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Malignant transformation of neurocutaneous melanosis (NCM) following immunosuppression

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Abstract

Neurocutaneous melanosis (NCM) is the condition of abnormal melanocyte deposition in the leptomeninges and brain parenchyma. Associated with congenital melanocytic nevi, NCM can result in neurologic deficits, hydrocephalus, and rarely, malignant transformation of cells. We present the case of a 16-year-old boy with NCM who developed malignant leptomeningeal melanoma following immunosuppression with a TNF α inhibitor. To our knowledge, this is the first reported case of a patient with known NCM undergoing malignant transformation after anti-TNF therapy.

Keywords

neoplasms-malignant; nevi-melanocytic; immunodeficiency

Introduction

Neurocutaneous melanosis (NCM) is a rare congenital disorder of melanocyte deposition in the leptomeninges and/or central nervous system (CNS) parenchyma. Approximately 15% of patients with multiple or large congenital melanocytic nevi (CMN) have NCM¹ though this may be an underestimate as only patients with high risk features are routinely referred for magnetic resonance imaging (MRI) and imaging may be less sensitive over time². Patients may be asymptomatic or can develop neurologic manifestations, typically in the first two years of life³. Common symptoms include those seen with increased intracranial pressure and hydrocephalus, such as headache, nausea, and vomiting. Patients may also develop seizures, developmental delay, or focal neurologic symptoms.

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Patients with CMN and NCM are at increased risk for the development of melanoma³. Risk of cutaneous melanoma is thought to be related to the size of CMN and number of satellite lesions⁴. In contrast, risk factors for malignant transformation of NCM are largely unknown. Below, we present the case of a 16-year-old boy with giant CMN (GCMN) and asymptomatic NCM who went on to develop leptomeningeal melanoma following immunosuppression with TNF α inhibition.

Case Description

A 16-year-old boy with GCMN and a known diagnosis of asymptomatic NCM was referred to pediatric neuro-oncology at Memorial Sloan Kettering Cancer Center after development of new neurologic symptoms.

At birth, the patient was diagnosed with a large melanocytic nevus on his back with multiple satellite lesions. This finding prompted a surveillance MRI of the brain at age three months. The MRI revealed T1 shortening at the left pontomedullary junction, cerebellar peduncle, and cerebellum, diagnostic of NCM. Over time, his nevus enlarged in size and he developed multiple new satellite lesions, totaling approximately 50 in all. He underwent multiple surgical resections in his first few years of life in an attempt to reduce nevus size (Figure 1).

The patient remained neurologically asymptomatic throughout childhood. At age 12, he had a surveillance MRI of the brain which demonstrated T1 shortening in the left temporal lobe consistent with his known diagnosis of NCM (Figure 2 A). A year later an MRI of the spine with and without gadolinium was obtained for intermittent neck and back pain in the setting of increased sports activity. The imaging did not reveal any abnormality (Figure 2 B) and his pain later resolved with physical therapy.

At age 15, the patient developed new symptoms of fatigue and hemorrhagic diarrhea. His mother suffered inflammatory bowel disease and a colonoscopy led to the same diagnosis. The patient was treated initially with balsalazide, an anti-inflammatory agent. Symptoms improved until he developed a hypersensitivity reaction requiring discontinuation. He then received a 160mg dose of adalimumab, a TNF α inhibitor. Within a day of receiving adalimumab, he developed severe intractable headache with associated nausea and photophobia. Symptoms persisted fourteen days before self-resolving and were attributed to adalimumab. Adalimumab was subsequently discontinued and patient was transitioned instead to infliximab in conjunction with prednisone. He remained on this regimen for two months until undergoing colectomy for refractory disease. Infliximab was discontinued prior to colectomy. Post-operatively he began a slow taper of prednisone.

Two weeks following surgery, while undergoing prednisone taper, our patient developed sudden onset severe headache, nausea, and vomiting, with symptoms most pronounced at night. He presented to a local emergency room and was discharged without imaging with a diagnosis of migraine. Over the subsequent weeks, symptoms persisted and he developed severe neck and back pain, tinnitus, intermittent diplopia, and numbness of the left leg. Four weeks following symptoms' onset, he was experiencing particularly severe headache with multiple episodes of vomiting and became difficult to rouse. He re-presented to an

emergency room where a non-contrast head CT demonstrated hyperdensity in the sulci, initially concerning for subarachnoid hemorrhage. Follow-up CT angiogram revealed sulcal enhancement, confirmed on a follow-up MRI (Figure 2 C). A lumbar puncture was performed with an opening pressure of 43 cmH₂O, 4 white blood cells (WBC) per high power field (HPF), 106 red blood cells (RBC) per HPF, 85 mg/dL protein, and 53 mg/dL glucose. An MRI of the spine demonstrated nodular T1 signal along the spinal cord and cauda equina, consistent with melanomatous deposits (Figure 2 D). Ultimately, CSF cytology was positive for malignant cells with epithelioid morphology and a degree of atypia exceeding what is expected of simple leptomeningeal melanocytosis. This was confirmed on repeat lumbar puncture which demonstrated 4 WBC per HPF, 1,345 RBC per HPF, 1,136 mg/dL protein, and 27 mg/dL glucose. Repeat cytology again demonstrated malignant cells, some of which were pigmented, felt to be morphologically compatible with melanoma (Figure 3). Unfortunately, marker studies could not be performed due to lack of material. Genetic sequencing of the cerebrospinal fluid was performed and found to be negative for alterations in 49 commonly mutated genes, including NRAS and BRAF.

The patient had a ventriculoperitoneal shunt (VPS) placed that alleviated symptoms of increased intracranial pressure. After discussion, he and his family elected not to pursue tumor-directed therapy and he died approximately 12 weeks after symptom onset.

Discussion

The relationship between melanoma and the innate immune system is a complex one. Melanoma is an immunogenic tumor and immunotherapy is a mainstay of treatment. Correspondingly, reactivation of latent melanoma in the setting of immunosuppression is a well described phenomenon. Patients with even remote histories of melanoma suffer recurrence post-transplant in up to 19% of cases ⁵.

TNF α is a pro-inflammatory cytokine of the innate immune system that functions in surveillance of malignancies and infection. Inhibition of TNF α is an important therapeutic strategy in the treatment of a number of inflammatory conditions including psoriasis, psoriatic arthritis, rheumatoid arthritis (RA), and inflammatory bowel disease. Given the role of TNF α , it has been postulated that its inhibition may be associated with the development or reactivation of cancer and an increased risk of malignancy.

In rat models, inhibition of TNF α promotes the growth of immunogenic colon tumors that are otherwise eliminated in immunocompetent rats ⁶. Clinically, support for a link between TNF α inhibition and malignancy is largely derived from retrospective data and case reports. A recent systematic review and meta-analysis of 3,493 RA patients from nine randomized controlled trials demonstrated a dose-dependent increase in malignancy risk with TNF α inhibition ⁷. In the pediatric population specifically, an association between TNF α inhibition and increased rates of hematologic malignancies, solid tumors, and melanoma, have been reported ⁸. Associations were most evident when TNF α inhibitors were used in conjunction with other immunosuppressants, such as in this patient.

The relationship between melanoma specifically and TNF α inhibitors has been discussed in several case reports. Katoulis and Kouklakis both report patients who developed de novo malignant melanoma several years after initiation of adalimumab^{9,10}. Khan et al similarly report a patient who developed malignant melanoma shortly following initiation of infliximab for RA¹¹. Similarly, Fulchiero et al. described two cases of patients with previously treated local disease (stage IB and IA), 6 and 9 years from definitive surgical treatment, respectively, who developed metastatic eruption following TNF α inhibition¹². Of interest, the diagnosis of inflammatory bowel disease itself has been associated with an increased risk of melanoma^{13,14} though there is evidence the association could be the result of immunosuppressive treatment¹³.

To our knowledge, the above case is the first to describe malignant transformation of NCM in the setting of immunosuppression. Notably, our patient did not have NRAS or BRAF mutations which have been reported in 75% and 13% of NCM patients, respectively¹⁵. Patients with GCMN and NCM are at increased risk of development of melanoma. Mechanism and triggers of this transformation have not been described but occurrence following TNF α inhibition suggests the innate immune system may play a role in prevention.

TNF α inhibitors have changed the management and improved quality of life of many patients suffering inflammatory conditions. However, their use should be balanced with the potential risk of malignancy. All patients should undergo surveillance monitoring. We would counsel careful consideration of these agents in patients who suffer pre-cancerous states or have latent malignancies.

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Figure 1.
GCMN following multiple surgical resections.

Figure 2.

(A) MRI of the brain (age 12) with L temporal T1 shortening, diagnostic of NCM in this clinical setting; (B) Normal contrast-enhanced MRI of the lumbar spine at age 13 years; (C) MRI of the brain at age 16 years after symptom onset reveals dilated temporal horns and nodular enhancement of the cerebellar folia. Enhancement corresponds to T1 shortening (not pictured), consistent with melanocyte deposition; (D) MRI of the lumbar spine at age 16 years with nodular areas of contrast enhancement, consistent with leptomeningeal deposits.

There is corresponding T1 hyperintensity on pre-contrast images suggestive of melanocyte deposition (not pictured).

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Figure 3.
Malignant cell present in cerebrospinal fluid