

# Intraocular Inflammatory Myofibroblastic Tumor With ALK Overexpression

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● We report a case of an intraocular inflammatory myofibroblastic tumor nearly filling the vitreous cavity of the eye of a 50-year-old man. The tumor was composed of a mixture of spindle cells and mixed inflammatory elements, including numerous plasma cells. The differential diagnosis included inflammatory pseudotumor and neoplastic mimics of this condition. Further investigation with immunohistochemistry revealed the mass to be composed of myofibroblasts, positive for smooth muscle actin stains and with weak anaplastic lymphoma kinase (ALK) expression in some tumor cells. Evaluation by fluorescence in situ hybridization revealed the tumor cells to have multiple copies of chromosome 2 and ALK but no rearrangement of the ALK gene. The authors propose that multiple copies of the ALK gene may be involved in inflammatory myofibroblastic tumor tumorigenesis, in addition to ALK gene rearrangements.

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Inflammatory pseudotumor of the orbit or eye is a rare disorder that is associated with serious visual disturbances.<sup>1–3</sup> The diagnostic entity “inflammatory pseudotumor” has undergone something of a revolution in recent years. What was once a heterogeneous group of poorly defined entities has been refined, and it presently encompasses several distinct biologic processes, including both benign, reactive conditions as well as neoplasms. The latter category includes spindle cell proliferations composed of myofibroblasts, which are termed “inflammatory myofibroblastic tumors” (IMTs). The neoplastic nature of IMT was confirmed by proving the presence of clonal abnormalities in the short arm of chromosome 2 in a subset of cases.<sup>2–5</sup>

Anaplastic lymphoma kinase (ALK), more commonly known for its association with anaplastic large cell lym-

phoma, is expressed in a small proportion of IMTs.<sup>4,5</sup> We report a case of an intraocular IMT that expressed ALK in tumor cells with multiple copies of chromosome 2 and the ALK gene by fluorescence in situ hybridization.

## REPORT OF A CASE

A 50-year-old African American man presented with pain and mass in the right eye, after a 2-year history of retinal detachment, progressive pain, and recurrent episcleritis of unknown etiology. Vision was limited to light perception only. The fundus could not be visualized on examination. Two years previously, surgery had been performed to repair a retinal detachment. No mass had been perceived at that time.

Twenty years previously, the left eye had been enucleated after repeated episodes of idiopathic iritis and episcleritis followed by retinal detachment and vision loss. Because of increasing pain, the eye was removed. The pathology from this eye was not available for review.

Radiologic and gross examination revealed the globe to be intact with no extension of tumor into the soft tissue. The enucleated eye was 2.5 × 2.3 × 2.0 cm, with a firm, tan mass filling most of the vitreous cavity (Figure 1). The mass was evaluated by routine histology (hematoxylin-eosin), cytochemical stains for microorganisms (periodic acid–Schiff, Grocott-Gomori methenamine-silver, acid-fast bacilli), and a panel of immunohistochemical stains (from Dako Corporation, Carpinteria, Calif, except as indicated), including CD3 (LabVision Corporation, Fremont, Calif), CD20, κ, λ, CD21, Epstein-Barr virus latent membrane protein (Cell Marque Corporation, Hot Springs, Ark), α-smooth muscle actin, anti-human muscle actin (HHF-35), and ALK. Fluorescence in situ hybridization using a probe for the ALK gene (located on chromosome 2) and a chromosome 2 centromeric probe was also performed (probes obtained from Vysis, Inc, Downer's Grove, Ill).

## RESULTS

The vitreous cavity was replaced with a dense spindle cell infiltrate with interspersed bands of collagen fibrosis and numerous inflammatory cells (Figure 2). There was extensive plasma cell infiltration of the retina, but tumor cells did not involve this layer. The choroid was diffusely infiltrated by both inflammatory cells and the spindle cell proliferation.

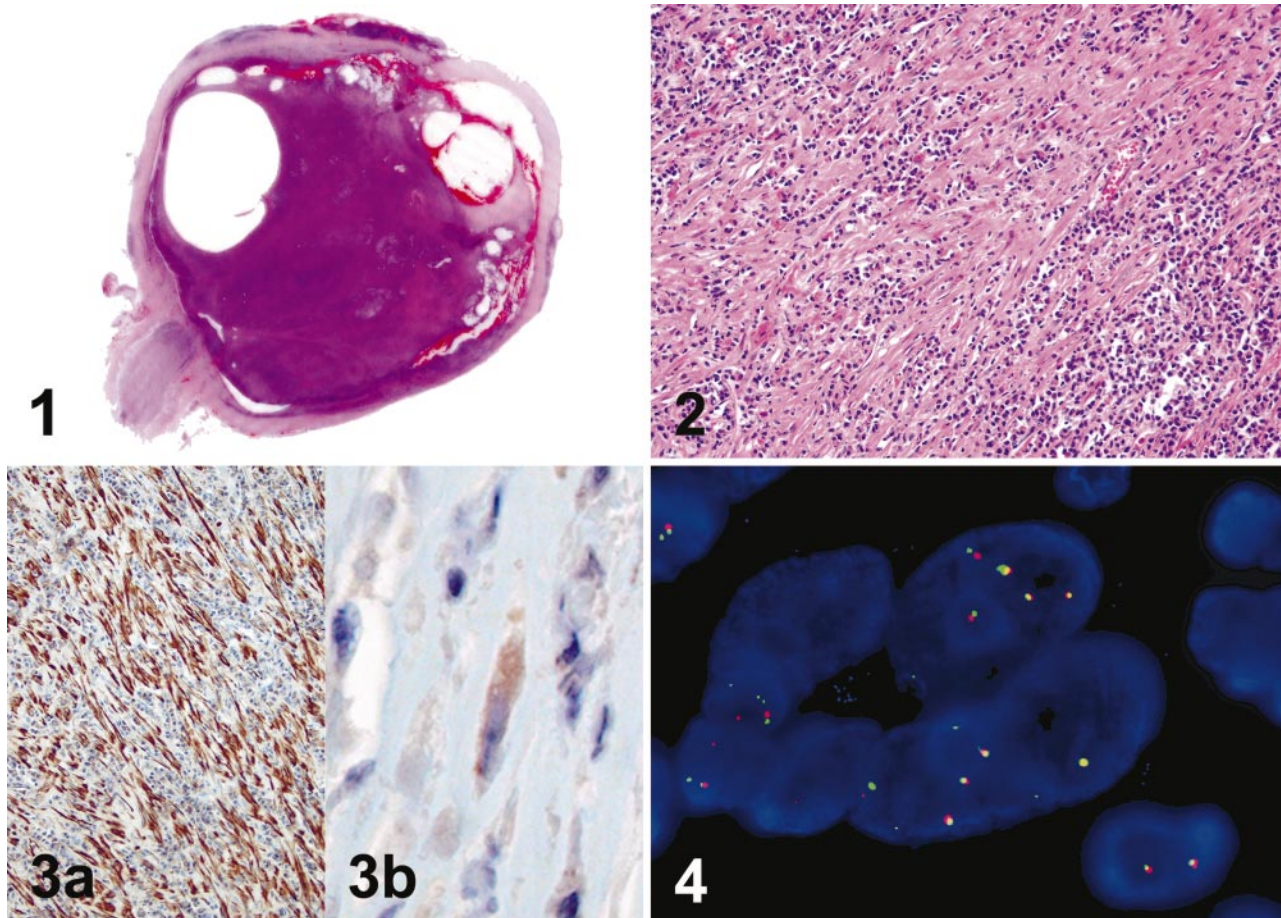
The spindle cells had blunt-ended nuclei, delicate nuclear chromatin, and inconspicuous nucleoli. The remainder of the cellularity consisted of abundant, mature-appearing plasma cells, scattered lymphocytes, histiocytes, and neutrophils. The inflammatory infiltrate extended into the optic nerve and to the outer surface of the eye.

No microorganisms were identified using special stains. Immunohistochemical stains for lymphoid markers (CD3,

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**Figure 1.** Whole mount of eye illustrating tumor essentially replacing vitreous cavity (hematoxylin-eosin, digital scan of glass slide, original magnification  $\times 1$ ).

**Figure 2.** Intermediate magnification of mass. Note the spindle cells (myofibroblasts), collagen fibrils, and inflammatory elements, including plasma cells (hematoxylin-eosin, original magnification  $\times 20$ ).

**Figure 3.** A, Staining for HHF-35, a marker of smooth muscle differentiation (HHF-35 immunohistochemistry, original magnification  $\times 20$ ). B, Staining for ALK protein showing weak, granular cytoplasmic staining (ALK immunohistochemistry, oil immersion, original magnification  $\times 100$ ).

**Figure 4.** Fluorescence in situ hybridization using ALK break-apart probe, detecting the ALK gene at 2p23. Multiple copies are seen in the large myofibroblastic cell (center), and only 2 copies are seen in adjacent inflammatory cell (lower right). There is no evidence of ALK gene rearrangement (split signals). The probe is designed to detect ALK rearrangements with a Spectrum Orange label on the telomeric side of the ALK gene and a Spectrum Green probe on the centromeric side of the gene. In cases with an ALK rearrangement, 2 signals, orange and green, are seen. Similar results were obtained with a chromosome 2 centromeric probe (not shown).

CD20) showed the lymphocytes to be a mixture of T and B cells. The lymphocytes and plasma cells were polyclonal ( $\kappa$ ,  $\lambda$ ). The spindle cells were strongly and uniformly positive for HHF-35 (Figure 3, a) and for  $\alpha$ -smooth muscle actin. ALK staining was weakly positive in a minority of the spindle cells (Figure 3, b). Staining for CD21, a marker of follicular dendritic cells, and for Epstein-Barr virus latent membrane protein was uniformly negative.

The fluorescence in situ hybridization results did not show evidence of an *ALK* translocation; however, 3 to 6 copies of both the *ALK* probe and a chromosome 2 centromeric probe were identified in approximately 20% of cells and 3 signals in approximately 10%, indicating additional copies of the chromosome 2 and the *ALK* gene (Figure 4).

#### COMMENT

Lesions of the orbit and eye with a mixture of spindle cell elements and mixed inflammatory elements are not

uncommon and fall under the general rubric of inflammatory pseudotumor. These lesions are composed of varying mixtures of acute inflammation, plasma cells, fibroblasts, and myofibroblasts. The differential diagnosis of inflammatory pseudotumor includes reactive proliferations rich in histiocytes, most often associated with an infectious etiology, neoplasms of dendritic cells, and neoplasms of myofibroblastic cells (eg, IMT). In contrast to IMT, the spindle cell component in inflammatory pseudotumor is more often a mixture of fibroblasts, myofibroblasts, and occasionally follicular dendritic cells. They are also more commonly rich in histiocytes. Many inflammatory pseudotumors are derived from infection-associated reactions of stromal elements with a typically intense inflammatory infiltrate. These "tumors" are nonclonal.

In IMT, the spindle cells are predominantly myofibroblasts that are positive for smooth muscle markers, and it has been reported in the orbital region.<sup>4</sup> Subsets of IMT have deregulation of the *ALK* gene located at chromosome

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2p23, although the exact mechanism by which the *ALK* gene participates in the pathogenesis of IMT is unclear. The multiple copies of chromosome 2, leading to amplification of the chromosome 2p23 region (*ALK* gene) in this case, and the lack of *ALK* rearrangement suggest that *ALK* overexpression, in addition to *ALK* rearrangement, may be a cause of IMT tumorigenesis.

In summary, we report a case of inflammatory myofibroblastic tumor of the vitreous cavity of the eye, with expression of *ALK* protein. In order to fully evaluate spindle cell lesions with inflammation of the eye and orbit, it may be necessary to consider this diagnosis and do ap-

propriate ancillary studies, including immunohistochemistry and fluorescence in situ hybridization.

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