

# Educational Case: Orbital B-Cell Lymphoma With Amyloid Deposition

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289520934089>.<sup>1</sup>*

## Keywords

pathology competencies, organ system pathology, hematopathology, white cell disorders, clinical features, extranodal lymphoma, orbital lymphoma, amyloid

Received May 31, 2019. Received revised January 26, 2020. Accepted for publication May 9, 2020.

## Primary Objective

*Objective HWC4.4: Extranodal Lymphoma:* Identify lymphomas most likely to present in or involve extranodal sites such as the gastrointestinal tract, bone marrow, blood, skin, or central nervous system.

Competency 2: Organ System Pathology; Topic HWC: Hematopathology: white cell disorders; Learning Goal 4: Clinical Features of Hematolymphoid Neoplasms.

## Patient Presentation

A 72-year-old female presents to the ophthalmologist with a history of elevated intraocular pressure for a follow-up visit after ophthalmic surgery aiming to decrease the intraocular pressure. She has a past medical history of hypertension and family history of glaucoma. She had been followed by her ophthalmologist for chronic increased intraocular pressure of the left eye, which her ophthalmologist felt was likely due to glaucoma, a condition where the drainage of aqueous humor from the eye is blocked, leading to increased pressure within the eye and optic nerve damage and causing vision loss. She recently underwent a selective laser trabeculoplasty, a surgery where laser energy is directed at the cells of the trabecular

meshwork, the structure which drains the aqueous humor, resulting in a gradual increased outflow of the aqueous humor through the trabecular meshwork over a period of a few months. This particular visit was a postoperative follow-up for an intraocular pressure check a few months after her selective laser trabeculoplasty.

## Diagnostic Findings, Part I

The intraocular pressure in her left eye remained elevated, while that of her right eye was within normal range. On physical examination, she was noted to have diplopia, proptosis, limitation of elevation/abduction of her eye, and no pain with orbital movement.

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**Figure 1.** Computed tomography of the sinus/orbit showing ill-defined mass in left retrobulbar and superonasal soft tissue (red arrow).

**Table 1.** Complete Blood Count With Differential.

White blood cell	$5.8 \times 10^9/L$ (3.8-10.6)
Hgb	15.3 g/dL (11.6-14.6)
Platelets	$249 \times 10^9$ (156-369)
Percent neutrophils	65.3% (44%-47%)
Absolute neutrophil count	18.9 (13-44)
Percent lymphocytes	18.9% (13%-44%)
Absolute lymphocyte count	1.1 (0.8-3.65)

## Questions/Discussion Points, Part 1

### What Do the Findings in the Physical Examination Indicate?

The findings of proptosis and diplopia indicate that something is pushing her eye forward, either increased fluid, inflammation, or a tumor within or behind the eyeball. The fact that she is unable to elevate or abduct her eye reveals that the unidentified process is also affecting her extraocular muscles. Pain with ocular movement is an infrequent symptom which is indicative of optic neuritis, or inflammation of the optic nerve, as can be seen with multiple sclerosis or neuromyelitis optica. When taken together, these findings were concerning for a mass within or behind the globe.

## Diagnostic Findings, Part 2

The ophthalmologist decided to obtain a computed tomography (CT) scan of the sinuses and orbits to investigate the possibility for a mass (see Figure 1). A complete blood count (CBC) with differential was also ordered to help rule out an infectious process causing eye swelling. The result of the CBC is shown in Table 1.

## Questions/Discussion Points, Part 2

### What Does the Computed Tomography Scan and Complete Blood Count Show? What Is the Next Step for This Patient?

A CT scan of the sinuses and orbits was performed which showed an ill-defined mass within the left retrobulbar, superonasal soft tissue and involving the left lacrimal gland (see Figure 1). The mass surrounded the left lateral rectus muscle and likely involved the superior oblique muscle. The mass did not deform the globe and did not appear to be calcified. The imaged paranasal sinuses were not involved. The visualized calvarium was intact. The CBC performed was within normal limits.

A biopsy of the left lacrimal gland was performed to diagnose the mass. The lacrimal gland was chosen as the biopsy site, as the lacrimal gland is a relatively superficial structure and the orbital mass was involving the gland on the CT scan.

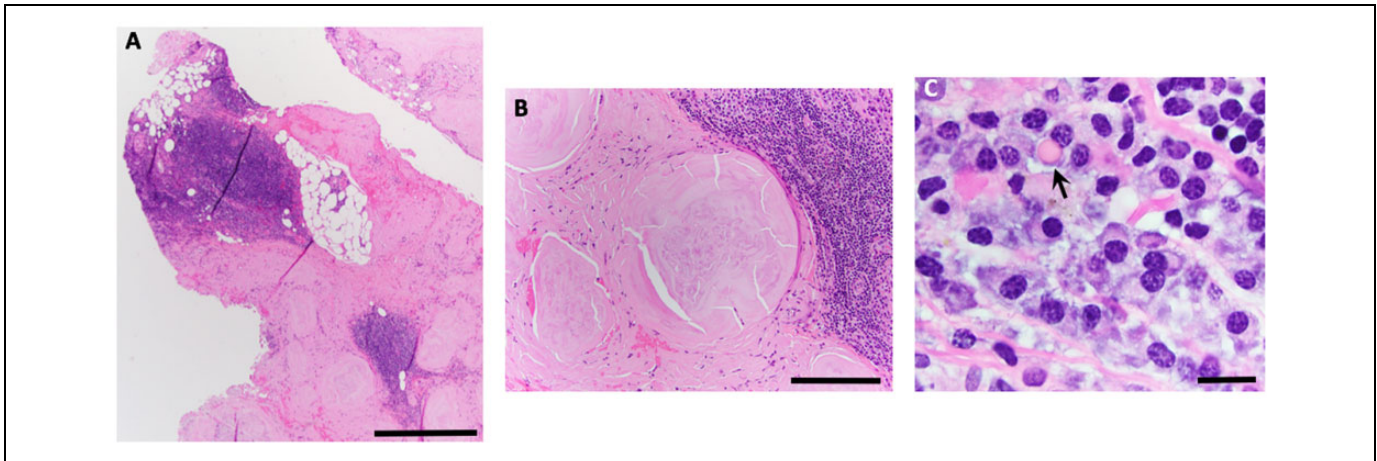
### What Is the Differential Diagnosis for an Orbital Mass in an Adult?

In adults, the differential diagnosis for an orbital mass includes infections, inflammatory conditions, and benign and malignant tumors. Infections are classified by their location: either orbital or preseptal, which involves the soft tissues anterior to the globe itself. Orbital or preseptal cellulitides can be caused by bacteria, such as *Staphylococcus aureus*, streptococci, anaerobes, or less commonly mycobacterial or fungal infections.<sup>2</sup>

Inflammatory conditions to examine include sarcoidosis, Sjögren syndrome, and vasculitides. Sarcoidosis can affect the globe itself or the periorbital tissues, including the lacrimal glands and extraocular muscles, and can even present as a soft tissue orbital mass.<sup>3</sup> Common findings on imaging include orbital masses and lacrimal gland involvement.<sup>3</sup> Patients with Sjögren syndrome typically present with a foreign body sensation in the eye or eye dryness and will rarely present with a mass lesion of the lacrimal gland, usually when a secondary lymphoma has developed. Patients with antineutrophil cytoplasmic autoantibody-associated vasculitides, such as granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, can also present with an orbital or periorbital pseudotumor.<sup>4</sup> Rarely, cryoglobulinemia-associated vasculitis can affect the orbit, but it rarely presents as a mass.

Tumors to consider are diverse and include both benign and malignant neoplasms. Due to the rapid cellular turnover in tumors, mass effect or cystic rupture can be seen in both benign and malignant tumors, which can lead to vision loss. Benign entities that should be considered include dermoid cysts, lymphangiomas, cavernous hemangiomas, and meningiomas.

There are several categories of malignant tumors to consider: lymphomas, melanomas, metastatic carcinomas, and primary central nervous system (CNS) tumors. Ocular lymphoma is not common and can be associated with immunodeficiency



**Figure 2.** H&E-stained sections of (A) lymphoplasmacytic aggregates with adjacent (B) acellular, amorphous eosinophilic material. C, A high-power image shows scattered plasma cells with the classic features of “clock-face” chromatin distribution and a perinuclear Hof. A plasma cell with a Russell body; an intracytoplasmic collection of immunoglobulin is identified (arrow). Scale bars measure 1 mm (A), 0.3 mm (B), and 25  $\mu\text{m}$  (C), respectively.

but can occur sporadically in the immunocompetent.<sup>5</sup> Primary ocular melanomas are also rare. Half of patients who have successful local treatments of primary uveal melanomas are at risk for metastases.<sup>6</sup> There are several important metastatic malignancies to consider, including lung and breast cancers.<sup>7</sup> Primary CNS tumors, such as medulloepitheliomas, can arise in the eye and behave in a relatively benign manner.

### Diagnostic Findings, Part 3

A lacrimal gland biopsy was performed and representative sections are seen in Figure 2.

### Questions/Discussion Points, Part 3

A lacrimal gland biopsy was performed, which showed mild chronic dacryoadenitis, but ophthalmology was concerned that the mass was not adequately sampled and proceeded with a more invasive, retrobulbar biopsy. This biopsy was received by the pathology department. The biopsy specimen consisted of multiple fragments of tan-pink soft tissue measuring 1.0 cm  $\times$  0.5 cm  $\times$  0.3 cm in aggregate.

Microscopic examination of the left orbital mass revealed extensive deposition of amorphous eosinophilic material which stained with Congo red and showed apple green birefringence upon polarization (see Figures 2 and 3). There were also scattered lymphocyte aggregates with an occasional follicle with associated germinal center, as well as admixed plasma cells surrounding the amorphous material. The lymphocytes were mostly small in size with rounded nuclei with occasional larger lymphoid cells within scattered follicles. The plasma cells demonstrated an eccentric nucleus and a perinuclear clearing, or Hof. As seen in Figure 4, the plasma cells stained positive for CD20, CD138, and CD19 and negative for cyclin D1 and CD56, whereas the background lymphocytes stained positive

for CD20 and CD19. Additionally, the plasma cells showed kappa light chain restriction.

### What Is the Most Likely Diagnosis Considering the Clinical and Pathologic Findings?

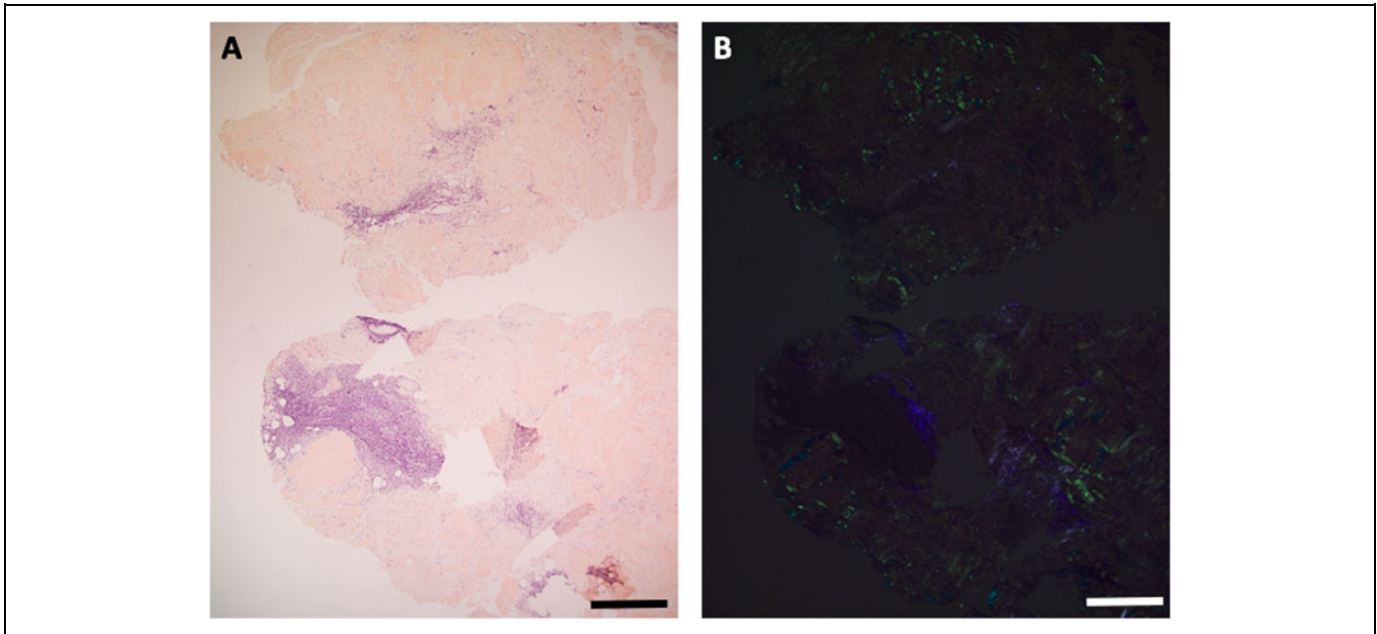
Both the clinical and histologic findings are most consistent with an extranodal ocular B-cell lymphoma with plasmacytic differentiation and associated amyloid deposition. The pertinent clinical features include an ill-defined ocular mass in an older adult, whereas the applicable histologic findings include a kappa light chain-restricted B-cell population expressing markers of plasmacytic differentiation surrounded by amorphous eosinophilic material.

### Where Are the Clinical Features, Locations, and Causes of Primary Extranodal Lymphomas?

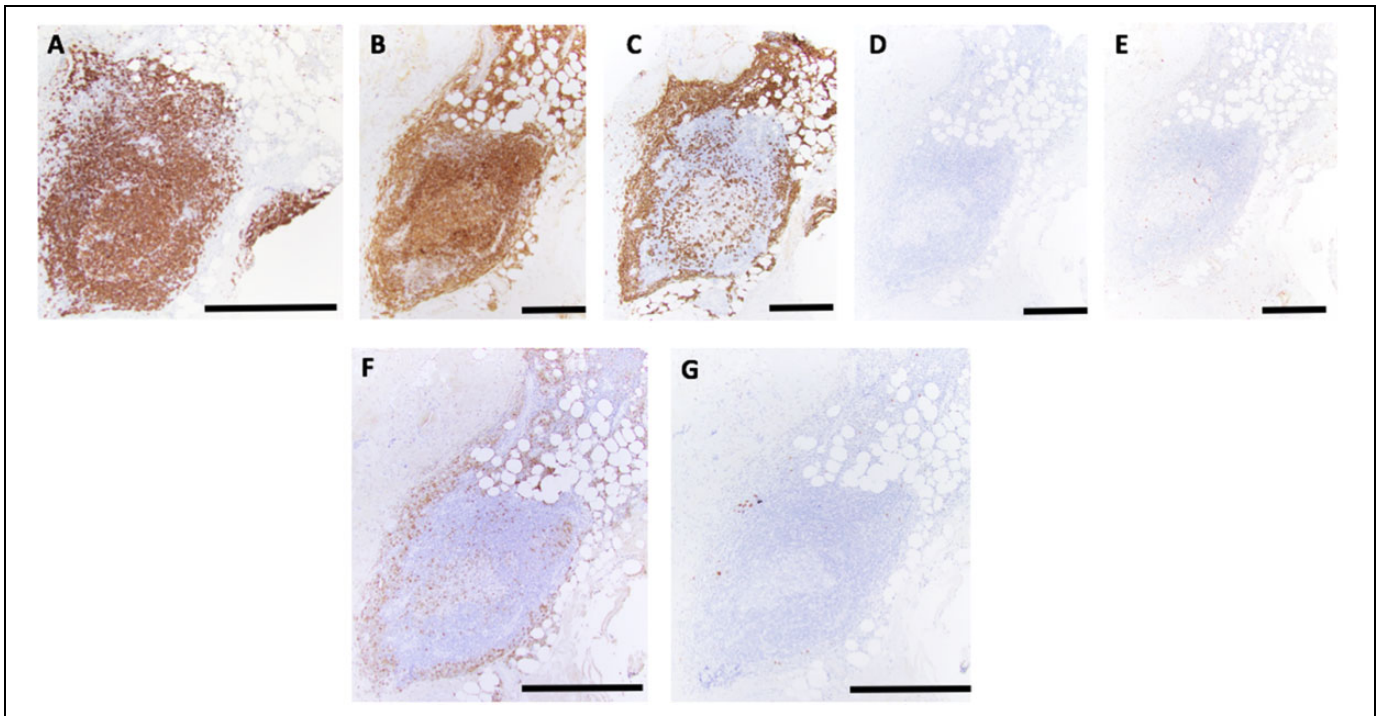
Extranodal lymphomas are also known as extranodal marginal zone lymphomas or extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas). These account for approximately 7% to 8% of B-cell lymphomas, with the highest incidence being in the seventh decade of life. Overall, they affect men and women equally, but salivary gland and thyroid lymphomas are more common in women.<sup>8</sup> Most frequently, primary extranodal lymphomas arise in the gastrointestinal tract.<sup>9-11</sup> Other sites include skin, testis, bone, and kidney.<sup>9-11</sup> Rare sites include the heart, bladder, prostate, ovary, breast, adrenal glands, thyroid, salivary glands, and the orbit.<sup>9-12</sup>

Chronic inflammation, from infection or autoimmunity, plays a role in the development of primary extranodal lymphomas. Over time, chronic inflammation and antigenic stimulation can lead to autonomous activation of B cells, leading to a proliferation of a clonal B-cell population, which can then acquire genetic alterations and develop into a lymphoma.<sup>12</sup>





**Figure 3.** Congo Red stained section (A) shows acellular material is congophilic and is (B) apple green birefringent upon polarization. Scale bars measure 1 mm.



**Figure 4.** Staining pattern of the lymphoid aggregate and plasma cells around the periphery: (A) CD20 stain highlights the B cells within the lymphoid follicle/aggregate, plasma cells at the periphery are negative; (B) CD19 is positive in both B cells and plasma cell areas; (C) CD138 highlights the plasma cells at the periphery; (D, E) lymphoid cells and plasma cells are negative for CD56 and cyclin D1. The plasma cells show (F) kappa light chain-restriction with (G) rare cells expressing the lambda light chain. Scale bars measure 0.5 mm.

Many lymphomas have been linked to specific etiologic agents, with the classic example being the association of chronic *Helicobacter pylori* infection with gastric MALT lymphoma. Sjögren syndrome and Hashimoto thyroiditis, autoimmune diseases

affecting the salivary/lacrimal glands and thyroid gland, respectively, are associated with lymphomas in their respective organs. In fact, patients with Sjögren syndrome have a 13- to 15-fold increased lifetime risk of lymphoma compared with the

overall population. Patients with Hashimoto thyroiditis carry a 70-fold lifetime risk of thyroid lymphoma.<sup>8</sup>

Overall, primary extranodal lymphomas tend to be slow growing and follow an indolent course. Reoccurrence of disease in these patients may occur after many years and at other extranodal sites. Transformation to a high-grade, aggressive lymphoma, such as diffuse large B-cell lymphoma, occurs in less than 10% of cases.<sup>8</sup>

### What Are the Clinical Features of Extranodal Orbital Lymphomas?

These lymphomas are typically seen in women between 50 and 70 years of age,<sup>12</sup> as is the case with our patient. Approximately 40% are located within the orbit, with 35% to 40% occurring in the conjunctiva, 10% to 15% involving the lacrimal gland, and approximately 10% located on the eyelid.<sup>12</sup> Conjunctival lymphomas may be initially responsive to topical steroids, which may lead to a misdiagnosis of chronic conjunctivitis.<sup>12</sup> Bilateral involvement of lymphoma is seen in 10% to 15% of affected patients.<sup>12</sup> Most patients (90%) present with localized disease, as our patient did, but up to 5% may have lymph node metastases. Around 10% to 15% present with advanced disease, such as bone marrow involvement.<sup>12</sup>

Physical examination findings vary with the site of involvement. Orbital lymphomas present as firm, rubbery masses that often lead to an insidious proptosis and may be accompanied by diplopia, decreased visual acuity, or periorbital edema. On physical examination, conjunctival involvement usually appears as a “salmon-pink patch,” a mobile mass involving the substantia propria and leading to conjunctival irritation. Lacrimal gland lesions result in inferionasal orbital displacement. Eyelid lymphomas may cause proptosis and usually involve the dermis or orbicularis muscle.<sup>12</sup>

There are conflicting data as to whether clinical staging or site of origin has prognostic impact.<sup>12,13</sup> It appears that plasmacytic differentiation of the neoplastic B cells does not appear to have a clinical prognostic significance.<sup>13</sup> Although there are currently no clinically validated prognostic markers, p53, BCL-6, and BCL-10 have been identified as potential indicators of negative outcome.<sup>12-16</sup>

### What Are the Causes of Extranodal Orbital Lymphomas?

The orbit and orbital adnexae do not contain lymphoid tissue under normal conditions, but lymphoid aggregates can appear under conditions of repeated stimulation of B cells by antigens, either through infections or autoimmune disorders, such as Sjögren syndrome.<sup>12,17</sup> As mentioned previously, the chronic stimulation of B cells can result in autonomous activation, leading to a proliferation of a clonal B-cell population, which can then acquire genetic alterations and develop into a lymphoma.<sup>12</sup>

A single etiologic agent for orbital lymphomas has not been identified. Debated possibilities include thyroid orbitopathy associated with autoimmune thyrotoxicosis,<sup>18</sup> chronic

conjunctivitis associated with household animal exposure,<sup>19</sup> and exposure to *H pylori* or *Chlamydia Pneumoniae*.<sup>20</sup>

### Describe the Molecular Features of Extranodal Orbital Lymphomas

The classic immunophenotype of the neoplastic cells in these lymphomas is CD20<sup>+</sup>, CD10<sup>-</sup>, CD23<sup>-</sup>, and BCL-6<sup>-</sup>. The cells are monoclonal with restriction for either the lambda or kappa light chains. There are typically interspersed CD3<sup>+</sup> T cells. Several characteristic translocations have been identified, involving the genes *API*, *MALT1*, *IGH*, *FOXP1*, and *BCL-10*. The most common translocation, seen in 15% to 40% of patients, is t(11;18)(q21;q21), which creates the API2-MALT1 fusion protein.<sup>12</sup> This translocation results in constitutive expression of the *MALT1* gene, a protein which is involved in the NF-kappaB signaling pathway that results in lymphocyte activation. This in turn promotes tumorigenesis and cell survival.<sup>12</sup>

### Diagnostic Findings, Part 4

Characterization of the amyloid performed at an outside institution indicated AL kappa type amyloid serum immunological studies, including immunoglobulin A (IgA), IgG, IgM, kappa and lambda light chains, and kappa:lambda ratio, were performed and were within normal limits. The patient also had serum and urine electrophoresis performed which did not detect a serum or urine monoclonal protein.

### Questions/Discussion Points, Part 4

#### What Is the Significance of the Amyloidosis?

Amyloidosis is the disease caused by accumulation of abnormal extracellular aggregates of low-molecular-weight proteins in beta-pleated sheets or amyloid fibrils which cause damage of affected organs.<sup>21-23</sup> Light chain amyloidosis (AL) is the most common type of amyloidosis affecting approximately 10 patients per million per year and is often the most lethal, as it can affect the heart, causing a restrictive cardiomyopathy.<sup>21-26</sup> The AL amyloidosis is caused by deposition of the immunoglobulin light chain by neoplastic plasma cells.<sup>21-26</sup> Serum amyloid A, an acute phase reactant, is implicated in amyloid A amyloidosis (AA), which is associated with chronic inflammatory diseases.<sup>21-23,27,28</sup> Other types of amyloidosis include hereditary, dialysis-related, systemic old age, and organ-specific amyloidosis.<sup>21-23,29-32</sup>

The patient's amyloid protein was classified as amyloid light chain, kappa type. The periocular soft tissue mass may represent localized AL amyloidosis, or it is possible that it is the first manifestation of systemic AL amyloidosis, which can be primary or secondary to plasma cell myeloma or rarely Waldenstrom macroglobulinemia or non-Hodgkin lymphoma.<sup>21-26</sup> The patient's serum and urine protein electrophoreses were unremarkable, along with the patient's serum immunoglobulin and light chains; absence of serum or urine



**Figure 5.** Posttreatment computed tomography showing stable to minimally decreased mass size (blue arrow).

monoclonal proteins occurs in less than 5% of patients with AL amyloidosis.<sup>21</sup> The clinical manifestations of AL amyloid are varied and depend on which organ is affected. There is commonly renal, cardiac, gastrointestinal, and neurological involvement.<sup>21-26</sup>

Diagnosis of amyloidosis usually occurs at biopsy, but imaging can sometimes be suspicious of amyloid deposition.<sup>21</sup> For patients with systemic involvement, fat pad biopsy is the recommended site with a sensitivity of 57% to 85% and a specificity of 92% to 100% for AL.<sup>21,33-37</sup> Amyloid deposits that are stained with Congo Red show characteristic apple green birefringence under polarized light.<sup>21-26</sup> Immunohistochemistry can be useful in characterizing amyloid type, particularly for amyloid A and transthyretin amyloid, but has less utility with AL amyloid, as the antigenic epitopes may be lost due to proteolysis during deposition and fibril formation.<sup>21,35</sup> Additional methods for characterizing amyloid type include mass spectroscopy and amino acid sequencing, which can be performed on formalin-fixed paraffin-embedded tissue via laser capture microdissection.<sup>21,33,34</sup>

Treatment of AL amyloidosis usually involves treating the underlying plasma cell neoplasm.<sup>21-26</sup> Options for treatment include chemotherapeutics, autologous stem cell transplantation, and radiotherapy for local involvement, among others.<sup>21-26,38</sup>

### Patient Follow-Up

The patient received radiation treatment, with a total dose of 24 Gy in 12 fractions using a 3D conformal treatment to cover the entire orbital region. At her follow-up after radiotherapy, she noted improved visual acuity, particularly in the left lateral visual field. Repeat CT sinus/orbit showed stable to minimal decrease in size of soft tissue mass (see Figure 5). The patient also began 4 courses of systemic chemotherapy with rituximab. Treatment with rituximab, a monoclonal antibody against CD20, particularly in combination with other agents such as idelalisib, has shown efficacy in systemic AL.<sup>39</sup> An

echocardiogram was performed, which showed no evidence of restrictive cardiomyopathy.

### Teaching Points

- The differential diagnosis for an orbital mass in an older adult includes infections, inflammatory conditions, and benign and malignant tumors.
- Extranodal marginal zone lymphomas tend to follow an indolent course, are caused by chronic inflammatory states, and occur most commonly in the gastrointestinal tract. Extranodal orbital lymphomas are rare.
- Ocular adnexal lymphomas typically occur in women between their fifth and seventh decades, are typically localized at presentation, and most commonly originate in the orbit or conjunctiva.
- It is postulated that orbital adnexal lymphomas develop from autonomously activated B cells that are chronically stimulated by infections or autoimmune disease.
- Amyloidosis is caused by accumulation of abnormal extracellular aggregates of low-molecular-weight proteins in tissues, with the most common types of amyloidosis being light chain (AL) and amyloid A (AA).
- The clinical manifestations of AL amyloid are varied, but there is commonly renal, cardiac, gastrointestinal, and neurological involvement.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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