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Diagnosis of Intravascular Lymphoma by a Novel Biopsy Site

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Abstract

Purpose—To report the first known case of intravascular lymphoma (IVL), a rare disease, diagnosed via lacrimal gland biopsy.

Design—Interventional case report.

Participants—Single patient case report.

Intervention—Bedside lacrimal gland biopsy.

Main Outcome Measures—Clinicopathologic diagnosis of IVL, a neoplasm with only a few prior reports of ophthalmic manifestations, via a novel biopsy site.

Results—A 70-year-old Chinese man with 6 months of progressive paraplegia complained of blurred vision in both eyes. He had unremarkable cerebrospinal fluid studies and magnetic resonance imaging that showed abnormal thoracic cord signal and periventricular brain white matter changes with a normal pituitary gland and stalk. Dilated fundus examination showed multifocal areas of intra- and subretinal hemorrhage with serous retinal detachment. The workup included serologies and 2 normal bone marrow biopsies but did not reveal the underlying etiology. Because of the continued high suspicion for a malignant process, we performed bedside transconjunctival biopsy of the lacrimal gland. This demonstrated large, atypical CD20-positive B cells confined to the vessel lumina, consistent with IVL, an unusual form of large B-cell lymphoma.

Conclusions—This case represents the first time that IVL has been detected via lacrimal gland biopsy, which may be a useful way to investigate cryptogenic neurologic processes. Furthermore, it is one of the only reported cases of ophthalmic IVL diagnosed before autopsy. IVL is a rare disease but has protean manifestations involving the central nervous system, skin, bone marrow, liver, and spleen. The eye should also be considered an end organ for involvement.

Intravascular lymphoma (IVL) is an uncommon, extranodal, diffuse, large B-cell lymphoma defined by intravascular proliferation of clonal lymphocytes with little to no involvement of

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organ parenchyma.^{1,2} These malignant lymphocytes characteristically are present only in small vessel lumina, especially capillaries.

The disease is usually widely disseminated at the time of diagnosis and follows an aggressive course. Intravascular lymphoma is divided into Western and Asian variants. Patients with the former tend to show more central nervous system and skin involvement, whereas those with the latter typically display hemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia.³ Typical laboratory findings include elevated serum lactate dehydrogenase levels, anemia, and, in the Asian variant, thrombocytopenia and hypoalbuminemia. Treatment consists of chemotherapy with anthracycline-based drugs and rituximab.¹

Although there have been reports of intraocular IVL, the eye is not considered one of the sites of disease in the hematologic literature.⁴ We report a new case of IVL diagnosed because of lacrimal gland biopsy, a previously unreported approach that provided the tissue diagnosis and could be done at the bedside using only topical anesthesia.

Methods

After written informed consent was obtained, the eyelid and ocular surface were prepped with 5% povidone iodine, and the eye was anesthetized with topical proparacaine and lidocaine 2% gel. With an assistant retracting the upper lid, the surgeon grasped the prolapsed conjunctiva and lacrimal gland with toothed forceps and obtained a 2×2-mm portion of conjunctiva and lacrimal gland.

The literature search for novelty of lacrimal gland biopsy was performed using PubMed, with the search terms “intravascular lymphoma” and “lacrimal.” It was expanded to include other terms for IVL, “neoplastic angioendotheliomatosis,” “angiotropic lymphoma,” and “intravascular lymphomatosis.” To ensure completeness, the terms “lacrimal gland” and “lacrimal gland biopsy” were also used as search terms. Furthermore, articles on ocular involvement by IVL were identified by searching for “intravascular lymphoma” and “eye,” “ophthalmic,” “ophthalmologic,” and “ocular” on PubMed. The resulting articles and their references were reviewed for any mention of lacrimal involvement or lacrimal biopsy.

Case Report

A 70-year-old Chinese man with a past medical history only of former tobacco use who was a missionary in South Africa for the previous 8 years complained of constipation then urinary retention 6 months before ophthalmologic consultation. He then noted leg weakness, numbness, and difficulty walking. He became paraplegic and was admitted to a hospital in South Africa. Magnetic resonance imaging (MRI) showed cervical and lumbar canal stenosis with abnormal cord signal in the thoracic spine at T7–8. Head MRI showed periventricular white matter changes with an unremarkable appearance to the lacrimal glands. He was given intravenous methylprednisolone then underwent lumbar decompression, with partial recovery of ambulation. Subsequent MRI still showed abnormal thoracic cord signal.

Two months before consultation, his legs became flaccid again, with no improvement with intravenous steroids. The patient had a bone marrow biopsy that was normocellular with negative flow cytometry. His family brought him to the United States, and he noted a “band sensation” progressively moving up his chest. A neurologist noted a sensory level at T8 on the right and T5 on the left with flaccid paraplegia of both legs and had the patient admitted to the hospital.

On admission, he was afebrile with a blood pressure of 90/60, pulse 71, respiratory rate of 18, and 95% oxygen saturation on room air. His lower extremity strength, reflexes, and sensation were absent.

His laboratory workup showed a white blood cell count of 3850, normocytic anemia with a hematocrit of 25%, and platelet count of 77 000. Peripheral blood smear was unremarkable, as was serum protein electrophoresis. The patient had a decreased sodium of 130 mEq/L thought to be from syndrome of inappropriate antidiuretic hormone hypersecretion. Total protein and albumin were low at 4.9 g/dL and 2.3 g/dL, respectively.

His endocrine workup was consistent with panhypopituitarism, but pituitary MRI did not show any mass or infiltration. Tests were negative for human immunodeficiency virus, human T-lymphotropic virus, Lyme, malaria, hepatitis B and C, *Brucella*, and schistosomes. Culture from his indwelling urinary catheter showed infection with multidrug-resistant *Pseudomonas aeruginosa*.

Cerebrospinal fluid showed only 1 white blood cell with normal flow cytometry and negative oligoclonal bands. Glucose was low at 19, and protein elevated at 113 mg/dL. Gram stain, polymerase chain reaction (for enterovirus, varicella zoster virus, cytomegalovirus, and herpes simplex virus), *Cryptococcus*, and fungal cultures were all negative. Serum antinuclear cytoplasmic antibody, anti-DNA antibody, and antibodies for SS-A/Ro, SS-B/La, Smith, and ribonucleic protein were negative. C3 and C4 were normal.

Chest computed tomography (CT) showed no bulky adenopathy and scattered subcentimeter calcified nodules. Brain MRI showed age-consistent atrophy and deep white matter ischemic changes (Fig 1), and spinal MRI showed abnormal cord signal in the midthoracic spine and conus medullaris (Fig 1, arrows).

The primary team suspected neurosarcoid and consulted ophthalmology to rule out ophthalmic manifestations. Near visual acuity was difficult to measure because of poor cooperation but was approximately 20/200 in the right eye and 20/400 in the left. There was no relative afferent pupillary defect. Motility was normal, and intraocular pressure was 21 on the right and 22 on the left. The anterior structures showed pale conjunctivae and nontender, prolapsable, and normal-sized lacrimal glands. The corneas were clear, and there was a mild cataract in the right eye. The left eye was pseudophakic.

Dilated fundus examination showed bilateral, multifocal sub-retinal and intraretinal hemorrhages with exudative retinal detachment (Fig 2). The presence of multifocal choroidal lesions in this age group was worrisome for lymphoma. Another possibility was

metastatic disease or syphilis, which the primary team had not considered. Tuberculosis could also have this type of appearance, with sarcoidosis being possible but unlikely.

Repeat bone marrow biopsy was unremarkable. Rapid plasma reagin was nonreactive, and fluorescent treponemal antibody-ABS was not sent as requested.⁵ Lumbar puncture was essentially unchanged, with negative mycobacterial and Venereal Disease Research Laboratory tests. Positron emission tomography was unremarkable, and CT was unchanged. Repeat MRI demonstrated possible new increased T2 signal at C6–7 and increased T2 hyperintensity of the thoracic cord.

At this point, the primary team asked ophthalmology to consider choroidal biopsy. Because of the high risk of this procedure, we first recommended bedside biopsy of the lacrimal gland to allow evaluation for both granulomatous and infiltrative processes such as lymphoma. We chose the right gland because of convenience and patient positioning. There was minimal bleeding, and the patient needed only postprocedure ointment and overnight patching.

Histopathologic evaluation showed a small portion of unremarkable lacrimal gland (not seen on the slide in Fig 3) with adjacent fibrovascular tissue containing small vessels (Fig 3, left). These vessels were focally distended by large, atypical, CD20-positive B cells with prominent nucleoli (Fig 3, center). Occasional mitotic figures and scattered apoptotic bodies were present among the atypical cells. Ki-67 immunostain revealed a high proliferation index (Fig 3, right). CD3 immunostain showed scattered T cells in the vessel lumina, but these were not enlarged or atypical in appearance. There was no infiltration of surrounding parenchyma by lymphoid cells, which were entirely contained within the vessels. These findings were consistent with a diagnosis of IVL.

The patient was referred to oncology, which initiated chemotherapy with rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine. Recent reports suggest that 3-year survival with chemotherapy including rituximab may be 60%, compared with just >30% with anthracycline-based chemotherapy without rituximab.^{1,6} Of note, the patient's lactate dehydrogenase then was elevated at 689 U/L, and C-reactive protein was 7.3 mg/dL. After 3 full cycles of chemotherapy, the patient did not have any improvement in his vision or his neurologic symptoms, and he and his family elected to move to a rehabilitation facility closer to home.

Discussion

This case represents the first time that IVL has been diagnosed via lacrimal gland biopsy. In previous reports, IVL has been detected through biopsy of the prostate, testicle, adrenals, brain, liver, gallbladder, and kidney.^{7–11} The Western variant is often diagnosed by skin biopsy and the Asian variant by bone marrow biopsy.^{12,13} Some advocate random skin biopsy if IVL is on the differential.¹⁴

Biopsy of the lacrimal gland offers a relatively uncomplicated way to obtain tissue in the evaluation of patients with cryptogenic neurologic processes where examination of other tissue such as cerebrospinal fluid or bone marrow biopsy have not yielded a satisfactory

explanation for the patient's presentation. The lacrimal gland is a highly vascular organ, and so assessment of the patient's hematologic and coagulative status before biopsy is important. In this case, there was minimal bleeding, with a taped overnight eye pad being the only dressing needed.

Infiltrative disease such as lymphoma and granulomatous disease such as sarcoidosis are both often in the differential diagnosis, and the lacrimal gland allows examination for both. In this case, the blood vessels within the specimen allowed diagnosis of IVL, an unusual condition.

Other than chest CT, the primary team did not choose to send other modalities for testing for sarcoidosis, such as serum angiotensin converting enzyme, lysozyme, or gallium scan, and it would be reasonable to exhaust those noninvasive techniques before considering lacrimal biopsy.

Using only topical anesthesia, we were able to perform the procedure in the patient's room with minimal discomfort. The greatest postprocedure concern is dry eye. The Schirmer test, which quantifies tear production, was not done before the procedure. Afterward, it did show less tear production in the biopsied eye (8 vs 17 mm at 5 minutes with anesthesia), but the patient denied any symptoms of dry eye, and it is hard to interpret this result without knowing the baseline.

The first cases of IVL in the ophthalmology literature described 3 patients diagnosed with IVL postmortem demonstrating (1) vitreous inflammation, (2) retinal artery occlusion, and (3) retinal pigment epithelium changes, vascular alterations, and macular edema with hemorrhages.¹⁵ In one reported case, a patient's bilateral choroidal abnormalities triggered a systemic workup, including chest CT, which led to diagnostic lung biopsy.⁴ Rare additional case reports have documented eye involvement, but the final diagnosis was made at autopsy or after treatment for other suspected disease.^{16–18}

Our patient's fundus findings were highly suspicious for lymphoma given his age and the bilateral choroidal involvement. However, there was nothing to indicate on examination that this patient had IVL instead of more common lymphoma subtypes. Continued suspicion of a malignant process was the key to a correct diagnosis here.

Intravascular lymphoma produces multiple neurologic manifestations, and this patient's paraparesis is consistent with a previously published case of spinal cord biopsyproven IVL.^{19,20} The conus medullaris is another known location of IVL involvement, and there are reports of panhypopituitarism.^{21,22}

Intravascular lymphoma is a rare diagnosis, but the eye should be considered an involved organ. When a patient with a presentation highly suspicious for lymphoma has an otherwise negative workup, the possibility of IVL should be entertained. Along with skin and bone marrow biopsy, lacrimal biopsy may be of value in the workup of a patient where both infiltrative neoplastic and granulomatous disease such as sarcoidosis are suspected.

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Figure 1.

Magnetic resonance imaging (MRI) from initial presentation to hospital, 1 week before ophthalmologic consultation. Brain MRI (top left) showed nonspecific periventricular lesions, and the cervical cord (bottom left) showed degenerative changes. The thoracic cord (center) showed a few areas of signal abnormality (arrows). The lumbar cord (right) showed enhancement of the conus medullaris (arrow).

Figure 2.

Fundus photographs taken at patient's bedside. The right eye (left) demonstrates multifocal hemorrhages and nerve fiber layer swelling with subretinal fluid (arrow) as well. The older, dehemoglobinized hemorrhage is yellow, with newer, surrounding hemorrhage also present. The left eye (right) demonstrates more nerve fiber layer swelling and hemorrhage that includes the macula. It also has an area of elevation along the inferotemporal arcade (arrow).

Figure 3.

Pathology from the lacrimal gland shows diffuse involvement of blood vessels by enlarged, atypical lymphocytes, all of which were contained within the blood vessels (left). CD20 staining (middle) confirms B-cell phenotype. Ki67 stain (right) indicates active proliferation of the intravascular abnormal lymphocytes.