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Necrotizing myositis in a rectus muscle arising in the setting of long-standing Langerhans cell histiocystosis and recent dabrafenib treatment

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ABSTRACT

Purpose: to describe an unusual case of necrotizing myositis in a rectus muscle, possibly related to BRAF inhibitor therapy.

Observations: An 18-year old man with neurodegenerative Langerhans cell histiocytosis (LCH), recently started on the BRAF inhibitor dabrafenib, presented with right eye pain. Magnetic resonance imaging (MRI) orbits revealed a rectus muscle mass concerning for LCH recurrence or malignancy. Dabrafenib was stopped, and incisional biopsy of the mass was performed. The mass was absent on post-operative MRI, so no further treatment was pursued. Histopathologic evaluation was initially concerning for sarcoma, but on further analysis, appeared more consistent with necrotizing myositis. The mass did not recur, nor did the patient develop other signs or symptoms concerning for myositis or malignancy over a 24-month follow-up period.

Conclusions: Necrotizing myositis has not been previously described in a rectus muscle or with BRAF inhibitor use, though myalgias and malignancies are established side effects. Necrotizing myositis may masquerade as sarcoma and should be on the differential diagnosis for a new mass in the setting of dabrafenib therapy.

1. Introduction

BRAF inhibitors (Dabrafenib [TAFINLAR, Novartis Pharmaceuticals Corp], Vemurafenib [ZELBORAF, Genentech], and Encorafenib [BRAFTOVI, Array BioPharma]) are relatively new biologic agents developed for metastatic or unresectable melanoma with the BRAF V600E or V600K mutation.[1] BRAF is a protein kinase active in regulating the RAS/RAF signalling pathway, which regulates cell growth, so mutations in the BRAF gene can cause cancer by allowing unregulated cell growth.[2] They have been used off-label for other advanced malignancies, including BRAF V600-positive non-small cell lung cancer,[3] glioma,[4] anaplastic thyroid cancer,[5] and hairy cell leukemia.[6] In addition to its use for malignancies, Vemurafenib was approved by the FDA for treatment of V600-mutant Erdheim Chester Disease (ECD), a rare non-Langerhans-cell histiocytosis, following the demonstration of prolonged efficacy in the VE-BASKET study.[7,8] Vemurafenib and other BRAF inhibitors have also been used with success in Langerhans cell histiocytosis (LCH) cases harboring the BRAF V600E mutation (50–60% of LCH cases have this mutation).[9,10] Indeed, there is an ongoing phase I/IIa clinical trial of Dabrafenib for the treatment of children with BRAF V600 mutation-positive tumors that includes an LCH group (NCT01677741).

While myalgias are a well-known side effect of Dabrafenib, we could not find a report of biopsy-proven necrotizing myositis attributed to this drug.[11] Necrotizing orbital myositis has not to our knowledge been reported in the English language literature. Here, we present an unusual case of lateral rectus muscle necrotizing myositis arising in the setting of long-standing Langerhans cell histiocystosis and Dabrafenib treatment, in which the myositis masqueraded as a sarcoma.

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2. Case report

An 18-year-old man with a history of neurodegenerative Langerhans cell histiocytosis presented to the emergency department (ED) with mild right eye pain, headache, and blurred vision. He had been diagnosed with LCH at age 5 months with skin histiocytosis, and was initially treated with topical steroid and emollient. At age 19 months, his disease returned with right external ear and zygoma involvement, which was treated with local radiation and systemic prednisone. Subsequent findings of central nervous system involvement led to treatment using the LCHIII protocol of prednisone, vinblastine, and 6-mercaptopurine.[12] Given continued disease progression, he received several other regimens including pentoxifylline, naturopathic care, vincristine and cytosine arabinoside, and finally rituximab, which was discontinued 2 years prior to presentation when no response was noted. As a result of the LCH, he suffered from hypopituitarism marked by central hypothyroidism, diabetes insipidus, and adrenocorticotropic hormone (ACTH) deficiency.

As an adolescent, he continued to experience gradual, ongoing neurologic decline. Molecular analysis of his skin biopsy specimen from infancy demonstrated the *BRAF* V600E mutation. He was started on dabrafenib in light of emerging evidence about the relationship between the *BRAF* V600E mutation and neurodegenerative LCH, and the therapeutic possibility of BRAF inhibition in this context.[13,14] Four weeks later, he developed right eye pain as described above and presented to the ED.

At the time of presentation, his vision was 20/20 in both eyes with no afferent pupillary defect, and normal intraocular pressure. His extraocular motility exam was notable for a mild deficit of supraduction of the right eye and a long-standing left beating nystagmus in left gaze of the left eye. His confrontational visual fields and dilated fundus exams were normal.

Magnetic resonance imaging (MRI) of the orbits revealed an enhancing, fusiform mass in the right lateral rectus muscle measuring 16 mm × 8 mm x 9 mm. This mass was located within his earlier radiation field and was concerning for LCH recurrence or, less likely, malignancy (Fig. 1). He was advised to stop taking Dabrafenib.

In order to establish a diagnosis, two weeks later the patient was taken to the operating room for incisional biopsy via lateral orbitotomy. The lesion appeared as a red-orange, bulbous area of the muscle. Inside, the lesion was noted to be friable and yellow within a fairly distinct capsule.

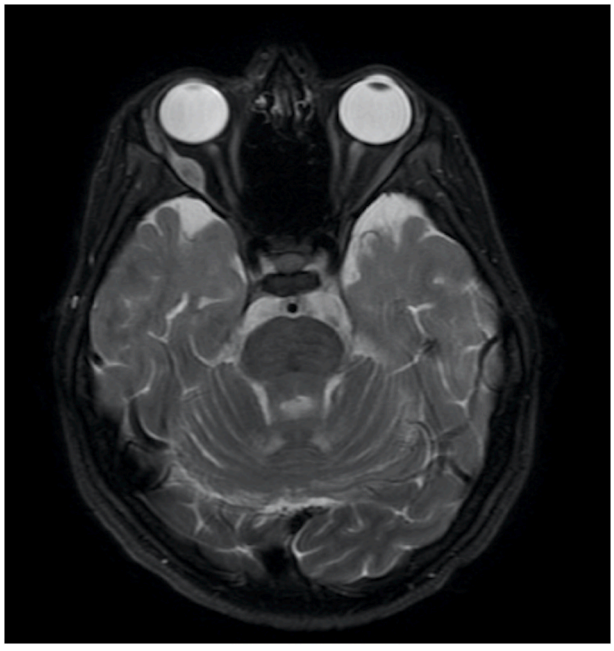

Fig. 1. T2-weighted fat supressed MRI image showing a contrast-enhancing, mildly hypointense right lateral rectus mass measuring 16 × 8 × 9 mm.

Initial evaluation of the pathologic specimen was suggestive of soft tissue sarcoma: there were many spindle-shaped or pleomorphic cells infiltrating skeletal muscle, and many large anaplastic cells with marked atypia (Fig. 2). Next generation sequencing was considered but could not be accomplished due to low sample volume. The differential diagnosis initially included radiation-related sarcoma, secondary neoplasia related to dabrafenib treatment, or other soft tissue sarcoma.

Initial discussion of treatment included the possible need for surgical resection, which would require orbital exenteration in order to ensure clear margins. Several weeks following biopsy, a repeat MRI orbit with contrast showed post-operative changes without clear evidence of residual tumor.

In light of the lack of recurrence of the lesion, which would be atypical for incompletely resected sarcoma, the specimen was reviewed again. The large cells were positive for desmin and negative for smooth muscle antigen (SMA), myogenin, CD1a, S100, and BRAF, and were surrounded by a mixed inflammatory infiltrate. The inflammatory cells were confirmed to be macrophages and T cells by CD68 and CD3 positivity with CD20 negativity. On review and consultation with expert colleagues, the pathology was found to be more consistent with necrotizing myositis than with sarcoma. Ragged muscle fiber margins with adherent leukocytes and vacuolization were noted. In this clinical setting, findings of increased numbers of nuclei; enlarged, atypical nuclei; and spindled and polygonal cells were determined to be reactive rather than anaplastic features.

After discussion with the patient and his family, the decision was made to perform surveillance MRI scans every 3 months and refrain from additional surgery or chemotherapy in the absence of signs of recurrence.

He has been followed now for 24 months following his biopsy and he has shown no sign of recurrence. He is not currently receiving any treatment for his neurodegenerative LCH. His medical treatment focuses on his endocrine and neuropsychiatric needs. His eye exam is stable.

3. Discussion

This unusual case of rectus muscle mass occurring in the setting of long-standing LCH while on Dabrafenib treatment was initially diagnosed as sarcoma based on biopsy findings. The patient had several risk factors for sarcoma, including long-standing Langerhans cell histiocytosis, which can rarely undergo malignant transformation to Langerhans cell sarcoma. Langerhans cell sarcoma is typically CD1a and S100 positive; however, the biopsy of this mass was negative for both markers.[15] Secondary malignancies are a well-established risk of BRAF inhibitor therapy via a mechanism of paradoxical MAPK pathway hyperactivation, and typically occur within the first 8 weeks of treatment.[16] These secondary malignancies are more commonly squamous cell carcinomas, though our patient was asked to stop BRAF inhibitor therapy due to the possible association.[11] Finally, the mass was within the field of his prior radiation therapy, which is a well-established risk factor for sarcoma development (most commonly leiomyosarcomas).[17]

Despite incomplete surgical resection, a post-operative MRI showed no definite residual mass, and the decision was made to follow the patient closely without additional treatment. This decision was made in part because clear surgical margins would have required orbital exenteration surgery, which is highly disfiguring and carries significant morbidity. The apparent involution of the lesion and its failure to recur over a two-year follow-up period prompted re-examination of the case and slides, at which point a diagnosis of necrotizing myositis was made as explained in the case description. No muscular weakness was detected, which is atypical for myositis, though this may be due to the very small focus of necrosis.

Necrotizing myositis of the extraocular muscles is very rare: no reports were identified in the English-language literature. Most cases of

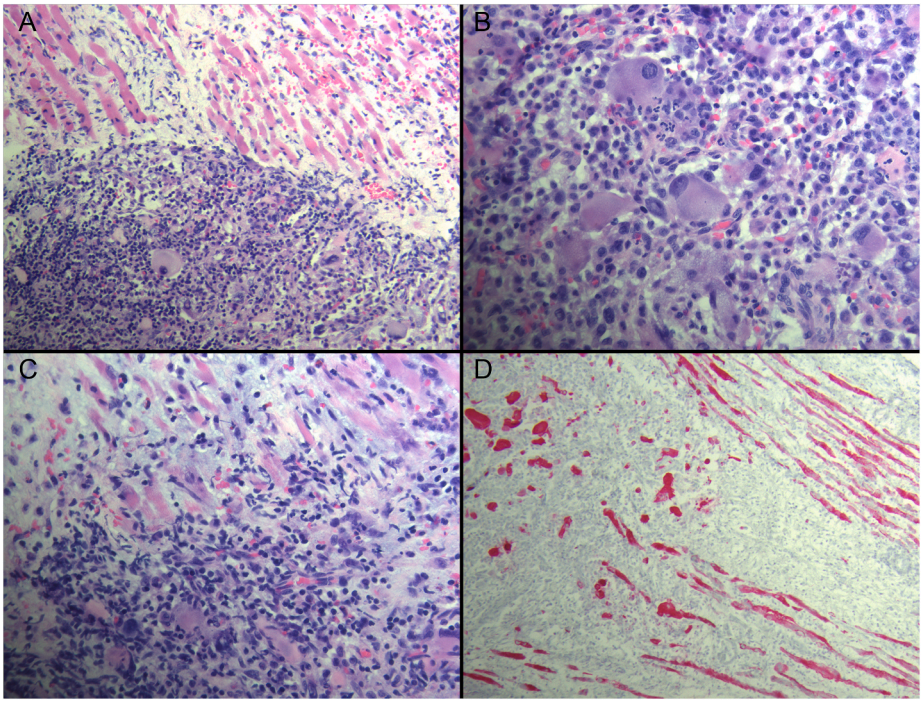

Fig. 2. Pathologic evaluation of orbital mass biopsy specimen. A) 20x hematoxylin and eosin (H&E) stain shows the interface of spindle to pleomorphic cells and skeletal muscle. B) 40x H&E stain highlights the enlarged, atypical, polygonal cells and background inflammation. C) 40x H&E stain shows myocytes assuming a more reactive morphology in the midst of inflammation. D) 10x desmin stain shows elongated and ragged cells, becoming more round, abnormal, and necrotic in appearance.

necrotizing myositis present as proximal muscle weakness without discrete masses.[18,19] They appear to be immune related, and are associated with elevated creatine kinase (CK), anti-signal recognition particle (SRP) antibodies, and anti-3hydroxy-3 methylglutarylcoenzyme A reductase (HMGCR) autoantibodies.[18] Histopathological findings in necrotizing myositis are fairly heterogenous, which may in part reflect biopsies being taken at different timepoints in the disease course or may reflect different underlying biochemical processes. Previous reports have described biopsy findings of necrotic myocytes with minimal surrounding infiltration, acute lymphocytic infiltrate,[20] or mixed inflammatory infiltrate, often macrophage-predominant with some T cells.[21–23]

Necrotizing myositis is a known side effect of immune checkpoint inhibitors (ICIs), with a rate of 1% reported with anti-programmed cell death protein-1 (PD-1) antibody use.[24–26] In a recent review of orbital myositis, McNab identified 17 reported ICI-associated cases.[27] Most patients were using ipilimumab, a checkpoint inhibitor that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), though none of these cases were biopsied and therefore it is unknown whether muscular necrosis occurred. Clinical findings were often similar to thyroid-associated orbitopathy. Case were typically treated empirically with anti-inflammatory medications and stopping the ICI.

The clinical findings of checkpoint inhibitor-associated necrotizing myositis can be similar to autoimmune cases, but the mechanism is unclear and there are no consistently associated antibodies. For example, steroid refractory dermatomyositis has been reported following combination Dabrafenib and Trametinib (a mitogen-activated protein kinase 1/2 [MEK1/2] inhibitor) therapy.[28] The authors noted that the MAPK/ERK pathway (in which MEK1, MEK2, and BRAF play important roles) is important for T-cell receptor signalling, so suppression of this pathway may impair the development of peripheral tolerance, thereby contributing to the development of an autoimmune state.

Another series of 54 ECD patients with BRAF V600E mutations treated with BRAF or MEK inhibitors reported rhabdomyolysis in 4/15 (27%) treated with cometinib, a MEK inhibitor, though only one patient had symptoms severe enough to stop treatment, and no masses were noted.[29] None of the 39 patients treated with BRAF-inhibitor monotherapy were found to have rhabdomyolysis. Our patient's presentation was quite different from these cases, though there may be a similar mechanism at play. Antibodies and CK levels were not tested at the time of the biopsy, though the patient had no symptoms suggestive of proximal muscle weakness or myalgias elsewhere in the body, and it is unlikely that such a focal area of myositis would cause a measurable elevation in CK levels. Electromyography can also be helpful in making a diagnosis of myositis but is not practical to perform on a rectus muscle.

It is unclear if the lesion at the center of this case would have involuted spontaneously as a result of cessation of dabrafenib alone, or if the incisional biopsy contributed to its resolution. Regardless, the lesion has not recurred, nor has myositis been identified elsewhere in this patient's body, without additional treatment.

4. Conclusions

In conclusion, this is an unusual case of necrotizing myositis of the lateral rectus muscle occurring in the setting of disseminated LCH, prior radiation, and dabrafenib use, which masqueraded as sarcoma. Necrotizing myositis should be considered on the differential diagnosis of a patient with a new muscular mass in the setting of BRAF-inhibitor treatment. Biopsy is necessary for diagnosis and may contribute to involution of the mass. The authors recommend stopping BRAF-inhibitor treatment, which also may contribute to lesion resolution.

Patient consent

The patient's legal guardian consented to publication of the case in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

CRediT authorship contribution statement

Suzanne W. van Landingham: Conceptualization, Methodology, Investigation, Writing - original draft, Project administration. **Diane Puccetti:** Conceptualization, Investigation, Resources, Writing - review & editing. **Heather Potter:** Investigation, Resources, Writing - review & editing. **David Gamm:** Resources, Writing - review & editing. **Eli L. Diamond:** Investigation, Resources, Writing - review & editing. **Mark J. Lucarelli:** Investigation, Resources, Writing - review & editing, Supervision.

Declaration of competing interest

Dr. van Landingham is a paid consultant of Horizon Therapeutics, on topics unrelated to the current work. The following authors have no financial disclosures: M.L., D.P., D.G., and H.P.

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