4
Platelet count (10^3/uL)	249	182-369
Neutrophil (%)	69.2	34.0-71.1
Eosinophil (%)	0.9	0.7-5.8
Lymphocyte (%)	25.9	19.3-51.7
Monocyte (%)	3.1	4.7-12.5
Immature granulocyte (%)	0.7	0-0.5
NRBC (/100 WB)	0	0-0.2
Comprehensive metabolic panel		
Sodium (mEq/L)	136	135-145
Potassium (mEq/L)	5.2	3.5-5.3
Chloride (mEq/L)	104	96-108
Carbon Dioxide (mEq/L)	23	23-30
Glucose (mg/dl)	**115**	70-100
Urea Nitrogen (mg/dl)	14	8.0-23
Creatinine (mg/dl)	0.6	0.6-1.2
Calcium (mg/dl)	**8.4**	9.2-11.0
Albumin (gm/dl)	**3.1**	3.8-5.0
Protein Total (gm/dl)	7	6.0-8.0
ALT (IU/L)	**39**	4.0-36
AST (IU/L)	**76**	8.0-33
Bilirubin Total (mg/dl)	1	0.1-1.2
Alkaline phosphatase (IU/L)	72	38-126

Abnormal results are bolded.

In the ED-Hospital day #1:

Patient was isolated and treated for possible meningitis with vancomycin, ceftriaxone, ampicillin, acyclovir and dexamethasone. A non-contrast computed tomography (CT) of the brain was negative. Results of cerebrospinal fluid obtained from lumbar puncture are shown in table 2. Her course was complicated by an episode of supraventricular tachycardia (SVT) requiring adenosine and diltiazem for control.

Table 2. Results of Analysis of Cerebrospinal Fluid

Variable	Results	Normal Range
Color	Colorless	Colorless
Appearance	Slightly Cloudy	Clear
Xanthochromia	Negative	Negative
Glucose (mg/dl)	33	40-70
Protein level (mg/dl)	71	15-45
White-cell count (cells/mm3)	246	0-5
Red-blood cell count (cells/mm3)	144	0-10
Neutrophils (%)	96	0
Lymphocytes (%)	3	60-70

She was transferred to the intensive care unit (ICU) 12 hours after arrival to the emergency room. Upon arrival to the ICU she became obtunded requiring emergent intubation.

Hospital day #2:

She remained febrile (T 100.8^{o}F) on mechanical ventilation with good oxygenation. On neurological exam she did not follow commands, did withdraw all extremities to pain and opened eyes spontaneously.

History of a positive tuberculin test was obtained. At the time she had a negative chest x-ray and was treated with nine months of isoniazid. In view of her cerebrospinal fluid (CSF) results and poor response to antibacterial, she was started on tuberculosis treatment with rifampin, pyridoxine, pyrazinamide and ethambutol.

CSF cultures, cryptococcal antigen and sputum acid-fast bacilli (AFB) smears were negative. Sputum was sent for mycobacteria PCR testing, HIV test was sent, CSF viral panel results were pending.

Hospital day #3:

Patient remained obtunded. Her vital signs were: T 98.4^{o}F HR 160 BP 107/75 RR: 19 100% O2 saturation on FiO2 30%. She had an episode of SVT followed by bradycardia. She went into cardiac arrest requiring CPR for 30 minutes before regaining a pulse. The patient was started on four pressors to maintain her blood pressure. Pupils became dilated and fixed. Electrocardiogram showed ST elevation in the lateral leads. Chest X-ray was consistent with pulmonary edema. Later that day, the patient had a second cardiac arrest. Pulse was obtained several minutes later. Brain computed tomography angiography (CTA) of head

showed diminished cerebral venous circulation and decrease in coronal medullary differentiation consistent with cerebral edema, right posterior fossa parenchymal hematoma (Figure 1,2) with mass effect and partial cerebellar tonsil herniation (Figure 2).

Patient was febrile (102.7^{0}F) did not respond to painful stimuli, did not open eyes spontaneously, and had absent corneal reflex with fixed dilated pupils. She was tachycardic, with bilateral rales, hypoactive bowel sounds. Antibiotics, acyclovir, anti-tuberculosis medications and steroids were continued. EEG was ordered.

Hospital day #4 and 5:

The patient was declared brain dead. Her family was informed. Pressure support was discontinued. Shortly afterwards the patient died. An autopsy was obtained.

What is your diagnosis?

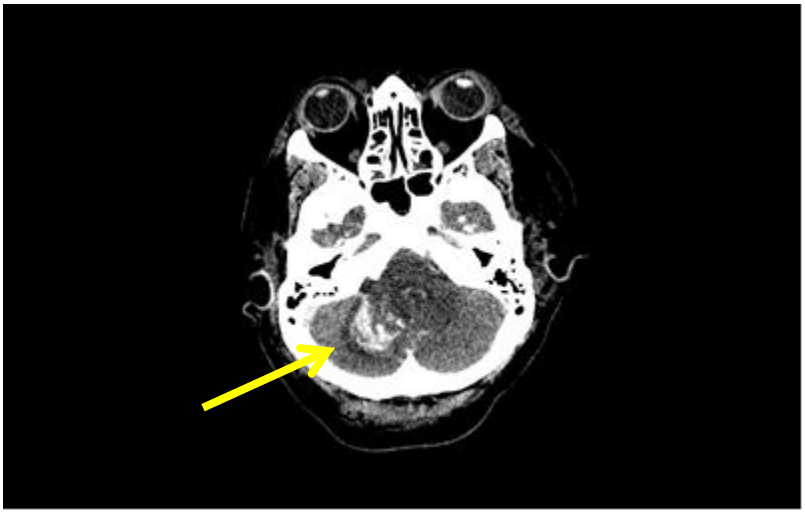


Figure1: CTA showing a cerebellar bleed

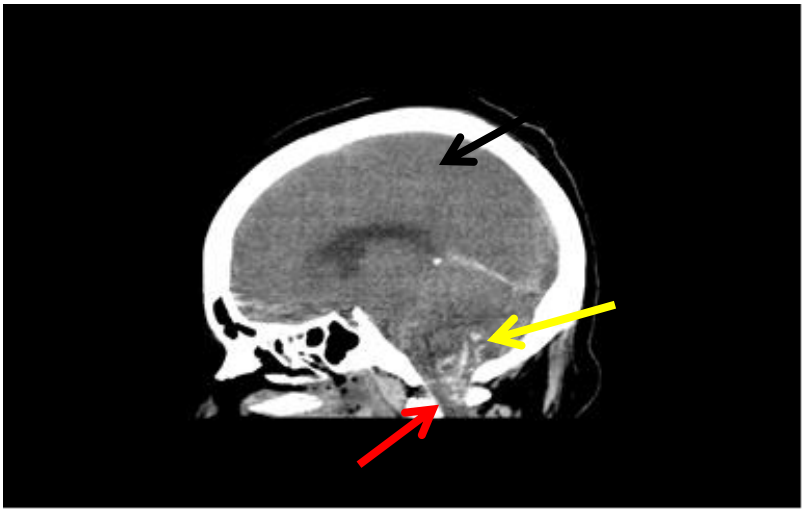


Figure2: CTA

-Decrease in coronal medullary differentiation consistent with cerebral edema (black arrow)

-Cerebellar bleed (yellow arrow) causing herniation of the cerebellum through the foramen magnum(red arrow)

Comments:

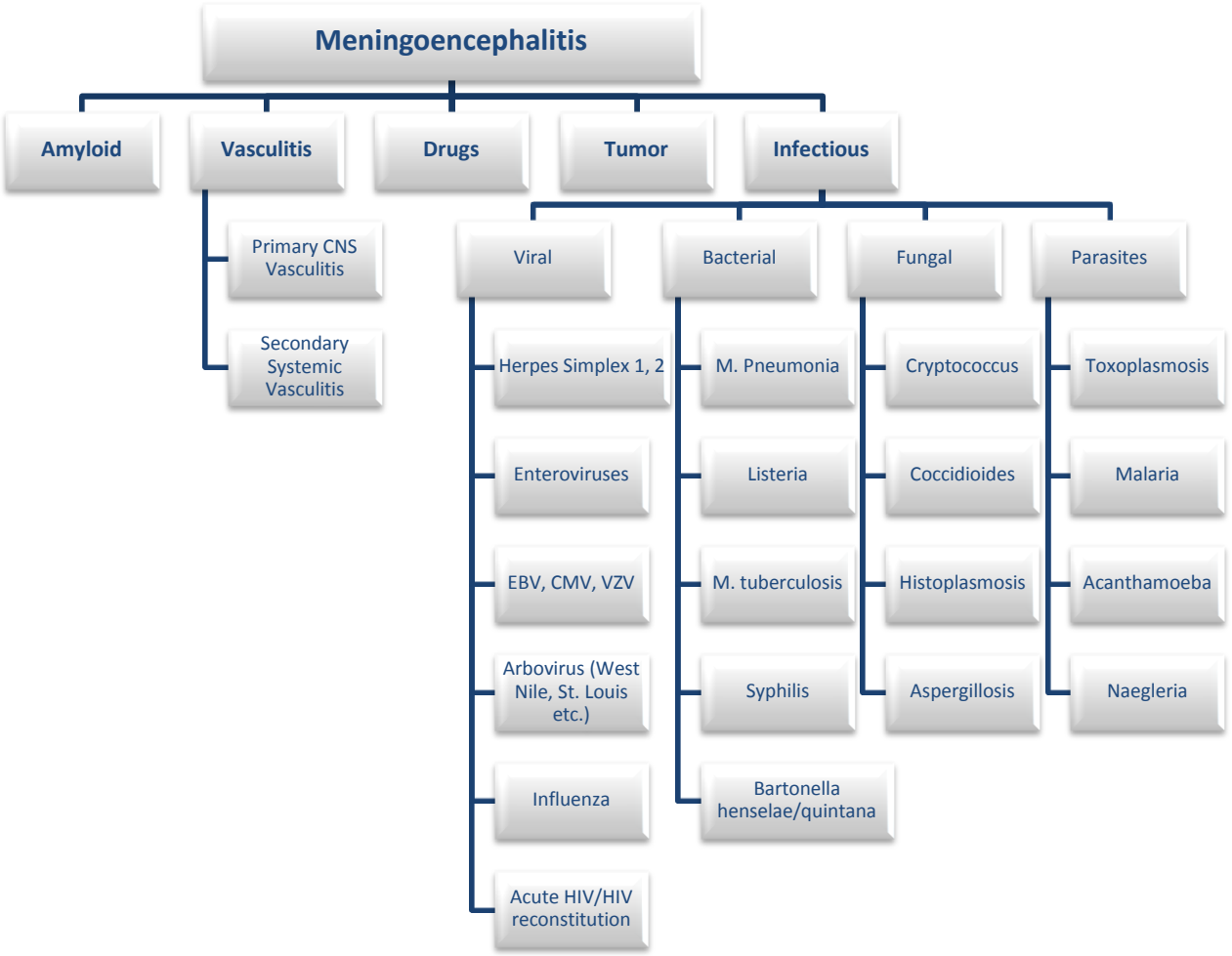
In summary, this was a 38 year old woman with a history of Sjogren's disease and rheumatoid arthritis on low dose steroid therapy, who presented with an abrupt onset of headache with meningeal signs, with elevated CSF white blood cells. Within hours she deteriorated, became comatose with evidence of cerebral edema and herniation. She died 4 days later despite broad antibiotic and tuberculosis treatment.

An extensive differential diagnosis was generated and is summarized in figure 3. Of the potential diagnosis, drugs, and parasites are less probable as her drug history and travel history are not consistent with these entities. Amyloid is seen in patients with long standing rheumatologic disease. Metastatic disease seems unlikely as the patient had no evidence of a primary tumor. However a primary central nervous system (CNS) malignancy or lymphoma has been reported in patients on immunotherapy with rheumatoid arthritis[1]. The remaining two broad categories are infectious (viral bacterial or fungal) and vasculitis.

The patient was tested for viral fungal and bacterial etiologies but all were negative. However many viral etiologies are not routinely tested nor have established diagnostic modalities requiring brain biopsy or post mortem culture for diagnosis. Some bacteria like streptococcus pneumonia are difficult to grow and require special media. However treatment with broad antibiotics failed to improve this patient's course. Lastly, an unusual fungal infection cannot be ruled out in an immunocompromised individual. This would require culture or tissue for diagnosis.

This patient has a history of both Sjögren's syndrome and rheumatoid arthritis. CNS vasculitis presents with a history of worsening headaches, progressive decrease in mental capacity or with stroke like symptoms. Initial CT scan did not show any pathology but the patient did not have an MRI or contrast scan. Her medical history did not have any evidence of peripheral nerve involvement but did have a prior history of bulimia and recent history of difficulty sleeping. Histology in CNS vasculitis reveals inflammation affecting the CNS arteries causing vasculitis, occlusion and thrombosis of these vessels. CNS vasculitis is a known but rare complication of rheumatoid arthritis but its presence is debated in Sjogren's disease[2].

Figure 3: Differential diagnosis of meningoencephalitis



Pathology results:

CSF viral panel and HIV tests were negative. CSF culture and mycobacteria cultures remained negative.

Autopsy showed acute hemorrhage of right cerebellum, deep grey matter and brain stem. Multiple foci of acute infarct with hypoxic ischemic changes are also seen in various regions of the brain. Microscopic sections showed acute vasculitis demonstrated by fibrinoid necrosis of the vascular walls with inflammatory infiltrate and fragmentation of neutrophilic nuclei (Figure 4). Occlusion of the vascular lumen with fibrinous material is also seen (Figure 4). These changes were seen in multiple small and medium size blood vessels which likely caused acute hemorrhage, infarcts and eventually brain edema and herniation of cerebellar tonsils.

The leptomeninges were mildly opaque, but exudate was not grossly seen. In the subarachnoid spaces, a sparse, very focal infiltrate of histiocytes was mixed with a few neutrophils (Figure 5). Gram stain and stain for fungi were negative.

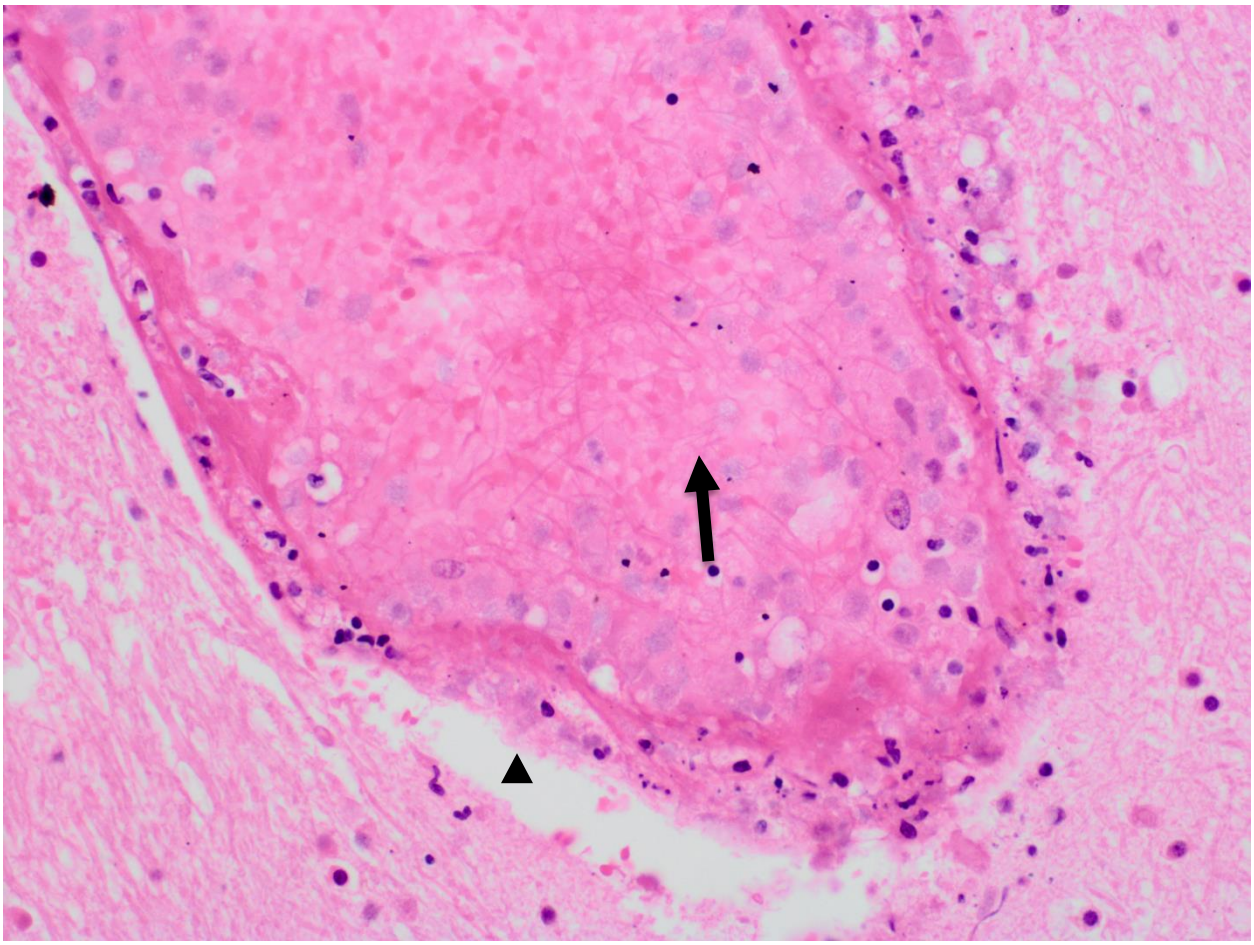


Figure 4. Vasculitis with fibrinoid necrosis and inflammatory infiltrate of vascular wall (arrowhead). Vascular lumen is occluded by fibrinous material (arrow). H&E 400x

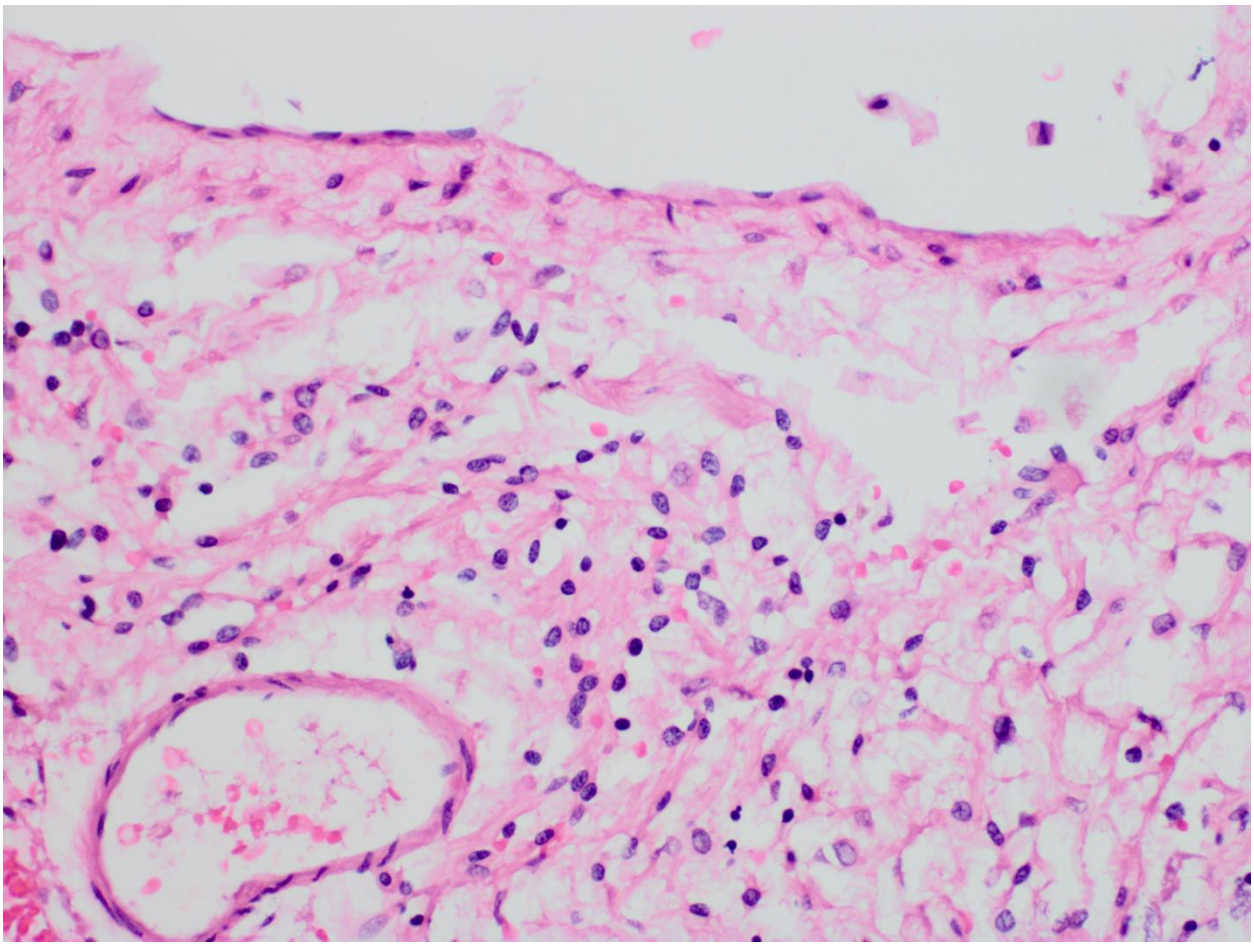


Figure 5. Sparse inflammatory cells and histiocytes in the subarachnoid space. H&E 400x.

Discussion:

CNS vasculitis involves inflammation of the arteries supplying the brain, spinal cord and it's covering the arachnoid and pia mater. Primary CNS vasculitis is distinguished from secondary vasculitis as there is no evidence of inflammation involving arteries outside the brain. In this case, the patient had evidence of both Sjögren's syndrome and rheumatoid arthritis: Sjögren's is characterized by lymphocytic infiltration mainly of the exocrine glands, while in rheumatoid arthritis the inflammatory cells mainly affect the synovial tissue.

The incidence of CNS involvement in Sjögren's syndrome varies from study to study[2, 3]. This is partly due to the use of different definitions for Sjögren's syndrome, for the spectrum of entities referred as CNS involvement, and for the contribution of other disease entities (for example Systemic Lupus Erythematosus) in patients with overlapping rheumatologic syndromes. In general CNS involvement occurs in 20% of patients[4]. It includes a spectrum of manifestations from mood and psychiatric disorders to focal disease such as cranial nerve dysfunction, or seizures, or involvement of the spinal cord causing in some instances acute transverse myelitis or a chronic progressive myelopathy[3]. In the 1994 study by Alexander et al[4], 63% of patients with CNS involvement also had peripheral nervous system symptoms. It is difficult to predict CNS involvement with known markers for Sjögren's syndrome although there is a reported correlation with anti-Ro and necrotizing angiitis[2]. CNS pathology usually involves small vessels. Work up can include CSF analysis, MRI or electroencephalography (EEG). Angiography is used to exclude other entities. CSF reveals lymphocytes, and occasionally the presence of oligoclonal bands (in which case

multiple sclerosis would need to be ruled out). MRI is especially useful in patients with focal symptoms. EEG is reported to be abnormal in one third of patients[2].

Involvement of the CNS in rheumatoid arthritis is rare but better described in the literature than for Sjögren's syndrome. In 2010, Pons et al[5] found only 12 published cases of patients with rheumatoid arthritis and CNS vasculitis. Since then four other cases have been published[6-8]. This case report would be the 17th case in the literature. The mortality for CNS involvement is high at almost 60%. 76% of patients had rheumatoid arthritis for five or more years. Five cases presented with seizures, 9 cases had focal findings mainly hemiparesis. Only one case description had symptoms similar to our patient: headache nausea and vomiting[8]. However unlike our case, symptoms were present for seven days. CT scan was consistent with left occipital infarction. The patient was treated with steroids but seven days later she had sudden onset of left sided weakness, visual field defects and confusion. CT scan showed several non-hemorrhagic infarctions and expansion of the previous noted occipital infarction. CSF had five white blood cells. A brain biopsy showed lymphocytic infiltration and small vessel vasculitis. The patient's symptoms stabilized but did not reverse with immunotherapy.

One notable feature of our case is the presence of elevated WBC in the CSF. It is unclear if this represented meningitis or was a manifestation of the active inflammation of the CNS parenchyma. The CT scans were without contrast therefore meningeal enhancement could not be determined. In addition, findings on pathology did not show an active meningeal process. Nevertheless there is a literature describing meningitis in patients with rheumatoid arthritis which has been published by Matsushima[9]. Most of these patients had long standing rheumatoid arthritis, enhancement on MRI, and pathology which showed meningeal lymphocytic infiltration, vasculitis or rheumatoid nodules.

Our case highlights the dramatic course that CNS vasculitis can have in a patient with a five year history of rheumatoid arthritis and Sjögren's syndrome. Her course was acute and notable for elevated CSF white cells and CNS vasculitis that quickly progressed to brain herniation and death despite being treated with steroids. It is important to include early on in the differential diagnosis of "meningitis," vasculitis in a patient with rheumatoid arthritis or Sjögren's syndrome as treatment can be initiated early in an attempt to stabilize the inflammatory process.

Pathologic diagnosis: Acute central nervous system vasculitis.

References:

1. Fukushima M, Katayama Y, Yokose N, Kura Y, Sawada U, Kotani A, Yoshino A. Primary central nervous system malignant lymphoma in a patient with rheumatoid arthritis receiving low-dose methotrexate treatment. Br J Neurosurg. 2013 Dec;27(6):824-6.
2. Soliotis FC, Mavragani CP, and Moutsopoulos HM. Central nervous system involvement in Sjogren's syndrome. Ann Rheum Dis 2004; 63:616-620.
3. Tobon Gj, Pers JO, Devauchell-Pensec V, and Youinou P. Neruological disorders in primary Sjogren's syndrome. Autoimmune disease 2012; Article ID 645967:1-11.
4. Alexander El, Ranzenbach MR, Kumar AJ et al. AntiRo (ss-A) autoantibodies in central nervous system disease associated with Sjogren's syndrome: clinical, neuroimaging, and angiographic correlates. Neurology 1994; 44:899-908.
5. Pons NC, Montala N, Valverde J, Brell M, Ferrer I, Martinez-Yelamos. Isolated cerebral vasculitis associated with rheumatoid arthritis. Joint Bone Spine 2010; 77:361-363.
6. Loya-de la Cerda DG, Aviles-Solis JC, Delagado-Monemayor MJ, Camara-Lemarroy CR, Galarza-Delgado DA. Isolated rheumatoid arthritis-associated cerebral vasculitis: a diagnostic challenge. Joint Bone Spine 2013;80:88-90.
7. Ozkul A, Yilmaz A, Akyol A, Kiylioglu N. Cerebral vasculitis as a major manifestation of rheumatoid arthritis. Acta Clinica Belgica 2015; 70(5):359-63.
8. Spath NB, Amft N, and Farquhar D. Carebral vasculitis in rheumatoid arthritis. Q J Med 2014; 107:1027-29.

9. Matsushima M, Yaguchi H, Niino M, et al. MRI and pathological findings in rheumatoid meningitis. J. Clin Neuroscience. 2010. 17-129-12.