Single-Organ Gallbladder Vasculitis

Characterization and Distinction From Systemic Vasculitis Involving the Gallbladder. An Analysis of 61 Patients

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Abstract: Systemic vasculitis (SV) involving abdominal structures usually has a poor prognosis. Gallbladder vasculitis (GV) has been reported as part of SV (GB-SV) and focal single-organ vasculitis (GB-SOV). We analyzed clinical and histologic characteristics of patients with GV to identify features that differentiate GB-SOV from the systemic forms of GV. To identify affected patients with GV we used pathology databases from our institution and an English-language PubMed search. Clinical manifestations, laboratory and histologic features, treatment administered, and outcomes were recorded. Patients were divided in 2 groups, GB-SOV and GB-SV. As in previous studies of single-organ vasculitis, GB-SOV was only considered to be a sustainable diagnosis if disease beyond the gallbladder was not apparent after a follow-up period of at least 6 months. Sixty-one well-characterized patients with GV were included (6 from our institution). There was no significant sex bias (32 female patients, 29 male). Median age was 52 years (range, 18–94 yr). GB-SOV was found in 20 (33%) and GB-SV in 41 (67%) patients. No differences were observed in age, sex frequency, or duration of gallbladder symptoms between groups. Past episodes of recurrent right-upper quadrant or abdominal pain and lithiasic cholecystitis were more frequent in GB-SOV patients, whereas acalculous cholecystitis occurred more often in GB-SV. In GB-SV, gallbladder-related symptoms occurred more often concomitantly with or after the systemic features, but they sometimes appeared before SV was fully developed (13.5%). Constitutional and musculoskeletal symptoms were reported only in GB-SV patients. Compared to GB-SOV, GB-SV patients presented more often with fever (62.5% vs 20%; $p = 0.003$) and exhibited higher erythrocyte sedimentation rate levels (80 ± 28 vs 37 ± 25 mm/h, respectively; $p = 0.006$). All GB-SV patients required glucocorticoids and 50% of them also received cytotoxic agents. Mortality in GB-SV was higher than in GB-SOV (35.5% vs 10%; $p = 0.05$). Nongranulomatous inflammation with fibrinoid necrosis of medium-sized vessels occurred equally in both groups (>90%). Forms of SV affecting the gallbladder included polyarteritis nodosa ($n = 10$), hepatitis B virus-associated vasculitis ($n = 8$), cryoglobulinemic (essential or hepatitis C virus-associated) vasculitis ($n = 6$), vasculitis associated with autoimmune diseases ($n = 6$), microscopic polyangiitis ($n = 4$), eosinophilic granulomatosis with polyangiitis (Churg-Strauss) ($n = 4$), IgA vasculitis (Henoch-Schönlein) ($n = 2$), and giant cell arteritis ($n = 1$).

GV is uncommon. Its histology most often consists of a nongranulomatous necrotizing vasculitis affecting medium-sized vessels. GB-SOV is usually discovered after routine cholecystectomy performed because of the presence of local symptoms, gallstone-associated cholecystitis, and contrary to GB-SV, GB-SOV is usually not associated with systemic symptoms. Acute phase reactants and surrogate markers of autoimmunity are usually normal or negative in GB-SOV. GB-SOV does not require systemic antiinflammatory or immunosuppressive therapy; surgery is adequate to achieve cure. GB-SV always warrants immunosuppressant therapy and is associated with high mortality. The finding of GV may precede the generalized manifestations of SV. Therefore, once GV is discovered, studies to determine disease extent and a vigilant follow-up are mandatory.

(*Medicine* 2014;93: 405–413)

Abbreviations: ACR = American College of Rheumatology, ANCA = antineutrophil cytoplasmic antibodies, CRP = C-reactive protein, EGPA = eosinophilic granulomatosis with polyangiitis, ESR = erythrocyte sedimentation rate, GB = gallbladder, GPA = granulomatosis with polyangiitis, GV = gallbladder vasculitis, HBV = hepatitis B virus, HCV = hepatitis C virus, MPA = microscopic polyangiitis, PAN = polyarteritis nodosa, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SOV = single-organ vasculitis, SV = systemic vasculitis.

INTRODUCTION

Abdominal structures are frequently involved in systemic vasculitides (SV),[24] including polyarteritis nodosa (PAN), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, IgA vasculitis (Henoch-Schönlein purpura), cryoglobulinemic vasculitis, Takayasu arteritis, and less frequently in giant cell arteritis or chronic periaortitis.[8,24,39,55,62,63] Gastrointestinal involvement is usually associated with a worse prognosis in these forms of SV.[46,57,62]

Abdominal territories may rarely be the site of a focal single-organ vasculitis (SOV).[24] SOV has been reported to occur in several locations within the abdominal cavity, including the esophagus, stomach, omentum, small and large intestine, appendix, pancreas, and gallbladder (GB).[24] In all these territories vasculitis has been reported to be cured with surgical excision alone.[24] An exception to these good outcomes with SOV is vasculitis that affects the small or large bowel. Whether it is part of SV or SOV, bowel vasculitis is associated with a high risk of severe morbidity and mortality.[46,54]

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José Hernández-Rodríguez was supported by a research award from Hospital Clínic of Barcelona, Spain; the RJ Fasenmyer Center for Clinical Immunology at the Cleveland Clinic, Cleveland, Ohio; the Ministerio de Ciencia e Innovación (SAF 11/30073), Spain. Gary S. Hoffman was supported in part by the Harold C. Schott Foundation. The other authors have no funding or conflicts of interest to disclose.

Results partially presented at the 16th International Vasculitis and ANCA Workshop, Paris, France, April 2013.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000205

GB vasculitis (GV) has been described in 8%–40% of patients with PAN[11,46] and in fewer than 2% of patients with other forms of SV.[46] GV has also been reported in patients with autoimmune diseases,[6,11,33,42,58] and some authors have attributed a worse prognosis to patients with GV and surrogate markers of autoimmunity.[6]

Previous attempts to classify SOV were based on vessel size[49] or histologic inflammatory patterns.[7] However, the revised Chapel Hill consensus conference guidelines for nomenclature and definitions of vasculitides[30] recommend that a specific type of SOV should be designated by the name of the involved organ and vessel type (for example, GB arteritis, cutaneous arteritis) and not utilize terms used for SV; because SOV is not a systemic disease, the terms PAN or giant cell arteritis of the GB would be misleading.

Previous studies of vasculitis affecting the breast,[26] gynecologic,[27] and testicular[25] structures, in which vasculitic lesions may be found as SOV or as part of SV, have already established that SOV forms can be cured with surgical excision. Therefore, the current study was designed to characterize clinical, laboratory, and histologic findings of patients with GV and to identify features that differentiate GB-SOV from the systemic forms of GV (GB-SV).

PATIENTS AND METHODS

Patient Selection

Patients with biopsy-proven GV were identified from the Cleveland Clinic Department of Anatomic Pathology database over a period of 22 years (from January 1986 to December 2007). Additional cases were identified from a search of cases published in the English-language literature (PubMed, National Library of Medicine, Bethesda, MD) from 1951 to June 2013. Terms used in the search included ''gallbladder,'' ''vasculitis,'' ''arteritis,'' ''angiitis,'' ''isolated,'' ''limited,'' ''giant-cell or temporal arteritis,'' ''polyarteritis nodosa,'' ''Wegener's granulomatosis,'' ''microscopic polyangiitis,'' ''Churg-Strauss syndrome,'' and ''Henoch-Schönlein purpura.'' Additional references from these articles were also included if they met inclusion criteria.

Data collected included clinical, laboratory, and imaging features at disease presentation, histology of the GB and other performed biopsies, treatment administered, and events during follow-up. Patients were included if there were histologic evidence of vasculitis and adequate data available to determine extent of disease (SOV or part of SV). Patients already diagnosed with SV and GB abnormalities, such as hydrops or cholecystitis, without resection proving GV were not included. Patients in whom clinical data were insufficient or duration of follow-up was not stated or was less than 6 months were also excluded. The study was approved by the Cleveland Clinic Institutional Review Board.

Clinical and Histopathologic Data Collection

We collected all significant clinical, laboratory, imaging, and histopathologic data, which were recorded in a standardized database. Clinical data included GB-related manifestations; constitutional symptoms such as malaise, fatigue, fever, and weight loss; musculoskeletal, cutaneous, or peripheral nervous system involvement and/or other features suggestive of SV; duration of symptoms prior to diagnosis of GV; and their chronology of appearance. Laboratory data recorded when available included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, hepatic enzymes, serum creatinine, urinalysis, hepatitis B and C virus (HBV/HCV) serologies, and surrogate markers of autoimmunity (for example, antinuclear antibodies, rheumatoid factor, ANCA, cryoglobulins, and complement levels). We also recorded all available information about imaging procedures, biopsy results, treatment, duration of follow-up, and outcomes.

GB specimens from the Cleveland Clinic patients with GV were formalin-fixed, paraffin-embedded, and stained with hematoxylin-eosin. Slides were re-examined by specialists in vascular pathology (CDT and ERR). All GB biopsies included in the study were categorized according to vessel size and pattern of inflammation, for example, small-sized or medium-sized and granulomatous or nongranulomatous, respectively.

Categorization According to the Disease Extent

Based on the presence or absence of associated systemic disease, patients with GV were classified as GB-SOV or GB-SV. GB-SOV diagnosis was made when vasculitis was limited to GB in the absence of systemic disease over a minimum follow-up period of 6 months. Cases reported as GB-SOV in whom follow-up was not reported or was less than 6 months were excluded. Diagnosis of GB-SV was based on additional evidence of biopsy-proven vasculitis in any territory other than GB or the presence of features noted in the 1990 ACR classification criteria[2] and 2012 Chapel Hill consensus conference on nomenclature for vasculitis.[30] Cases with GV and nonspecific constitutional or musculoskeletal symptoms alone or those in whom the clinicians used glucocorticoids with no proof of vasculitis elsewhere were not considered as SV.

Statistical Analysis

To achieve better comparisons of ESR and hemoglobin values we considered these parameters as binary variables (normal/abnormal). ESR was considered normal when the value was reported as ''normal'' or $\leq$20 mm/h, and abnormal when reported as ''high'' or ''abnormal'' or $>$20 mm/h. Hemoglobin levels were considered normal when the value was reported as ''normal'' or $\geq$12 g/dL, and abnormal when reported as ''low'' or ''abnormal'' or $<$12 g/dL.

With SPSS v. 18.0, the Fisher exact test and Student unpaired t-test were used for the comparison of categorical and continuous variables, respectively (p values ≤ 0.05 were considered statistically significant).

RESULTS

Cleveland Clinic Series

Six patients with GV were identified from the Cleveland Clinic Department of Anatomic Pathology database among 2080 GB specimens over 22 years (1986–2007). The frequency of vasculitis among all GB surgeries in our institution was 0.29%. Among these 6 patients, 4 presented with GB-SOV and 2 with GB-SV (HBV-associated vasculitis and cryoglobulinemic vasculitis) (Table 1).

Overall Results

Sixty-one well-characterized patients with GV were finally included. Among these, 32 were female and 29 male (Table 2). Six patients were identified by the Cleveland Clinic database search and 55 patients from the PubMed search. Originally, 83 cases were identified as GV in the literature; however, 28 patients were excluded: 15 patients from a single study,[6] 1 patient with IgA vasculitis (Henoch-Schönlein),[35] and 4 with

TABLE 1. Cleveland Clinic series of patients with vasculitis of the gallbladder

#	Age/Gender/ Race Type of vasculitis	Abdominal Symptoms*	Systemic Symptoms*	Duration of Symptoms	Diagnostic/ therapeutic procedures	Gallbladder histology	ESR mm/1st h	Hgb mg/dl	Other laboratory parameters	Medical treatment	Duration of follow-up (months)	Status at end of follow-up
1	45 yrs/F/W	Intermittent RUQ abdominal pain, mostly with fatty food	None	13 yrs	Abnormal cholescintigraphy	Non-granulomatous necrotizing arteritis, active and healed lesions	34	12	NL/Neg CRP, renal, hepatic function, RF/ANA	None	7	Alive
	SOV											No signs of vasculitis
2	80 yrs/F/W	RUQ abdominal pain and bloating	37.5°C. No systemic symptoms thereafter	1 week	Abdomen US/CT: lithiasic cholecystitis	Small muscular artery: non-granulomatous arteritis and FN	ND	12	CRP 17.8.	None	18	Alive
	SOV								NL renal, hepatic, pancreatic tests			No signs of vasculitis
3	39 yrs/F/AA	Acute onset of abdominal pain	Acute illness, 37.7°C.	1 day	Abdomen US: acalculous cholecystitis with perforation	Non-granulomatous vasculitis involving veins	11	NL	NL/Neg CRP, renal, hepatic tests. ANA, RF cryoglobulins, complement	None	192	Alive
	SOV		No previous symptoms									No signs of vasculitis
4	41 yrs/F/W	Chronic vomiting, abdominal pain	None	10 yrs	Abdomen US: cholelithiasis	Non-granulomatous necrotizing arteritis with acute and chronic lesions	19	9.8	NL CRP, renal hepatic function	PDN 60 mg/d, discontinued in 4 months	20	Alive
	SOV								Neg HBV			No signs of vasculitis
5	42 yrs/F/W	First admission: Abdominal pain, vomiting (3 weeks): cholecystitis and pancreatitis post-ERCP	Second admission: persistent abdominal pain, fever, arthritis	3 months	Abdomen CT/US: cholelithiasis.	Non-granulomatous arteritis	78	12.5	HBsAg positive Platelets 480000, NL/Neg CRP , ANA, ANCA, Complement, HIV, Chest XR	MPDN 50 mg/12 h followed by PDN 60 mg/d	-	Died (acute abdomen and hypovolemic shock due to SMA rupture)
	HBV associated vasculitis				ERCP caused pancreatitis	Necropsy: vasculitis of the kidneys, adrenal glands and mesenteric arteries						
6	60 yrs/M/W	None (exploratory laparotomy during work-up for cancer)	Fever, anorexia, weight loss, myalgias, peripheral neuropathy, TIA	4 months	EMG: severe axonal polyneuropathy	Numerous arteries and arterioles with acute non-granulomatous arteritis and FN	96	7.6	NL renal/urine. Increased LDH/GPT/ GOT.	Initial treatment: CYC 150 mg/d PDN 60 mg/d	3	Alive
	Cryoglobulinemic vasculitis				NL abdominal/brain CT, funduscopy, muscle biopsy				Positive cryoglobulins/ RF. ANA/HBV Neg			

Abbreviations: AA = African-American; ANA = Antinuclear antibodies; ANCA = Anti-neutrophil cytoplasmic antibodies; CRP = C-reactive protein; CT = Computed tomography; CYC = Cyclophosphamide; ERCP = Endo-Endoscopic retrograde cholangiopancreatography; ESR = Erythrocyte sedimentation rate; F = Female; FN = Fibrinoid necrosis; GB = Gallbladder; HBV = Hepatitis-B virus; HCV = Hepatitis-C virus; Hgb = Hemoglobin; HIV = Human immunodeficiency virus; M = Male; MPDN = Methylprednisolone; ND = Not determined; Neg = Negative; NL = Normal; PDN = Prednisone; RF = Rheumatoid factor; RUQ = Right upper quadrant; SMA = Superior mesenteric artery; SOV = Single-organ vasculitis; TIA = Transient ischemic accident; US = Ultrasound; W = White.

TABLE 2. Epidemiologic, clinical, therapeutic features and outcomes of 61 patients with gallbladder vasculitis*

Characteristics	All Patients with Gallbladder Vasculitis No. (%)	SOV of the Gallbladder No. (%)	Systemic Vasculitis with Gallbladder Involvement No. (%)	p Value†
Number of patients	61	20	41	
Age, yr‡	52; 59 (18-94)	55; 52 (19-86)	51; 48 (18-94)	NS
Sex (Female/Male)	32/29	12/8	20/21	NS
Abdominal presentation				
Recurrent RUQ or abdominal pain	16/59 (27.1)	10/19 (52.6)	6/40 (15)	0.004
Duration of abdominal symptoms, wk‡	9.5; 1 (0-60)	13.5; 3.5 (1-60)	7.6; 1 (0-56)	NS
Gallbladder diagnosis				
Gallstone-associated cholecystitis	24/59 (40.7)	10/19 (52.6)	14/40 (35)	NS
Chronic cholelithiasis	2/59 (3.4)	1/19 (5.3)	1/40 (2.5)	NS
Acalculous cholecystitis	27/59 (45.8)	7/19 (36.8)	20/40 (50)	NS
Bile duct obstruction	2/59 (3.4)	1/19 (5.2)	1/40 (2.5)	NS
No gallbladder symptoms§	4/60 (6.7)	0	4/40 (10)	NS
Presence of gallstones	26/59 (44.1)	11/19 (57.9)	15/40 (37.5)	0.17
Constitutional/Musculoskeletal symptoms	34 (55.7)	4 (20)	30 (73.2)	0.0001
Fever	29/60 (48.3)	4 (20)	25/40 (62.5)	0.003
Malaise	9/60 (15)	0	9/40 (22.5)	0.02
Weight loss	10/60 (16.7)	0	10/40 (25)	0.01
Musculoskeletal symptoms	14/60 (23.3)	0	14/40 (35)	0.001
Myalgias	5/60 (8.3)	0	5/40 (12.5)	0.15
Arthralgias	9/60 (15)	0	9/40 (22.5)	0.02
Other systemic involvement (skin, abdominal, renal, lung, head and neck, peripheral nervous system)	26/60 (43.3)	0	26/40 (65)	0.0001
Duration of systemic symptoms at the time of gallbladder surgery, wk‡	22; 4 (0-250)	0.3; 0 (0-1)	28; 8 (1-250)	NS
Chronology at presentation				
Only gallbladder symptoms	20 (32.8)	20 (100)	0 (0)	0.0001
Gallbladder followed by systemic symptoms	5/57 (8.8)	0	5/37 (13.5)	0.15
Systemic followed by gallbladder symptoms	18/57 (31.6)	0	18/37 (48.6)	0.0001
Concomitant presentation	14/57 (24.6)	0	14/37 (37.8)	0.001
Follow-up and Treatment				
Follow-up period, mo‡	25; 15 (0-192)	42; 21 (6-192)	17; 11 (0-156)	0.02
Glucocorticoid therapy	36/53 (67.9)	3 (15)	33/33 (100)	0.0001
Receiving glucocorticoids at end of follow-up	17/23 (73.9)	0/3 (0)	17/20 (85)	0.01
Additional cytotoxic drug¶	18/53 (34)	0	18/33 (54.5)	0.0001
Deaths during follow-up	13/51 (25.5)	2 (10)	11/31 (35.5)	0.05

Note: References for gallbladder SOV patients: 1, 3, 11, 15, 34, 37, 44, 48, 54, 59. References for patients with systemic vasculitis with gallbladder involvement: 4, 5, 9-12, 14, 16-20, 22, 23, 28, 31, 32, 38, 40, 42, 43, 45-48, 50, 51, 54, 56, 58, 60, 61.

Abbreviations: NS = not significant; SOV = single-organ vasculitis.

* Data from available cases.

† p Values were calculated between columns 2 and 3.

‡ Mean; median (range).

§ Abnormal US, exploratory laparotomy or necropsy.

¶ The additional immunosuppressant agent more frequently used was cyclophosphamide.

Kawasaki disease[13] did not have sufficient data and 8 cases classified as GB-SOV in whom inadequate follow-up[3,29,38,44,54] or an initial treatment with glucocorticoids and/or cytotoxic agents[33,42] could not guarantee the extent of GV. In addition, 3 patients previously diagnosed with autoimmune diseases (1 each with systemic lupus erythematosus [SLE],[42] rheumatoid arthritis [RA],[42] and mixed connective tissue disease[33]) did not have involvement of other tissues at the time of GV diagnosis.

Mean age at the time of GV diagnosis was 52 years (median, 49 yr; range, 18–94 yr). Race was noted in 40% of published cases, and 60% of the patients were white. GV has been also described in Asian, African American and Latino-American patients. Patients were followed for a mean of 25 months (median, 15 mo; range, 0–192 mo). Mean duration of GB-related (right-upper quadrant or abdominal) symptoms was 9.5 weeks (median, 1 wk; range, 0–60 wk) prior to diagnosis. Lithiasic cholecystitis and/or chronic cholelithiasis was the clinical presentation in 44% of patients,[3,4,11,14,17,19,31,34,38,40,46,48,50,51,61] 45.7% presented with acalculous cholecystitis,[1,3,5,12,16,18,20,22,23,28,32,36–38,42–48,51,58–60] 3.4% with bile duct obstruction,[10,15] and 6.7% did not exhibit abdominal symptoms; GV was discovered because of abnormal GB findings in imaging studies,[9,38] exploratory laparotomy (current study Patient 5), or necropsy.[56]

GB-related manifestations were the only expression of GV in 20 (33%) patients. Among patients with GV, abdominal symptoms were followed by systemic features in 5 (13.5%), systemic and GB manifestations were concomitantly present in 14 (37.8%), and systemic symptoms were the initial manifestation in 18 (48.6%) patients. Clinical and laboratory findings of the entire series are listed in Table 2 and Table 3, respectively.

Abdominal ultrasound and/or computed tomography were reported in 62% of patients. GV diagnosis was achieved after cholecystectomy (in 60 patients) or autopsy (1 patient). At the time of abdominal surgery, other regions with vasculitis involvement were found, including the small

TABLE 3. Laboratory, Imaging and Histologic Characteristics of 61 Patients With Gallbladder Vasculitis*

Characteristic	All Patients With GV No. (%)	GB-SOV No. (%)	GB-SV No. (%)	P†
Number of patients	61	20	41	
Laboratory results (positive)				
ESR >20 mm/h	23/25 (92)	3/5 (60)	20/20 (100)	0.033
Hemoglobin <12 g/dL	14/22 (63.6)	3/6 (50)	11/16 (68.8)	NS
Leukocyte count‡	15; 13.4 (5.8–40)	13.6; 14.2 (9.3–16.5)	15.5; 13.4 (5.8–40)	NS
Urinary abnormalities§	13/22 (59.1)	0/2 (0)	13/20 (65)	NA
HBsAg	8/31 (25.8)	0/8 (0)	8/23 (34.8)	NA
HCV Ab	2/11 (18.2)	1/2 (50)	1/9 (11.1)	NA
Cryoglobulins	6/13 (46.2)	0/2 (0)	6/11 (54.5)	NA
Hypocomplementemia	5/12 (41.7)	-	5/12 (41.7)	NA
Antinuclear antibodies	6/28 (21.4)	2/9 (22.2%)	4/19 (21%)	NS
Rheumatoid factor	6/23 (26.1)	1/8 (12.5)	5/15 (33.3)	NS
Antineutrophil cytoplasmic antibodies	5/17 (29.4)	0/3 (0)	5/14 (35.7)	NA
Patients with other diagnostic procedures				
Biopsies of other territories	27/59 (45.8)	4 (20)	23/39 (59)	0.0001
Abnormal arteriogram/MR-angiography	3/7 (42.9)	0/2 (0)	3/5 (60)	NA
Histopathology of vasculitis				
Histologic pattern				
Nongranulomatous vasculitis	58 (95.1)	17 (85)	41 (100)	NS
Granulomatous vasculitis	3 (4.9)	3 (15)	0	NS
Size of the vessels affected				
Medium-sized arteries	56/60 (93.3)	19/19 (100)	37 (90)	NS
Small-sized vessels	4/60 (6.7)	0	4 (10)	NS

Abbreviations: NA = not applicable; NS = not significant.
* From available cases.
† P values were calculated between columns 2 and 3.
‡ Mean; median (range).
§ Microscopic hematuria and/or red blood cell casts and/or proteinuria.

intestine,[43,46,48] pancreas,[54] liver and appendix.[11] In the patient in whom GV was diagnosed postmortem, autopsy revealed vasculitis in multiple organs.[56] In 3 patients autopsy was performed after the initial cholecystectomy, and findings included vasculitis of the superior mesenteric artery with arterial rupture (Patient 5) and vasculitis affecting multiple intraabdominal organs.[4,51] Twenty-seven patients underwent biopsies in other regions.[1,3,9–11,14,15,19,23,32,36,38,40,42,43,45,46,48,50,51,54,60] Abdominal angiography was performed in 7 patients and vascular abnormalities were detected in 3 who had GB-SV (Table 4).[9,10,12,37,46,54]

GB-SOV was found in 20 (33%) patients and GB-SV in 41 (67%). Forms of SV that affected the GB were PAN (n = 10),[4,12,22,32,38,45,46,51,54] HBV-associated vasculitis (n = 8),[10,11,17,38,46,56,60] cryoglobulinemic (essential or HCV-associated) vasculitis (n = 6),[9,14,19,36,50] MPA (n = 4),[5,31,38,40] EGPA (Churg-Strauss) (n = 4),[20,43,48,61] IgA vasculitis (Henoch-Schönlein) (n = 2),[23,28] giant cell arteritis (n = 1),[47] and vasculitis associated with autoimmune diseases (n = 6)[11,16,18,42,58] (see Table 4). Systemic diseases with associated vasculitis included RA (n = 3),[11,16,18] SLE (n = 2),[42,58] and systemic sclerosis (n = 1).[11] Main characteristics for the 41 patients with GB-SV are listed in Table 4.

Comparisons Between Groups

Epidemiologic and clinical features, treatment, and outcomes of both groups are depicted in Table 2. Laboratory, imaging and histologic characteristics are provided in Table 3. No differences were observed in age, sex or duration of GB symptoms between groups. Gallstone-associated cholecystitis and recurrent abdominal pain episodes occurred more frequently in GB-SOV than in GB-SV patients, who presented more often with acalculous cholecystitis. Whereas GB-related symptoms were the only manifestation in GB-SOV patients, in GB-SV patients local symptoms occurred more often together with or after the development of systemic features. Although 19% of GB-SV patients presented initially with GB symptoms, systemic features emerged from several days to 2 months. Clinical involvement of other organs was detected in 65% of GB-SV patients. Except for fever, which occurred in both groups (62.5% GB-SV vs 20% GB-SOV; p = 0.003), constitutional and musculoskeletal symptoms were reported only in GB-SV patients and occurred in 75% of them. ESR values were higher in GB-SV than in GB-SOV patients (80 ± 28 vs 37 ± 25 mm/h; p = 0.006). However, no differences were found in hemoglobin, leukocyte count, or CRP levels between groups. Surrogate markers for autoimmune diseases and hepatitis virus serologies were tested more frequently in GB-SV patients, in whom they were more frequently positive.

Angiographic studies were performed in 2 GB-SOV patients[37,54] and in 5 GB-SV patients,[9,10,12,46] and were suggestive of SV in 3 of them.[10,12,46] Among GB-SV patients, 23 (59%) had a biopsy performed in regions other than the GB[9–11,14,19,23,32,36,38,40,42,43,45,46,48,50,51,54,60,61] and 82% of them confirmed vasculitis. SV (including GV) was diagnosed at necropsy in 1 patient.[56]

Treatment and Follow-up

Among GB-SOV patients, only 3 received glucocorticoids for 6 to 16 weeks,[15,37] whereas all GB-SV patients were treated with glucocorticoids (p = 0.001),;[4,5,9,10,12,14,16–18,20,22,23,28,31,32,36,38,40,42,43,46–48,54,58,60,61] 54% of patients with SV also received cytotoxic agents[5,12,14,16,17,22,23,31,36,40,42,46,48,58,60] (see Table 2). Among GB-SV patients with adequate information, 17/20 patients were receiving glucocorticoid therapy at the end of

TABLE 4. Characteristics of the systemic vasculitides involving the gallbladder

Characteristics	Polyarteritis nodosa	HBV-associated vasculitis	Cryoglobulinemic (essential or HCV associated) vasculitis	Vasculitis associated with autoimmune diseases*	Microscopic polyangiitis	Eosinophilic granulomatosis with polyangiitis	IgA vasculitis	Giant cell arteritis
Number of patients	10	8	6	6	4	4	2	1
Age, yr †	45; 46 (18-71)	59; 60 (32-94)	49; 46 (33-64)	47; 50 (22-69)	57; 56 (40-76)	41; 38 (36-50)	64; 64 (53-75)	70
Sex (F/M)	4/6	4/4	1/5	4/2	1/3	2/2	0/2	0/1
Gallbladder presentation	Lithiasic/acalculous cholecystitis (2/6), lithiasic obstructive jaundice (1)	Lithiasic/acalculous cholecystitis (4/2), bile duct dilatation (1), necropsy (1)	Lithiasic/acalculous cholecystitis (3/1), no GB symptoms (2)	Lithiasic/acalculous cholecystitis (2/4)	Lithiasic/acalculous cholecystitis (3/1)	Lithiasic/acalculous cholecystitis (1/3)	Acalculous cholecystitis (2)	Acalculous cholecystitis
Duration of gallbladder symptoms, wk†	4; 1 (0-21)	9.5; 7.5 (0-21)	2; 1 (0-7)	2.5; 1 (1-7)	1; 1 (1-1)	13; 7 (1-30)	11; 11 (1-21)	56
Systemic manifestations	Fever (7), WL (4), malaise (2), arthralgias (2), skin nodules or rash (2), PN (1)	Fever (7), WL (1), malaise (1), arthralgias (3), myalgias (1), PN (2)	Fever (2), WL (2), malaise (2), arthralgias (2), myalgias (1), purpura (4), PN (3), lung (1), renal (2)	Fever (4), WL (1), malaise (1), arthralgias (1), myalgias (1), purpura (2), PN (1)	Fever (2), WL (1), malaise (2), arthralgias (1), myalgias (1), purpura (1), PN (1), renal (3)	Fever (2), myalgias (1), asthma (4), ENT (3), PN (3), lung infiltrates (1), renal (1)	Fever (1), arthralgias (1), purpura (2), renal (1)	Fever, WL, malaise, headache, scalp tenderness
Duration of systemic symptoms, wk†	7; 6 (4-12)	5; 3.5 (2-12)	67; 20 (1-250)	43; 24 (1-104)	18.5; 18.5 (1-36)	4; 4 (4-4)	3; 3 (3-3)	8
Chronology at presentation	Systemic first (4), GB first (3), concomitant presentation (1)	Systemic first (3), GB first (1), concomitant presentation (2)	Systemic first (4), concomitant presentation (1), no GB symptoms (1)	Systemic first (3), GB first (2)	Systemic first (1), GB first (1), concomitant presentation (2)	Systemic first (1), GB first (1), concomitant presentation (2)	Systemic first (1), GB first (1)	Concomitant presentation
Vasculitis proved in other territories	Other abdominal sites (6), skin (1), muscle (1)	Other abdominal sites (5)	Skin (1), kidney (2), muscle (2)	Skin (1), colon (1)	Skin (1), kidney (1)	Muscle (2), kidney (1)	Skin (1)	-
Positive arteriogram	Mesenteric and hepatic angiography (2)	Hepatic angiography (1)	-	-	-	-	-	-
Laboratory results								
ESR (mm/1st h)†	79 ± 39	64 ± 23	92 ± 6	93 ± 33	103 ± 25	53 ± 8	NR	99
Hemoglobin (g/dL)†	11.5 ± 2.1	12.1 ± 1.6	10.3 ± 3.8	11.4	9.4	11.6	NR	10.9
Others (positive/tested)	-	-	HCV (1/3)	ANA (2/4); RF (3/3)	ANCA (3/3)	ANCA (0/1)	-	-
Treatment	GC (7/8), AIS (3/7)	GC (6/6), AIS (3/6)	GC (4/4), AIS (3/4)	GC (5/5), AIS (4/5)	GC (4/4), AIS (3/4)	GC (4/4), AIS (1/4)	GC (2/2), AIS (1/2)	GC alone
Follow-up period, mo†	26; 12 (0-156)	18; 17 (0-48)	4.5; 0 (0-24)	14; 1 (0-42)	16; 15 (11-24)	24; 24.5 (0-47)	0	18
Deaths/Patients with follow-up	3/7	3/7	0/2	4/5	1/4	0/4	0/1	0/1

Abbreviations: AIS = additional immunosuppressant; ESR = erythrocyte sedimentation rate; GB = gallbladder; GC = glucocorticoids; HBV/HCV = hepatitis B/C virus; NR = Not reported; PN = peripheral neuropathy; WL = weight loss.

* Systemic diseases with associated vasculitis included rheumatoid arthritis (n=3), systemic lupus erythematosus (n=2) and systemic sclerosis (n=1).

† Continuous values as mean; median (range) or mean ± standard deviation.

follow-up.[10,12,16,20,23,38,40,43,46,47,58,61] Two (10%) GB-SOV patients died years later from unrelated conditions,[3,11] and 11/30 (37%) GB-SV patients died from complications derived from disease activity or infections.[4,11,16,18,38,46,51,56]

Histopathologic Features

Nongranulomatous inflammation with fibrinoid necrosis of medium-sized vessels occurred with equal frequency in both groups (>90%). A granulomatous vasculitic pattern was seen only in 3 GB-SOV cases.[1,37] Fibrinoid necrosis was described in 43 patients, 15 with GB-SOV (75%) and 28 with GB-SV (68.3%). The presence of a healed inflammatory pattern was often observed with acute lesions in the same biopsy in both GB-SV[9,19,38,43,51] and GB-SOV.[19,34,44,59] Artery aneurysms due to vasculitis have been reported in patients with GB-SOV.[3,44] No malignant lesions accompanied GV. Histopathologic results are summarized in Table 3. GB histopathology from 2 of our patients is illustrated in Figure 1.

DISCUSSION

GV is an uncommon condition that may be a site for SOV or part of SV.[24] GV was found in 0.29% of the cholecystectomies performed for cholecystitis or complicated cholelithiasis in our center, and in 0.04% of GB surgeries in a previous study.[11]

In 1979, Papaioannou et al described 47 cases of PAN with GB involvement.[47] Although two-thirds of patients had symptomatic cholecystitis, the extent of vasculitis was not delineated.[47] GB involvement in PAN has been reported in 8% of live patients[46] and in 10%–40% at necropsy studies.[41,53,64] In addition, GV has been observed in fewer than 2% of patients with other SV.[46] Occasionally, GV manifesting as acalculous cholecystitis and GB hydrops has been described associated with IgA vasculitis (Henoch-Schönlein)[23,28,35] and Kawasaki disease.[13]

SV or SOV may also exist in many other organs such as the aorta,[52] breast,[26] gynecologic organs,[27] and testicular structures.[25] We have previously analyzed features that helped to distinguish isolated from systemic vasculitis. The results are comparable to those found in the current study. GV occurs equally as a lithiasic or acalculous cholecystitis. However, recurrent episodes of abdominal pain and gallstone-associated cholecystitis occurred more often in GB-SOV, whereas acalculous cholecystitis tended to occur more frequently in GB-SV. Apart from the local GB-related symptoms common to both GV forms, GB-SOV is characterized by the absence of systemic (constitutional and musculoskeletal) manifestations, which predominate in patients with GB-SV. Although some GB-SOV patients may present with fever, high ESR, and anemia, these markers are clearly more common in GB-SV patients, who also present with clinical involvement of other regions.

GB-related symptoms usually are the only manifestations of GB-SOV. However, in 13.5% of GB-SV patients, abdominal symptoms may occur alone and may precede systemic symptoms for days or weeks. When GV is diagnosed, it is mandatory to perform a thorough examination ruling out a generalized process, and provide follow-up surveillance for possible emergence of systemic disease. In this regard, laboratory and other studies are of value. These include acute phase reactants, complete blood counts, liver and kidney function tests, urinalyses, viral serologies (HBV, HCV) as well as electromyography, imaging studies, and when clinically appropriate, markers of systemic autoimmune diseases (for example, ANCA, rheumatoid factor, complement, or cryoglobulins) and vascular imaging.

GV histopathology is commonly characterized by a nongranulomatous inflammation affecting medium-sized arteries in all GV patients. In addition, some histologic features, such as acute and healed vasculitic lesions and aneurysm formation, have been observed in both GB-SOV and SV patients. Therefore, histologic findings are not helpful in distinguishing the extent of disease in GV.

Some patients with SOV affecting intestinal arteries have been cured after surgical excision of the affected segment.[6,21] However, gastrointestinal SOV may have an increased risk of death, similar to that seen in SV.[46,54] Of note, GB-SOV patients do not require any treatment apart from GB excision and do not seem to have an increased mortality. Conversely, all GB-SV patients require glucocorticoid therapy, and most of them require an additional immunosuppressive agent. GB-SV is associated with a high mortality rate (35.5%): PAN, HBV-associated vasculitis, MPA, and vasculitis associated with autoimmune diseases are the SV in which mortality has been reported.[4,11,16,18,38,46,51,56] Similarly, a global series of patients with systemic necrotizing vasculitides (PAN, HBV-associated vasculitis, EGPA, and MPA) and gastrointestinal involvement reported a mortality rate of 26%.[46]

The main limitations of the current study relate to the retrospective collection of clinical and histologic data from different and heterogeneous sources. Final diagnoses have been based on different classification criteria or on authors' own criteria. Although cases of GB-SOV have a minimum follow-up

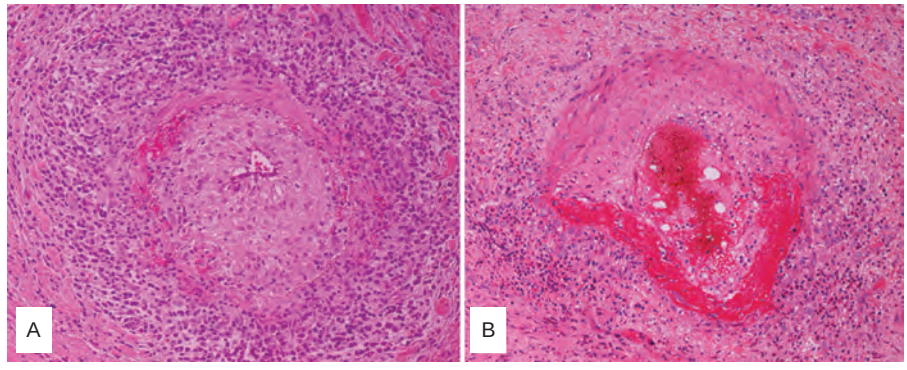

FIGURE 1. Nongranulomatous necrotizing vasculitis of medium-sized arteries of the gallbladder wall, from Patients 1 (A) and 2 (B) of the current series. Both arteries show lymphocytic infiltrates with neutrophils, muscular layer destruction with fibrinoid necrosis and intimal hyperplasia.

of 6 months, as reported in exceptional cases, the evolution to SV after this period is still possible.

In conclusion, GV is uncommon and may occur as a focal or generalized disease. GV histology is usually a nongranulomatous necrotizing vasculitis affecting medium-sized vessels. GB-SOV is usually discovered after routine cholecystectomy performed because of the presence of local symptoms, more often a gallstone-associated cholecystitis, and in contrast to GB-SV, GB-SOV is usually not associated with systemic symptoms or an increase in acute phase reactants. Laboratory markers of autoimmunity are usually normal or negative. GB-SOV does not require therapy other than surgery. GB-SV always warrants immunosuppressive-antiinflammatory medical therapy and is associated with high mortality. PAN, vasculitis associated with HBV, cryoglobulinemic vasculitis, and vasculitis secondary to systemic autoimmune diseases are the most frequent forms of GB-SV. The finding of GV may precede the generalized manifestations of SV. Therefore, once GV is discovered, a study of disease extent and a vigilant follow-up is mandatory to provide appropriate treatment if necessary.

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