Vasculitis of the Gastrointestinal Tract in Chronic Periaortitis

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Abstract: The term “chronic periaortitis” (CP), proposed by Mitchinson in 1984, comprises 3 main entities: idiopathic retroperitoneal fibrosis (IRF), inflammatory abdominal aortic aneurysms (IAAAs), and peri-aneurysmal retroperitoneal fibrosis (PRF).

The presence of constitutional symptoms, high acute-phase reactants, positive autoantibodies, and associated autoimmune diseases suggests a systemic inflammatory process. Histopathologic findings show vasculitis with fibrinoid necrosis involving the aortic vasa vasorum as well as the small and medium retroperitoneal vessels.

We reviewed the medical records of 608 patients with a diagnosis of vasculitis involving the gastrointestinal (GI) tract at the Mayo Clinic between January 1996 and December 2007. Only patients with biopsy-proven or typical angiographic findings of vasculitis localized to the GI tract were included.

Five patients were identified with evidence of CP (1 patient with PRF, 1 with IRF, and 3 with IAAAs). Three patients were men, and the median age at diagnosis was 49 years. The diagnosis of GI vasculitis and CP was made simultaneously in 4 patients. At the time of onset, all patients had abdominal pain and constitutional manifestations; the median erythrocyte sedimentation rate was 62.5 mm/1 h (range, 20–86 mm/1 h). All patients had evidence of mesenteric vasculitis at angiography. Three patients also had associated renal artery stenoses. Abdominal computed tomography showed spleen infarcts in 2 patients, bowel wall thickening in 1, and liver infarction in 1. Two patients underwent surgical intervention for acute abdomen; there was histologic evidence of small bowel infarcts and infarction of the spleen and liver in 1. Oral prednisone was administered to all 5 patients (median starting dose, 60 mg/d; range, 25–80 mg/d). Three patients also received immunosuppressive agents, 1 tamoxifen, and 1 anti-tumor necrosis factor therapy. All patients had at least 1 relapse or recurrence of vasculitis, but at last visit, GI vasculitis and CP were in remission in all 5 patients.

This study provides evidence that GI manifestations due to mesenteric vasculitis may be associated with CP. Vasculitic involvement of the renal arteries is also frequently present in these patients. Aggressive immunosuppressive treatment should be promptly initiated to forestall abdominal complications. These findings reinforce the hypothesis that a vasculitic process plays an important role in the pathogenesis of CP.

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Abbreviations: ANCA = antineutrophil cytoplasmic antibody, CP = chronic periaortitis, CRP = C-reactive protein, CT = computerized tomography, ENA = extractable nuclear antigens, ESR = erythrocyte sedimentation rate, FDG-PET = 18F-fluorodeoxyglucose-positron emission tomography, GI = gastrointestinal, HIV = human immunodeficiency virus, IAAA = inflammatory abdominal aortic aneurysm, IRA = inferior mesenteric artery, IRF = idiopathic retroperitoneal fibrosis, IV = intravenous, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, PRF = peri-aneurysmal retroperitoneal fibrosis, SMA = superior mesenteric artery.

INTRODUCTION

Chronic periaortitis (CP) is a clinical pathologic entity characterized by a fibroinflammatory reaction that extends from the adventitia of the abdominal aorta and the common iliac arteries into the retroperitoneum, and often leads to the encasement of adjacent structures (ureters, inferior vena cava).1,31,35,43 CP may be viewed as comprising 3 main entities: idiopathic retroperitoneal fibrosis (IRF), inflammatory abdominal aortic aneurysms (IAAAs), and peri-aneurysmal retroperitoneal fibrosis (PRF). These conditions have common clinical and histopathologic findings, and thus probably represent different manifestations of the same disease.

Although CP has traditionally been considered an exuberant local inflammatory response to atherosclerotic plaque antigens, its clinical presentation is characterized by constitutional symptoms and elevated inflammatory markers, which suggests a systemic inflammatory process as the underlying pathogenesis disease mechanism.35–37,45

Histopathologic findings typically reveal vasculitis with fibrinoid necrosis involving the aortic vasa vasorum as well as the small and medium-sized retroperitoneal vessels in most patients.1,12,6,31,44,46 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) studies in patients with CP have demonstrated large-vessel vasculitis involving the abdominal aorta and the common iliac arteries. In some patients, vasculitis also involved the thoracic aorta and/or its main branches.35 Furthermore, an association between CP and granulomatous necrotizing (antineutrophil cytoplasmic antibody [ANCA]-associated) vasculitis, polyarteritis nodosa, and Henoch-Schönlein purpura has been described in some patients.1,7,9,10,12,14,15,17,18,22,24,25,28,30,41,42,48 These findings raise the question of whether CP should be regarded as a form of idiopathic vasculitis.

As part of a recent review of 608 consecutive patients with vasculitis of the gastrointestinal (GI) tract seen at the Mayo Clinic (Rochester, MN) over 12 years,36 we identified 5 patients with evidence of CP at the time of the onset of GI symptoms. In the current report, we describe the clinical, laboratory, radiology, and pathology findings, as well as the treatment and outcome of these 5 patients. In addition, we review the relevant literature regarding the association between CP and established vasculitides.

PATIENTS AND METHODS

Identification of Patients

We conducted a retrospective medical record review of all patients seen at the Mayo Clinic from January 1, 1996, through December 31, 2007, who had a diagnosis of vasculitis involving...
the GI tract. Using the institution’s medical diagnostic linkage system, we screened the electronic medical records for a diagnosis of vasculitis in combination with key indexing terms. These terms included the following: mesenteric arteries, celiac artery, gastric artery, hepatic artery, splenic artery, esophagus, stomach, small intestine, jejunum, ileum, appendix, colon, rectum, gallbladder, pancreas, liver, and spleen. We reviewed the records of all identified patients with findings of vasculitis involving the GI tract and IRF, IAAA, and PRF.39 The study was approved by the Mayo Clinic Institutional Review Board.

Diagnostic Criteria

The presence of GI vasculitis was ascertained using the following criteria:

1) recent history or presence of acquired GI manifestations;
2) histopathologic evidence of vasculitis in a GI specimen; and/or
3) high-probability angiographic findings (smooth segmental narrowing, dilatation, occlusion, or aneurysms affecting 1 or more GI arteries in the absence of vessel changes suggestive of atherosclerosis or of vasculitis mimics such as fibromuscular dysplasia) with a report by the Mayo Clinic radiologist specifically stating that the angiographic findings were consistent with vasculitis.

Retroperitoneal fibrosis and IAAA were diagnosed by computerized tomography (CT) and magnetic resonance imaging (MRI). IAAAs were identified by the presence of aortic wall thickening and the presence of an inflammatory soft tissue cuff around the aneurysm.

Data Collection

The clinical records, radiologic images, pathologic specimens, and autopsy data were used to abstract detailed data, including CT and MRI, angiographic data, and results of biopsies. Available pathologic specimens were reviewed. In addition, information on treatment regimens, response to treatment, presence and number of relapses, follow-up functional status, and cause of death if relevant was retrieved from the clinical record whenever available. Response to therapy was based on documentation by the treating physician. Relapses were defined as an increase in or progression of disease activity requiring more aggressive therapy.

Review of the Literature

We searched the PubMed database (National Library of Medicine, Bethesda, MD) using the keywords “retroperitoneal fibrosis,” “chronic periaortitis,” “periaortitis,” “Takayasu arteritis,” “giant cell arteritis,” “polyarteritis nodosa,” “Wegener’s granulomatosis,” “microscopic polyangiitis,” “Churg-Strauss syndrome,” “Henoch-Schönlein purpura,” “cryoglobulinemic vasculitis,” “leukocytoclastic angiitis,” and “glomerulonephritis” to retrieve relevant clinical reports of the conditions of interest.

FIGURE 1. A, Mesenteric angiogram: there are numerous areas of luminal irregularity in multiple visceral branches of the superior mesenteric artery (arrows). Areas of smooth narrowing, as well as slight dilatation are seen. B, CT of the abdomen: retroperitoneal fibrosis around the aorta and proximal right ureter (ureteral stent present, arrow). C, Abdominal CT angiogram: beginning in the common hepatic and extending into the hepatic artery, the artery is dilated and irregular with areas of stenosis (arrows). D, Abdominal CT angiogram: the SMA is irregular with a thickened wall and areas of stenosis (arrow), including stenoses involving the origins of the jejunal and ilial branches.
Case 1

A 77-year-old man presented with deep vein thrombosis of the left lower extremity, following which he was anticoagulated. Four months later, he noted the onset of malaise, fever, fatigue, and anorexia. Over the next 3 months, he developed progressive abdominal pain, further appetite loss, diarrhea, and weight loss of 13 kg in 4 months, and was hospitalized. Upper endoscopy showed moderately severe reflux esophagitis and hiatal hernia. Colonoscopy showed a segmental area of ischemic colitis. Contrast-enhanced CT of the abdomen and pelvis revealed soft tissue thickening partially surrounding the thickened infrarenal abdominal aorta and circumferentially thickened inferior mesenteric artery (IMA) consistent with retroperitoneal fibrosis. A visceral angiogram showed abnormalities in the superior mesenteric artery (SMA) distribution with numerous areas of luminal irregularity (areas of smooth narrowing, as well as slight dilatation) in multiple visceral branches consistent with GI vasculitis (Figure 1A). CT of the chest was unremarkable. Left temporal artery biopsy was negative for arteritis. Hepatitis B and C serologies, ANCA, cryoglobulins, antinuclear, anti-DS-DNA and anti-extractable nuclear antigens (ENA) antibodies were negative. Erythrocyte sedimentation rate (ESR) was 86 mm/1 h, C-reactive protein (CRP) was 15 mg/dL (normal to 8 mg/dL), and hemoglobin was 8.9 gm/dL.

Based on these findings, diagnosis of GI tract vasculitis was made and treatment with prednisone 80 mg/d commenced. Two weeks later, the patient was feeling significantly better and had no fever and no abdominal cramping. Appetite, fatigue, and overall well-being were markedly improved. ESR and CRP were normal (8 mm/1 h and <0.3 mg/dL, respectively), and hemoglobin was 12.8 g/dL. The prednisone dose was tapered to 10 mg by 7 months following diagnosis with continued clinical remission. ESR and CRP were 17 mm/1 h and 1.02 mg/dL, respectively. The prednisone dose was further tapered, albeit very slowly because of the persistence of slightly elevated CRP values.

Twenty-one months later, the prednisone dose was 4 mg/d. Six months later, the patient developed bilateral hydrocele, creatinine increased to 1.8 mg/dL, and ESR and CRP to 35 mm/1 h and 8.4 mg/dL, respectively. The patient was still asymptomatic; however, MRI/MR angiography (MRA) of the chest and abdomen showed an area of aneurysmal ectasia of the infrarenal abdominal aorta and bilateral renal artery stenoses. There was a considerable amount of abnormal soft tissue enveloping the retroperitoneal vascular structures from just below the level of the renal arteries and extending inferiorly along the most proximal aspect of the right common iliac vessels. This soft tissue also extended to the aortocaval space and encircled the inferior vena cava at and below the level of the left renal vein, resulting in extrinsic compression and narrowing of the inferior vena cava in this region. There was compression of the upper right ureter with moderate pyelocalcetasis, which had developed from the prior CT. CT-guided biopsy of the paracaval retroperitoneal soft tissue was performed, which revealed changes consistent with retroperitoneal fibrosis (Figure 2A).

The patient remained asymptomatic, while the prednisone dose was kept at 4 mg/d. However, 3 months later retroperitoneal ultrasonography showed right hydro-ureteronephrosis. A right ureteral stent was placed (Figure 1B), prednisone was increased to 30 mg/d, and tamoxifen 20 mg/d was started. The prednisone dose was subsequently gradually reduced, and the stent was periodically changed. The patient remained clinically asymptomatic, while the extension of retroperitoneal soft tissue and the size of the aneurysm remained unchanged on the several subsequent CT scans of the abdomen and pelvis.

Three years later therapy consisted of prednisone 5 mg/d and tamoxifen 20 mg/d. At this follow-up, there was still evidence of bilateral hydroceles, but the right one had become more tense and fuller. There was a modest increase in CRP and ESR (3.3 mg/dL and 35 mm/1 h, respectively), and some concern that fibrosis on CT might be worse. Therefore, the prednisone was increased to 10 mg/d and methotrexate, 15 mg/wk substituted for the tamoxifen. At the most recent follow-up visit 3 months later, there had been no recurrence of symptoms attributable to GI vasculitis or retroperitoneal fibrosis, and ESR and CRP were 5 mm/1 h and 0.4 mg/dL, respectively.
Case 2

A 63-year-old man was seen for a second opinion regarding a previous diagnosis of possible vasculitis dating back 25 years. At that time, he had developed a systemic inflammatory illness with fever, night sweats, fatigue, generalized aching, and loss of appetite with nausea and abdominal pain. He underwent an extensive evaluation including muscle biopsy, temporal artery biopsy, and mesenteric angiogram, which were all unrevealing. He was started empirically on prednisone 60 mg/d with complete resolution of symptoms. Since that time, prednisone had been continued, generally at a dose of 10 mg/d, with few interruptions. Over all these years, there had been no clear evidence of major organ involvement.

At the time of initial evaluation at the Mayo Clinic, the patient was taking prednisone 10 mg/d and had no clear-cut symptoms suggestive of an underlying systemic vasculitis or connective tissue disease. Mild renal insufficiency was noted (creatinine, 1.6 mg/dL). Physical examination revealed only degenerative changes of the hands.

Investigations at that point included MRA of the chest vessels, which was negative. MRA of the abdomen showed stenosis of the proximal celiac artery, high-grade stenosis of the origin of the IMA, and mild to moderate stenosis of the proximal right renal artery. There was soft tissue thickening around the abdominal aorta, beginning at the origin of the SMA and extending inferiorly to near the aortic bifurcation. Minor lymphadenopathy was noted in the retroperitoneum.

CT urogram confirmed the presence of soft tissue thickening in the retroperitoneum at and just inferior to the level of the renal veins with associated lymphadenopathy. Soft tissue thickening was also present along a nonopacified segment of the proximal left ureter. ESR and CRP were elevated (55 mm/1 h and 6.2 mg/dL, respectively), while immune serologies (ANCA, antinuclear antibodies, cryoglobulins) were all negative. A diagnosis of mesenteritis was made. Therapy was continued at prednisone dose 10 mg/d.

At the last follow-up 2 years later, CT urogram was unchanged. The prednisone dose was 5 mg/d. The patient was clinically asymptomatic, and creatinine was stable at 1.5 mg/dL; however, the ESR remained persistently elevated (72 mm/1 h).

Case 3

A 59-year-old woman was hospitalized because of abdominal pain, fever, and fatigue. Two years earlier, she had begun to experience postprandial abdominal pain and persistent diarrhea. The pain was described as a hot burning sensation relieved by avoidance of food. She also had nausea with weight loss (15 kg), mainly in the last year. An angiogram was performed with evidence of right renal artery stenosis, 95% stenosis of the origin of the celiac axis, and complete occlusion of both the SMA and IMA. CT scans of the abdomen showed aneurysmal dilatation, diffuse wall thickening, and a periarteric cuff of inflammatory soft tissue surrounding the infrarenal abdominal aorta. A diagnosis of retroperitoneal fibrosis associated with GI tract vasculitis was made. Therapy was continued at prednisone dose 10 mg/d.

At the last follow-up 2 years later, CT urogram was unchanged. The prednisone dose was 5 mg/d. The patient was clinically asymptomatic, and creatinine was stable at 1.5 mg/dL; however, the ESR remained persistently elevated (72 mm/1 h).
origins of the celiac artery and SMA with poststenotic dilata-
tion, and stenosis of the right renal artery. Diffuse aorta wall
thickening and periaortic inflammatory changes present on the
first CT were improved. ESR was 110 mm/1 h, CRP 4.1 mg/dL,
and creatinine 1.3 mg/dL. Immunologic tests (antineutrophil,
anti-DS-DNA, anti-ENA antibodies, ANCA, cryoglobulins, and
rheumatoid factor) were negative. A diagnosis of GI tract vascul-
itis was made, and the prednisone dose was increased to 40
mg/d. Two months later, ESR and CRP were elevated at 70 mm/1
h and 2.1 mg/dL. Despite an occasional dull ache in the epi-
gastrum, the patient had regained some weight.

Three months later, CT scan revealed an increase in size of
the aortic aneurysm and a slight worsening of the right renal
artery stenosis. Therefore, cyclophosphamide pulse therapy 1 g
intravenously (IV) administered monthly was started, while the
prednisone was maintained at 40 mg/d. Two months later, a
repeat CT angiogram of the abdomen showed worsening of
vasculitis with occlusion and diffuse wall thickening of the celiac
axis distal to the left gastric artery, occlusion at the origin of the
right renal artery, and high-grade stenosis at the origin of the left
renal artery. Left renal and spleen infarcts were also observed.
ESR and CRP were 97 mm/1 h and 12.1 mg/dL, respectively.
The crampy abdominal pain recurred, and the patient was treated
with IV pulses of methylprednisolone 120 mg/d for 8 days. At
this point, the patient underwent surgical repair of the abdominal
aortic aneurysm and reconstruction of the mesenteric and renal
arteries with 4 bypasses.

Three months later, tapering of the prednisone dose to
20 mg/d was initiated. ESR and CRP were 30 mm/1 h and
0.4 mg/dL, respectively. Six months later, while on prednisone
2.5 mg/d, the patient developed malaise, fatigue, and decreased
appetite. Her ESR was 99 mm/1 hour and CRP 4.3 mg/dL. The
prednisone dose was increased to 30 mg/d. At the last follow-up
visit 4 months later, the prednisone dose was reduced to 15 mg/d
without further recurrence of symptoms.

Case 5

A 23-year-old man developed fatigue and left upper
quadrant abdominal pain unrelated to food intake or activity
without changes in bowel habit. Physical examination showed
mild left upper tenderness with no rebound tenderness or
guarding and easily palpable abdominal aortic pulse. An abdo-
men CT scan performed 3 weeks later showed a 4.9-cm intra-
renal abdominal aortic aneurysm with diffuse wall thickening
and a surrounding periaortic inflammation, consistent with
IAAA. The internal iliac arteries and the IMA were occluded.
ESR was 20 mm/1 h; immunologic (antineutrophil antibodies,
ANCA, and cryoglobulins) and microbiologic (syphilis IgG and
IgM, human immunodeficiency virus [HIV], hepatitis virus B
and C) tests were negative. Genetic consultation failed to reveal
any evidence of connective tissue dysplasia such as Ehlers-
Danlos or Marfan syndromes.

A diagnosis of GI tract vasculitis associated with IAAA
was made, and prednisone 60 mg/d was started with resolution
of the abdominal pain. The prednisone dose was gradually re-
duced. Three months later, while on prednisone dose, 10 mg/d,
the patient underwent surgical repair of the abdominal aneurysm.
Pathology of the excised aneurysm wall showed marked ad-
ventitial fibrosis and chronic inflammation with medial thinning
and focal medial loss (Figure 2B). IgG4 staining showed no increase in IgG4 plasma cells.

Four months later, the prednisone was withdrawn, but
soon thereafter mid-epigastric waxing and waning abdominal
pain unrelated to food intake reappeared. ESR was 16 mm/1 h
and CRP 1.05 mg/dL. One month later, intermittent fever with
occasional night sweats developed. By 4 months later, CRP was
found to be increased at 3.75 mg/dL, while ESR was 11 mm/1 h.
CT angiography of the chest and abdomen showed new mural
thickening of the jejunal vessels, near-complete occlusion and
focal aneurysmal dilatation of the SMA, and stenoses and dilata-
tion of multiple distal SMA branches and the hepatic artery
(Figures 1C and D). The IMA and the iliac arteries remained
chronically occluded. Prednisone was restarted at the dose of
60 mg/d in addition to methotrexate 17.5 mg/wk with complete
resolution of the clinical manifestations.

Two months later, when the prednisone dose was reduced
to 15 mg/d, the patient reported progressively increasing ab-
dominal pain. An abdominal CT scan showed segment occlusion
in the mid-SMA. The patient was then started on adalimumab
40 mg every 2 weeks by subcutaneous injection and responded

| TABLE 1. Clinical and Laboratory Findings of the 5 Patients With Chronic Periaortitis and Gastrointestinal Vasculitis |
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| Patient/ Age/ Type of CP | Distribution of CP | Ureteral Involvement | Clinical Symptoms | Gastrointestinal Symptoms | Time From GI Symptom Onset to Diagnosis | Time Between CP and GI Vasculitis Diagnoses | ESR* (mm/h) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1/77/M PRF | Periaortic and periaortic | Unilateral | Fever, fatigue, anorexia, left leg deep vein thrombosis, bilateral hydrocele | Abdominal pain, diarrhea, anemia, weight loss (13 kg in 4 mo) | 1 mo | Simultaneously | 86 |
| 2/38/M IRF | Periaortic | Unilateral | Fever, fatigue, anorexia, diffuse arthromyalgia, night sweats | Abdominal pain, anemia | 25 yr | Simultaneously | 55 |
| 3/59/F IAAA | Periaortic | — | Fever, fatigue, lower back pain | Abdominal pain, abdominal angina, diarrhea, anemia, weight loss (15 kg in 1 yr) | 17 wk | Simultaneously | — |
| 4/49/F IAAA | Periaortic | — | Fatigue, anorexia, fever | Abdominal pain, anemia, weight loss (7 kg in 1 yr) | 18 wk | 3 mo | 70 |
| 5/23/M IAAA | Periaortic | — | Fatigue, fever | Abdominal pain | 1 mo | Simultaneously | 20 |

*Before the start of therapy.
very well. Prednisone was subsequently tapered and was completely discontinued 5 months after starting adalimumab. Approximately 10 months after starting adalimumab, methotrexate was discontinued due to abnormal liver function tests. At his last follow-up visit (31 months from diagnosis), the patient was on monotherapy with adalimumab and had been off prednisone for 6 months. At that time, he was asymptomatic and had normal ESR and CRP. CT imaging of the intraabdominal vessels showed stable findings with no disease progression.

RESULTS

Demographic, Clinical Features, and Laboratory Investigations

Of the 608 patients diagnosed at the Mayo Clinic between 1996 and 2007 with vasculitis of the GI tract, 5 patients also had CP (1 patient with PRF, 1 with IRF and 3 with IAAAs) at the time of the onset of GI manifestations. Table 1 shows the clinical characteristics and laboratory findings of the 5 patients described in detail above. Three were men. The mean age at diagnosis was 49 years. GI vasculitis and CP were diagnosed simultaneously in 4 patients. The time from onset of GI manifestations to diagnosis of GI vasculitis was 1 month for 2 patients; the median interval was 17 months.

All patients had abdominal pain. Four patients had nausea, 3 weight loss, 2 diarrhea, and 1 abdominal angina. Constitutional features (fatigue, anorexia, fever, diffuse arthralgia, and/or myalgia) were present in all patients, while lower extremity deep vein thrombosis, bilateral hydroceles, and night sweats occurred in 1 patient each. Unilateral hydronephrosis occurred in 1 patient, requiring a urethral stent. Patient 3 developed an acute abdomen due to small bowel obstruction caused by ischemic strictures requiring exploratory laparotomy. In this patient, upper endoscopy showed ischemic gastritis and duodenitis. Patient 1 had a colonoscopy that demonstrated ischemic colitis.

ESR before therapy was elevated in 4 of the 5 patients with available data (median value, 62.5 mm/1 h). Immunologic tests (antinuclear antibody, ANCA, cryoglobulins, anti-DSDNA, anti-ENA, and rheumatoid factor) were negative in all 5 patients.

Radiology Results

Table 2 shows the findings of conventional angiography, MRI and/or MRA, and CT and/or CT-angiography at presentation. In all patients multiple lesions were detected affecting multiple GI arteries. The most commonly involved blood vessel was the IMA (4/5), followed by the SMA (3/5). Three patients had unilateral renal artery stenosis.

At presentation, 2 patients (Patients 3 and 5) had IAAA, while Patients 1 and 4 developed aneurysmal enlargement during the follow-up. The latter 2 patients had evidence of inflammation of the infrarenal aorta at presentation. Patient 2 already had soft tissue thickening in the retroperitoneum and some degree of retroperitoneal lymphadenopathy that remained stable during the follow-up. CT evidence of spleen infarcts was present in 2 patients (Patients 3 and 4), liver infarction in 1 (Patient 3), and small and large bowel wall thickening in 1 (Patient 3).

Pathology Results

Pathology specimens were available for 3 patients. Patient 1 had a CT-guided biopsy of the retroperitoneal soft tissue mass that confirmed the diagnosis of IRF (Figure 2A). In Patient 3,

| TABLE 2. Imaging and Pathology Findings |
|----------------------------------------|
| **Patient** | **Angiography** | **MRI/MRA** | **CT/CT Angiography** | **Pathology** |
| 1 | Numerous areas of smooth narrowing and dilatation in multiple visceral branches in the SMA distribution | — | Soft tissue thickening partially surrounding the thickened infrarenal abdominal aorta and circumferentially thickened IMA | Retroperitoneal fibrosis |
| 2 | Moderate/severe stenoses of proximal celiac artery, IMA at the origin, and proximal right renal artery. Soft tissue mass surrounding infrarenal abdominal aorta | — | CT-urogram: soft tissue thickening in the retroperitoneum, extending along the left ureter; some retroperitoneal adenopathy | |
| 3 | 95% stenosis of the origin of the celiac axis, complete occlusion of both SMA and IMA, and right renal artery stenosis | — | Aneurysmal dilatation and diffuse wall thickening of the infrarenal aorta, and periaortic cuff of soft tissue inflammation | Small bowel, liver, and spleen infarcts |
| 4 | High-grade stenoses at the origins of the celiac artery, SMA (with poststenotic dilatation), and right renal artery | — | Infrarenal abdominal aorta with diffuse wall thickening and periaortic cuff of soft tissue inflammation | |
| 5 | — | — | Infrarenal abdominal aortic aneurysm with diffuse wall thickening and periaortic cuff of soft tissue inflammation, occlusions of internal iliac arteries, and IMA | Abdominal aorta aneurysm wall: marked adventitial fibrosis, chronic inflammation with medial thinning, and focal medial loss; IgG4 staining showed no increase in IgG4 plasma cells |
histologic examination of surgically removed abdominal samples showed small bowel infarcts and infarction of the spleen and liver. Finally, in Patient 5, histologic examination of a specimen of the abdominal aorta wall performed during aneurysm repair showed marked adventitial fibrosis and chronic inflammation (Figure 2B) with medial thinning and focal medial loss. IgG4 staining showed no increase in the amount of IgG4 plasma cells infiltrating the tissue.

**Treatment and Outcome**

Three patients underwent surgical intervention. Patient 3 had aorto-mesenteric bypass and resections of small bowel, part of the left liver, and spleen. Two patients (Patients 4 and 5) had repair of the abdominal aneurysm. Patient 4 also had reconstruction of mesenteric and renal arteries with 4 bypasses. A right ureteral stent was placed in Patient 1.

All 5 patients received oral prednisone. The median starting dose was 60 mg/d (range, 25–80 mg/d). The details of treatment and status of patients at last follow-up are shown in Table 3. In 1 patient oral prednisone therapy was preceded by pulse methylprednisolone therapy (120 mg/d for 8 d, Patient 4). The median duration of oral prednisone therapy was 37 months (range, 11 mo to 27 yr). Two patients were treated with prednisone alone, and 3 were treated with corticosteroids and immunosuppressive agents. Two patients (Patients 1 and 5) received methotrexate (15 mg/wk for 3 mo and 17.5 mg/wk for 12 mo, respectively), and 1 patient (Patient 4) received oral azathioprine (200 mg/d for 22 mo) that was subsequently switched to monthly IV cyclophosphamide pulse therapy (1 g/mo for 15 mo) because of a relapse. Patient 1 was also treated with tamoxifen (20 mg/d for 36 mo), and Patient 5 with the anti-tumor necrosis factor agent adalimumab.

Overall, all 5 patients had at least 1 relapse or recurrence. Response to therapy was noted in all patients, even after relapses or recurrences.

Patient 1 responded well to prednisone therapy with resolution of GI and constitutional manifestations; however, he had 2 relapses when the prednisone dose was reduced to 4 mg/d and 5 mg/d, respectively. The first relapse was characterized by the appearance of bilateral hydroceles. Abdomen MRI/MRA showed worsening of retroperitoneal fibrosis, aneurysmal ectasia of the infrarenal aorta, and bilateral renal artery stenoses. Therefore, the prednisone dose was increased to 30 mg/d, and tamoxifen 20 mg/d was started.

The second relapse occurred 3 years later. Right hydrocele was worse at inspection (more tense and fuller) and there was some concern that fibrosis might have worsened as assessed by CT. The prednisone dose was increased from 5 mg/d to 10 mg/d, and methotrexate 15 mg/wk was substituted for tamoxifen. At last follow-up 3 months later, the patient was in remission on this same therapy.

Patient 2 had been on prednisone therapy for 27 years. During the first 25 years, the dose was 10 mg/d. Attempts to taper and discontinue the corticosteroid therapy failed due to recurrences of abdominal pain. However, during the last 2 years the patient was able to gradually reduce the prednisone dose to 5 mg/d without suffering a disease relapse. At the last follow-up visit, CT urogram was unchanged.

Patient 3 was treated with prednisone only. Five years after stopping therapy, she had a recurrence characterized by small bowel ischemic obstruction as well as liver and spleen infarctions. Small bowel resection, resection of part of the left liver, and splenectomy were subsequently necessary. The patient responded well to surgical intervention. At last follow-up visit, 2 months later, she was in remission on prednisone 5 mg/d, which had been started 4 months previously because of generalized arthralgia and/or myalgia.

Patient 4 was successfully treated at disease onset. The first relapse occurred 20 months after starting treatment, while she was taking prednisone 10 mg/d. MRI/MRA showed a rapidly enlarging abdominal aneurysm and stenoses of the celiac artery, SMA, and right renal artery. The prednisone dose was increased to 40 mg/d, and GI symptoms markedly improved. The second relapse occurred 5 months later, while she was still taking prednisone 40 mg/d because of persistent abdominal pain. The relapse was characterized by an increase in size of the abdominal aneurysm and worsening of the right renal artery stenosis on CT angiogram. IV cyclophosphamide pulse therapy (1 g/mo) was started, and azathioprine discontinued, while prednisone was maintained at the dose of 40 mg/d.

Two months later, the patient had the third relapse. She complained of crampy abdominal pain, and a CT angiogram revealed occlusion of the celiac artery and right renal artery, high-grade stenosis of the left renal artery, and left renal and spleen infarcts. IV methylprednisolone pulse therapy was started, and she underwent an abdominal aortic aneurysm repair and reconstruction of the mesenteric and renal arteries with 4 bypasses. The GI symptoms resolved. Nine months later, when the oral prednisone dose was reduced to 2.5 mg/d, she developed constitutional symptoms and the ESR level increased to 99 mm/1 h. The prednisone dose was increased to 30 mg/d. At patient’s last follow-up visit, 4 months later, the prednisone dose was reduced to 15 mg/d, and she was clinically asymptomatic.

Patient 5 was initially treated with prednisone only. However, 5 months after stopping therapy, prednisone had to be restarted at the dose of 60 mg/d with methotrexate 17.5 mg/wk because of recurrence of GI and constitutional symptoms. CT angiogram showed new mural thickening of the jejunal vessels, near-complete occlusion and focal aneurysmal dilatation of the SMA, and stenoses/dilatation of multiple distal SMA branches and the hepatic artery.

The patient responded well and symptoms resolved, and the prednisone was again gradually tapered. However, 2 months later, taking prednisone 15 mg/d, abdominal pain reappeared and increased in intensity, while an abdominal angiogram showed a new vasculitic lesion in the SMA. The patient subsequently went into remission with anti-tumor necrosis factor therapy, and at the last follow-up visit he was able to discontinue prednisone.

**DISCUSSION**

We describe here 5 patients with vasculitis of the GI tract affecting medium-sized arteries associated with CP. GI vasculitis and CP were diagnosed concomitantly in 4 patients, suggesting that a common vasculitic process was involved in the pathogenesis of both conditions. This hypothesis is further supported by the simultaneous worsening of mesenteric vasculitis and/or renal artery stenoses and CP observed in most of the relapses. Still, the link between GI vasculitis and CP remains largely a matter of debate.

CP was originally interpreted as an exuberant local inflammatory reaction to atherosclerotic plaques in the abdominal aorta. However, the presence of constitutional manifestations, elevated inflammatory markers, and, sometimes, of various autoantibodies in CP patients reported in subsequent studies appears to point away from a localized and toward a systemic inflammatory process. Consistent with this hypothesis, a recent study demonstrated that all patients with CP had evidence on FDG-PET of grade 2+ or 3+ vascular uptake in the abdominal aorta and/or iliac artery, consistent with widespread large-
| Patient | Surgical Treatment | Medical Treatment | Follow-Up Imaging (Time From GI Vasculitis Diagnosis) | Status at Last Follow-Up | Follow-Up* |
|---------|--------------------|-------------------|-----------------------------------------------------|--------------------------|------------|
| 1       | Colonoscopy: ischemic colitis Right ureteral stent | Oral prednisone (initial dose, 80 mg/d) for 75 mo. Tamoxifen (20 mg/d) for 36 mo. Methotrexate (15 mg/wk) for 3 mo. | MRI/MRA (32.5 mo): inflammatory aneurysm of infrarenal abdominal aorta; bilateral renal artery stenoses; soft tissue mass enveloping the retroperitoneal vascular structures and extending along right common iliac vessels to aortocaval space; compression of inferior vena cava and right ureter with hydro-ureteronephrosis; bilateral renal artery stenoses. CT abdomen (71.5 mo): no changes of the extension of retroperitoneum soft tissue mass and aneurysm size. | Remission of GI symptoms. Stable RPF and abdominal aorta aneurysm. In therapy with prednisone 10 mg/d and methotrexate 15 mg/wk | 83 mo |
| 2       | —                  | Oral prednisone (initial dose, 60 mg/d) for 27 yr | CT-urogram (24 mo): unchanged. | Remission of GI symptoms. Stable RPF. In therapy with prednisone 5 mg/d | 27 yr |
| 3       | Upper endoscopy: ischemic gastritis and duodenitis Aorto-mesenteric bypass. Resections of small bowel, part of the left liver and spleen | Oral prednisone (initial dose, 25 mg/d) for 11 mo | Angiography (one mo): new stenoses of multiple SMA branches, right hepatic and left gastric arteries. CT abdomen (3 wk): diffuse wall thickening of alimentary tract from the stomach to the mid-transverse colon consistent with ischemic changes. CT abdomen (68 mo): infarction of the spleen and lateral segment of the left hepatic lobe, and ischemic thickening of the mid-distal small bowel loops. | Remission of GI symptoms. Stable abdominal aorta aneurysm. In therapy with prednisone 5 mg/d | 8 yr |
| 4       | Repair of abdominal aneurysm; reconstruction of mesenteric and renal arteries with 4 bypasses | Oral prednisone (initial dose, 40 mg/d) for 40 mo. IV methylprednisolone (120 mg/d) for 8 d. Azathioprine (200 mg/d) for 22 mo. IV cyclophosphamide (1 g/mo) for 15 mo. | CT angiography (3 mo): increase in size of aortic aneurysm and worsening of right renal artery stenosis. CT angiography (5 mo): occlusion and diffuse wall thickening of celiac artery, occlusion of right renal artery at the origin, and high-grade stenosis of left renal artery at the origin. Left kidney and spleen infarcts. | Remission of GI symptoms. Stable abdominal aorta aneurysm. In therapy with prednisone 15 mg/d | 38 mo |
| 5       | Repair of abdominal aneurysm | Oral prednisone (initial dose, 60 mg/d) for 14 mo. Methotrexate (17.5 mg/wk) for 12 mo. Adalimumab (40 mg sq every 2 wk) for 11 mo. | CT angiography (12 mo): mural thickening of the jejunal vessels, near total occlusion and aneurysm of SMA, and stenoses/dilatation of multiple distal SMA branches and hepatic artery. CT angiography (14 mo): new 3 cm segment of occlusion in mid-SMA. | Remission of GI symptoms. In therapy with adalimumab 40 mg sq every 2 wk | 31 mo |

*From the onset of symptoms.
### TABLE 4. Association Between Chronic Periaortitis and Vasculitides Reported in Literature

| First Author Year (Reference) | No. of Patients | Retroperitoneal Findings | Vasculitides |
|-------------------------------|-----------------|--------------------------|--------------|
| **Large vessel**              |                 |                          |              |
| Kuwana 1992 (21)              | 1               | Bilateral ureteral obstruction with bilateral hydronephrosis CT: periaortic retroperitoneal mass<br>and thickening of the aortic wall | Stenosis/dilatation of aortic arch, left renal artery, and splenic artery |
| Le Moal 2001 (23)              | 1               | CT: thoracic-abdominal periaortitis | Biopsy-negative large-vessel giant cell arteritis |
| Salvarani 2005 (40)           | 3               | Left ureteral obstruction with hydronephrosis in 1 case CT and FDG-PET: perversual soft tissue mass involving the abdominal aorta and iliac arteries in all 3 patients, inflammatory abdominal aneurysm in 1 patient | Involvement of thoracic aorta and/or its branches (vascular uptake on FDG-PET) |
| Vaglio 2008 (47)              | 14              | CT, MRI, FDG-PET: perversual soft tissue mass involving the abdominal aorta and iliac arteries | Involvement of the thoracic aorta and its branches (9 patients had thoracic periaortitis, 2 thoracic periaortitis and pericarotid involvement, 3 thoracic aneurysm) |
| **Medium vessel**             |                 |                          |              |
| Hellstrom 1966 (14)           | 1               | Bilateral ureteral obstruction with hydronephrosis Pathology: fibro-inflammatory tissue showing necrotizing vasculitis | Necrotizing vasculitis involving small arteries of gallbladder, liver, and testis Polyarteritis nodosa (probable) |
| Carton 1969 (7)               | 1               | Biopsies during bilateral lumbar sympathectomy: necrotizing vasculitis of the medium-sized arteries accompanying the sympathetic chain Autopsy: mediastinal and retroperitoneal fibrosis | Polyarteritis nodosa |
| Météhni 1988 (28)             | 1               | Bilateral ureteral obstruction with hydronephrosis CT: retroperitoneal perianeurysmal mass | Polyarteritis nodosa Polyarteritis nodosa |
| Bourgault 1989 (5)            | 1               | Left ureteral obstruction with hydronephrosis CT: retroperitoneal mass Pathology: fibrotic tissue | Polyarteritis nodosa |
| Hautekeete 1990 (12)          | 1               | Bilateral ureteral obstruction with hydronephrosis CT: soft tissue mass around the aortic prosthesis, reaching forward toward the mesentery | Polyarteritis nodosa |
| Iino 1992 (17)                | 1               | Pathology: aortic dissection with necrotizing vasculitis in the vasa vasorum of the adventitia and media of the thoracic aorta | Polyarteritis nodosa |
| van Bommel 2002 (48)         | 1               | CT: retroperitoneal mass surrounding the inferior cava vein and abdominal aorta | Polyarteritis nodosa |
| **Small vessel**              |                 |                          |              |
| Baker 1978 (3)                | 1               | Left ureteral obstruction with hydronephrosis Pathology: fibro-inflammatory tissue with necrotizing vasculitis involving small and medium-sized arteries | Wegener granulomatosis |
| Hollingworth 1980 (15)        | 1               | Bilateral ureteral obstruction with hydronephrosis Inferior venocavagram: blockage at the same level as ureteral blockage CT: no mass in the region corresponding to inferior cava venal and ureteral obstruction | Wegener granulomatosis |
| Metselaar 1985 (29)           | 1               | Left ureteral obstruction with hydronephrosis Pathology: fibro-inflammatory tissue showing necrotizing vasculitis | Wegener granulomatosis |
| Leche 1985 (22)               | 1               | Bilateral ureteral obstruction with acute renal failure Pathology: inflammatory tissue with vasculitis | Wegener granulomatosis |
| Adelizzi 1986 (1)             | 1               | Bilateral ureteral obstruction with right hydronephrosis Pathology: inflammatory tissue with prevalent lymphocytes, granulomas, and numerous scattered eosinophils | Wegener granulomatosis |
| Sieber 1990 (41)              | 1               | CT and aortogram: left lateral periaortic mass near the aortic bifurcation Exploratory laparotomy: inflammatory aortic aneurysm extending from the renal arteries to the aortic bifurcation Aneurysmal wall biopsy specimen: granulomatous inflammatory process | Wegener granulomatosis |

(Continued on next page)
vasculitis involving these arteries.\(^40\) Vasculitis of the thoracic aorta and/or its branches was documented by FDG-PET, CT angiography, and MRA in 34% of 41 consecutive Italian CP patients,\(^41\) while reports of aortic arch syndrome in CP appear to confirm that CP may also affect the thoracic aorta.\(^21,23\) (Table 4).

Along the same lines, autopsy studies have shown that the adventitial inflammation and fibrosis seen in CP may not be limited to the abdominal aorta, but may also involve the thoracic portion.\(^40\)

Histologic evaluation of these cases has failed to reveal significant differences between IAAA and IRF apart from an increase in aortic diameter in the former.\(^35\) In IAAAs, histopathologic findings demonstrate that most of the thickening of the aortic wall is due to an enlargement of the adventitia caused by a marked inflammatory reaction.\(^35\) The inflammatory infiltrate of the aortic adventitia may have a diffuse or follicular pattern. The nodular aggregates of inflammatory cells (mainly lymphocytes) are usually centered around the adventitial vasa vasorum, which show evidence of vasculitis with fibrinoid necrosis.\(^8,26,31,44\) This inflammatory histopathologic pattern has been found in all 3 CP subsets. These findings are in keeping with a local immune response to an antigen probably localized in the adventitia.

Taken together, imaging and histologic evidence suggest that CP may represent a large-vessel vasculitis involving the abdominal aorta and common iliac arteries, which in some patients may spread to the thoracic aorta and/or its branches. This vasculitis may be triggered by a yet-unknown inciting antigen in the adventitia.

In addition to large-vessel involvement, there is emerging evidence that medium- and small-sized arteries may also be affected in CP.\(^5,44\) Vaglio et al.\(^44\) found vasculitis with fibrinoid necrosis involving small- and medium-sized retroperitoneal vessels in most of the IRF patients undergoing surgery. Similarly, the cases in the current study provide evidence that medium-sized vessels located outside the retroperitoneum may be affected, albeit infrequently, in CP. Various case reports\(^1\) have described the involvement of medium- and small-sized vessels as part of established vasculitides, particularly granulomatous, ANCA-related necrotizing vasculitis and polyarteritis nodosa, in association with CP (see Table 4).

### TABLE 4. (Continued)

| First Author | Year (Reference) | No. of Patients | Retroperitoneal Findings | Vasculitides |
|--------------|------------------|----------------|--------------------------|--------------|
| ter Maaten   | 1993 (42)        | 1              | Left ureteral obstruction | Wegener granulomatosis |
|              |                  |                | Pathology: necrotizing granulomatous vasculitis |              |
| Middleton   | 1994 (30)        | 1              | Right ureteral obstruction with hydrenephrosis | Wegener granulomatosis |
|              |                  |                | CT: soft tissue retroperitoneal mass extending bilaterally along the course of the ureters from just below the kidney to the common iliac arteries |              |
| Fink        | 1994 (10)        | 1              | Right ureteral obstruction with hydrenephrosis | Wegener granulomatosis |
|              |                  |                | CT: thickened ill-defined tissue around the aorta, extending to the right iliac artery |              |
| Blockmans   | 2000 (4)         | 1              | CT: dilatation of the distal part of abdominal aorta, thickened aortic wall, a patent excentric lumen surrounded by a hypodense rim | Wegener granulomatosis |
| Izzedine    | 2002 (18)        | 1              | Left ureteral obstruction with hydrenephrosis | Wegener granulomatosis |
|              |                  |                | Pathology: inflammatory tissue with necrotizing granulomatous vasculitis |              |
| de Roux-Serratrice | 2002 (9) | 1 | CT: ectasia of infrarenal aorta and periaortic inflammatory infiltration | Wegener granulomatosis |
| Carels      | 2005 (6)         | 1              | CT: 4-cm aneurysm of the distal part of the aorta with inflammation of the surrounding adipose tissue | Wegener granulomatosis |
| Levin       | 2006 (24)        | 1              | CT, CTA, FDG-PET: periaortic soft tissue mass | Wegener granulomatosis |
| Akman       | 1983 (2)         | 1              | Bilateral ureteral obstruction with hydrenephrosis | Henoch-Schönlein purpura |
| Vaglio      | 2002 (46)        | 2              | 1st case: Left ureteral obstruction with hydrenephrosis | ANCA-positive rapidly progressive GMN |
|              |                  |                | CT: periaortic mantle of soft tissue density surrounding the left ureter |              |
|              |                  |                | 2nd case: Right ureteral obstruction with hydrenephrosis |              |
|              |                  |                | CT and US: aneurysmal dilatation of the abdominal aorta and perianeurysmal mantle of soft tissue density surrounding the right ureter |              |
| Martinez-Odriozola | 2008 (27) | 1 | Bilateral ureteral obstruction with ureterohydronephrosis | ANCA-positive rapidly progressive GMN |
|              |                  |                | CT: retroperitoneal soft-tissue mass surrounding the aorta and extending longitudinally from renal arteries to common iliac arteries |              |
|              |                  |                | Pathology: fibrosis and a chronic inflammatory infiltrate |              |

Abbreviations: CTA = computed tomography angiography, US = ultrasonography, GMN = glomerulonephritis.
These observations suggest a link between CP and vasculitides of small- and medium-sized vessels. Specifically, most reported patients with vasculitis and CP presented with ureteral obstruction and hydronephrosis (Table 4). Ureteral involvement has been described as an extrarenal urogenital manifestation of ANCA-related necrotizing granulomatous vasculitis and polyarteritis nodosa.\(^{16}\) Vasculitis may be the cause of ureteral obstruction because of the direct vasculitic involvement leading to fibrosis.\(^{34}\) On the other hand, IgG4-related retroperitoneal fibrosis and IgG4-bearing plasma cell infiltration of various organs arise in the context of the so-called IgG4-related sclerosing disease, a condition characterized by extensive T-lymphocyte infiltration of the tissue. The role of IgG4 in the pathogenesis of IgG4-related sclerosing disease remains unclear, but the limited evidence available so far suggests that IgG4 infiltration might play a role in only a minority of all AAA/CP cases.

GI involvement due to mesenteric vasculitis is common in polyarteritis nodosa and may be associated with a poor outcome, particularly in patients who develop an acute abdomen syndrome.\(^{25}\) In fact, peritonitis, bowel perforation, GI ischemia or infarction, and intestinal occlusion have been found to be significantly associated with increased mortality in a cohort of patients with GI manifestations and systemic necrotizing vasculitides.\(^{33}\) Two patients in the current study underwent surgery for GI manifestations. One patient had severe mesenteric vasculitis with complete occlusion of both mesenteric arteries and severe obstruction of celiac artery at its origin. Despite aortomesenteric bypass and corticosteroid therapy, she developed spleen and liver infarctions as well as small bowel obstruction due to ischemic strictures, which required small bowel resection and partial liver resection and splenectomy. The second patient had repair surgery of the mesenteric and renal arteries with 4 bypasses for complete occlusion of the celiac and right renal arteries and severe stenoses of superior mesenteric and left renal arteries. Left renal and spleen infarcts were also present.

These observations suggest that mesenteric vasculitis associated with CP is probably as severe as that seen in other established vasculitides. Therefore, it is critical that physicians endeavor to recognize this condition promptly, because early, aggressive immunosuppressive treatment may prevent abdominal complications.

GI manifestations were successfully treated in most of our patients with corticosteroid therapy, which was combined with immunosuppressive chemotherapeutic agents in 3 patients and with anti-tumor necrosis factor agent in 1. At last visit, GI vasculitis and CP were in remission in all 5 patients. In most cases, relapses and recurrences were associated with tapering of corticosteroid therapy. Patients usually responded promptly to an increase in the dose or reintroduction of corticosteroids, sometimes associated with immunosuppressive agents. One relapse responded to the introduction of anti-tumor necrosis factor therapy. Our experience supports the use of corticosteroid treatment in CP, which usually results in the resolution of symptoms and regression of the retroperitoneal mass.\(^{43}\)

In conclusion, the results of the current study suggest that GI medium-sized vasculitis occurs in the context of CP. Awareness of this uncommon but potentially serious manifestation may aid the clinician in recognizing it and thus starting aggressive treatment early, which may prevent severe complications.

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