Case 196: Immunoglobulin G4–related Disease¹

A 71-year-old woman presented to the emergency department of our hospital with a headache of several days duration and increasing difficulty elevating her gaze but without ocular pain or changes in visual acuity. The patient did, however, report a history of bilateral orbital masses 10 years prior to the current admission. The patient reported the lesions were nonneoplastic at biopsy and had been successfully treated with steroids. The patient also reported a prior history of kidney problems several years ago that required imaging and prompted interventional treatment. In addition, she reported a remote history of lung resection. On physical examination, the patient had nonfluctuant supraorbital masses and limited upgaze, without exophthalmos or pupillary abnormality. Relevant additional findings included marked thyromegaly and clear but decreased breath sounds in both upper lung zones. The patient did not have respiratory complaints, and she was comfortably breathing room air. Laboratory tests showed normal thyroid function and an antithyroglobulin antibody level of less than 1 IU/mL (normal range, 0–40 IU/mL), a creatinine level of 1.5 mg/dL (132.6 μmol/L) (normal range, 0.4–1.1 mg/dL [35.4–97.2 μmol/L]), an erythrocyte sedimentation rate of 105 mm/hr (normal range, 0–20 mm/hr), and a C-reactive protein level of 37.9 mg/L (361 nmol/L) (normal range, 0–5.0 mg/L [0–47.6 nmol/L]). Various imaging examinations were then performed.

Additional Laboratory Data

Protein electrophoresis showed an elevated immunoglobulin G level of 2673 mg/dL (26.73 g/L) (normal range, 700–1600 mg/dL [7–16 g/L]) and, specifically, an elevated immunoglobulin G4 (IgG4) level of 216 mg/dL (2.16 g/L) (normal range, 4–86 mg/dL [0.04–0.86 g/L]).

History

Unenhanced multidetector computed tomography (CT) of the head (5-mm transverse images with 2-mm coronal and sagittal reconstructions) showed bilateral homogeneous soft-tissue attenuation masses (Fig 1, A) in the superolateral aspects of the orbits in the expected location of the lacrimal glands. The masses involved both orbital and palpebral portions of the glands. The adjacent bony structures were intact. Additional sagittal reconstructions showed the mass effect of these lesions on the superior and lateral recti muscles (Fig 1, B). There was no cerebral abnormality.

Thyroid ultrasonography (US) showed a diffusely heterogeneous and enlarged thyroid gland (Fig 2). Fine-needle aspiration biopsy of several small thyroid lesions was performed a few years before the current admission and revealed benign “mixed micro- and macrofollicular lesions with cystic degeneration on a background of lymphocytic thyroiditis.” Images obtained with retrograde urography (Fig 3) several years before

¹From the Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215 (Y.G., A.A.B.); and Department of Pathology and Laboratory Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass (M.A.S.).
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Figure 1: Unenhanced head CT images. A, Axial image shows bilateral lacrimal gland masses without osseous expansion or erosion (arrows). B, Sagittal image shows substantial mass effect on the superior and lateral recti muscles (arrow).

Figure 2: A, Transverse and, B, sagittal US images of the right thyroid lobe and, C, transverse and, D, sagittal US images of the left thyroid lobe show diffuse enlargement of the gland and heterogeneous echo texture.

Figure 3: Retrograde urography captured on coronal fluoroscopic images shows contrast opacification of the, A, right and, B, left urinary collecting systems with upstream hydronephrosis (open arrows), smooth narrowing of the proximal ureters, and normal-caliber ureters (arrows). These findings were interpreted as consistent with retroperitoneal fibrosis.

the current admission showed smooth long segmental narrowing of bilateral proximal ureters with upstream hydronephrosis, which is highly consistent with a diagnosis of retroperitoneal fibrosis. This finding prompted ureteral stent placement.

Chest radiographs showed multiple large bilateral well-circumscribed and solid pulmonary masses (Fig 4, A) in the subpleural lungs and mediastinal lymphadenopathy (Fig 4, B). There was mild cardiomegaly after coronary artery bypass graft surgery, but no other cardiovascular abnormality was identified.

Subsequent unenhanced multidetector CT of the chest (5- and 1.25-mm axial images with 5-mm coronal and sagittal reconstructions) showed the true extent of the homogeneous masses with extensive pleural surface contact (Fig 5). Within the masses, there was no central necrosis or air bronchogram. However, there were small foci of calcifications within the masses (Fig 6). Mild mediastinal
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Figure 4: A, Frontal and, B, lateral chest radiographs show bilateral multiple solid and circumscribed large pulmonary masses (white arrows) and mediastinal lymphadenopathy (black arrow). There are cardiomedial- tinal clips and sternotomy wires related to prior coronary arterial bypass surgery. There is no lung volume asymmetry and no interstitial or alveolar abnormality within the aerated lungs.

Figure 5: A, Coronal chest CT image. B, C, Sagittal CT images of the left (B) and right (C) lungs. All images show large homogeneous pleural-based pulmonary masses (arrows).

Figure 6: Axial unenhanced chest CT image shows bilateral lung masses with associated calcifications (arrows) and prevascular and precarinal lymphadenopathy.

Biopsy of the lung masses was performed (Fig 7) and yielded cordlike hyalinized collagens admixed with an inflammatory infiltrate that included neutrophils, eosinophils, lymphocytes, macrophages, and plasma cells (Fig 7, A and C). An increased fraction of plasma cells expressed the IgG4 isotype (Fig 7, B and D). No microorganisms were identified with Gram, methenamine silver, or acid-fast staining. There was no evidence of amyloid at Congo red or sulfated Alcian blue staining and no birefringent polarizable material. Thus, these findings were consistent with a diagnosis of pulmonary hyalinizing granuloma, which was formerly considered a form of inflammatory pseudotumor but is currently recognized as a manifestation of so-called systemic IgG4-related autoimmunity.

Discussion

At unenhanced CT, the clinical presentation of difficulty elevating gaze was found to be secondary to bilateral lacrimal gland soft-tissue masses without bony involvement. Common causes of lacrimal gland masses include benign and malignant epithelial neoplasms, lymphoma, pseudotumor, and sarcoidosis (1). Less common causes include entities such as Sjögren disease, thyroid orbitopathy, choroma, posttransplantation lymphoproliferative disease, and sickle cell disease (2–4).

Epithelial tumors (pleomorphic adenomas or adenoid cystic carcinomas) are unilateral mass lesions in the lacrimal gland with associated bony changes. This is incompatible with the 10-year history of bilateral lacrimal gland masses present in this patient. Orbital sarcoidosis is bilateral, infiltrative, and associated with ocular abnormalities, which were absent in this patient who had no clinical or laboratory evidence of sarcoidosis. Orbital involvement in Sjögren disease can affect both lacrimal glands in a particular patient; however, the Sicca syndrome of dry eye and dry mouth was absent in this patient. Chloromas are extramedullary tumors of immature myeloid cells, most commonly associated with acute myeloid leukemia. They usually arise in the orbit and extend to the lacrimal gland, with aggressive bony destruction. However, none of these findings were present in this patient. Posttransplantation lymphoproliferative disease and sickle cell disease involving the lacrimal gland are exceedingly rare, and both diseases were inconsistent with the clinical history of this patient. Finally, lymphoma and pseudotumor can involve both lacrimal glands in an infiltrative pattern without bony destruction; hence, both entities remain considerations. Biopsy of the lacrimal gland masses ultimately revealed nongranulomatous inflammation and enabled us to exclude lymphoma and confirm pseudotumor.
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Figure 7: Representative histologic images of the lung obtained with open surgical resection. A, C, Hematoxylin-eosin–stained slices show dense hyalinized fibrosis with mixed inflammatory infiltrate, including neutrophils, eosinophils, macrophages, lymphocytes, and plasma cells. B, D, IgG4-specific staining shows an increased fraction of plasma cells expressing the IgG4 isotype (brown stain). A and B were obtained with \( \times 100 \) magnification; C and D were obtained with \( \times 400 \) magnification.

Figure 8: Diagnostic criteria for IgG4-related disease (IgG4-RD). To convert serum IgG4 level to SI units (grams per liter), multiply by 0.01.

Concurrent thyromegaly in this patient was a challenging finding. Graves thyroid orbitopathy typically manifests as enlargement of the extraocular muscles and increased intraorbital fat, but it can involve the lacrimal gland (2). Laboratory findings of normal thyroid function tests and negative antithyroglobulin antibodies, however, enabled us to exclude Graves disease in this patient. A prior thyroid biopsy had, indeed, revealed lymphocytic thyroiditis.

Chest radiography, which was initially performed to assess for possible sarcoidosis, revealed bilateral large solid pulmonary masses, which were further characterized on CT images to be well-defined, homogeneous, and pleural-based lesions. There were relatively small intrallesional calcifications and associated mediastinal lymphadenopathy. The differential considerations for large bilateral pulmonary masses are broad but consist of two main categories: inflammatory and neoplastic disease. Inflammatory diseases include sarcoidosis, histoplasmosis, antineutrophil cytoplasmic antibody–associated granulomatous vasculitis, rheumatoid-related nodules and masses, the nodular form of amyloidosis, and pulmonary hyalinizing granuloma. Neoplastic diseases include primary lung carcinoma, mesothelioma, lymphoma, solitary fibrous tumor of the pleura, pulmonary chondroma, and atypical metastases. Infectious diseases, such as fungal infection, were less likely, given the lack of clinical symptoms and laboratory indicators. To differentiate between these entities, CT-guided percutaneous biopsy and subsequent surgical resection were performed in 2002 and revealed pulmonary hyalinizing granuloma. Additional percutaneous biopsies of lung masses were reportedly performed at other institutions after the initial resection because of intervening enlargement or positron emission tomographic positivity of the lung masses.

Mild renal dysfunction was a long-standing problem in this patient. Retrograde urography performed several years earlier revealed smooth narrowing of the bilateral upper ureters; this finding was highly consistent with a diagnosis of retroperitoneal fibrosis and required bilateral ureteral stent placement.

The spectrum of imaging findings in this patient included lacrimal gland pseudotumors, lymphocytic thyroiditis, bilateral pulmonary hyalinizing granulomas, mediastinal lymphadenopathy, and retroperitoneal fibrosis. In the setting of an elevated IgG4 level, these findings are consistent with a diagnosis of IgG4-related disease, which is a recently recognized multiorgan system disorder. IgG4-related disease is an uncommon immune-mediated systemic fibroinflammatory condition that can affect any organ system. Although pancreatic involvement with diffuse or focal occasionally masslike gland enlargement, which sometimes has a capsulelike low-attenuation rim and pancreatic ductal narrowing, was not present in this patient, it is common in the setting of IgG4-related disease, and the link between autoimmune pancreatitis and elevated IgG4 is well established (5). Renal involvement is also well known in IgG4-related disease, most commonly IgG4-related tubulointer-
Histologically, the disease is characterized by a lymphoplasmacytic infiltrate that is positive for IgG4-bearing plasma cells at IgG4-specific staining in affected organs, as well as by an elevated serum IgG4 level (7). Given the overlap with other diseases, the limitations of using only IgG4 level in the diagnosis have been acknowledged (7). In this patient, multiple biopsies were performed to exclude primary malignancies of the lacrimal gland, thyroid, and lung over many years in the absence of a unifying diagnosis. This appears to be a typical experience in patients with IgG4-related disease. However, after exclusion of primary neoplasms and inflammatory diseases, specific diagnostic criteria recently have been proposed by Okazaki et al (8) (Fig 8) to facilitate diagnosis, minimize invasive procedures, and expedite care. This patient, who has mass lesions in two organs, an elevated serum IgG4 level, and abundant IgG4-rich plasmacytes at lung biopsy, met all three diagnostic criteria, which is highly consistent with the diagnosis of IgG4-related disease (Fig 8). Prompt diagnosis and management of IgG4-related disease are necessary to prevent sclerosis and permanent organ damage. In the absence of a unifying diagnosis, this patient experienced chronic orbital symptoms and underwent initial lung resection with multiple subsequent lung biopsies over a decade.

The mainstay of therapy is glucocorticoid administration, which typically produces rapid initial treatment response (9). Immunosuppression is used more frequently to manage recurrent disease, as maintenance steroid therapy is controversial (9). Ongoing clinical trials of immune modulators, such as rituximab, may prove promising for disease relapse (10–12). Serum IgG4 levels and clinical symptoms are used to follow treatment response (9).

This patient received 30 mg of prednisone twice daily with some improvement and was discharged 1 week after admission. She was then followed-up with rheumatology at another institution. IgG4-related disease is an uncommon entity. The puzzling clinical presentation and long delay in diagnosis, as seen in this patient, are typical. Thus, radiologists should become more familiar with this complex multiorgan fibroinflammatory disease, since we are able to review imaging findings over a long period of time in some patients and are in a unique position to help suggest or establish this unifying diagnosis.

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Congratulations to the 112 individuals and nine resident groups that submitted the most likely diagnosis (IgG4-related disease) for Diagnosis Please, Case 196. The names and locations of the individuals and resident groups, as submitted, are as follows:

**Individual responses**

Pablo J. Abhona, MD, Irvine, Calif
Osamu Abe, MD, PhD, Itabashi-ku, Tokyo, Japan
Gholamali Afshang, MD, Tinsley Park, Ill
Stephane Alland, MD, Aix En Provence, Bouches De Rhone, France
Albert J. Alter, MD, PhD, Blanchardville, Wis
Roshan K. Arjal, MD, Wahan, China
Guis S. Astacio, MD, Rio de Janeiro, Brazil
Asim K. Bag, MD, Homewood, Ala
Thomas J. Barloon, MD, Iowa City, Iowa
Itasso Barral Juez, MD, Donostia, Gipuzkoa, Spain
Dhiraj Baruah, MD, Wauwatosa, Wis
Gustav A. Blomquist, MD, Lexington, Ky
Eric L. Bressler, MD, Minnetonka, Minn
Douglas C. Brown, MD, Virginia Beach, Va
Ian A. Burgess, MD, North Sydney, New South Wales, Australia
Jose Antonio Camilo Machado, Sr, MD, Goiania, Goias, Brazil
Daniel Castellon, MD, Faubelabada, Madrid, Spain
Phillip M. Cheng, MD, MS, Caliver City, Calif
Michael H. Childress, MD, Silver Spring, Md
Mauro C. Corral, MD, El Paso, Tex
Jean-Nicolas Dacher, MD, Rothenburg, Germany
David A. Lisle, MBBS, Brisbane, Queensland, Australia
Stephan V. Manghisi, MD, Closter, NJ
Gerasimos Maroulis, MD, Aachen, Germany
Kamen Kuramoto, MD, Tachikawa, Tokyo, Japan
Mario A. Laguna, MD, Milwaukee, Wis
Karl J. Lehmann, MD, Karlsruhe, Germany
David A. Lisle, MBBS, Brisbane, Queensland, Australia
Stephan V. Manghisi, MD, Closter, NJ
Gerasimos Maroulis, MD, Aachen, Germany
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Kamen Kuramoto, MD, Tachikawa, Tokyo, Japan
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Stephan V. Manghisi, MD, Closter, NJ
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David A. Lisle, MBBS, Brisbane, Queensland, Australia
Stephan V. Manghisi, MD, Closter, NJ
Gerasimos Maroulis, MD, Aachen, Germany
Kamen Kuramoto, MD, Tachikawa, Tokyo, Japan
Mario A. Laguna, MD, Milwaukee, Wis
Karl J. Lehmann, MD, Karlsruhe, Germany
David A. Lisle, MBBS, Brisbane, Queensland, Australia
Stephan V. Manghisi, MD, Closter, NJ
Gerasimos Maroulis, MD, Aachen, Germany
Kamen Kuramoto, MD, Tachikawa, Tokyo, Japan
Marios Primetis, MD, Athens, Greece
Mantosh S. Rattan, MD, Cincinnati, Ohio
Ryan P. Rehbock, MD, Dundas, Ontario, Canada
Andre F. Robin, MD, Piracicaba, Brazil
Daniel Romeu Vilar, MD, Bertamirans, A Coruna, Spain
Stefan Roosendaal, MD, PhD, Amsterdam, the Netherlands
Akihiko Sakata, MD, Kyoto, Japan
Steven M. Schultz, MD, Fort Worth, Tex
Anthony J. Scueller, MD, Johnstown, Pa
Matthew P. Shaquirol, MD, Charlottesville, Va
Hideki Shima, MD, Narita, Chiba prefecture, Japan
Taro Shinomo, MD, Osaka, Japan
Ichiro Shirouzu, MD, Tokyo, Japan
Michael S. Siegfried, MD, Glencoe, Ill
David F. Sohel, MD, La Jolla, Calif
James D. Sprinkle Jr, MD, Spotsylvania, Va
Hongliang Sun, MD, Beijing, China
Ayako Tamura, MD, Tokyo, Japan
Eiko Tanaka, MD, Yokohama, Japan
Douglas L. Teich, MD, Brookline, Mass
Eugene Tong, MD, Austin, Tex
Ulysse S. Torres, MD, Body Bassitt, Brazil
Meric Tuzun, MD, Ankara, Turkey
Christopher P. Vittore, MD, Belvidere, Ill
Haruo Watanabe, MD, Gyjju, Japan
Noritaka Yamakawa, Kyoto, Japan
Toshihide Yanoaka, MD, Kyoto, Japan
Koji Yamashita, MD, Fukuoka, Japan
Yi Yang, MD, Suzhou, Jiangsu, China
Kurata Yasuhisa, MD, Kobe, Hyogo, Japan
Satoru Yoshida, Muroran, Hokkaido, Japan
Keneko You, Gyjju, Japan

**Resident group responses**

Hospital: University of Fuendaburad
Radiology Residents, MD, Madrid, Spain
ICESP Residents, Sao Paulo-SP, Brazil
Johns Hopkins Medical University Radiology Residents, Baltimore, Md
Mater Dei Hospital Radiology Residents, Msida, Malta
Mie University Hospital Radiology Residents, Tsu, Mie, Japan
Prince of Songkla University Radiology Residents, Songkla, Thailand
Sint Antonia Nieuwegein Radiology Residents, Nieuwegein, the Netherlands
Tsukuba University Hospital Radiology Residents, Tsukuba, Ibaraki, Japan
Virginia Commonwealth University Radiology Residents, Richmond, Va