Vasculitis and the gastrointestinal tract

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Abstract

Vasculitis, defined as a non-infectious inflammatory disorder of blood vessels, can affect vessels of any type in any organ. The gastrointestinal (GI) tract may thus also be involved. In systemic disorders as mixed connective tissue disease (MCTD) and systemic lupus erythematodes (SLE), patients may present with symptoms of gastrointestinal disfunction such as motility disorders, caused by alterations in the connective tissue. True vasculitis however also occurs in the GI tract. Severe, occlusive damage often leads to ischemia that may result in ulceration and perforation. Non-occlusive vascular disease may lead to vascular leakage resulting in oedema and haemorrhage. Those patients often present with diarrhoea or symptoms of bleeding.

GI involvement is frequent in Henoch-Schönlein purpura and also often noted in polyarteritis nodosa (PAN), microscopic polyangiitis, Wegener's syndrome and Churg-Strauss syndrome. Furthermore, GI vasculitis has also been described in giant cell arteritis, Takayasu's disease, Buerger's disease and leucocytoclastic vasculitides as essential mixed cryoglubulinemia, lupus vasculitis, rheumatoid disease, MCTD, drug-induced vasculitis and Behçet's disease. The diagnosis and classification of vasculitis relies upon a combination of clinical, serological, haematological, radiological and histological findings. Establishing a precise diagnosis can be difficult but is important because treatment and prognosis can be highly variable. (Acta gastroenterol. belg., **2002**, 65, **204-212**).

Key words : gastrointestinal (GI) tract, vasculitis.

Definition

True vasculitis is defined by **eosinophilic degeneration of the vessel wall** (fibrinoid necrosis) and **infiltration of the vessel wall by leucocytes**, with neutrophils, nuclear dust, and extravasated red cells in the vessel wall and the adjacent stromal tissue (fig. 1) (1,2). The term is applied to "noninfectious inflammatory" disorders of blood vessels. Vasculitis has many causes, which result in only a few histologic patterns. Vessels of any type, in any organ can be affected and this results in a wide variety of clinical signs and symptoms. The diagnosis of vasculitis can be difficult because the clinical picture can be highly variable and the demonstration of vasculitis in histologic specimens is not always easy. However, a precise diagnosis is important, because the prognosis and treatment can be highly variable.

A diagnosis of vasculitis is based upon a combination of clinical, radiological, biochemical – haematological – serological and histological findings. Most patients present with clinical signs and symptoms refering to multiple systems such as a combination of skin lesions, nephritis and abdominal pain which can occur in both Henoch-Schönlein's disease and microscopic polyangiitis. A complete biological screening involves testing for evidence of inflammation (sedimentation rate, CRP, alfa2 globulins, haptoglobin), an immunological bilan (electophoresis and quantification of immunoglobulins), screening for immune complexes and complement (CH50, C3, C4), screening for autoantibodies (antinuclear antibodies, L.E. factor, rheumatoid factor, antiphospholipids), screening for infections (Hepatitis B & C, parvovirus, HIV, rickettsia, streptococci....), testing for antineutrophil cytoplasmic antibodies (ANCA's), screening for factors which promote clotting and for evidence of vascular endothelial damage (factor VIII, ICAM-I, VCAM-I). Involvement of large and medium-sized vessels by vasculitis can be demonstrated by means of arteriography and other imaging techniques. Skin biopsies can reveal signs of small vessel vasculitis. Endoscopic biopsies of the gastrointestinal tract are more likely to be negative. They are indeed usually composed of mucosa and the blood vessels in the mucosa are mainly capillaries. Small arterioles are present in the small intestinal mucosa, or at the level of the muscularis mucosae in the other segments. Rectal biopsies were indeed negative in many patients with established systemic vasculitis (3). The establishment of the involvement of larger vessels requires surgical samples.

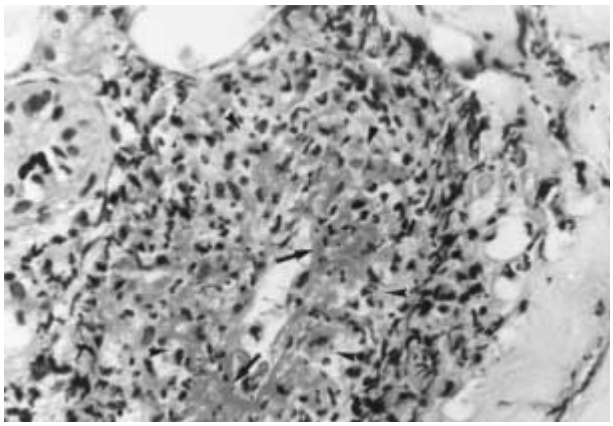

Fig. 1. — Necrotising vasculitis : the vesselwall (arrowheads) is infiltrated by neutrophils and lymphocytes. There is also fibrinoid degeneration of the vessel wall (arrows).
Original magnification × 400.

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Microscopic diagnosis - problems

The minimum criteria for a diagnosis of vasculitis have remained controversial but it is in general accepted that there must be two components : a) an inflammatory cell infiltrate ; b) evidence of vascular injury. The absence of inflammation thus precludes the diagnosis of vasculitis, even in the presence of vascular alterations. Yet, in a late, healing state, inflammatory infiltration may be minimal.

Like many other inflammatory conditions, vascular injury is a continuum. The spectrum ranges from endothelial cell swelling and leakiness to frank fibrinoid necrosis and fibrin deposition. The cells involved are dynamic and the degree of vascular injury resulting from any given insult is likely to be dose-related. The definition of "vascular injury" is therefore at present not clear and not precise. This depends partly on the techniques used for the assessment of vascular injury (routine microscopy or EM ; clinical evaluation or microscopy). Pathologists usually require a certain degree of injury manifested by deposition of fibrinoid material and / or necrosis of the vessel wall. However, certain changes such as extravasation of erythrocytes and edema due to leakiness, thrombosis and infiltration of the vessel wall can occur without fibrinoid necrosis of the vessel wall. The term "vasculopathy" may be used to describe vascular alterations without clear inflammation. Another major problem is the difference between primary and secondary vascular injury. Secondary vasculitis can occur in different inflammatory conditions, such as a peptic ulcer of the stomach or a cholecystitis, when local blood vessels are affected by the inflammatory process. The occurrence of vascular lesions in otherwise severely inflamed tissue should therefore not be confused with genuine vasculitis.

There is considerable overlap between the histological appearances in different genuine forms of vasculitis. A reliable histological classification is further difficult because of lack of histologic specificity and the variability of the spectrum of histologic changes depending on the stage of the disease and its activity and treatment. In some cases a differential diagnostic scheme based on the histology can be helpful but in general this type of classification is not very useful (Table I).

Classification

Vasculitis has many causes, although they result in only a few histologic patterns (4). Blood vessels may be involved in a disease process as a result of tissue injury (secondary lesions), via the effect of soluble mediators of the inflammatory process such as cytokines and other mediators, or specific components of blood vessels may be a target for immune attack (as a result of altered antigenicity following inflammation or through some aberrancy of the immune response). The process may be antibody-mediated or T cell mediated. While the former has been clearly identified in several types of vasculitis such as Henoch-Schönlein syndrome, the latter is less well recognized.

Table 1. — **Classification of vasculitis according to infiltrate**

I : Vascular damage - vasculopathy : scant inflammatory cells
II : Vasculitis : lymphocytes predominant
"lymphocytic vasculitis"
lupus erythematosus
angiocentric lymphomas
cytomegalovirus inclusion disease
Behçet's syndrome
III : Vasculitis : neutrophils predominant
small vessel leukocytoclastic vasculitis
polyarteritis nodosa
Behçet's syndrome
III : Vasculitis : mixed cell types / and or granulomas
Churg-Strauss
Wegener
Giant cell arteritis
Secondary vasculitis

The histological lesions are variable in time and the clinical presentation will depend upon the size of the vessels involved as well as upon the widespread systemic or more localized nature of the disease. The protean clinical manifestations, combined with the etiologic nonspecificity of the histologic lesions complicate the diagnosis of specific features of vasculitis. This is problematic because different vasculitides with indistinguishable clinical presentation (for instance Henoch-Schönlein and microscopic polyangiitis) may have different prognosis and treatment. A general classification covering all these aspects that is easily applicable in clinical practice is however at present not available. One approach is to categorize the noninfectious vasculitides on the basis of the predominant type of vessel affected but other types of classification can be proposed. A classification based on vessel size has been proposed by an international conference and more recently attempts have been made to combine the classification according to vessel size with etiologic criteria (Table II) (4,5).

The classification of noninfectious vasculitis according to vessel size was introduced for clinical reasons and it is still important to identify the type and size of inflamed vessels and to determine whether the inflammatory reaction is focal or involves a considerable length of the vessels (4). These variables will have an influence upon the clinical presentation and the diagnostic techniques which can be used (1,2). Involvement of larger vessels is frequently associated with severe clinical syndromes. In the GI tract, especially, involvement of larger "mesenteric vessels" can be associated with complications such as necrosis, infarction and perforation.

Large vessel vasculitis was also the first type of vasculitis which has been described (6). For years, vasculitis was known as "periarteritis nodosa", a term firstly used for a condition characterized by nodular inflammatory lesions in medium-sized and small arteries throughout the body. The name was later changed into "polyarteritis nodosa (PAN)" because the vascular wall

Table 2. — **Major Categories of noninfectious vasculitis (vasculitis induced by infections generating pathogenic immune complexes is included)**

Large vessel vasculitis
– Giant Cell arteritis
– Takayasu's disease
– Buerger disease (Thromboangiitis obliterans)
Medium-sized vessel vasculitis
– Polyarteritis nodosa (PAN)
– Kawasaki syndrome
Small vessel vasculitis
– Infections
– Immunologic injury
– ANCA-associated small vessel vasculitis
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic Polyangiitis (MPA)
Drug-induced anca small-vessel vasculitis
– Immune complex mediated small vessel vasculitis
Henoch-schönlein purpura
Essential cryoglobulinemia
Lupus vasculitis
Rheumatoid vasculitis
Drug induced immune complex vasculitis
Infection induced immune complex vasculitis
Behçet's disease
Sjögren's syndrome vasculitis
Goodpasture syndrome
Serum-sickness vasculitis
– Paraneoplastic small vessel vasculitis
– Inflammatory bowel disease vasculitis

Table 3. — **Major immunological disorders of blood vessels**

	PAN	Wegener	LE	Churg-Strauss	Hypersensitivity vasculitis
	ANCA +	ANCA +	Auto-antibodies	ANCA +	–
Age	any age chiefly middle mean age	adults 50yrs	young or middle age	middle age	adults
Sex ratio	3M/1F	M > F	8F/1M	M > F	M = F
Aorta	–	–	–	–	–
Arteries	++	+ or ++	+	+	–
arterioles	+	+	++	++	+
capillaries	–	+	++	+	++
veins	–	++	+	++	+
surgical	GI	?	GI	?	?

itself is inflamed at various levels. By the 1950s many investigators had realized however, that there was a variety of clinically distinct forms of vasculitis and that small vessels could also be involved. Small vessel vasculitis was refered to as either "hypersensitivity vasculitis" or "microscopic periarteritis" (7). The latter is now commonly known as microscopic polyangiitis (MPA).

Some of the "noninfectious inflammatory" disorders of blood vessels are the result of inflammation secondary to an immunological reaction at the endothelial surface of the affected vessel. This can be induced by an infection, but in many cases the underlying pathogenesis is poorly understood. Based upon data related to the pathogenesis "vasculitis" can be subdivided into secondary vasculitis, immunological disorders and inflammatory disorders of uncertain origin (Table III). Abnormal deposits of immunoglobulins are detected in some distinct forms of vasculitis such as "Henoch-Schönlein". Viral antigens such as Hepatitis B antigen (or bacterial and fungal antigens) can be found in immune complexes or in association with vasculitis in PAN. In vitro studies have shown the occurrence of a separate class of antibodies against endothelial cell antigens in Lupus and Wegener's disease.

The identification of the ANCA's has further greatly influenced subclassification of vasculitis. ANCA's are common in Wegener's disease, in Churg-Strauss vasculitis (70%) and in MPA (80%). They are rare in Kawasaki's disease and occasionally found in Lupus, and Takayasu's disease. ANCA's are specific for antigens in neutrophil granules and monocyte lysosomes. They can be detected with indirect immunofluorescence microscopy by using alcohol-fixed neutrophils as substate. This produces two major staining patterns : cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). Specific immunochemical methods demonstrate two major antigen specificities in patients with vasculitis : antimyeloperoxidase (MPO-ANCA) and antiproteinase 3 (PR3-ANCA). The majority of c-ANCAs (90%) react with proteinases and most p-ANCAs (90%) are specific for myeloperoxidase (MPO-ANCA). Wegener's granulomatosis is usually associated with c-ANCA (PR3-ANCA) and only rarely with p-ANCA, whereas MPA (microscopic polyangiitis, see : polyarteritis nodosa) and Churg Strauss show the opposite pattern (more likely p-ANCA positive).

Gastrointestinal involvement in vasculitis

Clinical Presentation

Vascular injury can result in lesions of variable severity, depending on the number, size and type of vessels involved (arterial vs. venous), the extent of vascular damage, the intensity of the inflammation, the type of inflammatory infiltrate (neutrophils vs lymphocytes) and other parameters. In the gastrointestinal tract, severe "occlusive" vascular damage leads to ischemic damage, which may result in necrosis and / or ulceration. "Nonocclusive" vascular disease may be associated with damage to the structural integrity of the vessel wall and may lead to leakage of blood, resulting in edema and hemorrhage (clinically seen as purpura, or petechiae when the lesions are less than 3 mm or as gastrointestinal bleeding). There may be a combination of both types of lesions (Table IV).

The clinical presentation of gastrointestinal vasculitis may thus be variable (2). Lower or upper gastrointestinal bleeding is common but patients may also be hospitalized because of perforation. 18 patients (27%) out of a series of 65 patients with systemic vasculitis had major gastrointestinal complaints. These included 13/25 patients with PAN (8 classic PAN ; 17 microscopic PAN), 4/36 Wegener's granulomatosis and 1/4 with

Table 4. — **Ischemia of the GI tract**

Occlusive disease	Non occlusive disease
Atherosclerosis	
Arterial thrombosis	
Mesenteric thrombosis	
Arteritis (rare)	
Giant cell arteritis	
Takayasu's disease	
Buerger's disease	
PAN	Wegener's
LE	Microscopic polyangiitis
Churg-Strauss	
Rheumatoid disease	Immune complex mediated vasculitis
Miscellaneous	
Hypertension	
Amyloidosis	
Mechanical obtruction	

Churg-Strauss disease. Abdominal pain was present in 14 patients (3 with PAN ; 8 with microscopic PAN ; 3 Wegener). Nine patients complained of diarrhea (2 with PAN ; 4 with microscopic PAN ; 2 Wegener ; 1 Churg Strauss) and blood was observed in 8 (3 with PAN ; 3 with microscopic PAN ; 1 Wegener ; 1 Churg Strauss). A positive biopsy was obtained in 8 patients (4 / 4 with PAN ; 2/2 with microscopic PAN ; 1/1 Wegener ; 1/1 Churg Strauss). The diagnosis was primarily made on the basis of renal or skin biopsies (8). The frequency of GI involvement varies however highly.

Different forms of vasculitis

Large vessel vasculitis

Giant cell arteritis (synonyms : Cranial arteritis, Temporal arteritis)

Giant cell arteritis is an inflammatory disorder of uncertain origin which primarily affects large- and medium-sized arteries. The classical clinical example is "temporal arteritis" of the elderly, presenting with pain and tenderness of the forehead, and possible sudden visual impairment. Five major diagnostic criteria have been proposed by the American Rheumatism association. They include age over 50, recent localized headache, temporal artery tenderness, a positive biopsy and erythrocyte sedimentation rate over 50 mm/hr. When three of these criteria are met a positive diagnosis is likely. For the GI tract a positive biopsy can only be obtained in surgical specimens, given the size of the vessel involved.

Histologically the involved arteries show an inflammatory process that may extend throughout the entire arterial wall. It is composed mainly of lymphocytes and macrophages. Some of the latter may be multinucleated but giant cells are not always present. Neutrophils may be present. The infiltrate is unevenly distributed. There is fragmentation of the lamina elastica and elastophagocytosis by the giant cells. In late stages there may be only thickening of the intima.

GI involvement is rare. Mesenteric involvement is usually associated with temporal arteritis. The clinical picture is dominated by small bowel ischemia or frank infarction. In a series of 248 patients with giant cell arteritis, 15% had involvement of the aorta including the superior mesenteric artery (8,9).

Takayasu' s disease

This is a condition which is commoner in women. It typically presents before the age of 40 and mostly affects the aortic arch and its major branches. Splanchnic involvement may occur.

The pathologic features are a chronic inflammatory process extending from the outer aspect of the artery (lymphocytes and macrophages, some giant cells and plasma cells) with most changes seen in the adventitia and media (thrombosis is uncommon) ; the elastic structure of the media is destroyed ; the intima is thickened by oedematous connective tissue with little cellular infiltration. In the later stage there will be a predominance of the fibrous component with scarring.

Involvement of the abdominal aorta may lead to intestinal ischemia because of occlusive arterial lesions. Intestinal involvement is rare but has been reported even in association with idiopathic inflammatory bowel disease (8).

Thromboangiitis obliterans (Buerger disease)

In Buerger disease both arteries and veins are affected. The disease is more common in male smokers in the third and fourth decades. Pathologically there is occlusion of the vessels by distinctive inflammatory thrombi with microabscesses and giant cells. Familial cases occur and cell mediated sensitivity to types I and III collagen may be found. The gastrointestinal tract is only rarely affected. There are a few well documented cases of mesenteric involvement leading to small bowel necrosis or (segmental) colonic involvement (with inflammation and ulceration of transverse and sigmoid colon) or even perforation and peritonitis (10,11).

Medium-sized vessel vasculitis

Polyarteritis Nodosa (PAN)

The first description dates back from 1866 when a case of a 27-year old man with fever, abdominal pain, muscle disease, peripheral neuropathy and renal disease was reported (6). The authors termed the fatal illness "periarteritis nodosa" because of the cellular infiltrate in the periphery of the vessel wall and referring to nodular protuberances along the course of medium-sized muscular arteries. In 1903 the term "polyarteritis" (PAN) instead of periarteritis was proposed because inflammation was present within all levels of the affected vessel. Classic PAN is : "a systemic, necrotizing vasculitis, primary affecting muscular arteries and resulting in lesions of various ages, often with focal aneurysms". Over the

Table 5. — **Gastrointestinal Involvement in systemic vasculitis (overall +/- 27%)**

Large Vessels	Medium-sized	Small vessels
– Giant cell arteritis : 15% – Takayasu's : rare – Buerger : rare	PAN : 25% - 2/3	Wegener's : 50% symptoms : rare Churg-Strauss : 60-70% MPA : 50% Henoch-Schönlein : 60-80% Cryoglobulinaemia ass : 30% rare in GI tract common in liver Rheumatoid disease : 10% Lupus : 50% Connective tissue disease < 1% Drugs associated Paraneoplastic
Major Complic	Major Complic (6-15%) Minor complic GI bleeding (50%)	Major Complic : rare Minor complic GI bleeding (80%)

years different forms have been distinguished. These include the "classic" and the "microscopic" form.

The characteristic lesions of classic PAN are : a panarteritis involving medium-sized and small arteries ; small segments of the muscular arteries are involved and the lesions are in different stages of development. Early lesions are characterized by degeneration of the arterial wall - partial to complete destruction of the external and internal elastic laminae ; deposition of fibrinoid material ; infiltrate in and around the vessel, composed largely of neutrophils (showing evidence of leukocytoclasis or white blood cell necrosis), often with some eosinophils. In the later stage there are intimal proliferation ; thrombosis leading to ischemia and ulceration and an infiltrate with lymphocytes, histiocytes and plasma cells.

GI complaints are noted in about 25 % to 60% of the patients. They include abdominal pain, nausea, vomiting, anorexia and diarrhea. Vascular occlusion can lead to ischemia with ulceration and infarction of the bowel wall and hemorrhage. In a series of 30 cases 17% had melena and 10% hematemesis (12). The frequent occurrence of GI bleeding was also noted in another series where 50% of the patients had GI bleeding (13). Serious complications such as "intestinal infarction" occur in about 6-15% of all patients (8). "Related lesions" have been described such as " Cryptogenic Multifocal stenosing ulcerations of the small intestine" (14).

Small vessel vasculitis - anca associated

Wegener's granulomatosis, Churg-Strauss syndrome and the microscopic polyangiitis are closely related. They are all three frequently ANCA-associated and the ANCA-associated small-vessel vasculitis is the most common primary systemic small-vessel vasculitis in adults (4). There are however ANCA negative cases. The three types are histologically very similar. They involve preferentially venules, capillaries and arterioles and may also involve arteries and veins.

Wegener's granulomatosis is differentiated from the other two by the presence of necrotizing granulomatous inflammation (fig. 2) in the absence of asthma ; Churg-Strauss is differentiated by the presence of asthma, eosinophilia and necrotizing granulomatous inflammation and MPA is differentiated by the absence of granulomatous inflammation and asthma.

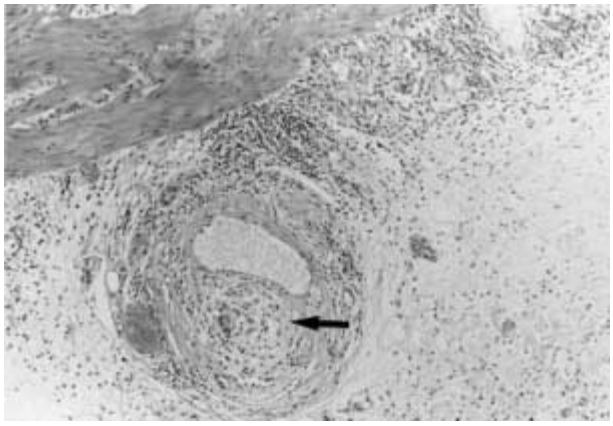

Fig. 2. — Granulomatous vasculitis : the vessel wall is infiltrated by lymphocytes. Furthermore, there is a loosely arranged granuloma in the vessel wall (arrow).
Original magnification × 100.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis, initially reported by Klinger in 1931 and later described in more detail by Wegener, is defined by a triad of features : systemic necrotizing "angiitis", necrotizing inflammation of the respiratory tract, and necrotizing glomerulonephritis (limited forms without glomerulonephritis may occur) (4,15,16).

Gastrointestinal involvement appears uncommon (17). Gastrointestinal manifestations were present in 4 patients out of a series of 36, but only one patient experienced bleeding (3). In an autopsy review of 59 fatal cases of patients with Wegener's granulomatosis, histologic evidence of gastrointestinal involvement

was found in 23 but symptoms (nausea, abdominal pain, blood loss) had been infrequent (2).

Churg-Strauss (CSS)
(synonyms : allergic granulomatous angiitis ; allergic granulomatosis and angiitis, Churg-Strauss vasculitis CSV)

Churg Strauss vasculitis is a nonhereditary disease with unclear underlying pathomechanisms. Immunologic defects have been reported but because of the rarity of the disease there are no data in large studies. Immunologic alterations reported include : derangement of CD95 system (FAS) (resistance to apoptosis) and an increase in CD4- CD8- T cells (18). The definition of the disease is unclear because of an overlap with other systemic vasculitides such as PAN and Wegener, and with other inflammatory conditions exhibiting eosinophils. CSS is mainly a focal disease. In the original publication asthma, hypereosinophilia, necrotizing vasculitis and extravascular granulomas were the major characteristics (19).

Clinically CSS is now often defined by the presence of asthma, hypereosinophilia, (more than 10 percent eosinophils in the blood or 1.5 X 109 eosinophils per liter) and systemic vasculitis involving two or more extrapulmonary organs (20). Approximately 70% of patients with CSS have ANCA (MPO-ANCA in the majority of cases).

The incidence of CSS is similar in males and females (with mild predilection for males). CSS usually presents in the third or fourth decade of life, in several phases (asthma or allergic rhinitis : prodromal phase ; hypereosinophilia with eosinophilic pneumonitis or gastroenteritis : second phase ; systemic vasculitis : third phase) the three phases not necessarily occur sequentially.

GI involvement has been reported in two larger series, one including 154 patients with CSS (21) and one with 146 cases (22) (Table VI). In a Japanese series 21 cases had multiple ulcers (stomach n = 11 ; small intestine n = 16 ; colon n = 7) sometimes presenting with perforation (12 / 21 cases) (21). The small intestine was the most common site of involvement. Endoscopically, colonic ulcers were shallow and irregular in size. Other clinical manifestations are cholecystitis, gastric ulcer, pseudopolyps in the colon consistent with ulcerative colitis, allergic granulomas in the stomach, liver and omentum (8). The GI lesions may have features of eosinophilic gastroenteritis. Histologically necrotizing vasculitis (infiltration of the wall by eosinophils and granulomatous lesions in the wall of the vessels) and granulomas in the extravascular tissue are present. The granulomas are composed of histiocytes and frequently multinucleated giant cells centered around degenerating collagen fibres. In the central portion there may be also disintegrated cells, particularly eosinophils. Extravascular granulomas are not present in all cases according to the literature. In the Japanese series they were reported in 48% of cases.

Table 6. — **Gastrointestinal disease in Churg-Strauss syndrome**

	Japanese series (20)	Western series (19)
89% Japanese (67/75)		
abdominal pain	67% (50/75)	59% (41/66)
bleeding	47% (35/75)	18% (11/67)
diarrhoea	32% (24/75)	33% (24/72)

The granulomas are not a prerequisite for the diagnosis (and can occur in other conditions - rheumatoid arthritis etc.) (2).

Related lesions have been reported as “necrotizing granulomatous vasculitis – isolated or limited form of CSS in the gastrointestinal tract” (22). In this case, involvement of small arteries and veins was noted and the lesions were limited to the GI tract. Whether this can be regarded as genuine CSS is unclear.

Microscopic polyangiitis

Microscopic polyangiitis (MPA) (less appropriate synonyms : microscopic polyarteritis nodosa, hypersensitivity angiitis, microscopic form of periarteritis, microscopic form of PAN) has been distinguished from classic PAN because it is a systemic small-vessel vasculitis typically associated with focal necrotizing glomerulonephritis with crescents (in classic PAN ischemic glomerular lesions are more common).

However, there are many cases with overlapping features and therefore it may not be logic to make a strict distinction between classic PAN and microscopic polyangiitis. On the other hand, in MPA, ANCAs (p-ANCAs or MPO-ANCA) may play a role in inducing the vasculitis. pANCAs are positive in over 80% of the MPA cases (8). The differential diagnosis includes vasculitis occurring in viral hepatitis, especially B but C may also be involved (in some studies 5% of PAN have hepatitis C) (23). Tests for pANCA have been found to be positive in a patient presenting with colonic ulcers due to vasculitis and hepatitis C (23).

Small vessel vasculitis, immune complex mediated

Hypersensitivity vasculitis (Leucocytoclastic vasculitis, LCV)

This is a large heterogeneous group, frequently associated with immune complexes. Pathologically it is mainly a neutrophilic / leucocytoclastic vasculitis. Various names such as “hypersensitivity vasculitis” and “leucocytoclastic vasculitis” have been used for this group. The term “hypersensitivity vasculitis” is confusing because it has also been used for small vessel vasculitis in general or MPA (4,7). The condition affects small vessels (especially postcapillary venules) and is characterized by a combination of vascular damage and an infiltrate composed largely of neutrophils. Because there is often fragmentation of nuclei (karyorrhexis or leucocytoclasis) the term leucocytoclastic vasculitis

(LCV) is frequently used. There may be swelling of endothelial cells and deposits of strongly eosinophilic strands of fibrin can be found within and around the vessel walls. In severe cases luminal occlusion may be noted.

The immune-complex aetiology (antibody mediated) is often invoked to explain this type of small vessel vasculitis and different distinct clinical syndromes can be distinguished such as "Henoch-Schönlein purpura", "Cryoglobulinemia associated vasculitis" and "connective tissue disease" associated vasculitis. Therefore it is indicated to specify the diagnosis. Leucocytoclastic vasculitis, not associated with Henoch-Schönlein purpura can involve the gastrointestinal tract (24).

Henoch-Schönlein Purpura (IgA deposits)

Henoch-Schönlein purpura is characterized by "peculiar skin lesions", arthritis, abdominal pain and renal disease. It frequently occurs in childhood (six months to seven years old). It is characterized by vascular deposition of IgA-dominant immune complexes.

Two-thirds of the cases are known to experience such GI symptoms as colicky abdominal pain and bleeding. Symptoms can be so acute that surgical intervention is considered (25). GI bleeding may be found in up to 80% of cases if tests for occult blood are performed serially. The necrotizing arteritis may also cause acute cholecystitis and acute pancreatitis. Gastrointestinal symptoms may precede the recognition of skin lesions.

Essential Mixed Cryoglobulinemia (Deposition of cryoglobulin)

Essential mixed cryoglobulinemia is a distinctive syndrome of purpura, arthralgias, weakness and diffuse vasculitis. The diagnosis is based on determining the presence of cryoprecipitable serum proteins – that is, two or more immunoglobulins of different classes which have the ability to reversibly precipitate at low temperatures. Cryoglobulins can occur in association with a primary GI process, particularly hepatic disease (hepatitis B and especially C, which is thought to be etiologic) but also adult celiac disease and IBD (mainly ulcerative colitis). Symptoms in this disease appear to result from immune complex formation and deposition which incites a vasculitis involving small and medium-sized vessels. GI involvement is common in essential mixed cryoglobulinemia. It usually affects the liver and spleen. Intestinal involvement is less common and is generally felt to be a late and often catastrophic manifestation of the disease due to severe vasculitis. Occasionally, the disorder mimics IBD both clinically and radiographically. Abdominal pain was present in 20% of patients in a series of 40 patients. Yet an unequivocal diagnosis of visceral vasculitis secondary to essential mixed cryoglobulinemia is rare (4 cases up to 1991). The clinical picture was either that of intestinal infarction or of IBD (26). The presence of complement abnormalities, especially a very low level of early components (C4) with normal or slightly low C3 is diagnostically useful.

Lupus vasculitis

Intestinal manifestations of systemic lupus erythematosus (SLE) are recognized in more than 50% of the patients. They include a variety of conditions and symptoms such as protein-loosing and abdominal pain. Anorexia and weight loss may occur in more than 50% of patients with active disease. Lupus enteritis may affect the oesophagus and the stomach although the small bowel and colon are more commonly involved. Severe complications such as ischemic colitis are uncommon although frequently reported (27). There may be dysmotility of the oesophagus leading to symptoms of reflux ; of the stomach, leading to gastric outlet obstruction ; of the small intestine resulting in pseudo-obstruction. Peritonitis may occur as part of the serositis of lupus. It may be generalized, sometimes giving rise to ascites, or localized leading to perihepatitis or perisplenitis. Acute pancreatitis is also documented. Adhesions, ulcer, ileus, protein-losing enteropathy, malabsorption and variable degrees of small and large bowel ischemia are known to occur (28). Gastointestinal vasculitis occurs in approximately 2% of patients with SLE but has a 50% mortality (28).

Rheumatoid Disease

Rheumatoid disease (RA) should be considered in the differential diagnosis of both small and large vessel vasculitis. It is a systemic disease with inflammation of the joints as the major manifestation but extra-articular manifestations are a common finding. Involvement of the GI tract might be expected and is observed in about 10% of patients (6). The usual presentation is with acute abdominal pain, associated with intestinal ulceration and sometimes perforation and peritonitis. Rarely, rheumatoid disease may be associated with a malabsorption syndrome.

Although serious complications of vasculitis like ulcers, gangrene and perforations may occur, these are rare. Apart from disorders due to vasculitis, less serious manifestations can be ascribed to the disease itself. An example of this are hypergastrinemia and the high percentage (30%) of oesophageal motility disorders found in RA (29). Extrinsic factors, mainly the use of NSAIDS may however influence the percentage of some of these manifestations (29).

Rectal biopsy may help to identify the disease and GI involvement (30). In one series, the presence of necrotising arteritis on rectal biopsy was associated with poor prognosis.

Mixed Connective Tissue Disease (MCTD)

MCTCD is a syndrome characterized by overlapping features of progressive systemic sclerosis (PSS, scleroderma), sytemic lupus erythematosus and polymyositis

(PM), and unusually high titres of antibodies directed against the ribonucleoprotein fraction of extractable nuclear antigen. In a series of 61 patients with MCTD one case of colonic and small bowel perforations due to vasculitis was reported. Gastrointestinal manifestations of MCTD were however much more common (heartburn 48%, dysphagia 38% ; distal oesophageal aperistalsis 17%) (31).

Drug-induced vasculitis

A number of drugs have been associated with colonic ischemia (conjugated estrogen, ergotamine derivatives, catecholamines, dextroamphetamine, digoxin, vasopressin, cocaine and its derivatives, methamphetamine). Most of them modify splanchnic blood flow (32). Drugs that have been implicated in cutaneous leucocytoclastic vasculitis include penicillins, aminopenicillins, sulfonamides, allopurinol, thiazides, retinoids and quinolones. In addition, drugs as propylthiouracil and hydralazine appear to cause vasculitis by inducing ANCA (4).

Behçet's Disease

Behçet's disease is an unusual condition, originally defined by the presence of recurrent oral and genital ulcers and relapsing iritis but now recognized as a multisystem disorder. A diagnosis is based upon the presence of recurrent oral and genital ulcers, the occurrence of skin lesions (erythema nodosum...) and a positive pathergy test. Susceptibility to Behçet's disease is strongly associated with the presence of the HLA-B51 allele. Environmental factors such as infections (Herpes, Hepatitis C, Parvovirus B19...). have also been implicated in its pathogenesis. Lymphocytic function is abnormal. Behçet's disease is not a chronic disorder but rather one consisting of recurrent attacks of acute inflammation. (33) Gastrointestinal involvement, although infrequent, has been identified throughout the alimentary tract. Between 0.48% and 1.2% of patients with established Behçet's disease can have gastrointestinal lesions (25/2031 patients ; 1.23% and 16/3316 patients ; 0.48% in Japanese series ; 0/130 patients in a German series and 5/496 patients ; 1%, in a Turkish series) (33). Numerous cases of colitis associated with Behçet's disease have been recognized (34). Microscopic examination of colectomy specimens reveals extensive mucosal ulceration with varying longitudinal, fissuring and aphthoid configurations, usually occurring within a background of normal or focally inflamed mucosa, and associated with a lymphocytic vasculitis involving submucosal veins. Intestinal perforation, including oesophagus and small intestine, is a common complication. Many of the features of Behçet's disease are suggestive of Crohn's disease but colitis in Behçet usually lacks the transmural inflammation, aggregated lymphocytes and submucosal fibrosis. These differences are reflected in differences in the frequency of perforations (34,35).

Entero-colic lymphocytic phlebitis, possibly different from Behçet's disease (because of lack of systemic involvement) has been reported (36). Intestinal venulitis has also been described in cases of drug-related angiitis.

Paraneoplastic vasculitis

Neoplasias are rarely associated with vasculitis syndromes. Overall, cancer is found in approximately 5% of patients with vasculitis. Only a few reports of vasculitis associated with adenocarcinoma have been published. These include four cases of adenocarcinoma of the colon with cutaneous vasculitis in two patients and mesenteric vasculitis (necrotizing) in two other patients. The pathogenesis of vasculitis in cases with malignancy is unknown. It has been suggested that tumour antigens may provoke host reactions and give rise to antigen-antibody complexes that produce inflammation. Another possible mechanism is a direct destructive effect of cancer cells on the vascular wall (37). Lymphoproliferative and myeloproliferative disorders can also induce vasculitis.

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