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Management of anaplastic lymphoma kinase positive orbito-conjunctival inflammatory myofibroblastic tumor with crizotinib

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Inflammatory myofibroblastic tumor (IMT) is a distinct mesenchymal neoplasm of myofibroblastic spindle cells associated with an inflammatory infiltrate formed by lymphocytes, eosinophils, and plasma cells in a myxoid or collagenous stroma. This tumor has a predilection for children and young adults and most commonly occurs in the lungs, retroperitoneum, abdomen, and pelvis. Ocular and orbital involvement is exceedingly rare. We describe a case of IMT in a 7-year-old girl involving the cornea, conjunctiva, and the anterior orbit treated with crizotinib, resulting in complete tumor remission.

The etiopathogenesis of inflammatory myofibroblastic tumor (IMT) is unknown; however, gene rearrangements on the short arm of chromosome 2 at 2p23, the site of the anaplastic lymphoma kinase (*ALK*) gene, are found in about 50%-70% of IMT cases.[1,2] These abnormalities generally lead to aberrant ALK protein overexpression, which are detectable by immunohistochemistry.[1,2] Crizotinib is an orally bioavailable ATP-competitive inhibitor of the ALK receptor tyrosine kinase, a member of the insulin growth factor receptor superfamily.[2]

Case Report

A 7-year-old girl presented at the Ocular Oncology Service of Hacettepe University Hospital with a painless mass on the nasal part of her right eye that had been growing slowly for many months. She had no history of trauma, and her past medical history was unremarkable. Systemic work-up for tuberculosis and autoimmune disorders was negative. On ophthalmological examination, her best-corrected visual acuity was 20/80 in the right eye and 20/20 in the left eye. In the primary gaze position, she had a right esotropia of 60^{Δ} and completely limited abduction of the right eye. There was a richly vascularized and ill-defined superonasal bulbar conjunctival tumor invading the cornea with diffuse vascular ingrowth (Figure 1A). The mass was immobile and hard in consistency. Dilated fundus examination showed superonasal choroidal elevations in the right eye. Orbital magnetic resonance imaging (MRI) studies showed a crescent-shaped mass at the medial side of right eye (Figure 1B).

Histopathological examination of an incisional biopsy specimen showed inflammatory cells consisting of lymphocytes, plasma cells, and histiocytes scattered in a hyalinized connective tissue together with myofibroblastic spindle cells (Figure 2A), which showed positive cytoplasmic immunoreactivity for ALK (Figure 2B), positive immunostaining for α-SMA (Figure 2C), and vimentin (Figure 2D). Desmin staining was weak; s-100 was negative. The Ki-67 proliferation index was 5%.

Since complete surgical resection was impossible, the patient was started on oral crizotinib at a dosage of 125 mg twice daily. The tumor regressed steadily over the course of 1 year (Figure 3A-B) and complete response was declared based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[3] Crizotinib was discontinued at the end of the year; however, 3 months later tumor recurrence was noted in the form of minimal diffuse thickening of the nasal conjunctiva. Crizotinib was prescribed 250 mg twice daily for 6 months, resulting in total clinical and radiological remission (Figure 3C). No tumor recurrence was found during the next 14 months' follow-up, and corneal neovascularization regressed notably (Figure 3D). The patient's final visual acuity was 20/30 in the right eye with -1.00 $+2.50$ $\times 135$ correction; ocular motility was entirely unrestricted. She had a residual esotropia of $<10^{\Delta}$. Crizotinib therapy was well tolerated and no drug-related adverse effects were observed.

Discussion

IMT is a neoplasm of intermediate biological potential due to its frequent multifocal nature, development of local recurrences in 25% of patients even after surgical excision, and the risk, albeit low, of distant metastases.[1,2] Constitutional symptoms may be present in 15%-30% of patients.[4] Moreover, the *ALK* gene deregulation, which results in proliferation of fibroblasts and myofibroblasts, may be associated with a more aggressive behavior and malignant potential.[1,2,4]

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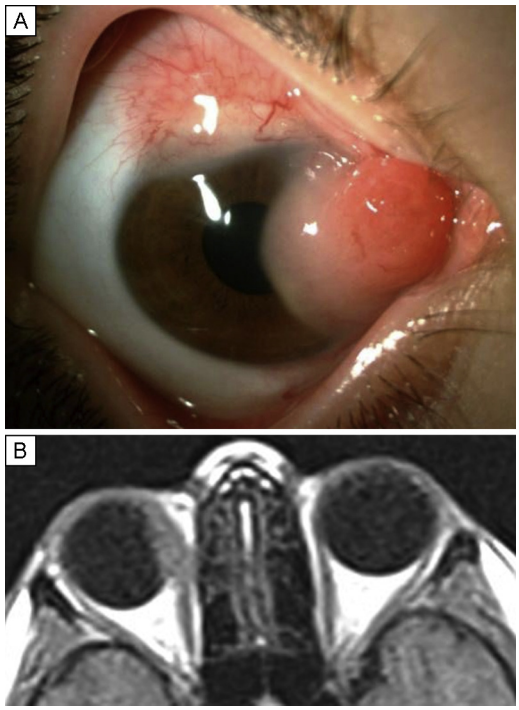

FIG 1. A, Right eye of the patient: the main bulk of the tumor is on the nasal side, but the whole lesion involves almost half of the ocular surface with full-thickness corneal infiltration. B, T1-weighted axial magnetic resonance imaging (MRI) scan showing the anterior orbital tumor affecting the sclera and the insertion of the right medial rectus muscle.

Fewer than 10 cases of primary and isolated either orbital or intraocular biopsy-proven IMTs have been reported in the literature.[4-7] Complete surgical excision with clear margins appears to be the treatment of choice. A well-delineated, superolateral intraconal ALK-positive IMT was completely excised in a patient who did not have any recurrence for 28 months.[8] Debulking of the orbital tumor in an 8-month-old provided a recurrence-free survival of 2 years.[7] In contrast, enucleation was performed in a 31-year-old woman who presented with a white intraocular mass.[5]

In patients in whom complete surgical removal was not feasible, other treatment modalities have been used: corticosteroids, nonsteroidal anti-inflammatory drugs, antibiotics, immunomodulators, chemotherapy, and low-dose radiotherapy alleviated signs and symptoms with varying success rates.[4-9] Systemic corticosteroids yield rapid response, with 31%-78% of tumors disappearing completely in 24-48 hours; but corticosteroids are associated with a high relapse rate.[5] Low-dose radiotherapy (10-20 Gy) may provide tumor control in 67%-87% of patients.[5] A 10-year-old boy whose tumor was very similar to our case was treated with a combination of corticosteroids and 20 Gy radiotherapy[9]; however, vascularized scar tissue remained in the superior cornea.[9] Favini and colleauges[6] reported treating an anterior

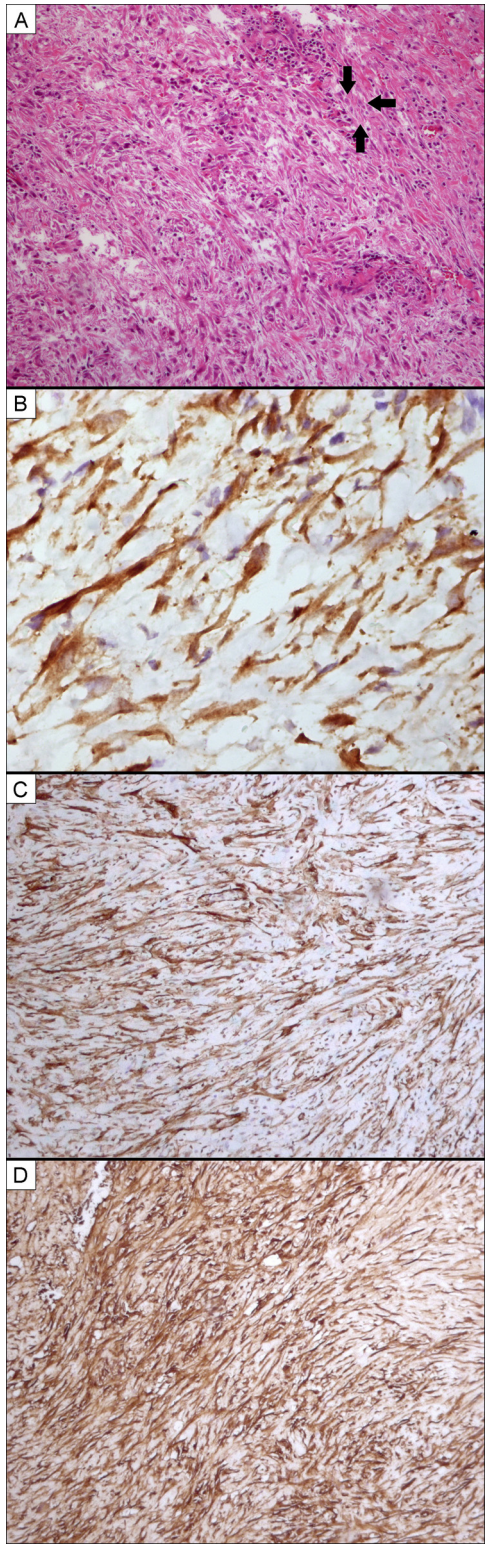

FIG 2. Histopathological evaluation of the specimen. A, Spinde-shaped myofibroblastic cells with large vesicular nuclei (arrows) admixed with inflammatory cells in an eosinophilic stroma (hematoxylin and eosin, original magnification ×100). B, Positive intracytoplasmic immunostaining for anaplastic lymphoma kinase (original magnification ×400). C, smooth muscle actin positivity (original magnification ×200). D, vimentin positivity (vimentin, original magnification ×200).