A 67-year-old man with type 2 diabetes mellitus and hyperlipidemia was evaluated for unintentional weight loss of 28 lb (12.7 kg) and increasing fasting blood glucose values over the past 6 months. A computed tomography scan showed diffuse enlargement of the pancreas with peripheral hypoenhancement but no discrete mass. Soft tissue surrounded the infrarenal abdominal aorta, extended along the common iliac arteries, and obstructed the left ureter, causing hydronephrosis. He was referred for evaluation of possible malignancy. Laboratory studies including immunoglobulin G4 (IgG4) levels are shown in the Table. Fine-needle aspiration of the pancreas showed no malignancy. Colonoscopy results 8 months ago were normal.

### Table. Patient’s Laboratory Values and Reference Ranges

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Values</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.7</td>
<td>13.5-17.5</td>
</tr>
<tr>
<td>Mean corpuscular volume, μm³</td>
<td>84.1</td>
<td>81.2-95.1</td>
</tr>
<tr>
<td>White blood cell count, /µL</td>
<td>6800</td>
<td>3500-10 500</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>11</td>
<td>0-22</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>134</td>
<td>70-100</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>70</td>
<td>45-115</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>19</td>
<td>12-31</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>18</td>
<td>10-45</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.6</td>
<td>0.9-1.4</td>
</tr>
<tr>
<td>CA 19-9, U/mL</td>
<td>17.1</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Immunoglobulin G, total, mg/dL</td>
<td>1530</td>
<td>600-1500</td>
</tr>
<tr>
<td>Immunoglobulin G, subclass 4, mg/dL</td>
<td>391</td>
<td>8-140</td>
</tr>
</tbody>
</table>

**Abbreviation:** CA, carbohydrate antigen.

SI conversions: to convert alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase to μkat/L, multiply by 0.0167; creatinine to μmol/L, multiply by 88.4; fasting glucose to mmol/L, multiply by 0.0555.

**Answer**

A. Test results indicate presence of IgG4-related disease.

**Test Characteristics**

IgG4-related disease is a relapsing, immune-mediated, multiorgan, fibroinflammatory disease (characterized by intense inflammation and fibrosis) that presents similarly to a nonspecific malignant, infectious, and inflammatory condition. IgG4 is a subclass of IgG that accounts for less than 5% of the total IgG in healthy adults. The sensitivity of any elevation of IgG4 for diagnosing IgG4-related disease is approximately 70% and the specificity is 85%. Some criteria for diagnosing IgG4-related disease use a 2-fold elevation of IgG4 levels as the threshold for a positive test, in which case the sensitivity is approximately 60% and the specificity is 90%. Because the prevalence of IgG4-related disease is low (4.6 cases per 100 000), the positive predictive value of IgG4 elevation is only 36%.

The precise role of IgG4 in the pathogenesis of IgG4-related disease remains unknown. Elevated IgG4 levels in IgG4-related disease may result from type 2 helper cell activation, in response to prolonged exposure to an unknown antigen. The 2018 Medicare reimbursement for the IgG4 assay is $9.90.

**Application of Test Results to This Patient**

Individual organ manifestations of IgG4-related disease were previously regarded as unrelated disease entities (eg, autoimmune pancreatitis, IgG4-associated cholangitis, Mikulicz disease, retroperitoneal fibrosis, orbital pseudotumor, periglandular disease, IgG4-related tubulointerstitial nephritis) but are now considered part of a single disease process that involves various organs. Multiple organs may be involved successively or at the same time. IgG4-related disease typically affects males in a 3:1 ratio. An isolated elevation of IgG4 levels is not diagnostic of IgG4-related disease, but a combination of elevated IgG4 levels and typical imaging features (diffuse/localized swelling of the pancreas with peripheral hypoenhancement) is diagnostic, as in this patient with autoimmune pancreatitis and retroperitoneal fibrosis. In such typical cases,
a biopsy is not required for diagnosis. However, as manifestations of IgG4-related disease are often mass forming, a fine-needle aspiration should be performed to rule out malignancy.

IgG4-related disease can also be diagnosed based on characteristic history. However, samples from fine-needle aspiration are typically inadequate for histologic diagnosis of IgG4-related disease. Tissue diagnosis of IgG4-related disease requires preserved architecture, such as that obtained from a core or wedge biopsy or resection specimens. Histologic findings are similar across affected organs and are characterized by lymphoplasmacytic infiltration, storiform (cartwheel) fibrosis, and obliterator phlebitis. Staining the histopathology specimen facilitates calculation of the absolute number and relative proportion of IgG4+ cells from the total number of IgG+ plasma cells, which are components of the histologic criteria for IgG4-related disease.8

What Are Alternative Diagnostic Testing Approaches?
Specific laboratory tests alone cannot diagnose IgG4-related disease. Approximately 60% of patients with IgG4-related disease have elevated serum IgE levels, approximately 25% have elevated inflammatory markers such as C-reactive protein, and approximately one-third have elevated levels of eosinophils and antinuclear antibody.4 Levels of IgG4 are unreliable for assessing response to treatment and can rebound above normal in up to 70% patients after withdrawal of glucocorticoid treatment.9 Even patients with a false-positive elevation of IgG4 (ie, not related to underlying IgG4-related disease) can have improvement in IgG4 levels with steroids, presumably due to reduced inflammation.10 Therefore, IgG4 levels cannot be used to measure responsiveness to therapy. Repeat imaging, along with specific laboratory testing, depending on the organ involved (eg, liver biochemistries in cases with autoimmune pancreatitis or IgG4-associated cholangitis) are often the best indicators of response to treatment.

Patient Outcomes
The patient was prescribed prednisone, 40 mg daily, for 1 month followed by a prednisone taper over 8 weeks. Repeat computed tomographic scan 2 weeks after starting treatment showed significant improvement in pancreatic inflammation. A ureteral stent was placed for ureteral stenosis due to retroperitoneal fibrosis and left hydronephrosis. At 3-month follow-up, liver biochemistry levels were normal. At 6-month follow-up, pancreatic changes and hydronephrosis had resolved, and the ureteral stent was removed. The patient had a relapse 3 years after presentation, which was treated again with corticosteroids. The patient was relapse free at his most recent follow-up (3 months ago).

Clinical Bottom Line
- Immunoglobulin G subgroup 4 (IgG4)-related disease is a relapsing, immune-mediated, fibroinflammatory disease (characterized by intense inflammation and fibrosis) that resembles malignant, infectious, and inflammatory conditions in its presentation and can affect multiple organs.
- Elevated IgG4 levels are insufficient for diagnosing IgG4-related disease. In the case of pancreatic involvement from IgG4-related disease (ie, autoimmune pancreatitis), a combination of elevated IgG4 levels and characteristic imaging features can lead to a diagnosis without biopsy.
- Alternatively, a core or wedge biopsy can be obtained for a histologic diagnosis of IgG4-related disease. Histology is similar across all involved organs.
- Corticosteroids should be used for treating the initial episode and relapses.
- Levels of IgG4 commonly increase after treatment. An isolated elevation in IgG4 levels is insufficient evidence for relapse in the absence of other clinical data.

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.
Published Online: December 20, 2018. doi:10.1001/jama.2018.16665
Conflict of Interest Disclosures: The authors report no disclosures.
Additional Contributions: We thank the patient for sharing his experience and for granting permission to publish it.

REFERENCES