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Title: Plexiform Neurofibroma with Activating KRAS Mutation and Segmental Presentation Involving the Unilateral Eyelid

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Running head:

Segmental presentation of a plexiform neurofibroma with activating KRAS mutation

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Prescis:

The authors describe the case of a right upper eyelid sporadic plexiform neurofibroma with perineuriomatous features molecularly driven by an activating *KRAS* mutation and inactivating mutation in *PHF6*.

Abstract:

Plexiform neurofibromas are classically thought to be pathognomonic for neurofibromatosis type 1. However, isolated forms may occur, particularly as a manifestation of segmental neurofibromatosis related to post-zygotic mosaicism in the *NF1* gene. Most cases occur on the head and neck, trunk, and extremities with very few cases reported in the periorbital area. The authors report a case of plexiform neurofibroma with perineuriomatous features of the right upper eyelid in a patient with no other stigmata of neurofibromatosis. While suggestive of segmental neurofibromatosis, genetic analysis revealed activating *KRAS* mutation and inactivating mutation in *PHF6* with no evidence of *NF1* mutation in germline or tumor tissue. Neither *KRAS* nor *PHF6* have been previously reported in association with neurofibroma.

Neurofibromatosis type 1 (NF1) is a systemic phakomatosis with heterogeneous neurologic, ophthalmologic and cutaneous findings. Patients with typical disease features limited to one or more body segments without systemic involvement of the disease are referred to as having segmental (localized) NF1, driven by sporadic postzygotic mosaicism of the pathogenic mutation. The authors report a case of a unilateral plexiform neurofibroma affecting the first branch of the trigeminal nerve, clinically and histologically suggestive of segmental neurofibromatosis (NF), although genetically found to have an activating KRAS mutation. Collection and evaluation of patient information for this case report were conducted in compliance with the Health Insurance Portability and Accountability Act.

Case Presentation:

A 68-year-old man presented with bilateral blepharoptosis and a slowly progressive, painless right upper eyelid lesion of two-year duration. Past family, medical and ocular history were non-contributory. Notably, the patient had been in a car accident ten years prior and reported glass embedded in the forehead and brow.

Examination was notable for thickened, confluent, flesh-colored papules of the right upper eyelid, brow, and forehead with a beaded appearance (Fig 1A), as well as right worse than left blepharoptosis. Slit lamp exam was unremarkable and neither eye had Lisch nodules. No café-au-lait macules or freckling of the axillary or inguinal regions were noted.

The patient underwent bilateral levator advancement surgery with simultaneous upper eyelid blepharoplasty. The excised anterior lamellar tissue of the upper eyelids, along with an incisional biopsy of the right forehead lesion, were sent for histopathologic review. Histopathologic examination showed a bland spindle cell proliferation within the dermis on a background of homogenous collagen fibers (Fig 1B). Multiple small tumor nodules involving adjacent peripheral nerves were also noted (Fig 1C). Immunohistochemical stains supported the diagnosis of plexiform neurofibroma with focal perineuriomatous features (Figs 1D-F). Lack of diffuse neurofilament in the smaller nodules argues against traumatic neuroma (not shown). There was no evidence of malignancy. Genetic testing was then performed using a clinically validated next-generation sequencing assay (UCSF500; see table in Supplementary Digital Content 1 which displays full list of genes assessed).[1] The plexiform neurofibroma harbored an activating missense hotspot mutation in the *KRAS* (p.Q61R) oncogene and an inactivating frameshift mutation in the *PHF6* (p.A113fs) tumor suppressor gene. There were no alterations in the *NF1* gene in either the germline or tumor tissue.

The patient had no family history of neurofibromatosis and no additional findings indicative of systemic NF1. Complete excision of the lesion was deferred given preserved eyelid architecture and aesthetic appearance acceptable to the patient.

Discussion:

Inactivating germline mutations in the *NF1* tumor suppressor gene on chromosome 17q11.2 are responsible for generalized NF1 with autosomal dominant inheritance. Segmental NF is a subtype of neurofibromatosis that is the result of postzygotic somatic mosaicism. Historically,

the cutaneous findings in segmental NF were unilateral, dermatomal, and noninheritable, although variations from this presentation have subsequently been described and have led to a broadening definition of disease with classification into additional subtypes.[2] The embryologic timing of genetic mutation is thought to be the main driver of the ultimate clinical picture and may be responsible for this variation in phenotype: mutations that occur earlier in development produce a generalized NF1 phenotype while mutations that occur after tissue differentiation may lead to a more localized clinical manifestation.[3]

Several case series of segmental NF demonstrate that solitary plexiform neurofibromas are responsible for 7–17% of cases and occur largely on the scalp, head and neck, abdominal, and pelvic regions.[3-5] Listernick et al. described a case of segmental NF in which the patient presented with a plexiform neurofibroma affecting the right upper eyelid and forehead with examination revealing additional sequelae of NF1 including Lisch nodules of the right iris and ipsilateral sphenoid wing dysplasia.[6] However, there have been few reported cases of isolated plexiform neurofibroma of the eyelid as described in the present one.

Genetic analysis of the patient's tumor did not show mosaicism in the *NF1* gene as expected based on the clinical and histopathologic findings. This is consistent with the genetic findings described by Ruggieri et al. (2004) in which none of their 72 cases of segmental NF demonstrated a mutation in *NF1*.[5] This disparity may suggest that segmental NF1 is actually genetically heterogeneous and may follow a different pathogenetic mechanism than previously thought. The present case did display an activating missense mutation in *KRAS* (p.Q61R) and an inactivating frameshift mutation in tumor suppressor and chromatin binding protein *PHF6*.

Activating *KRAS* mutations are expected to increase the downstream MAP kinase pathway activity and have been reported in other tumors which frequently harbor *NF1* mutations. Interestingly, the inactivation of the *NF1* gene and the activation of the *KRAS* gene have similar downstream effects (both promote the RAS-RAF-MAPK pathway). However, *KRAS* alterations have rarely been reported in association with NF1 syndrome.

KRAS mutations have been described in many benign and malignant tumors including sporadic schwanommas,[7] mucosal hybrid perineurioma/hyperplastic polyp of the colon,[8] and more recently and relevant to the present case, localized hypertrophic neuropathy (LHN). LHN is a rare Schwann cell proliferation of a single nerve of the extremities driven by KRAS-mediated RASopathy with somatic mosaicism.[9] An additional histopathologically similar lesion to consider is the hybrid peripheral nerve sheath tumor (HPNST) which contains mixed components of neurofibroma, schwannoma and perineurioma. The current patient's tumor did not have a prominent histopathologic "onion bulb" component and had areas of weak EMA and GLUT1 with retained SOX10 and S100 staining, differentiating the present tumor from LHN and HPNST, respectively. Finally, alterations in the PHF6 protein have been classically described in in T-cell acute lymphoblastic leukemia but have not been reported in neurofibromas.

To the authors' knowledge, this is the first described case of a patient presenting with a sporadic plexiform neurofibroma with perineuriomatous features driven by mutations in *KRAS* and *PHF6*.

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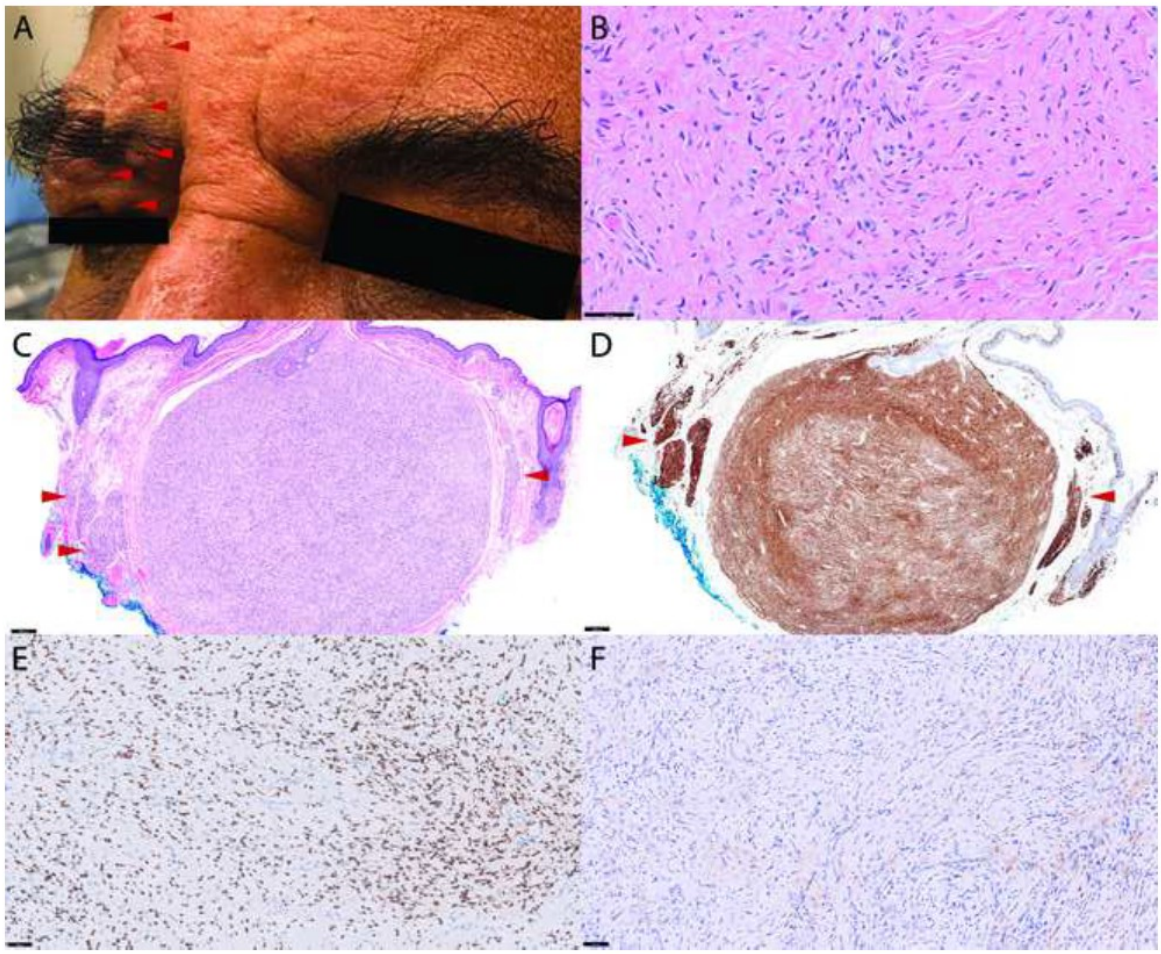
Figure 1*:*

A 68-year-old male presented with plexiform neurofibromas of the right periocular area. Thickened, confluent, flesh-colored papules (arrow heads) of the right upper eyelid, brow, and forehead with a beaded appearance **(A).** Histopathologic examination demonstrated a bland spindle cell proliferation within the dermis on a background of homogenous collagen fibers (hematoxylin and eosin, 200x magnification) **(B)**. In addition to a main, well-circumscribed nodule, multiple small tumor nodules (arrow heads) involving adjacent peripheral nerves were also noted (hematoxylin and eosin, 50x magnification) **(C)**. S100 stain highlighted both the main nodule and adjacent smaller nodules (arrow heads, 50x magnification) **(D)**. High-power (400x magnification) image of SOX10 stain shows staining in majority of the spindled cells **(E)**. Epithelial membrane antigen staining highlighted only focal staining in some areas, suggesting perineuriomatous features, but a well-established perineurioma component is not identified (400x

magnification) **(F)**.



Supplemental Digital Content 1. Full list of genes assessed in the UCSF500 genetic panel.pdf