

# Autoimmune Pancreatitis in the Setting of Multifocal Castleman Disease in an HIV-Negative, HHV-8–Negative, 70-Year-Old Man

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## Introduction

Castleman disease (CD), also known as angiofollicular lymph node hyperplasia and giant lymph node hyperplasia, was first described in 1956 by Dr. Benjamin Castleman as localized mediastinal lymph node proliferation. Nodal hyperplasia has been described as hyaline vascular (80–90%), plasma cell (10–20%), and mixed.<sup>1</sup> CD is a rare disease with no racial or sex predominance.<sup>2</sup> Clinical characteristics of patients with CD can range from no symptoms in unifocal cases to systemic complaints, including autoimmune sequelae in multifocal presentations.<sup>2,3</sup> Development of multifocal CD most commonly occurs in patients with a documented human herpesvirus 8 (HHV-8) infection. Multifocal CD has been described in patients with other immunosuppressive conditions, such as human immunodeficiency virus (HIV), lymphomas, and autoimmune diseases.<sup>2</sup> Laboratory findings include anemia, thrombocytopenia, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), increased liver enzymes, hypoalbuminemia, and polyclonal hypergammaglobulinemia.<sup>2,4</sup>

There have been numerous reports of both unifocal and multifocal CD in the pancreas.<sup>3,5-7</sup> Most commonly, CD produces masses in the head of the pancreas.<sup>3,5-8</sup> Biopsy of these pancreatic masses have demonstrated lymphoplasmacytic tissue with evidence of sclerosis. This pathology is often found in autoimmune pancreatitis (AIP).<sup>5</sup>

AIP is most commonly seen in men during their sixth and seventh decades and among patients of Asian descent.<sup>9</sup> Presenting symptoms of AIP include obstructive jaundice with or without abdominal pain, mild

attacks of pancreatitis, weight loss, and other nonspecific symptoms. Focal or diffuse swelling of the pancreas and diffuse or segmental narrowing of the pancreatic duct may be seen on imaging.<sup>10</sup> Studies have documented that elevated levels of immunoglobulin (Ig) G4 (>280 mg/dL) are highly associated with AIP; however, IgG4 levels within normal limits do not exclude a diagnosis of AIP.<sup>11</sup> Elevated IgG4 levels have also been documented in patients with other autoimmune conditions, such as atopic dermatitis, pemphigus vulgaris, and parasitic diseases.<sup>12</sup> Castleman-like lymphadenopathy has been reported in patients with IgG4-related systemic diseases, including AIP.<sup>9,12,13</sup> A diagnosis of AIP is often made by using either the HISORt (histology, imaging, serology, other organ involvement, and response to steroids) criteria<sup>14</sup> or the 2008 Asian Diagnostic Criteria for AIP.<sup>15</sup>

We report a case of multifocal CD in the setting of chronic AIP. The patient completed 3 cycles of rituximab (Rituxan, Genentech/Idex Pharmaceuticals), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) plus 3 cycles of rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). His CD and AIP have remained in remission for 2.5 years.

## Case Presentation

A 70-year-old Asian man with hypertension, diabetes mellitus type II, and a history of a cholecystectomy presented to his primary care provider with vague abdominal pain, anemia, and a 20-pound weight loss of unclear etiology in May 2009. Guaiac testing was negative for occult blood. Initial laboratory work showed anemia (hemoglobin=10.3 g/dL). Platelets (294 k/μL) and white blood cells (7.9 k/μL) were normal. Eosinophil percent and absolute eosinophils were elevated (7.7% and 608 k/μL, respectively). Laboratory work also showed hyperparaproteinemia and an IgG level greater than 4,000 mg/dL.

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**Figure 1.** Abdominal computed tomography demonstrated diffuse enlargement of the pancreas with nonspecific fat stranding of the pancreatic tail and mesenteric lymphadenopathy.

The patient was referred to a gastroenterologist for an additional workup. A biopsy taken during an upper endoscopy demonstrated active chronic gastritis, and subsequent testing revealed infection with *Helicobacter pylori*. No malignant polyps were found during colonoscopy. Endoscopic ultrasound (EUS) revealed a diffuse, heterogeneous, infiltrative process of the pancreas. A computed tomography (CT) scan of the abdomen and pelvis found diffuse pancreatic enlargement with nonspecific fat stranding of the pancreatic tail (Figure 1). Subsequent endoscopic retrograde cholangiopancreatography (ERCP) showed a prominent ampullary mass. Pathology was negative for malignancy, and IgG4 staining was not conducted on the specimen. Criterion 1 (diffuse enlargement of the pancreas with narrowing of the pancreatic duct as seen on ERCP) and criterion 2 (IgG elevation) of the 2008 Asian Diagnostic Criteria for AIP were met.<sup>15</sup> These findings, in conjunction with hyperparaproteinemia, eosinophilia, a negative workup for other known causes of pancreatic disease, demographic factors (eg, Asian descent), and the reported history (eg, minimal lifetime alcohol consumption and no prior episodes of pancreatitis), strongly supported a diagnosis of AIP.

Follow-up positron emission tomography (PET)/CT of the neck, chest, and abdomen detected bilateral hypermetabolic axillary, retroperitoneal, obturator, and inguinal nodes. The largest and most hypermetabolic nodes were in the external iliac and inguinal chains. Of note, no hypermetabolic nodes were detected in the mediastinum, no pulmonary nodules were present, and no hypermetabolic activity was detected in the bone marrow. At this time, the primary care provider referred the patient to an oncologist (Dr. Firozvi).

In addition to his aforementioned medical history, the patient was given a new diagnosis of AIP. He denied alcohol, tobacco, or illicit drug use. On physical examination, he

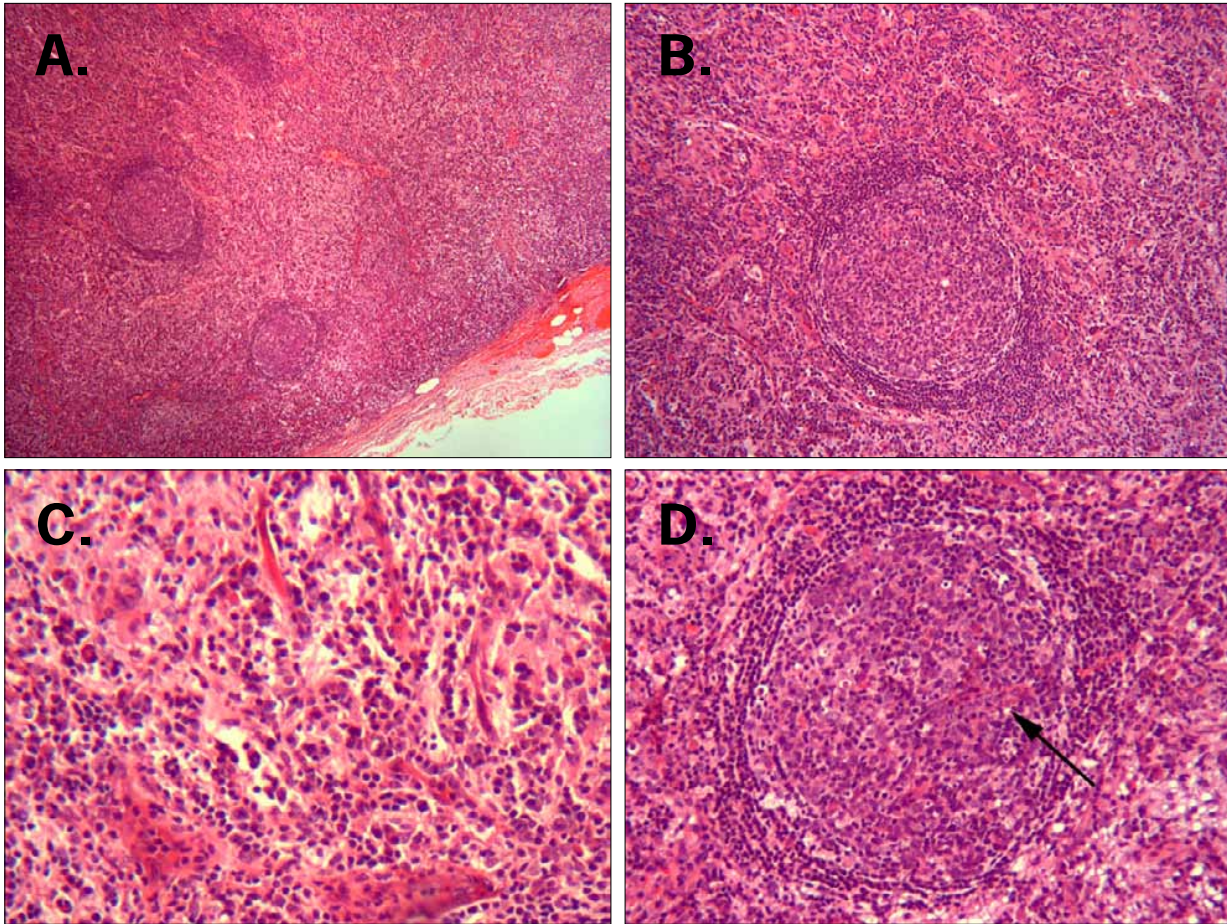
was thin but appeared healthy. Cardiovascular, pulmonary, and abdominal examinations were within normal limits. No adenopathy was observed. Additional laboratory tests revealed marginally elevated protein (8.5 g/dL) and low albumin (2.9 g/dL). Total bilirubin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, amylase, and lipase were normal. Serum protein electrophoresis detected a paraprotein spike in the gamma region (IgG total=3,530 mg/dL), with elevation of IgG1 (1,910 mg/dL), IgG2 (2,010 mg/dL), and IgG3 (481 mg/dL). IgG4 was within normal limits (39.6 mg/dL). Serum IgE was also elevated at 3,014 kU/L. Serum IgA and IgM were normal (125 mg/dL and 56 mg/dL, respectively). The patient was Coombs positive without evidence of hemolysis and had an elevated CRP (10 mg/L), ESR (128 mm/hr), haptoglobin (228 mg/dL), and beta-2 microglobulin (6.56 mg/L). Rheumatoid factor and antinuclear antibody (ANA) were within normal limits. Tests for HIV, HHV-8, hepatitis A, hepatitis B, and hepatitis C were negative. Carcinoembryonic antigen and cancer antigen 19-9 were not elevated.

Bone marrow biopsy revealed a slightly hypercellular marrow with no involvement of a lymphoproliferative disorder or plasma cell dysplasia. Neither fluorescent in-situ hybridization nor flow cytometry detected cellular abnormalities. Immunohistochemical analysis of the bone marrow did not reveal any significant increase in B cells or plasma cells. An inguinal lymph node biopsy showed reactive hyperplasia with Castleman-like features (Figure 2). Scattered lymphoid follicles with germinal centers containing blood vessels, as well as follicles with concentric lymphocyte ringing in the mantle zones, were present. Plasma cells were positive for CD138 with expression of kappa and lambda without light chain restriction, nonspecific findings in CD, or other malignant conditions. Histiocytes were reactive to CD68. No organisms were isolated. As such, the patient was diagnosed with multifocal CD and started on his first of 6 cycles of R-CHOP. Filgrastim (Neupogen, Amgen) was given as needed for chemotherapy-induced neutropenia. A PET/CT scan performed after the patient's third cycle of R-CHOP found decreased size of all lymph nodes and minimal hypermetabolic activity. At this time, the chemotherapy regimen was changed to R-CVP due to severe bone marrow suppression. Following 6 cycles of treatment, restaging CT showed interval resolution of pancreatic enlargement, an interval decrease in nodal size, and complete resolution of uptake of axillary, retroperitoneal, pelvic, and inguinal lymph nodes. After 2.5 years, his CD and AIP have remained in remission.

## Discussion

To our knowledge, concurrent CD and AIP has been reported only once in the literature,<sup>5</sup> but prior reports of





**Figure 2.** Inguinal lymph node biopsy showed Castleman-like features with expansion of the paracortical zone by an infiltration of plasma cells, histiocytes, and blood vessels. A) Inguinal lymph node biopsy demonstrating prominent germinal centers and expansion of the paracortical areas (4x objective). B) “Onion skinning” of the mantle zone cells (10x objective). C) Plasma cell infiltration of the paracortical zone with an associated increase in blood vessels (40x objective). D) Blood vessels (arrow) penetrating the germinal center (40x objective).

pseudo-pancreatic tumor development in CD are more prevalent.<sup>3,6,7</sup> Prior studies have documented a strong association among multifocal CD, HIV positivity, and HHV-8 positivity.<sup>2,16-18</sup> Interestingly, the other reported case<sup>5</sup> of concurrent multifocal CD and AIP also occurred in an HIV-negative and HHV-8–negative man in his 70s.

As previously stated, multifocal CD has been associated with autoimmune conditions. Researchers have suggested that inflammatory mediators, such as human interleukin-6 (IL-6), stimulate B-cell proliferation in CD and contribute to many of the systemic symptoms associated with multifocal CD.<sup>2,16</sup> Upregulation of IL-6 occurs in many diseases, including HHV-8 and AIP.<sup>1,2,18</sup> Although the exact mechanism of AIP is unknown, Park and associates<sup>19</sup> recently proposed a cascade stimulated by molecular mimicry by *H. pylori*. Once self-autoantigens activate antigen-presenting cells, initiation of AIP occurs through cellular immune-mediated reactions, and pro-

gression of AIP occurs through the humoral response in which regulatory T cells stimulate IL-6 and, ultimately, IgG4 production.<sup>19</sup>

While multifocal CD and AIP are undoubtedly separate diseases, similarities in their pathology, histology, and clinical findings (Table 1) suggest some connection. The multiple reports of Castleman-like lymphadenopathy occurring in AIP and pancreatic plasmacytic infiltration occurring in patients with multifocal CD raises the question as to whether AIP increases the risk of multifocal CD.

The diffuse nature of multifocal CD makes surgical removal impossible, and its poor prognosis mandates an aggressive treatment regimen. Due to its low incidence rate, the most effective regimen for CD remains unknown. Corticosteroids are commonly used in the treatment of CD, but the effect is often transient, with CD recurring upon cessation of corticosteroids.<sup>2</sup> Treatment of pancreatic lesions associated with CD varies based on the presence

**Table 1.** Common Characteristics of Multifocal Castleman Disease and Autoimmune Pancreatitis<sup>2,7,12</sup>

	<b>Multifocal Castleman Disease (angiofollicular lymph node hyperplasia)</b>	<b>Autoimmune Pancreatitis Type 1 (lymphoplasmacytic sclerosis)</b>
Most Common Symptoms	Hepatosplenomegaly, lymphadenopathy, frequent fevers, night sweats, weakness, anorexia, weight loss	Abdominal pain, anorexia, weight loss, jaundice, new onset of diabetes
Other Symptoms	Jaundice with pancreatic masses	Lymphadenopathy
Plasma Cell Proliferation	Yes	Yes
<b>Lymph Node Evaluation</b>		
Imaging	Diffuse lymph node enlargement throughout body	Diffuse lymph node enlargement throughout mediastinum and abdomen
Biopsy	Hyperplastic germinal centers with sheets of polyclonal plasma cells in the interfollicular region of the node	Castleman disease–like lymphadenopathy (ie, lymphadenopathy with follicular hyperplasia)
<b>Pancreatic Evaluation</b>		
Imaging	Enhancing mass on the pancreas	Diffuse enlargement of the pancreas or mass on the pancreas
Biopsy	Hyalinized vasculature intermixed with plasma cell infiltrates in the interfollicular zone of the pancreas	Whorled pattern of dense fibrosis intermixed with plasma cell infiltration

of unifocal or multifocal CD. Removal of the pancreatic mass in unifocal CD is curative in most cases.<sup>7</sup> Single-agent (eg, cyclophosphamide, vinblastine, or etoposide) or multi-agent (eg, CHOP or CVP) chemotherapy has been used to treat multifocal CD.<sup>2</sup> More recently, rituximab has been used alone and as adjuvant therapy for multifocal CD. The patient described in this case study was treated with multi-agent chemotherapy (R-CHOP and R-CVP). In this case, the high-dose prednisone included in the chemotherapy regimen also acted as therapy for the AIP. He experienced an appropriate response during therapy, as evidenced by decreased size and uptake of lymph nodes, as well as decreased pancreatic prominence. Despite aggressive treatment, the disease relapsed, which is the case for most patients with multifocal CD.

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# Review

## Autoimmune Pancreatitis, IgG4-Related Disease, and Castleman Disease: Is There a Link?

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### Introduction

The intriguing case reported by Gatti-Mays and colleagues<sup>1</sup> is located at the crossroads of 3 enigmatic diseases: autoimmune pancreatitis (AIP), immunoglobulin (Ig) G4-related disease, and Castleman disease (CD). The first 2 diseases were recognized and partly characterized only within the last 2 decades. Multicentric CD, formerly a rare disease among elderly patients, has shown an increased incidence in recent years following the pandemic of human immunodeficiency virus (HIV) infection. These 3 clinical entities share distinctive features, including unknown etiology and association with a broad spectrum of autoimmune manifestations, and they provide a diagnostic challenge for the clinician as they simulate neoplastic and infectious diseases.

### Autoimmune Pancreatitis

Although rare, AIP is being increasingly recognized as a distinct clinical entity worldwide. The disease predominantly affects men in the sixth and seventh decades of life. The largest series were reported from Japan and China, where the disease seems to have a higher prevalence compared to the Western world.<sup>2,3</sup> AIP often presents with jaundice and nonspecific abdominal discomfort or, occasionally, with ultrasound images suggestive of pancreatic cancer. Pancreatic enzyme elevation, steatorrhea, and diabetes may be present at onset. Computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP) are usually included in the diagnostic workup. Characteristically, imaging studies show a diffuse or segmental enlargement of the pancreas, occasionally with a mass, that is associated with pancreatic and bile duct narrowing. No specific serologic markers of AIP exist; however, high serum levels of IgG or IgG4 (>140 mg/dL) are required for diagnosis.

At a pathologic level, 2 types of AIP can be distinguished: type 1, also known as lymphoplasmacytic sclerosing pancreatitis, which is characterized by periductal

lymphoplasmacytic infiltrate, rich in IgG4 cells (usually more than 50% of the plasma cell infiltrate); storiform fibrosis; and obliterative phlebitis; and type 2, also known as granulocyte epithelial lesion pancreatitis, which presents with predominant neutrophilic infiltrate in the lobule and duct, without IgG4 plasma cell infiltrate.<sup>4</sup> Type 1 is by far the most frequently encountered AIP, especially in the Far East, while type 2 is more frequently diagnosed in the Western world. The 2 types are not distinguishable by CT or MRI; moreover, type 1 AIP is often associated with other systemic manifestations of IgG4-related disease. Finally, the response to steroid therapy is prompt and complete in type 1, but appears to be sluggish and partial in type 2.<sup>5</sup>

In order to define the diagnostic features of AIP, a number of diagnostic guidelines have been established, taking into account imaging, serology, and pathologic findings. Examples include the HISORt (histology, imaging, serology, other organ involvement, and response to steroids) criteria<sup>5</sup> and the 2008 Asian Diagnostic Criteria for AIP.<sup>6</sup>

### IgG4-Related Disease

Originally strictly associated with AIP, IgG4-related disease is a novel clinical entity that is now recognized to affect other organ systems. Involvement of the salivary glands, periorbital tissues, breast, prostate, thyroid, pericardium, kidneys, lymph nodes, meninges, aorta, skin, and lung has been reported.<sup>7</sup> A number of diseases, including Mikulicz's syndrome, Riedel's thyroiditis, and retroperitoneal fibrosis, now fall within the spectrum of IgG4-related disease.<sup>7</sup> All of the above conditions share some unifying pathologic features that are characteristic of IgG4-related disease, such as a lymphoplasmacytic infiltrate with storiform fibrosis (ie, fibrosis with a swirling pattern), obliterative phlebitis, and a moderate eosinophilic infiltrate; in addition, serum and/or tissue elevation of IgG4 is common; serum IgG4 greater than 135 mg/dL and/or more than 50% IgG4/IgG-stained plasma cells in the tissue affected are typically observed. In Japan, the prevalence is 0.8 cases per 100,000 people.<sup>7</sup> The true incidence of the disease is likely higher worldwide.

The etiology of IgG4-related disease is unknown. Although several autoantigens have been identified in affected tissues, their role in the pathogenesis of the disease is not clear. A Th2 cell pattern of cytokine expression (interleukin-4, interleukin-5, interleukin-10, and interleukin-13) has been consistently noted at the tissue level<sup>8</sup>; eosinophilia and elevated serum IgE levels are frequently present.

Clinically, the symptoms of the disease are related to the organ involved. Some patients may only experience swelling of the salivary and lacrimal glands, whereas radiologic studies in other cases have incidentally revealed swelling of an internal organ.

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Therapy should be tailored to each patient. The involvement of vital organs requires immediate treatment, while a policy of watchful waiting may be appropriate in cases of indolent nodal swelling. First-line therapy with steroids tends to be rapidly effective, although recurrence is not rare. In these cases, B-cell depletion with the anti-CD20 antibody rituximab (Rituxan, Genentech/Idex Pharmaceuticals) appears to be very promising.<sup>9</sup>

### Castleman Disease

CD encompasses a group of disorders characterized by polyclonal B-lymphocyte proliferation, often associated with autoimmune manifestations. Clinically, the disease is classified into 2 major subgroups: localized form, which is more common in young patients, and multicentric disease, which occurs more frequently in older patients, as well as in HIV-positive patients. The 3 recognized pathologic variants of CD are hyaline vascular, mixed, and plasma cell. Usually, the hyaline-vascular type is observed in the localized or unicentric form of the disease, whereas the plasma-cell variant is characteristically associated with multicentric CD.<sup>10,11</sup> The etiology of the disease is unknown; however, the reactivation of HHV-8 consistently observed in HIV-positive patients and in approximately half of HIV-negative cases suggests that an immunodeficient state may drive B-cell proliferation. High serum levels of interleukin (IL) 6 and vascular endothelial growth factor (VEGF) are commonly found in multicentric CD, as are acute phase reactants, anemia, thrombocytopenia, hypoalbuminemia, and polyclonal hyperglobulinemia. Patients with multicentric CD often complain of systemic manifestations, such as fever, night sweats, malaise, and weight loss. A physical examination may reveal hepatosplenomegaly, peripheral lymphadenopathy, ascites, and pleural effusion. Multicentric CD has a poor prognosis if untreated. The most common causes of death are infections, Kaposi sarcoma, malignant lymphoma, and epithelial neoplasia. Common therapeutic approaches include systemic chemotherapy, anti-IL-6 receptors (eg, tocilizumab, [Actemra, Genentech]), and anti-CD20 antibodies (eg, rituximab). Rituximab has been shown to induce a high percentage of complete and sustained remissions in HHV-8-associated CD of both HIV-positive and HIV-negative type.<sup>11,12</sup>

### Conclusion

The case described by Gatti-Mays and coworkers<sup>1</sup> undoubtedly met the Asian criteria for AIP<sup>6</sup>; however, IgG4 serum levels were normal and IgG4 immunostaining of the tissue specimen was not available. Thus, it is not entirely certain whether this case can be included in the broad spectrum of IgG4-related disease. Furthermore, no extrapancreatic manifestations of IgG4-related disease were reported in this patient. Nevertheless, this case is remarkably similar

to that reported by Maithel and associates.<sup>13</sup> Both are examples of type 1 AIP in the context of HIV-negative, HHV-8-negative multicentric CD. AIP presents a high variability at both the clinical and pathologic level. Recent data suggest that, in addition to types 1 and 2, a “mixed” type with intermediate pathologic features could exist.<sup>14</sup> This implies that AIP is not exclusively a manifestation of IgG4-related disease, but may also arise independently or in the context of other diseases often characterized by the presence of autoimmune phenomena, such as multicentric CD. In fact, a number of autoimmune manifestations are associated with CD.<sup>15</sup> They usually subside after treatment and remission of the disease. In this context, Mascaro and associates<sup>16</sup> described a remarkable case involving a patient in whom pemphigus and systemic lupus erythematosus disappeared and remained in remission off therapy for 6 years after excision of a Castleman nodal mass of the unicentric hyaline-vascular type. Thus, it seems that the autoimmune manifestations observed in CD are the result of the disease itself and not mere coincidences. Finally, when it comes to treating patients with both diseases, whatever the pathologic type of AIP, the challenge is to induce a stable remission of multicentric CD. In this regard, treatment with rituximab appears to be of considerable value.<sup>10,12</sup>

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