Title

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Journal

Proceedings of UCLA Health, 25(1)

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Publication Date

2021-03-17

CLINICAL VIGNETTE

Melanoma Presenting as Dizziness and Falls

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A 77-year-old man presented to a community hospital with altered mental status, dizziness, and multiple falls for three days. He had and recurrent mechanical falls for at least three years. Past medical history includes: alcohol dependence with stage II liver fibrosis, pancreatic insufficiency, 30-pack/year tobacco use, cervical disc disease, and fine bilateral upper extremity tremors. Two years prior to this hospitalization, brain imaging to evaluate his fine tremors, showed moderate microvascular ischemic disease but no masses. Evaluation on this admission included MRI of the brain, which demonstrated several new bilateral enhancing nodules concerning for metastases. CT chest, abdomen, and pelvis on the same day demonstrated periaortic lymph nodes and two pancreatic masses concerning for malignancy. Four days later, he underwent endoscopic ultrasound and biopsy of the pancreatic masses, which found metastatic malignant melanoma with "negative for BRAF V600E" by immunohistochemistry.

Skin exam in search of the primary lesion, revealed a nontender, 3 cm raised, lobulated, tan-pink polypoid left thigh lesion, which was biopsied and confirmed melanoma. Repeat MRI of the brain 9 weeks later demonstrated multiple enhancing lesions throughout the brain, ranging in size from 3 mm to 16 mm, with associated vasogenic edema and a 6 mm rightward shift of midline structures. The patient was evaluated by Oncology and Palliative Care specialties, who noted that the patient's goal was to be able to maintain his current functional status "for two more good years," and to avoid treatment that might cause significant debility or pain. Prior to his presentation, the patient was able to walk around his apartment, perform his own cooking, and drive short distances.

Three and a half months after diagnosis, the patient started palliative-intent treatment with pembrolizumab immunotherapy, with the goal to prolong survival and delay additional symptoms from his cancer. The patient was later started on stereotactic radiosurgery (SRS) radiation therapy of his brain. After three cycles of pembrolizumab, a surveillance PET/CT demonstrated a reduction in size of the largest pancreatic mass by approximately 50% and a significant decrease in uptake in the supraclavicular, anterior mediastinal, duodenal, mesenteric, left adrenal and deep pelvic area lymph nodes, suggesting a favorable response to treatment. Subsequent brain MRI three months later demonstrated near complete resolution of the enhancing lesions with only a couple of 2-3 mm lesions with significantly decreased vasogenic edema, and no midline shift.

At the last follow-up, the patient had regained his prior functional status and tolerated treatment well, having only occasional bowel urgency and a rash on the inner thigh that improved with hydrocortisone cream.

Discussion

Melanoma is the fifth most common cancer in the United States, and the incidence of melanoma is increasing. There are four major subtypes of invasive cutaneous melanoma: superficial spreading (accounting for approximately 70 percent), nodular (the second most common), lentigo maligna, and acral lentiginous which is the most common in darker pigmented individuals, including African Americans and Asians.[1]

Early diagnosis and treatment of melanoma is associated with improved morbidity and survival. Classically, the ABCD (asymmetry, border irregularity, color variegation, diameter >6 mm) pneumonic has been a part of clinical practice and public health education. In 2004, "E" (evolution) was added to the criteria to highlight that rapidly changing/appearing moles may signify melanoma. However, melanoma, such as the nodular subtype, can present with uniform color, no pigmentation (amelanotic/pink hue), no changes in color, symmetric borders, and a relatively small size in diameter.[2] This can make early detection difficult, as the differential diagnosis broadens to include: common melanocytic nevus, lentigo, basal cell carcinoma, pigmented actinic keratosis, seborrheic keratosis, and keratoacanthoma.

Cutaneous melanoma prognosis is not only related to tumor size, but tumor thickness (i.e. Breslow depth), both of which increase the probability of metastases.[3] Predictive factors for brain and CNS metastases, include: male gender, age >60, deeply invasive or ulcerated primary lesions, visceral tumor metastasis, elevated serum lactate dehydrogenase (LDH), melanomas of unknown origin, and primary melanomas arising from the head, neck, trunk, or abdomen.[4] Melanoma brain metastasis can be asymptomatic or present with headache, neurologic deficits, and/or seizures.

Prognosis of untreated melanoma with brain metastasis is often less than 6 months, but with response to new treatments such as immunotherapy, prognosis can be extended from months to years. Current treatment options using checkpoint inhibitor immunotherapy including as programmed cell death receptor 1 [PD-1] inhibitors and cytotoxic T lymphocyte-associated

protein 4 [CTLA-4] inhibitors and targeted therapy (BRAF plus MEK inhibitors) have superseded previous treatment regimens, such as interleukin-2 and some cytotoxic chemotherapy, while also reducing toxicity. Monotherapy with PD-1 inhibitors (pembrolizumab, nivolumab) has shown 5-year survival rates of 44 percent, as well as up to 52 percent when combined with ipilimumab (a CTLA-4 inhibitor).[5] In patients who achieved a complete response to pembrolizumab, researchers reported 91% two-year disease-free survival after discontinuation of immunotherapy.[6]

Approximately half of cutaneous melanomas have a V600 mutation in the BRAF gene. In combination with downstream MEK, BRAF activates the mitogen-activated protein kinase (MAPK) pathway, resulting in oncogenesis. Targeted therapy, such as dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binibetinib, focus on this pathway and is especially important for patients with extensive tumor burden and disease-related symptoms.[7]

For patients with metastatic melanoma, systemic therapy utilizing checkpoint inhibitor immunotherapy and targeted therapy have dramatically improved prognosis, especially since these agents have activity at all sites of disease, including the brain. Therefore, patients with small (<1 cm) and minimally symptomatic or asymptomatic brain metastases are increasingly considered to be candidates for immediate systemic therapy with deferred locoregional therapy such as radiation or surgery.[8]

Potential adverse reactions to checkpoint inhibitor immunotherapy includes fatigue, dermatologic/mucosal toxicity including pruritus, dermatitis, vitiligo, alopecia, mucositis, dry mouth, enterocolitis, hepatitis, pneumonitis, and endocrinopathies such as thyroid toxicity, hypophysitis, and adrenal insufficiency.[9] Some of these adverse reactions can be managed with as-needed medications—i.e. loperamide for mild colitis, hydroxyzine for pruritus, topical glucocorticoid creams for mild-moderate dermatitis—but more serious reactions may necessitate systemic steroids and evaluation for opportunistic infections.

Case Outcome

This patient with advance melanoma presented with altered mental status, dizziness, and multiple falls, rather than cutaneous symptoms. He was negative for a BRAF gene mutation, and was started on pembrolizumab, PD-1 inhibitor, which is typically administered for a minimum of 6 months and a maximum of 2 years in the absence of toxicity. After only a few treatments with pembrolizumab, imaging demonstrated significant response to treatment. Overall, he has tolerated treatment well, having only mild reactions of fecal urgency and a localized rash.

REFERENCES

1. **Eroglu Z, Ribas A**. Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. *Ther Adv Med Oncol*. 2016 Jan;8(1):48-56. doi: 10.1177/1758834015616934. PMID: 26753005; PMCID: PMC4699264.
2. **American Academy of Dermatology Ad Hoc Task Force for the ABCDEs of Melanoma, Tsao H, Olazagasti JM, Cordoro KM, Brewer JD, Taylor SC, Bordeaux JS, Chren MM, Sober AJ, Tegeler C, Bhushan R, Begolka WS**. Early detection of melanoma: reviewing the ABCDEs. *J Am Acad Dermatol*. 2015 Apr;72(4):717-23. doi: 10.1016/j.jaad.2015.01.025. Epub 2015 Feb 16. PMID: 25698455.
3. **Breslow A**. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970 Nov;172(5):902-8. doi: 10.1097/00000658-197011000-00017. PMID: 5477666; PMCID: PMC1397358.
4. **Bedikian AY, Wei C, Detry M, Kim KB, Papadopoulos NE, Hwu WJ, Homsi J, Davies M, McIntyre S, Hwu P**. Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma. *Am J Clin Oncol*. 2011 Dec;34(6):603-10. doi: 10.1097/COC.0b013e3181f9456a. PMID: 21150567.
5. **Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hogg D, Hill A, Márquez-Rodas I, Haanen J, Guidoboni M, Maio M, Schöffski P, Carlino MS, Lebbé C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bastholt L, Rizzo JI, Balogh A, Moshyk A, Hodi FS, Wolchok JD**. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2019 Oct 17;381(16):1535-1546. doi: 10.1056/NEJMoa1910836. Epub 2019 Sep 28. PMID: 31562797.
6. **Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, Hwu WJ, Weber JS, Gangadhar TC, Joseph RW, Dronca R, Patnaik A, Zarour H, Kefford R, Hersey P, Zhang J, Anderson J, Diede SJ, Ebbinghaus S, Hodi FS**. Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma. *J Clin Oncol*. 2018 Jun 10;36(17):1668-1674. doi: 10.1200/JCO.2017.75.6270. Epub 2017 Dec 28. PMID: 29283791.
7. **Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA**. The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma: Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway. *Arch Pathol Lab Med*. 2020 Apr;144(4):500-522. doi: 10.5858/arpa.2019-0561-RA. Epub 2020 Feb 14. PMID: 32057276.
8. **Sloot S, Chen YA, Zhao X, Weber JL, Benedict JJ, Mulé JJ, Smalley KS, Weber JS, Zager JS, Forsyth PA, Sondak VK, Gibney GT**. Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. *Cancer*. 2018

Jan 15;124(2):297-305. doi: 10.1002/cncr.30946. Epub 2017 Oct 12. PMID: 29023643; PMCID: PMC7771556.

9 **Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, Postow MA, Wolchok JD**. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015 Dec;26(12):2375-91. doi: 10.1093/annonc/mdv383. Epub 2015 Sep 14. Erratum in: *Ann Oncol*. 2016 Jul;27(7):1362. PMID: 26371282; PMCID: PMC6267867.