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Major review

Orbital lymphaticovenous malformations: Current and future treatments

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ABSTRACT

Orbital lymphaticovenous malformations consist of abnormal vascular channels lined by endothelial cells with a spectrum from venous to lymphatic characteristics. They may be venous-dominant or lymphatic-dominant. These lesions continue to present management challenges. Total excision or obliteration is not always achievable, recrudescence is common, and interventions carry a risk of damaging normal structures. Patients likely benefit most from a multidisciplinary approach, including both surgical and nonsurgical (e.g., sclerosants and liquid polymers) therapeutic modalities. Targeted biologic therapy would be ideal; nevertheless, this goal is complicated by the heterogeneous venous–lymphatic and stromal characteristics of these lesions. Ideally, antiangiogenic agents targeting both lymphatic and blood vascular endothelial cells will be developed to treat these lesions and reduce their regrowth. Further studies are warranted to enhance our understanding of these orbital lesions with regard to their angiogenic (proliferative) activities and profiles of marker expression, with a goal to produce effective medical therapies.

1. Introduction

Vascular anomalies (malformations) are disorders of vasculogenesis that affect arteries, capillaries, veins, or lymphatics caused by dysfunctional signaling processes that regulate proliferation, differentiation, maturation, apoptosis, and adhesion of vascular cells.[186] During the past two decades, advances in genetic and molecular characterization have yielded an evolving understanding of their pathogenesis. This knowledge has informed the development and refinement of the International Society for the Study of Vascular Anomalies classification system that categorizes these anomalies as vascular tumors and vascular malformations (Table 1).[35,102,117] They are further divided into slow-flow and fast-flow. The third level of division separates lesions based on their vascular components into arterial, capillary, venous, and lymphatic malformations, or combinations of these elements.[35,102,117]

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This classification defines the difference between vascular tumors and vascular malformations by evidence of endothelial cell proliferation in the latter (Table 2). *Vascular tumors* are lesions with endothelial proliferation (with or without dysplasia or anaplasia). *Vascular malformations*, in contrast, evolve by dysmorphogenesis and exhibit normal endothelial cell turnover.

This system is not perfect, as some anomalies may cross categories. In other words, endothelial mitotic activity is not always diagnostically useful. For instance, infantile hemangiomas, which are categorized as vascular tumors, lose their mitotic activity during the involutional phase. Conversely, some of the vascular malformations may have scattered foci of active capillary or lymphatic proliferation.[68,93,120,144]

We summarize the current knowledge related to the development of lymphatic vessels and lymphaticovenous malformations and present a brief description of current surgical and nonsurgical therapeutic options for management, with special focus on the development of targeted biologic therapies.

2. Case presentation

The following case presentation of a lymphaticovenous lesion documents its growth and changing management over a 14-year period. In addition, it demonstrates the development of a clearer understanding of the pathophysiology, assessment techniques, and underlying pathogenesis. The clinical picture, imaging, management, and histopathology outline the various mechanisms of persistence and progression of these lesions including recurrent thrombosis (phleboliths),[112] inflammation, mixed lymphatic and venous components, intralesional hemorrhage, as well as lymphatic and vascular angiogenesis.

A 48-year-old white woman presented with a recurrent complex lymphaticovenous malformation in her left orbit. The patient was first seen in March 2000, with longstanding painless left proptosis (Figs. 1A and 1B). The visual acuity was 20/30 in the right eye and 20/70 in the left eye with a minimal cataract. Examination of extraocular motility revealed limitation in upgaze to 25° and abduction to 20°. Hertel exophthalmometry was 18 mm in the right eye and 33 mm in the left eye (base 103 mm), with 3 mm downward displacement and an interpalpebral fissure of 12 mm. The left proptosis increased 3 mm to 36 mm with Valsalva maneuver. The contrast magnetic resonance image (MRI) showed a 4.2 x 3.5 cm intraconal mass that extended superolaterally in the orbit (Figs. 1C and 1D). The patient underwent a combined circumferential panorbitotomy with significant debulking and drainage of cysts of a mutinodular mass (2.6 x1.8 x1.4 cm) off adjacent structures except apically, where it was attached to the optic nerve and lateral rectus muscle. There was left corectopia postoperatively. At the 1 year postoperative visit, there was 3 mm left hypoglobus, with 2 mm inward displacement and exophthalmometry measurements of 20 mm OD and 26 mm OS, with no change on Valsalva maneuver, a denser cataract, lower eyelid scleral show of 2 mm, and a sluggish left pupil measuring 4 mm compared with 2 mm in the right (Figs. 1E and 1F). The MRI with contrast, which was done 2 years after surgery, demonstrated reduction of the lateral mass (Figs. 1G and 1H). Two years later she underwent surgery to address lower eyelid retraction utilizing a cartilage graft.

The patient was stable for 10 years and had undergone cataract and strabismus surgery. She returned in November, 2011, having noted increased bulging and a bluish left inferotemporal mass—including tearing, pressure, and discomfort (Figs. 2A and 2B). On physical examination, her vision was 20/25 in the right eye and 20/100 in the left eye (There was posterior capsule opacification). Her exophthalmometry

Table 1 – Current classification of vascular anomalies and malformations[35,117,120]

Vascular neoplasms (or vasoproliferative)	Malformations	
	Slow flow	Fast flow
Infantile hemangioma	- Capillary malformation Cutis marmorata telangiectatica congenita Telangiectasias	- Arterial malformation Aneurysm Atresia Ectasia Stenosis
- Congenital hemangioma Rapidly involuting congenital hemangioma Noninvoluting congenital hemangioma	- Lymphatic malformation Microcystic Macrocystic Primary lymphedema	- Arteriovenous malformation Capillary malformation-arteriovenous malformation Hereditary hemorrhagic telangiectasia PTEN-associated vascular anomaly
- Hemangioendotheliomas Kaposiform hemangioendothelioma - Other	- Venous malformation Cerebral cavernous malformation Cutaneomucosal venous malformation Glomuvenous malformation Verrucous hemangioma	- Combined malformations Capillary- ateriovenous malformations Capillary-lymphatic ateriovenous malformations
- Pyogenic granuloma	- Combined malformations Capillary-venous malformation Capillary-lymphatic malformation Capillary-lymphatic-venous malformation Lymphatic-venous malformation	