DR. ELIZABETH A. BRADLEY: I'm Dr. Elizabeth Bradley with the Mayo Clinic Department of Ophthalmology, and today we'll be talking about IgG4-related diseases of the orbit. We'll start with the case, that of a 56-year-old woman who presented with right eye swelling for one year, diplopia for six months, her left eye had been bloodshot for three months, and she had a three-day history of left flank pain.

Her past medical history was significant for chronic sinusitis for 20 years, asthma for five years, non-insulin-dependent diabetes mellitus, and controlled hypothyroidism. Her past surgical history was significant for a right submandibular gland biopsy 9 years previously and an orbital biopsy 10 years previously.

This had been her appearance at that time of the previous right orbital involvement 10 years prior. At that time, she underwent right lacrimal gland biopsy, which revealed dacryoadenitis with a reactive lymphoid hyperplasia, and this responded to intralesional steroid injection until her most recent presentation.

Her clinical exam was significant for a visual acuity of 20/60 on the right and 20/30 on the left. She did not have an Afferent Pupillary Defect. She does have right ptosis, as seen in the slide, as was a right upgaze deficit. She also had 2 millimeters of left proptosis and left conjunctival injection temperley. She had a right cataract, which explained the 20/60 vision, and the remainder of her intraocular examination was normal.

Because of orbital finding, she underwent orbital MRI scanning, which revealed diffusely enlarged lacrimal glands bilaterally and left lateral rectus muscle enlargement. Her 2003 lacrimal gland biopsy was re-evaluated. The H&E stain on the left shows a marked lymphoplasmacytic infiltrate. And on the right is the IgG4 immunostain showing many IgG4 positive plasma cells.

The patient was referred to hematology for IgG4-related disease. Labs were drawn including a serum IgG4 level, which was markedly elevated at 1,790 milligrams per deciliter with the upper range of normal being 120 milligrams per deciliter. The patient then underwent CT scanning of the chest, abdomen, and pelvis.

Her CT scanning of the chest showed left axillary lymphadenopathy. In the

abdomen, there was the fullness of the pancreatic tail and retroperitoneal and iliac lymphadenopathy shown on this slide. Additionally, she had partial urinary obstruction from retroperitoneal soft tissue infiltration, which explained her three-day history of flank pain.

The patient was treated with 40 milligrams of prednisone daily for four weeks as initial therapy, and although she had a good initial response, she flared on 30 milligrams daily, and prednisone also exacerbated her hyperglycemia. She therefore, was changed to treatment with Rituximab, which was started two months after diagnosis. Her initial treatment was 800 milligrams weekly for four weeks, followed by a maintenance dose every two months.

This slide illustrates her treatment response, and we can see that the soft tissue swelling has markedly improved as has the conjunctival injection and the left proptosis. Perhaps more impressive is her radiographic response with complete resolution of the soft tissue swelling superiorly and normalization of the left lateral rectus muscle.

So what is IgG4-related disease? It is a fibroinflammatory disease that was first described in 2003 in this description of cases of autoimmune pancreatitis related to IgG4. And the disease has a characteristic histopathology across many organ systems.

The slide describes the epidemiology and general clinical features of IgG4-related disease. It is a disease of middle age with male predominance. Patients present subacutely with few constitutional symptoms. Patients typically have a history of allergy or atopic disease, and lesions can be either tumefactive or fibrotic.

Many diseases fall under the umbrella of IgG4-related disease. From an orbital standpoint, we're familiar with Mikulicz's syndrome, eosinophilic anglocentric fibrosis, an inflammatory suda tumor. Other common systemic conditions include autoimmune pancreatitis and retroperitoneal fibrosis.

What do we know about the IgG4 molecule? It's the least common immune globulin. And unlike the other immune globulins, it does not bind complement, it does not form immune complexes, and overall appears to have anti-inflammatory properties.

For these and other reasons, its role in IgG4-related disease appears to be secondary, not primary or causal. Serum levels do not correlate with disease severity, and in fact, 1/3 of patients may have normal IgG4 levels. Within the individual patient, however, serum levels can be followed for treatment response.

Because of the difficulty making the diagnosis based on serum IgG4 levels, the primary diagnosis is made based on histopathology. Changes can include a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis, although the latter is rarely seen in orbital disease.

Secondary diagnostic criteria are tissue and serum IgG4 levels and IgG4 to IgG levels. This slide shows typical histopathology from orbital specimens. On the left is the dense lymphoplasmcytic infiltrate seen in our patient's lacrimal gland biopsy. On the right is an example of storiform fibrosis.

This slide shows tissue stained with the IgG4 immunostain. The left panel shows an IgG4 to IgG plasma cell ratio greater than 40%. The right panel shows more than 50 IgG4 positive plasma cells per high-power field.

A range of ocular findings can be seen in IgG4-related disease. Our patient exemplified the eyelid and periocular fullness that is seen in the vast majority of patients. She also had strabismus and proptosis, which are seen in about 1/3 of patients. About 10% of patients will have optic neuropathy or scleritis. Patients can also have xanthelasma-like deposits in the eyelid skin as well as numbness related to involvement of the infraorbial nerve. And 10% of orbital cases are associated with a malt-type lymphoma.

I'd like to run through a series of clinical images that show this range of ocular findings. The first is that of a 45-year-old male with pancreatitis and eyelid swelling who had undergone previous lacrimal gland debulking. And you can see upper eyelid fullness, particularly on the left and those xanthelasma-like changes of the skin. This patient also had significant swelling of the right parotid gland and the submandibular gland. This image is that of a 57-year-old woman with asthma and chronic sinusitis who presented with eyelid swelling, and she bilateral lacrimal gland involvement as well as the xanthelasma-like change of the skin.

This patient is a 69-year-old gentleman with a 30-year history of autoimmune

pancreatitis and new diplopia who presented with proptosis as well as marked swelling of the infraorbital nerves bilaterally. This patient also had optic neuropathy related to the IgG4-related disease. The top panel shows his visual field before treatment with Rituximab, and the bottom panel shows clearing of the visual field post-Rituximab.

Several treatment options are available for IgG4-related disease. Patients without organ-threatening disease can be observed. Most patients with orbital disease, however, will be treated. Our initial treatment is prednisone, 40 milligrams daily. Patients who become steroid dependent or who have steroid-related side effects are typically treated with Rituximab delivered as 1 gram every one to two weeks for two to four doses with a maintenance dose every two months for two years.

We also have experience with intralesional steroid, specifically Triamcinolone or Kenalog, 40 milligrams per ml delivered in a 1 to 1 and 1/2 cc dose into the lacrimal gland. In all cases, treatment failure can be associated with fibrotic disease.

This slide illustrates intralesional steroid response. The left panel is the patient before treatment, and the right is after Kenalog injection showing significant reduction in the lacrimal gland swelling.

To summarize IgG4-related disease of the orbit, consider IgG4-related disease in patients with the following conditions-- multi-system orbital disease, particularly in the context of pancreatic, biliary, or GU disease or other soft tissue swelling; patients with bilateral orbital disease and a history of allergy or atopic disease; and patients who have radiographic evidence of extraocular muscle, lacrimal gland, and infraorbital nerve involvement.

The ophthalmologic findings are periocular, not intraocular with IgG4-related disease, and the majority of patients will have elevated serum IgG4 levels, but a significant minority will have normal serum IgG4 levels. Tissue is needed to make the diagnosis of IgG4-related disease with specific findings including lymphoplasmacytic infiltrate, storiform fibrosis, and IgG4 positive plasma cells. 10% of lacrimal gland disease is associated with lymphoma, and current treatments for IgG4-related disease include local or systemic steroid and Rituximab.

Once again, I'm Dr. Elizabeth Bradley with the Mayo Clinic Department of Ophthalmology. Thanks very much for listening.