Erdheim-Chester Disease as a Mimic of IgG4-Related Disease
A Case Report and a Review of a Single-Center Cohort

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Abstract: Immunoglobulin-G4 (IgG4)–related disease (IgG4RD) is a fibro-inflammatory disorder characterized by tissue-infiltrating IgG4+ plasma cells, and, often, high serum IgG4. Several autoimmune, infectious, or proliferative conditions mimic IgG4RD. Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis, characterized by foamy histiocytic infiltration, fibrosis, and chronic inflammation. ECD and IgG4RD manifestations may overlap.

A patient presented with huge fibrous retroperitoneal masses causing compression on neighboring structures; the case posed the challenge of the differential diagnosis between IgG4RD and ECD mainly because of a prominent serum and tissue IgG4 response.

Retroperitoneal biopsy led to the diagnosis of ECD; the V600E BRAF mutation was found. Treatment with the BRAF inhibitor vemurafenib was started.

Treatment failed to induce mass regression and the patient died after 3 months of therapy. Prompted by this case, we examined serum and tissue IgG4 in a series of 15 ECD patients evaluated at our center, and found that approximately one-fourth of the cases have increased IgG4 in the serum and often in the tissue.

The differential diagnosis between IgG4RD and ECD can be challenging, as some ECD patients have prominent IgG4 responses. This suggests the possibility of common pathogenic mechanisms between ECD and IgG4RD.

INTRODUCTION
Immunoglobulin-G4 (IgG4)–related disease (IgG4RD) is an idiopathic, systemic, fibro-inflammatory condition histologically characterized by storiform fibrosis, dense lymphoplasmacytic infiltrates rich in IgG4+ plasma cells, tissue eosinophilia, and obliterative phlebitis. IgG4RD lesions usually develop as pseudo-tumoral masses and affect different organ systems, the most common of which include the pancreas and the biliary tree (sclerosing pancreatitis and cholangitis), the retroperitoneum (retroperitoneal fibrosis [RPF]), the salivary glands (sclerosing sialoadenitis), the lymph nodes, and the retro-orbital space.12 The disease spectrum is extremely variable and ranges from organ-limited, asymptomatic lesions to disseminated multisystemic forms that require prompt immunosuppressive treatment.5

The differential diagnosis of IgG4RD can be particularly challenging, given that several neoplastic (eg, lymphomas, pancreatic cancer), autoimmune (eg, large and small-vessel vasculitis, Sjögren syndrome), and fibro-inflammatory (eg, idiopathic RPF) disorders can clinically mimic IgG4RD.3 In addition, a number of diseases show high IgG4 serum levels4,5 and/or significant tissue infiltration by IgG4+ plasma cells.6

Erdheim-Chester disease (ECD) is an extremely rare but increasingly recognized form of non-Langerhans cell histiocytosis, of which approximately 600 cases have been reported in the literature.4 ECD is usually a systemic disease, with predilection for long bones, cardiovascular system, retroperitoneum, central nervous system, and endocrine glands, and is histologically characterized by tissue infiltration by CD68+CD1a-“foamy” histiocytes along with diffuse lymphoplasmacytic infiltrates and abundant fibrosis.8 ECD is included among the differential diagnoses of IgG4RD.3 However, serum IgG4 levels and tissue infiltration by IgG4+ plasma cells have never been investigated in ECD.

We here report the complex case of a patient who presented with huge perirenal retroperitoneal fibrous lesions, which posed the challenge of the differential diagnosis between ECD and IgG4RD, due to the presence of a prominent tissue and serum IgG4 response.

This intriguing case prompted us to re-evaluate serum and tissue IgG4 in a series of ECD patients recruited at our center, to explore the clinical and histopathological significance of IgG4 in ECD.

CASE REPORT
In 2014, a 55-year-old man was referred to the Nephrology Unit of Parma University Hospital for bilateral perirenal masses, which caused left-sided ureteral obstruction needing
permanent stenting; the perirenal lesions had been diagnosed in 2011. Since then, they did not significantly enlarge; on computed tomography (CT), they had a cranio-caudal extension of 32 and 28 cm on the left and right sides, respectively, and showed mild contrast enhancement (Figure 1A–C). Moreover, the patient had type 2 diabetes and flaccid paralysis of lower limbs along with neurogenic bladder due to a trauma injury that had occurred in 1980.

At first observation at our center, physical examination revealed a nontender, greatly enlarged abdomen (waist circumference 134 cm) with huge palpable masses; no superficial lymph nodes or cardio-thoracic abnormalities were found. Routine laboratory tests showed a normal white blood cell count (WBC 9180/\mu L; neutrophils 69%), a hemoglobin of 10.3 g/dL, normal liver function tests and coagulation, a serum creatinine of 0.5 mg/dL, and no proteinuria; C-reactive protein (CRP) was 83 mg/L (normal <5), erythrocyte sedimentation rate (ESR) 73 mm/h, and albumin 2.2 g/dL. Cryoglobulins, complement fractions C3 and C4, antinuclear antibodies, and antineutrophil cytoplasmatic antibodies (ANCAs) were negative or normal; total IgG levels were elevated (2831 mg/dL), particularly IgG4 (912 mg/dL; normal <135 mg/dL). IgE levels were 712 IU/mL (normal <100 IU/mL). The patient had no history of atopy. Common neoplastic markers (carcinoembryonic antigen [CEA], carbohydrate antigen 19.9 [CA 19.9], alpha-fetoprotein and prostate-specific antigen [PSA]) and fecal occult blood were negative. Whole body 99Tc-bone scan was also negative. Positron emission tomography (PET)-CT with 18F-fluorodeoxyglucose showed that the perirenal masses had a moderate metabolic activity (maximum standardized uptake value 4.7) and detected no other metabolically active lesions. A percutaneous biopsy of the right perirenal mass was then performed.

Histology revealed abundant fibrous tissue substituting the perirenal fat with perivascular clusters of foamy histiocytes which were immunohistochemically CD68⁺, S100⁺, and CD1a⁺. The tissue was also infiltrated by numerous lymphocytes and plasma cells. IgG4 staining was positive on >40% of the CD138⁺-infiltrating plasma cells (Figure 1D–F). The lymphoplasmacytic infiltrate was diffused throughout the biopsy specimen, and also aggregated in pseudo-nodular structures, although classical germinal centers were absent. No signs of obliterator phlebitis were detected. Granulomas were also absent. Overall, the histopathological picture was consistent with ECD. However, the presence of an IgG4⁺ plasma cell-rich infiltrate, the abundant fibrosis (although without a storiform pattern), the serum IgG4 elevation, together with the retroperitoneal location of the lesions, their mass-forming appearance, and the absence of long bone involvement (later confirmed by X-rays and CT), which is typical of ECD, made IgG4RD a potential differential diagnosis. Based on the definitions provided in the consensus statement on the pathology of IgG4RD, this case could be considered histologically as “probable” IgG4RD. We eventually made the diagnosis of ECD essentially on the basis of foamy histiocytic infiltration.
We next performed pyrosequencing on the biopsy specimens to assess the V600E BRAF mutation, which is found in about 55% of ECD patients. This mutation tested positive; thus the patient was started on the specific V600E-BRAF inhibitor vemurafenib, which has proven effective in most ECD patients bearing this mutation. However, probably due to the compressive effects of the huge abdominal masses on different structures including the gastrointestinal tract, the deep vessels, and the urinary tract, the patient’s clinical conditions progressively deteriorated; he developed severe and recurrent urinary tract infections and deep pressure ulcers which became chronically infected, and died after 3 months of vemurafenib treatment.

**REVIEW OF OUR ECD COHORT**

To investigate the IgG4 immune response in ECD, we studied all ECD cases diagnosed at or referred to the Nephrology Unit of the University Hospital of Parma between 2004 and 2015, whose serum IgG4 had been measured at diagnosis or during active disease. Where sufficient material from diagnostic biopsies was available, we performed tissue immunostaining of IgG4 and the plasma cell marker CD138, to assess the extent of IgG4⁺ plasma cell infiltration and the proportion of IgG4⁺ plasma cells out of the total number of CD138⁺ plasma cells. We used the anti-CD138 rather than the anti-IgG antibody because the former gives less background staining and, as already reported, it is believed that the vast majority of tissue CD138⁺ plasma cells are IgG⁺. For this reason, some authors use the IgG4/CD138 cut-off ratio (instead of the proposed IgG4/IgG) of 40% to define lesions as IgG4-related. Parma Ethics Committee approved the study.

Of the 25 ECD patients seen at our unit during the study period, 15 had serum IgG4 levels measured at diagnosis or during active disease, and were therefore enrolled in the study. This case series includes the index case reported above. The diagnosis of ECD was made following Veyssier-Belot criteria. All patients underwent an extensive clinical and radiological assessment aimed at screening the sites potentially involved by the disease. Imaging studies included ⁹⁹Tc-bone scintigraphy, long-axis radiographs (and bone CT or magnetic resonance imaging [MRI], when there was no apparent bone involvement on scintigraphy or radiographs), high-resolution lung CT, facial bone CT, contrast-enhanced abdominal CT or MRI, brain MRI, and echocardiography. ¹⁴⁻¹⁶ ¹⁸F-fluorodeoxyglucose PET and cardiac MRI were performed when available, as previously described. Routine laboratory tests, including CRP and ESR, and an array of endocrine tests, were also performed. Serum IgG and IgG4 levels (normal <135 mg/dL) were measured using standard nephelometric methods, as reported.

Tissue biopsies were stained using primary antibodies for IgG4 (Zymed, San Francisco, CA; dilution 1:100) and for CD138 (Bio Care Medical, Concord, CA; dilution 1:200). After immunohistochemical detection, the tissue sections were mildly counterstained with Harris hematoxylin.

All the 15 enrolled patients had a biopsy-proven diagnosis of ECD (Supplementary Figure 1, http://links.lww.com/MD/ A997). Unstained slides from diagnostic biopsies were available for IgG4 and CD138 immunohistochemical analysis in 10 cases. All patients had multisystemic involvement. The frequencies of their main clinical manifestations reflect those reported in previous series and are described in detail in Table 1. Four of the 15 studied patients (26.7%), including our index case (patient #10), had high serum IgG4 levels; in all 4 cases, serum IgG4 were well above the upper limit of normal (Table 1). Three of these 4 cases (#10, #11, and #13) were also examined immunohistochemically, and 2 of them (#10 and #11) showed an IgG4⁺/CD138⁺ plasma cell ratio exceeding the cut-off of 40%. These 2 cases also showed abundant fibrosis, although without a storiform pattern, a diffuse mononuclear cell infiltrate, and some lymphoid follicles. All of them had typical foamy histiocytic infiltration. The remaining patient (#13) with high serum IgG4 and available biopsy only had a mild plasma cell infiltration in the affected tissue (bone); it must be acknowledged, however, that bone lesions in ECD usually harbor a less prominent inflammatory infiltrate than do lesions in other affected sites. Interestingly, 3 of the 4 patients (#8, #10, #11) with high serum IgG4 had clinical features that typically belong to the spectrum of IgG4RD, such as RPF, pericarditis, soft-tissue fibrous lesions, and retro-orbital involvement.

None of the patients with normal serum IgG4 levels showed a significant tissue infiltration by IgG4⁺ plasma cells (Table 1).

**DISCUSSION**

Erdheim-Chester disease and IgG4RD are uncommon disorders; therefore their diagnosis can be particularly challenging. Both are frequently characterized by multisystemic involvement and an extremely variable clinical course, which usually progresses over months to years, with lesions often appearing metachronously. Interestingly, both diseases are characterized by mass-forming, tumor-like lesions, particularly in the retroperitoneum, mesentery, meninges, and orbits. However, both can also have a diffusely infiltrative pattern, such as that observed in the lungs. Distinctive clinical features of ECD include symmetric long bone involvement with osteosclerotic lesions. However, although rarely, bone lesions in ECD can either be absent (as observed in 3 cases of our series) or atypical (affecting the ribs, the spine), which makes the differential diagnosis difficult. On the other hand, pancreatic and biliary tract involvement, presenting as chronic pancreatitis and sclerosing cholangitis, are typical IgG4RD lesions that have never been reported, to the best of our knowledge, in ECD. Finally, RPF usually has peri-aortic and peri-ilar distribution in IgG4RD, whereas in ECD, it affects not only the periaortic space but also the perirenal fat, with the classical appearance of “hairy kidneys.”

Given this possible clinical overlap, histology remains crucial in differentiating ECD and IgG4RD. There may also be histological similarities between the 2 diseases, mainly the presence of abundant fibrosis, the diffuse or pseudonodular inflammatory infiltrate rich in mononuclear cells, and the absence of cellular atypias. However, fibrosis in IgG4RD tends to be storiform and with thicker collagen bands than in ECD. The presence of CD68⁺ CD1a⁺ foamy histiocytes is particularly suggestive of ECD, whereas they are usually absent in IgG4RD; nevertheless, it is well-recognized that lesional tissue in ECD often lacks the classic foamy histiocytic infiltrates. Histiocytes can be elongated and with nonfoamy appearance; cases showing fibrosis alone with only scant histiocytes have been reported.

Our index case and the review of our cohort show that a prominent IgG4 immune response can be observed in ECD. An increase in serum IgG4 was seen in 27% of the patients included in our series, which is a substantial proportion if we consider that even in IgG4RD the percentage of patients with serum IgG4 elevation does not exceed 70%, with normal levels being more common among patients with a probable rather than among those with a definite diagnosis of IgG4RD. Unfortunately,
### TABLE 1. Main characteristics of the Erdheim-Chester disease patients and their IgG4 status

| Patient No. | Age (yrs), Sex | Bone Location | Cardiovascular Manifestations | Retro-peritoneum | Endocrine System | CNS | Other | Serum IgG4 mg/dL | Serum IgG4/Total IgG | Diagnostic Biopsy Site | IgG4+/CD138+ Plasma Cells on Biopsy |
|-------------|---------------|---------------|-------------------------------|-----------------|-----------------|-----|-------|-----------------|---------------------|---------------------|-----------------------------|
| 1           | 47, M         | Long bones (upper and lower limbs) | Pericarditis with tamponade, atrial mass, coated aorta | Perirenal and periaortic fibrosis | Hyperprolactinemia | Skin nodules | 67 | 4% | Skin | 5% |
| 2           | 44, M         | Long bones (lower limbs), skull and facial bones, left clavicle | Pericarditis with tamponade, atrial mass, coated aorta | Perirenal and periaortic fibrosis, bilateral hydronephrosis | Diabetes insipidus, hypothyroidism, hypogonadism | Interstitial lung disease | 11 | 1% | Perirenal | 2% |
| 3           | 43, M         | Long bones (lower limbs) | Coated aorta, myocardial infiltration with coronary involvement, atrial mass | Periaortic and perirenal fibrosis, bilateral hydronephrosis, mesenteric involvement | Hypogonadism | 21 | 2% | Brain | NA |
| 4           | 42, F         | Long bones (upper and lower limbs), facial bones | Coated aorta, myocardial infiltration with coronary involvement, atrial mass | Periaortic and perirenal fibrosis, bilateral hydronephrosis, mesenteric involvement | Hypogonadism | 4 | 1% | Intestinal wall and peri-intestinal tissue | 3% |
| 5           | 71, M         | Long bones (upper and lower limbs) | Pericarditis with massive pericardial effusion, myocardial infiltration with coronary involvement, coated aorta | Perirenal fibrosis | Exophthalmos | 10 | 1% | Perirenal | NA |
| 6           | 46, M         | Long bones (upper and lower limbs), facial bones | Pericarditis with massive pericardial effusion, myocardial infiltration with coronary involvement, coated aorta | Perirenal and periaortic fibrosis, bilateral hydronephrosis, mesenteric involvement | Exophthalmos | 11 | 1% | Perirenal | 5% |
| 7           | 60, M         | Long bones (upper and lower limbs), iliac wings, spine | Pericarditis, myocardial infiltration with coronary involvement, coated aorta | Perirenal and periaortic fibrosis, bilateral hydronephrosis, mesenteric involvement | Diabetes insipidus | Meningeal thickening | 64 | 3% | Orbital | NA |
| 8           | 41, M         | Atypical lesion in the left iliac bone | Pericarditis, myocardial infiltration | Perirenal and periaortic fibrosis, bilateral hydronephrosis, mesenteric involvement | Exophthalmos, optic nerve involvement, xanthelasmas | 309 | 27% | Perirenal | NA |
| 9           | 72, M         | Long bones (upper and lower limbs) | Perirenal fibrosis and left-sided hydronephrosis | Perirenal fibrosis | Exophthalmos, optic nerve involvement, xanthelasmas | 36 | 3% | Perirenal | 5% |
| Patient No. | Age (yrs), Sex | Bone | Cardiovascular | Retro-peritoneum | Endocrine System | CNS | Other                              | Serum IgG4, mg/dL | Serum IgG4/Tot IgG | IgG4<sup>+</sup>/CD138<sup>+</sup> Plasma Cells on Biopsy |
|------------|----------------|------|----------------|------------------|-----------------|-----|------------------------------------|------------------|-------------------|-----------------------------------------------------------|
| 10 (index case) | 56, M          |      |                | Perirenal fibrosis, bilateral hydronephrosis |                 |     |                                    | 912              | 32%               | 45%                                                       |
| 11         | 49, F          |      |                |                  |                 |     |                                    | 684              | 32%               | Skin and subcutaneous tissue                             |
|            |                |      |                | Perirenal fibrosis, bilateral hydronephrosis | Exophthalmos, zygomatic and peri and retro-orbital masses, sinusitis, xanthelasmas |
| 12         | 63, F          | Long bones (lower limbs) | Pericarditis, thoracic periaortitis |                  | Supra/infratentorial and pons infiltration, multiple spinal cord lesions | 15               | 1%                | Bone 0                                                     |
| 13         | 59, M          | Long bones (upper and lower limbs) | Pericarditis, myocardial infiltration, coated aorta |                  | Supra/infratentorial and pons infiltration, multiple spinal cord lesions | 297              | 20%               | Bone 10%                                                   |
| 14         | 70, F          | Long bones (lower and upper limbs) | Pericarditis, myocardial infiltration, coated aorta | Perirenal, perisduen gland, and periaortic fibrosis, bilateral hydronephrosis | Diabetes insipidus | Exophthalmos, lung nodules | 65               | 4%                | Lung nodule NA                                             |
| 15         | 50, M          | Long bones (upper and lower limbs) | Coated aorta | Perirenal and peri-aortic fibrosis, bilateral hydronephrosis |                 | 17               | 2%                | Perirenal 0                                                |

CNS = central nervous system, NA = not available for review and for immunohistochemical detection of IgG4 and CD138.
only 3 of these 4 patients had diagnostic biopsies available for IgG4 immunostaining. However, 2 of them had a prominent IgG4+ plasma cell infiltrate, with an IgG4+/CD138+ cell ratio greater than 40%, the cut-off ratio most often used to define IgG4-related lesions.9

A high proportion of tissue-infiltrating IgG4+ plasma cells is indicative but not specific for the diagnosis of IgG4RD, as it can also be observed in other conditions such as rheumatoid synovitis, carcinoma-associated inflammatory responses, and also in ANCA-associated vasculitides such as granulomatosis with polyangiitis (Wegener) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).3,6 This is why the diagnosis of IgG4RD requires not only the demonstration of an IgG4-rich infiltrate but also other histological lesions such as storiform fibrosis, tissue eosinophilia, and obliterative phlebitis.9 However, the presence of a pronounced IgG4 response, often considered a disease epiphenomenon, may provide clues to the pathogenic mechanisms of the disease. The switch from other IgG subclasses, particularly IgG1, to IgG4, is usually driven by T-helper 2 (Th2) responses, with up-regulation of classical Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, and also by an increased production of immune-regulatory cytokines such as IL-10 and transforming growth factor (TGF)-β.5 This is apparently in contrast with the purported pathogenesis of ECD, which seems to be mainly driven by Th1-dominant responses.21 However, the recognition of an IgG4 (and consequently Th2-dominant) immune response in ECD may identify a subset of patients with a distinct pathogenesis and possibly different therapeutic targets. Interestingly, this is in analogy with the findings observed in other histiocytoses, namely sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease (RDD). Several studies showed that IgG4+ plasma cell-rich infiltrates can be found in both nodal and extranodal RDD lesions, and these cases are thought to represent a distinct disease subset.22,23

Our study has limitations, mainly due to the small sample size, which is clearly related to the rarity of ECD. Therefore, our results must be taken with caution and warrant confirmation by larger studies. In conclusion, our findings suggest that, although in a minority of cases, ECD can be characterized by a prominent IgG4 response, both in the serum and the affected tissues. This makes the differential diagnosis between ECD and IgG4RD even more challenging, and underlines the importance of a thorough clinical and histopathological evaluation of the protein manifestations of these 2 diseases.

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