ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic autoimmune disorder that has been defined in various organs. The disease is characterized by typical clinicopathological features including a dense lymphoplasmacytic infiltrate rich in IgG4 positive plasma cells, storiform fibrosis, obliterator phlebitis, and often an elevated serum IgG4 level. Esophageal IgG4-RD is rare, and its presentation as a solid mass is even more rare. Only 15 previous cases of IgG4-related esophageal disease have been described. We herein present a case of giant IgG4-related pseudotumor of the esophagus resected with endoscopic submucosal dissection (ESD) and a review of the literature. The patient was a 67-year-old man who was admitted to our hospital for assessment of progressive dysphagia. Upper gastrointestinal endoscopy revealed a 9 cm mass in the cervical esophagus. In the previous two hospitals, the patient's mass could not be diagnosed despite repeated biopsies. Because of concerns regarding malignancy, endoscopic submucosal dissection was performed. Histopathological examination showed dense lymphoplasmacytic infiltration with predominant IgG4-positive plasma cells on a sclerotic background. The patient was diagnosed with IgG4-RD. During the follow-up, no residual mass was detected but the patient was diagnosed with lung adenocarcinoma. We present a unique case of giant IgG4-related pseudotumor of the esophagus. Resection with ESD of such a big mass of IgG4-RD in the esophageal region has never been reported before in the literature.

Keywords: IgG4, IgG4-related disease, Esophagus, Endoscopic submucosal dissection, Autoimmune

INTRODUCTION

IgG4-related disease (IgG4-RD), originally described in the pancreas by Sarles et al. in 1961 (1), is a fascinating clinical entity of unknown etiology characterized by high serum IgG4 concentrations and tumefaction or tissue infiltration by IgG4-positive plasma cells. The disorder is recognized as a systemic disease characterized by specific histopathological findings that include the presence of predominant IgG4-positive plasma cells in a background of intense lymphoplasmacytic infiltration, storiform fibrosis, and obliterator phlebitis (2). It has been reported in almost any organ and tissue in the body including the pancreatobiliary system, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast (3–5). The clinical presentation depends on the site of involvement (6). Involvement of the esophagus is extremely rare. Sometimes esophageal IgG4-RD may mimic malignancy both clinically and radiologically, especially when it forms a mass (7–9). We herein present a unique case of giant IgG4-related pseudotumor of the esophagus resected with endoscopic submucosal dissection (ESD) and a review of the literature.

CASE REPORT

A 67-year-old Caucasian man presented with progressive dysphagia to solids over the last 2 years. His past medical history was uneventful. He had no other autoimmune diseases. He was an ex-smoker with a smoking history of 43 pack-years. The patient had previously visited 2 different hospitals, where he underwent upper gastrointestinal endoscopy, neck computed tomography (CT), and FDG positron emission tomography (PET) because of the suspicion of malignancy. Upper gastrointestinal endoscopy revealed a mass-forming lesion prolapsing into the lumen of the cervical esophagus. The neck CT demonstrated a suspicion of gastrointestinal stromal tumor (GIST) and no concomitant lymphadenopathy. FDG-PET showed that the SUVmax of the mass was 10.0. Because of the suspicion of esophageal cancer, multiple biopsies were taken from the mass. However, the biopsy specimens were evaluated as squamous epithelial hyperplasia and inflammatory granulation tissue histologically which did not explain the tumoral nature of the lesion.

The patient presented to the gastroenterology department of our hospital. The physical examination was unremarkable.
All laboratory data were within normal limits. Upper gastrointestinal endoscopy revealed an approximately 9 cm polypoid tumor partially obstructing the esophageal lumen, located about 15 cm from the incisors (Figure 1). Because of the obstruction and the concerns regarding malignancy, endoscopic removal of the lesion was planned.

He underwent a successful ESD. After marking the lesion, a mixture of saline, indigocarmin and hyaluronic acid was locally injected into the submucosal space to elevate the lesion. The borders were marked circumferentially using a needle knife tip (DualKnife™; Olympus, Tokyo, Japan) and careful dissection of the lateral borders and submucosal space was performed. En bloc removal of the lesion was performed successfully and it was sent to the pathology department for histological evaluation. Cauterization for bleeding was accomplished and enteral feeding was started in order to allow the esophageal mucosa to heal.

Gross examination of the resected specimen revealed a polypoid tumor that measured 9x7x5 cm with mucosal surface erosion and a tan-white, solid, partially rubbery cut surface (Figure 1). Histological examination showed dense lymphoplasmacytic inflammation, lymphoid follicles with prominent germinal centers, and proliferation of small vessels on a sclerotic background beneath the ulcerated squamous epithelium (Figure 2). The inflammation consisted of abundant plasma cells admixed with some eosinophils (Figure 3). Stromal sclerosis resembling storiform fibrosis that is characterized by a whorled pattern of fibrosis was observed (Figure 4). Blood vessels showed partially luminal obliteration by aggregated inflammatory cell infiltration but there was no manifest obliterative phlebitis (Figure 5). There were reactive mucosal changes adjacent to the ulcer. Immunohistochemically, cytokeratin AE1/AE3, CD117, ALK, CD3, CD20, bcl2, CD10, CD38, kappa, lambda, IgG and IgG4 stains were performed. Stains for cytokeratin AE1/AE3, CD117, ALK were all negative in the lesion. A possible lymphoproliferative neoplasm was excluded by CD3, CD20, bcl2 and CD10 staining. CD38 revealed abundant plasma cells demonstrating a polyclonal staining pattern including the expression of both kappa and lambda. IgG4 immunostaining revealed 60 IgG4+ plasma cells per high-power field (HPF) (Figure 6). The ratio of IgG4+/IgG+ plasma cells was > 40%.

With the help of histopathological findings raising concern for IgG4-RD, the serum IgG4 level was checked afterwards. Ten days after the ESD procedure, the patient's serum IgG4 level was found to be elevated at 179 mg/dL (reference range, 0-125 mg/dL). Based on comprehensive diagnostic criteria for IgG4-RD (10), the patient was finally diagnosed...
The patient did not receive any medication including corticosteroid therapy after the ESD procedure. He underwent neck and thorax CT two months after the ESD procedure. Neck CT showed no residual mass but unexpectedly the thorax CT showed a solid mass with an irregular spiculated contour of 24 mm size in the perihilar area of the lower lobe in the left lung. FDG-PET showed that SUVmax of the mass was 14.68 and there were concomitant hypermetabolic lymph nodes in the mediastinum. Due to the suspicion of lung cancer, bronchoscopy was performed. However, the mass could not be sampled despite repeated bronchoscopies. Bone scintigraphy showed a lesion suspicious in terms of metastasis in the left iliac crest. Biopsy taken from the lesion was evaluated as adenocarcinoma favoring the lung as primary origin. The patient received chemotherapy but unfortunately, 21 months after the ESD procedure, he passed away with unknown cause, and no autopsy was performed.

**DISCUSSION**

IgG4-RD is an immune-mediated fibroinflammatory condition that has been described in a variety of organs (11). According to the comprehensive diagnostic criteria for IgG4-RD (10), 3 criteria were proposed for a diagnosis of IgG4-RD: (1) involvement with diffuse/localized swelling or masses in single or multiple organs; (2) an elevated serum IgG4 concentration (≥135 mg/dl); (3) histopathological findings that include a ratio of IgG4+/IgG+ plasma cells > 40% and >10 IgG4+ plasma cells/HPF in addition to marked lymphoplasmacytic infiltration and fibrosis. A diagnosis of IgG4-RD is definite in patients who fulfill the comprehensive diagnostic criteria for IgG4-RD (10). As our case fulfilled all 3 criteria and was a solid pseudotumor, our patient was diagnosed as definite IgG4-related pseudotumor of the esophagus.

In IgG4-related pancreatitis, especially in resection specimens, it has been reported that >30 IgG4+ plasma cells per HPF have acceptable specificity, and >50 IgG4+ plasma cells per HPF is highly specific. However, it is emphasized that the appropriate cut-off point may vary from organ to organ (12).

In 2019, American College of Rheumatology/European League Against Rheumatism developed the classification criteria for IgG4-RD as validated in a wide cohort of patients (13). The classification criteria for IgG4-RD are divided into 4 steps that include entry criteria, exclusion criteria, inclusion criteria, and total inclusion points. These steps contain the details from clinical, serological, radiological, and pathological evaluations. However, to obtain a relatively
### Table I: Summary of reported cases of IgG4-related esophagitis.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age, years</th>
<th>Symptoms</th>
<th>Imaging findings</th>
<th>IgG4 cells/HPF</th>
<th>IgG4/IgG ratio</th>
<th>Serum IgG4</th>
<th>Diagnostic modality</th>
<th>Outcome</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>23</td>
<td>Dysphagia and weight loss</td>
<td>Intraluminal mass and esophageal stricture</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
<td>Esophagectomy</td>
<td>Uneventful postoperative course</td>
<td>Lopes et al. (7)</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>63</td>
<td>Dysphagia and weight loss</td>
<td>Diffuse friability, ulceration and irregular stricture</td>
<td>200</td>
<td>NA</td>
<td>138 mg/dL (RR: 6-121 mg/dL)</td>
<td>Esophagectomy</td>
<td>Uneventful postoperative course</td>
<td>Lee et al. (15)</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>63</td>
<td>Odynophagia and dysphagia</td>
<td>Circumferential severe ulcerative esophagitis</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>EGD biopsy</td>
<td>Small response to prednisolone and Rituximab</td>
<td>Dumas-Campagna et al. (17)</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>33</td>
<td>Dysphagia and weight loss</td>
<td>Intraluminal mass and esophageal stricture</td>
<td>12</td>
<td>NA</td>
<td>264 mg/dL (RR: &lt; 135 mg/dL)</td>
<td>US-guided needle biopsy</td>
<td>Improved after prednisolone</td>
<td>Oh et al. (8)</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>60</td>
<td>Acid reflux</td>
<td>Intraluminal mass</td>
<td>&gt;50 &gt;30%</td>
<td>1590 mg/L (RR: 80-1400 mg/L)</td>
<td>EGD biopsy</td>
<td>Partial response to steroid therapy</td>
<td>Yang et al. (9)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>76</td>
<td>Dysphagia and weight loss</td>
<td>Circumferential erosion and stricture</td>
<td>&gt;10 &gt;40%</td>
<td>9.8 mg/dL (RR: 4.8-105 mg/dL)</td>
<td>Esophagectomy</td>
<td>Uneventful postoperative course</td>
<td>Mori et al. (16)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>47</td>
<td>Dysphagia</td>
<td>Stricture with friable mucosa</td>
<td>110</td>
<td>60</td>
<td>Normal level</td>
<td>EGD biopsy</td>
<td>Improved after prednisolone and mycophenolate mofetil</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>79</td>
<td>Dysphagia</td>
<td>Stricture with friable mucosa</td>
<td>70</td>
<td>50</td>
<td>Normal level</td>
<td>EGD biopsy</td>
<td>Improved after prednisolone and mycophenolate mofetil</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>48</td>
<td>Dysphagia</td>
<td>Multiple rings and stricture</td>
<td>50</td>
<td>80</td>
<td>Normal level</td>
<td>EGD biopsy</td>
<td>NA</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>63</td>
<td>Dysphagia</td>
<td>Dilated distal esophagus with erosive esophagitis</td>
<td>50</td>
<td>60</td>
<td>NA</td>
<td>EGD biopsy</td>
<td>Uneventful post Botox injections and steroid therapy</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>18</td>
<td>Dysphagia</td>
<td>Unremarkable endoscopy</td>
<td>60</td>
<td>80</td>
<td>NA</td>
<td>EGD biopsy</td>
<td>NA</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>67</td>
<td>Dysphagia</td>
<td>Esophageal nodule and esophagitis</td>
<td>50</td>
<td>90</td>
<td>NA</td>
<td>EGD biopsy</td>
<td>NA</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>52</td>
<td>Dysphagia</td>
<td>Dilated distal esophagus and diverticulum</td>
<td>90</td>
<td>90</td>
<td>NA</td>
<td>Esophagogastrectomy</td>
<td>Postesophagectomy stricture</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>58</td>
<td>Epigastric pain</td>
<td>Severe erosive esophagitis</td>
<td>50</td>
<td>60</td>
<td>NA</td>
<td>EGD biopsy</td>
<td>NA</td>
<td>Obiorah et al. (14)</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>56</td>
<td>Dysphagia and weight loss</td>
<td>Stricture and mucosal abrasion</td>
<td>&gt;50 &gt;90%</td>
<td>171.0 mg/dL</td>
<td>Esophagectomy</td>
<td>Uneventful postoperative course and improved after prednisolone</td>
<td>Jang et al. (18)</td>
<td></td>
</tr>
</tbody>
</table>

NA: Not available, RR: Reference range, EGD: Esophagogastroduodenoscopy.
In conclusion, IgG4-RDE can present with a mass and may lead to a misdiagnosis of malignancy, both clinically and radiologically. Diagnosis of IgG4-RDE requires a careful sampling of the lesion in order to perform a correct histopathological examination. However, it may be difficult to diagnose IgG4-RDE with small endoscopic biopsy specimens in some patients. In cases of suspicion, the biopsy/resection specimens should be stained with IgG4 and IgG immunohistochemically and the serum IgG4 level of the patient should be checked. In patients with an esophageal mass, consideration of IgG4-RDE in the differential diagnosis by the clinicians and pathologists will ensure the correct diagnosis and prevent unnecessary overtreatment.

CONFLICT of INTEREST
None of the authors have any conflicts of interest to declare.

AUTHORS’ CONTRIBUTIONS
Concept: NE, Design: NE, DUK, Data collection or processing: DUK, EG, Analysis or Interpretation: NE, FA, Literature search: NE, DUK, Writing: NE, DUK, EG, Approval: NE, DUK, EG, FA.

REFERENCES


