CASE 2015 1

Clinical History:
This 54yo right handed woman had a recent near gross-total resection of a right parieto-occipital glioblastoma. The tumor was characterized as IDH1-wild-type, EGFR amplified, Met non-amplified, MGMT methylated, and positive for mutations in PTEN and TP53. Approximately 1 month following her initial resection, before the initiation of chemoradiation, she presented to an outside hospital ED complaining of worsening cognition, visual-spatial deficits, right-sided headache, nausea, vomiting, and gait difficulties. Imaging showed a large cystic and solid lesion in the right parietal lobe with multiple foci of nodular enhancement associated with 8mm of midline shift. She underwent re-resection for presumed recurrent tumor.

Material submitted:
One H&E stained slide

Points for discussion:
1. Diagnosis
2. Pathogenesis and prognosis
Submitted by:
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Clinical History:
The patient is an 18 year old woman with a complex past medical history significant for dilated cardiomyopathy diagnosed at 3 months of age, pulmonary hypertension, and moderate bilateral hearing loss. She underwent orthotopic heart transplant at 17 years of age followed by multiple complications including renal insufficiency, DRESS syndrome, and pulmonary nocardiosis. At 18 year of age she presented with several months of right facial pain and hyperalgesia involving the right tongue, gums, teeth and ear. A root canal and extraction of 3 teeth was performed, however the pain persisted. The pain became daily and she started to develop right eye pain. She was diagnosed with trigeminal neuralgia. Subsequently, an MRI was performed revealing a contrast enhancing, extra-axial, 20 mm mass lesion in Meckel's cave. The mass abutted the trigeminal nerve and extended through the foramen ovale. The patient underwent a right subtemporal craniotomy with subtotal excision of the mass.

Material submitted:
MRI images prior to resection and H&E stained section of the resected lesion

Points for discussion:
1. Diagnosis
2. Prognostic features
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Clinical History:
The patient was a 42-year-old male with complicated history of rapidly progressive neurologic deterioration. Imaging studies demonstrated bi-hemispheric abnormalities. He was treated for presumptive diagnosis of tumefactive multiple sclerosis with Solumedrol, plasmapharesis, and Cyclophosphamide but showed no improvement. The initial brain biopsy showed features consistent with a “macrophage-rich lesion,” although it was unclear whether the biopsy was representative. In the intensive care unit, the patient developed septic shock with fevers up to 106 degrees Fahrenheit, and he was managed with pressors and broad-spectrum antibiotics.

Autopsy findings:
Not available

Materials submitted:
1. One (1) unstained slide of cerebral cortex and white matter
2. One (1) postmortem image

Points for discussion:
1. Pathologic findings
2. Pathogenesis of this disorder
3. Relationship of pathologic lesions to neuroradiographic findings
Clinical History:
The patient was a 73-year-old man with a past medical history of angioimmunoblastic T-cell lymphoma diagnosed in 2009 and treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone with complete remission in 2010. He developed treatment-related acute myeloid leukemia in 2012 that was unresponsive to chemotherapy. He also had chemotherapy-induced cardiomyopathy with an ejection fraction of 25% and treatment-related chronic kidney disease. In April 2014, he underwent a non-myeloablative haploidentical bone marrow transplant.

He presented to the hospital approximately two months after for one episode of aphasia, which had been preceded by gait instability, lightheadedness and altered mental status for about 1 week. Vital signs showed a blood pressure of 105/60 and hypothermia (34.9 °C). White blood cell count was low with a left shift. On neurologic exam, he had depressed consciousness and was disoriented. He also had multifocal myoclonus, bilateral tremor more evident with intention than at rest, and dysmetria. There were no focal neurologic findings. He was admitted, but no acute intracranial changes were present on CT scan. In the hospital, he had rapid worsening of his mental status with respiratory failure requiring intubation. Bone marrow biopsy showed an aplastic marrow and suspected graft failure. He developed polymicrobial bacteremia and septic shock, and his family decided to make him comfort care. He died approximately one month after the recent hospitalization.

Autopsy findings:
Bone marrow profoundly hypocellular

Material submitted:
1 H&E stained section of the hippocampus

Points for discussion: 1. Differential Diagnosis
2. Pathogenesis
Clinical History: A 54 year-old Caucasian male, status post renal transplant 10 years prior due to IgA nephropathy chronic immunosuppression (CellCept and prednisone), presented with progressive left sided weakness. He had first noticed weakness and clumsiness in his left hand about 5-6 weeks prior to admission with more recent onset of tripping over his left foot and severe headaches. He had slowly developed more difficulty with his daily activities including handwriting, dressing, and grooming. Initial MRI scans showed a new enhancing right frontal mass with extensive edema. He denied any loss of consciousness, confusion, seizures, and changes in vision or hearing. He had no relevant travel history, no exotic pets, and lived in a rural area of Nebraska. A biopsy of the lesion was performed.

Material submitted:
   1. Initial MRI images of brain (T1 and T2 coronal FLAIR post gadolinium enhancement)
   2. H&E section of biopsied lesional tissue (virtual slide)

Points for discussion:
   1. Differential diagnosis
   2. Diagnosis
   3. Treatment considerations
Clinical History: A 35 year old African-American man was referred to the Manhattan HIV Brain Bank (MHBB) with 5 years of slowly progressive gait disturbance and dysarthria. He had been diagnosed with HIV, which was sexually-acquired, around the same time his neurologic symptoms began. He was poorly adherent to antiretroviral medications, reaching a CD4+ nadir of 16. Other medical conditions included hypertension, asthma, anxiety and depression. Social history was significant for chronic cocaine dependence, several incarcerations, and periods of homelessness with extreme social alienation. In his 20s he had been a boxer, and had sustained a total of 3 knockouts. There was no known family history of neurologic disease, however both his parents had died in their 50’s (mother of cardiac disease, father of unknown causes), and he had no full siblings.

Neurologic examination at presentation revealed grossly normal mental status. Cranial nerve examination was significant for mild dysarthria, decreased facial expression, slow saccades, and mild impairment of upward gaze. Motor exam revealed normal strength and tone in his upper extremities, but in the lower limbs there was mild symmetric weakness involving both distal and proximal muscles, and mild to moderate spasticity. Vibratory sense was mildly reduced in the toes, but sensory examination was otherwise normal. Cerebellar examination was normal in the upper extremities, and limited by weakness and spasticity in the lower extremities. Gait was wide-based and unsteady. Clinical diagnostic evaluation revealed normal serum folate and B12, and negative RPR. MRI of the brain was interpreted as normal. Somatosensory evoked potentials were consistent with myelopathy. He refused a lumbar puncture. A diagnostic molecular test was performed. The patient was followed in the MHBB for the next 15 years, until his death at the age of 50. During this time his neurologic course was steadily progressive. Within two years, at age 37, he had developed nystagmus, dysmetric saccades, progressive ataxia involving the trunk, spasticity involving the upper extremities, worsening dysarthria and hypophonia, and peripheral neuropathy. Repeat MRI of the brain demonstrated a mild, diffuse cerebral and cerebellar atrophy, and more marked brainstem atrophy. By age 42, the patient was wheelchair bound, unable to bear weight on his legs. At age 43, he was institutionalized for care. At the time of his death (due to pneumonia and sepsis), he was bed bound with a tracheostomy, and was able to communicate only through blinking his eyes.

Autopsy findings: The brain weighed 1150 grams with its dural cap. The ventricular system was diffusely dilated with a fenestrated septum pellucidum, the contours of the caudate nuclei were normal. There was remarkable atrophy of the pons, pallor of the substantia nigra and multiple, ill-defined gray plaques in the cerebral and cerebellar white matter. The spinal cord was extremely atrophic.

Material submitted: 1. Images of the medial aspect of the fixed brain cut in sagittal orientation, and fixed coronal sections of a half hemisphere at the level of the caudate and globus pallidus. 2. H&E slide of the spinal cord.

Points for discussion: 1. What was the diagnostic molecular test? 2. Is the neuropathology typical of this disorder?
CASE 2015-7

Submitted by: Rachael Vaubel, Eoin Flanagan, Caterina Giannini and Joseph Parisi
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Clinical History: The patient is a 55 year old man who presented with a three month history of progressive gait unsteadiness with numbness and tingling of his feet and fingertips as well as right foot weakness. His medical history was significant for an unintentional 25-pound weight loss over the past year, hypertension, 80 pack-year smoking history, and a small bowel resection for perforation 12 years prior.

Neurologic examination showed a severely ataxic gait, positive Romberg sign, loss of vibration and proprioception in his feet, and decreased pinprick sensation in his feet without a sensory level. His hip and knee flexion strength was mildly decreased bilaterally. His reflexes were brisk in the upper extremities and absent in the lower extremities.

Laboratory studies were significant for a microcytic anemia with a hemoglobin of 9.3 g/dL and MCV of 72.9 fL. Tissue transglutaminase antibodies were positive and endoscopic biopsy confirmed a diagnosis of celiac disease. Additional laboratory studies including vitamin B12, thiamin, and vitamin E levels, serum protein electrophoresis, fasting glucose and hemoglobin A1C, liver function tests, electrolytes, TSH, ANA, paraneoplastic antibody panel, PSA, PET-CT, as well as serology for Anaplasma, Erlichia, Babesiosis, and Lyme disease were all unrevealing. CSF examination was normal.

Head CT and MRI were unremarkable. Spine MRI showed a very subtle T2 signal hyperintensity within the dorsal columns (white arrow) but no other abnormalities. Additional laboratory studies were performed which led to a diagnosis for his neurologic symptoms. Five months later, he collapsed suddenly and died.

Autopsy findings: Autopsy disclosed a ruptured basilar tip aneurysm with severe subarachnoid hemorrhage.

Material submitted: H&E slide of the spinal cord. MRI image.

Points for discussion:
1. Etiology and Pathogenesis
2. Neuropathologic findings and differential diagnosis
Clinical History:

The patient is a 26-year-old man with a medical history of 10 years of progressive right lower extremity weakness and recent onset of urinary dysfunction. A recent neurologic examination was positive for right lower extremity weakness, diminished pinprick and touch sensation, and patellar and Achilles tendon areflexia. Non-contrast magnetic resonance imaging (MRI) of the lumbar spine showed a 9 cm intramedullary tumor that extended from T9 to T12 vertebrae. The tumor had a cystic component distally, and it was isointense compared to the cord on T1 sequences and hypointense on T2 sequences. A biopsy was performed and submitted for evaluation.

Material submitted:

1) One hematoxylin-eosin-stained slide
2) Two hematoxylin-eosin photographs from areas not represented on the slide

Points for discussion:

1) Differential diagnosis
2) Ancillary studies
Clinical History:
This 71-year-old female had a 6-month history of worsening speech function with paraphasic errors. The initial CT scan of the head was interpreted to show multiple left sided lesions in the superior and posterior fossa, suspicious for metastases. The metastatic work-up failed to reveal a primary source. Subsequent MR imaging a month later showed this to be a left-sided, complex dural-based mass extending both supra- and infra-tentorially, measuring up to 7.5 cm in maximum dimension. A follow-up CT scan, just a month later, showed a 0.5 cm enlargement in the maximum dimension with progressive narrowing of the fourth ventricle. Neurological deterioration that included right hemiparesis, unsteady gait and worsening aphasia necessitated surgical resection.

Material submitted:
Image from MRI study and an H&E section of cerebellar mass

Points for discussion:
1. What is the histological differential diagnosis of this lesion?
2. What highly specific and sensitive immunohistochemical and molecular techniques could be used to definitively resolve this differential diagnosis?
3. What is the pathophysiological basis for the diagnostic immunohistochemical staining pattern of this lesion?
Clinical History:
The patient is a 62-year-old man with a history of coronary artery disease and hypertension who was in his usual state of health until 2 weeks prior to admission, when he developed decreased appetite, neck and back pain, nausea, and vomiting. Shortly after admission to an outside hospital, he had a tonic-clonic seizure and was intubated. MRI showed extensive irregular gyriform parenchymal abnormalities in the bilateral cerebral hemispheres and extensive leptomeningeal enhancement throughout the basilar cisterns as well as coating the surface and insinuating the sulci of the bilateral cerebral hemispheres. A lumbar puncture was significant for elevated protein (539 mg/dL, normal range = 15 – 45 mg/dL); a Gram stain was negative. He was treated for meningitis, including tuberculous meningitis, for several days. He showed minimal clinical improvement and was extubated. One week after extubation, he developed altered mental status and was re-intubated. MRI demonstrated communicating hydrocephalus with persistent diffuse leptomeningeal enhancement. A repeat lumbar puncture showed an elevated opening pressure. A VP shunt was placed and he was transferred to our hospital for further care. Upon admission, his physical exam was significant for an inability to follow commands and a mild left-sided facial droop. He moved all extremities spontaneously and withdrew to pain. He remained intubated while his work-up continued. His intracranial pressure remained elevated. Eleven days after admission, he underwent a left frontal craniotomy for subdural and intraparenchymal biopsies (provided for your review). After the brain biopsies, he experienced a slow but progressive decline in his neurological status. His mental status fluctuated between coma and minimal consciousness. He required serial aspirations of CSF to control his intracranial pressure. A repeat MRI thirteen days after admission revealed persistent hydrocephalus, diffuse leptomeningeal enhancement, progressive areas of cortical restricted diffusion, and vascular irregularities on MR angiography. Two weeks later, he was transitioned to comfort care and died the following day. An autopsy was requested by his family.

Material submitted:
One representative hematoxylin and eosin-stained slide from the left frontal brain biopsy.
One representative UNSTAINED slide from the dorsal brainstem (post-mortem).

Points for discussion:
1. Discuss the differential diagnosis.
2. Discuss the process seen in the biopsy and correlate it with the autopsy findings.
3. Review the clinical settings in which these features can be seen.