CLINICAL VIGNETTE

Limbic Encephalitis: A Paraneoplastic Case of Metastatic Melanoma

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Case Presentation

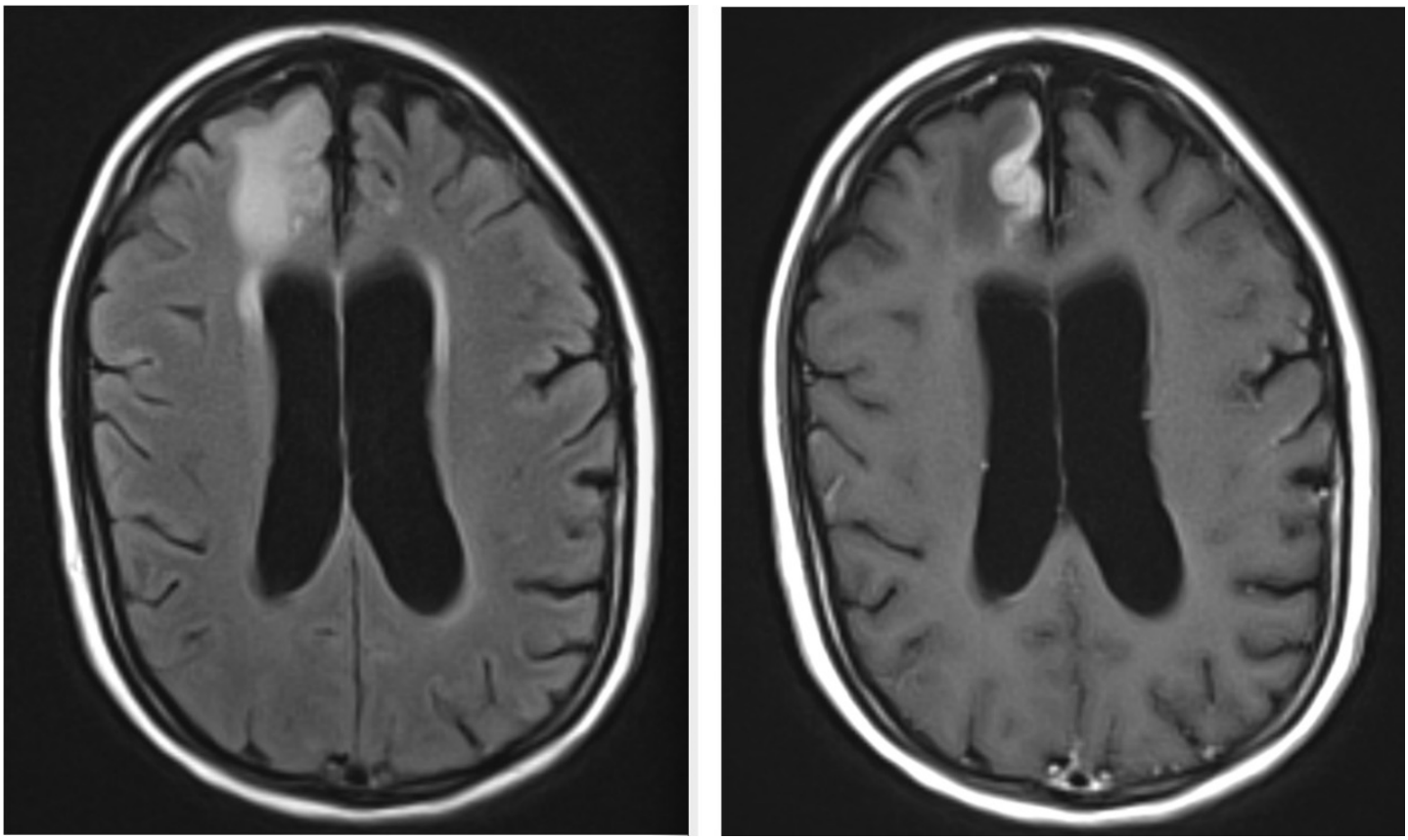
A 58-year-old woman with a history of alcohol use disorder, hypertension, and GERD presented to the emergency department after several weeks of progressively worsening personality changes, fatigue, slurred speech, dysphagia, and confusion. The patient had been traveling across the country for work in Napa Valley, California and North Carolina a few months prior to presentation. Her husband noted the patient had intermittent episodes of agitation, intrusive thoughts, and slurred speech. She had abstained from alcohol over the last year and reported URI-like symptoms in the midst of her travels associated with ear pain. During an ED visit 2 weeks prior to presentation, an MRI/MRA of the brain showed evidence of an old, right frontal lobe infarction and multiple chronic microvascular changes suggestive of left sided cerebellar strokes. She was sent home on amoxicillin for acute otitis media. The patient subsequently developed an episode of confusion and returned to the ED. No repeat imaging was performed, and the patient was referred to outpatient neurology for further evaluation. Neurology examination was notable for persistent dysarthria, drooling, gait abnormalities and confusion, as well as limb shaking. She was directed to the ED for further evaluation of possible embolic phenomena vs. seizure disorder.

On arrival to the emergency department, her vitals were T 36.7C, HR 78, BP 156/118, RR 16, SpO2 96% on room air. Neurological exam was limited due to lack of cooperation, but notable for poor orientation, dysarthria, drooling and lack of facial droop. The patient was awake, writhing with spontaneous movement of all her limbs but lacked awareness. A repeat MRI brain with and without contrast was notable for focal right frontal gliosis with cortical laminar necrosis suggestive of an old yet healing frontal lobe infarction (see clinical images). The patient's EEG was difficult to interpret given the significant amount of motion artifact but was deemed grossly normal without seizure activity. Lumbar puncture revealed clear and colorless fluid with an opening pressure of 10cm H20. The CSF analysis revealed a lymphocytic predominant pleocytosis with a WBC count of 17 cells/mL (74% lymphocytes), no RBCs, glucose level of 43 mg/dL, protein of 84 mg/dL. Flow cytometry was without monotypic B-cell, and a paraneoplastic antibody panel was negative. Transthoracic echocardiogram with bubble showed no significant findings.

The patient's symptoms progressively worsened throughout her admission. After discussion with radiology, the primary working diagnosis was limbic encephalitis secondary to an autoimmune disease versus a paraneoplastic process. CT chest, abdomen, pelvis with and without contrast did not identify a primary cancer. The patient was started on methylprednisolone 1g/day for the next 5 days followed by plasmapheresis for 5 days. Her symptoms failed to improve, and her agitation increased. Repeat MRI revealed enlarging ventricles with evidence of leptomeningeal disease extending to the cervical spine and hyperintensities on the cortical surfaces mostly over the right frontal lobe. In preparation for a lumbar drain, the patient was transferred to the ICU and intubated given concern for poor airway protection. After further discussion with the patient's spouse, it was discovered that the patient had a history of lentiginous melanoma in situ of the right cheek three years prior to presentation. She did not have a wide excision, but rather her lesion was only resected to its depth and treated with topical imiquimod. This was the patient's preference given her background as an actress and the concern for facial scarring. She had been lost to dermatological follow up. Neurosurgery was consulted for a brain biopsy in the areas of the frontal hyperintensity seen on MRI. The findings revealed infiltrating pleomorphic cells with prominent melanocytic pigment, consistent with metastatic melanoma and oncology was consulted.

The patient underwent a whole-body PET/CT. The results did not show definite evidence of focal abnormal FDG uptake in the facial soft tissues. There was intense FDG activity noted in the previously described ill-defined right superior frontal cortical hyperdensity. There was no suspicious extracranial FDG activity suggestive of malignancy. The patient was started on the combination of ipilimumab/nivolumab along with whole brain radiation therapy (WBRT). After the first round of WBRT, the patient's mental status significantly improved. She was noted to be more interactive with her family. The patient remained hospitalized for another month due to complications related to septic shock from acute cholangitis requiring ICU level of care and recurrent episodes of status epilepticus. Ultimately, the patient required placement of a trach, G-tube and VP shunt. Her respiratory status slowly improved, and she was able to be weaned off of mechanical ventilation. Her overall prognosis remained poor, and she was discharge to a long-term acute care facility and died 6 months after her initial presentation.

Clinical Images



Shown are two transverse images of the first MRI brain with and without contrast completed at initial ED presentation. These images show what appeared to be an area of right frontal gliosis (reactive changes seen with deposition of new glial cells) and an area of T1 signal hyperintensity in the left frontal and insular region, initially believed to represent cortical laminar necrosis from a prior infarction.

Discussion

Melanoma is an increasingly common malignancy, and although it is most often diagnosed as a localized disease, metastases are common.[1] The average lifetime risk for developing melanoma in most western countries is as high as 1 in 50, making it the fifth and sixth most common cancer in men and women, respectively.[1] The most important risk factors include number of nevi, male sex, lighter skin type, exposure to ultraviolet radiation, family history of melanoma, immunosuppression, and genetic susceptibility.[1,2] Although it only represents a small percentage of all skin cancers (~3%), it accounts for the vast majority of deaths (~65%).[3]

Lentiginous melanoma (LM) is a type of slow growing melanoma that often occurs in chronically sun-exposed areas of skin.[2,4] The early stage of the disease is confined to the epidermis (*in situ)* and often enlarges horizontally before eventually growing vertically to invade the dermis.[2] In this early stage, there is little risk of any lymph node involvement. Progression to invasive disease does occur with roughly 50 % of *in situ* cases if left untreated, but it often takes many decades.[2] Fortunately, the prevalence of invasive disease is low due to early recognition and treatment.

When a patient presents with a suspicious lesion, a narrow excision is needed to confirm the diagnosis and to provide information about the lesion's thickness (Breslow depth).[5] Per guidelines, the deeper the lesion, the larger the surrounding margins must be during excision.[5] This is known as a wide local excision and remains the gold standard of treatment of local disease.[3,5]

The Breslow depth also helps determine the need for sentinel lymph node biopsy.[5] Typically, melanomas greater or equal to a thickness of 1 mm require sentinel lymph node biopsy (SLNB).[5] A negative SLNB is associated with lower risk of locoregional recurrence.[6] Our patient had no report of either a wide excision or a sentinel lymph node biopsy. Interestingly, data from the Surveillance, Epidemiology, and End-Results (SEER) program in the mid-2000s highlighted that guideline-based margin excisions, sentinel lymph node biopsies, and even lymphadenectomies (with positive SLNB) were only being performed 58%, 53%, and 69% of the time, respectively.[3] This was more likely related to tumor location (i.e. head and neck primary), age (i.e. over 60), and otherwise good prognostic signs (i.e. no palpable lymph nodes, lack of ulcerations, etc.).[3,7] We suspect that our patient's *in situ* disease was over her cheek

and the excision may have been shallower and narrower than necessary to best align with her treatment goals. Moreover, the absence of concerning prognostic signs, she may have foregone the SLNB.

Patients with excised *in situ* lesions technically do not require additional surveillance but should continue to see their dermatologist for routine screening given their increased risk for new lesions.[8] Unfortunately, recurrences also occur. Patients with primary diagnoses of non-metastatic melanoma who underwent lymph node surgery had an 18.6% chance of recurrence within 23.1 months,[9] with 1.6% developing distant recurrences.[9] One of the most concerning and common sites for a distant recurrence or metastasis is the brain.[10] In those with advanced disease, it can account for up to 44% of cases[10] with a median survival of four to five months.[10] Seizures are the most common presenting symptom. Other manifestations include headaches, focal neurological deficits, altered mental status, and aphasia.[9] Some tumors may also present as stroke mimics, with 5-10% of tumors having a stroke-like time course.[11]

Although our patient presented with symptoms concerning for a stroke, including dysarthria, drooling, and poor orientation, the onset was not sudden but rather progressive. Her MRI revealed periventricular hyperintensities and her initial CSF analysis was consistent with an inflammatory process. Our preliminary working diagnosis was limbic encephalitis.[12] The next challenge was to distinguish between viral, autoimmune or paraneoplastic processes. The turnaround time for CSF analysis of common viral infections (HSV, HHV-6) and paraneoplastic antibodies was 48 hours. Each viral PCR result was negative, and the paraneoplastic antibody panel tested negative for IgG against Hu (Anti-Hu) - though these are known to be negative in up to 40% of cancer related cases.[12] In addition, the patient's CT of the chest, abdomen, and pelvis did not reveal an obvious primary neoplastic process. Given the time sensitive treatment of autoimmune limbic encephalitis, our team quickly initiated a combination of steroids and consulted hematology for plasma-pheresis. Unfortunately, the patient's symptoms worsened, providing evidence against an autoimmune process. The additional history of melanoma resection from her spouse increased suspicion for a paraneoplastic process with metastatic melanoma, the most probable cancer.

This was a challenging case with a wide differential diagnosis that took our teams over a week to decipher. We started with ruling out medical emergencies including ischemic/ hemorrhagic stroke, acute bacterial meningitis, seizures and moved towards less imminent and rarer diseases. Frequent reassessments of the patient and how she responded to different therapies were crucial elements of the evaluation. This was an important learning point for our team. The biggest takeaway from this case was to start with a thorough history and to use that information to guide pretest probability for given conditions. This may have saved considerable resources and time, though it remains unclear of the impact on the patient's outcome.

REFERENCES

1. **Rastrelli M, Tropea S, Rossi CR, Alaibac M**. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In Vivo*. 2014 Nov-Dec;28(6):1005-11. PMID: 25398793.
2. **Quintanilla-Dieck MJ, Bichakjian CK**. Management of Early-Stage Melanoma. *Facial Plast Surg Clin North Am.* 2019 Feb;27(1):35-42. doi: 10.1016/j.fsc.2018.08.003. PMID: 30420071.
3. **Pavri SN, Clune J, Ariyan S, Narayan D**. Malignant Melanoma: Beyond the Basics. *Plast Reconstr Surg.* 2016 Aug;138(2):330e-340e. doi: 10.1097/PRS.0000000000002367. PMID: 27465194.
4. **King R**. Lentiginous melanoma. *Arch Pathol Lab Med*. 2011 Mar;135(3):337-41. doi: 10.5858/2009-0538-RA.1. PMID: 21366457.
5. **Joyce KM**. Surgical Management of Melanoma. In: **Ward WH, Farma JM**, editors. *Cutaneous Melanoma: Etiology and Therapy [Internet]*. Brisbane (AU): Codon Publications; 2017 Dec 21. PMID: 29461771.
6. **Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, Jahkola T, Bowles TL, Testori A, Beitsch PD, Hoekstra HJ, Moncrieff M, Ingvar C, Wouters MWJM, Sabel MS, Levine EA, Agnese D, Henderson M, Dummer R, Rossi CR, Neves RI, Trocha SD, Wright F, Byrd DR, Matter M, Hsueh E, MacKenzie-Ross A, Johnson DB, Terheyden P, Berger AC, Huston TL, Wayne JD, Smithers BM, Neuman HB, Schneebaum S, Gershenwald JE, Ariyan CE, Desai DC, Jacobs L, McMasters KM, Gesierich A, Hersey P, Bines SD, Kane JM, Barth RJ, McKinnon G, Farma JM, Schultz E, Vidal-Sicart S, Hoefer RA, Lewis JM, Scheri R, Kelley MC, Nieweg OE, Noyes RD, Hoon DSB, Wang HJ, Elashoff DA, Elashoff RM**. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. *N Engl J Med*. 2017 Jun 8;376(23):2211-2222. doi: 10.1056/NEJMoa1613210. PMID: 28591523; PMCID: PMC5548388.
7. **Wasif N, Gray RJ, Bagaria SP, Pockaj BA**. Compliance with guidelines in the surgical management of cutaneous melanoma across the USA. *Melanoma Res*. 2013 Aug; 23(4):276-82. doi: 10.1097/CMR.0b013e32836254bd. PMID: 23695440.
8. **Elias ML, Behbahani S, Maddukuri S, John AM, Schwartz RA, Lambert WC**. Prolonged overall survival following metastasectomy in stage IV melanoma. *J Eur Acad Dermatol Venereol.* 2019 Sep;33(9):1719-1725. doi: 10.1111/jdv.15667. Epub 2019 Jun 3. PMID: 31070816.
9. **Tarhini A, Ghate SR, Ionescu-Ittu R, Manceur AM, Ndife B, Jacques P, Laliberté F, Nakasato A, Burne R, Duh MS**. Postsurgical treatment landscape and economic burden of locoregional and distant recurrence in patients with operable nonmetastatic melanoma. *Melanoma Res*. 2018 Dec;28(6):618-628. doi: 10.1097/CMR.0000000000000507. PMID: 30216199; PMCID: PMC6221390.

10. **Goldlust SA, Hsu M, Lassman AB, Panageas KS, Avila EK**. Seizure prophylaxis and melanoma brain metastases. *J Neurooncol*. 2012 May;108(1):109-14. doi: 10.1007/s11060-012-0802-y. Epub 2012 Feb 5. PMID: 22311106.
11. **Arakawa A, Mitsutake A, Hideyama T, Sato T, Katsumata J, Seki T, Maekawa R, Ohno M, Narita Y, Shiio Y**. A central nervous system metastasis of melanoma with stroke-like onset of left-lower quadrantanopsia. *J Gen Fam Med*. 2020 Feb 11;21(3):77-79. doi: 10.1002/jgf2.301. PMID: 32489760; PMCID: PMC7260162.
12. **Tüzün E, Dalmau J**. Limbic encephalitis and variants: classification, diagnosis and treatment. *Neurologist*. 2007 Sep;13(5):261-71. doi: 10.1097/NRL.0b013e31813e34a5. PMID: 17848866.