Gastrointestinal aspects of vasculitides

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Abstract | Systemic vasculitides are caused by inflammation of blood vessels and can affect any organ and any part of the gastrointestinal tract, hepatic and biliary system, as well as the pancreas. These disorders can cause a wide array of gastrointestinal manifestations, from asymptomatic elevated transaminase levels and mild abdominal pain to potentially life-threatening bowel perforations and peritonitis. A diagnosis based solely on gastrointestinal symptoms is challenging as these manifestations are not specific. Conversely, diagnostic and therapeutic delays can be rapidly detrimental. In this article, we review the epidemiology, characteristics and management of the main gastrointestinal manifestations of systemic vasculitides, including polyarteritis nodosa and antineutrophil cytoplasm antibody-associated vasculitides, as well as isolated vasculitides limited to the gastrointestinal tract.

Vasculitides are a heterogeneous group of diseases that are characterized by inflammation of blood vessel walls and are classified by the type and size of the predominantly involved vessels, which influence the area and type of ischaemic injury[1]. When considering the gastrointestinal aspects of vasculitides, large-vessel vasculitides can cause widespread intestinal or other organ infarctions, whereas small-vessel vasculitides mainly affect intramural arteries and can cause focal, segmental ischaemia and ulcerations[2].

Gastrointestinal manifestations of vasculitides range from mild abdominal pain to more severe and potentially life-threatening peritonitis and bowel perforations. The frequency and type of these gastrointestinal manifestations vary among vasculitides, the most common and suggestive of which are summarized in TABLE 1. The manifestations can occur at diagnosis or at the time of a relapse, and are sometimes isolated. In 1996, the Five Factor Score (FFS) identified severe gastrointestinal manifestations as major predictors of mortality in polyarteritis nodosa, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (EGPA), along with severe involvement of the central nervous system (CNS), heart and/or kidneys (serum creatinine level >15.8 mg/l and/or proteinuria >1 g per 24 hours)[3]. Despite improvements in the survival of patients with vasculitis over the past few decades, with advances in the medical and surgical management of vasculitides, gastrointestinal manifestations remain a serious problem. This Review focuses on the gastrointestinal manifestations of systemic vasculitides and their management, as well as single-organ gastrointestinal vasculitis.

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Large-vessel vasculitides

Takayasu arteritis

Takayasu arteritis predominantly affects the aorta and/or its major branches, especially the subclavian and common carotid arteries. Stenotic lesions are found in >90% of patients with Takayasu arteritis and aneurysms in ~25%[1,4].

Epidemiology. Takayasu arteritis predominantly affects females in their 20s or 30s and is most common in Japan, Southeast Asia, India and Mexico[5]. In 2012, the prevalence in Japan was >40 cases per million[6]. The annual incidence in North America is 1–3 cases per million, much lower than in Asia[7].

Gastrointestinal features. Gastrointestinal manifestations of Takayasu arteritis are rare and occur mainly in the small or large intestine, spleen or, more rarely, as liver ischaemia due to stenoses or occlusion of large or medium gastrointestinal arteries (FIG. 1). In a retrospective study of 126 patients with Takayasu arteritis, 16% had abdominal pain, 4% had mesenteric ischaemia and 14% had abdominal bruits[8]. On imaging, ~25% of patients had stenotic or occlusive lesions in the coeliac and/or superior mesenteric arteries. Aorto-oesophageal fistula due to Takayasu arteritis has also been described[9]. One study of 40 patients with Takayasu arteritis found elevated alkaline phosphatase levels in 73%, possibly indicating some ischaemic liver involvement[10].

Several cases of Takayasu arteritis coexisting with IBD have been reported, suggesting a possible association. In a North American cohort of 160 patients with Takayasu arteritis, eight (5%) had IBD, compared

Key points

- Gastrointestinal manifestations are rarely the predominating features of systemic vasculitides but can rapidly become life-threatening
- Gastrointestinal involvement is rare in large-vessel vasculitides and is mainly due to large-vessel stenosis or occlusion, with long-segment gastrointestinal tract ischaemic manifestations
- Small-vessel vasculitides can cause various gastrointestinal manifestations, including mucosal purpura (risk of haemorrhage), patchy granulomatous or ischaemic ulcerations that can mimic IBD and can perforate
- Liver involvement is rarely clinically significant in systemic vasculitides, except for rare infarcts due to large or medium-sized vasculitic occlusions and Budd–Chiari syndrome in patients with Behçet's disease
- Treatment of gastrointestinal manifestations must be prompt, adapted to the severity of the disease and conducted in collaboration with general surgery and interventional radiology as needed
- Patients with single-organ gastrointestinal vasculitis must be followed closely for the development of systemic vasculitis, although such a progression is observed in a maximum of one-quarter of patients over the subsequent 5 years

with an estimated prevalence of 0.2% of Crohn's disease in the general population[11]. Evidence of genetic overlap between Takayasu arteritis and ulcerative colitis also exists as they share *HLAB*5201* as a genetic determinant[12]. IBD diagnosis usually precedes that of Takayasu arteritis (in 69% of cases, by a median of 4 years)[11]. Neither IBD nor Takayasu arteritis seem to feature worse outcomes when they do coexist.

Management. Glucocorticoids (0.5–1.0 mg/kg body weight per day of a prednisone-equivalent for the initial dose, followed by a gradual taper) are the mainstay treatment for active Takayasu arteritis, but glucocorticoid-dependency and relapse are common when tapering[13]. Methotrexate (15–25 mg per week) remains the first-line glucocorticoid-sparing agent but there is limited evidence for its efficacy[14]. Cyclophosphamide (2 mg/kg body weight per day orally, or intravenous pulses of 7.5–15.0 mg/kg body weight on days 1, 15 and 29, then monthly for a maximum of 6 months total) and mycophenolate mofetil (1–3 g per day) have also been used for refractory cases[15,16]. Retrospective studies support the use of anti-TNF agents for refractory Takayasu arteritis, especially infliximab (5–10 mg/kg body weight per infusion at days 1, 15 and then monthly) and adalimumab (40 mg subcutaneous injection every 2 weeks)[14]. Tocilizumab (an anti-IL-6 receptor monoclonal antibody; 8 mg/kg body weight intravenously per month) was also effective in a series of 49 patients with Takayasu arteritis, although 29% eventually needed to switch to another biologic agent[17]. A randomized double-blind trial evaluating the efficacy of abatacept (10 mg/kg body weight intravenously on days 1, 15 and 29, then monthly) was completed in 2015 with the results expected in early 2017 (REF. 18).

Severe gastrointestinal manifestations of Takayasu arteritis should be treated aggressively with high-dose glucocorticoids and often another immunosuppressant, mainly anti-TNF agents. Open surgery and endovascular treatments might be needed, especially in patients with symptomatic coeliac or mesenteric artery stenosis. The main setback to vascular surgery is the high rate of restenosis: 15–30% at 5–20 years for open surgery; and 30–70% at 5–10 years after angioplasty[4]. The 5-year complication rate is increased sevenfold for patients with active inflammation at the time of revascularization and/or those who are not on glucocorticoids at the time of the procedure[4].

Giant cell arteritis

Giant cell arteritis (GCA) also affects the aorta and/or its major branches, with predilection for the branches of the carotid and vertebral arteries[1]. Aortitis can occur in 10–25% of patients with GCA[19].

Epidemiology. GCA is most common in Western countries and mainly affects white individuals[19]. The incidence of GCA increases with age and peaks at 70–80 years[20].

Gastrointestinal features. Mesenteric vessels are rarely affected in GCA. A systematic review of the literature found only 12 GCA cases (75% with a positive temporal artery biopsy result) with mesenteric involvement resulting in small bowel infarction[21]. More than 50% of these patients had both cranial and abdominal symptoms, the latter often predominating over the former. Isolated cases of infarction of the large bowel have been described and can present with nonspecific fever, abdominal pain or as an acute abdomen. Tongue necrosis can also occur and manifest as dysphagia, lingual pain, swelling and/or gangrene.

Abdominal pain in patients with GCA can also result from abdominal aortic aneurysm and dissection. The median time from the diagnosis of GCA to the development of abdominal aortic aneurysm or dissection is 6–7 years[22]. All patients with GCA should be screened for aortic aneurysm at diagnosis and for a minimum follow-up period of 5 years thereafter[23].

One-third to one-half of patients with GCA show asymptomatic liver enzyme level abnormalities, especially elevated alkaline phosphatase levels without any prognostic significance, as well as mildly raised transaminase levels in 10–40% of patients[24]. These abnormalities might result from injury to bile duct epithelial cells due to adjacent arteritis[25]. Portal tract hepatic arteritis[26] or granulomatous inflammation of the liver[27] are exceedingly rare but can cause fever and gastrointestinal symptoms before cranial symptoms suggestive of GCA occur.

Management. Similar to Takayasu arteritis, glucocorticoids are the cornerstone of treatment for GCA, often with another immunosuppressant in case of severe gastrointestinal manifestations, and surgery and/or endovascular procedures if needed. Patients with GCA tend to be older than those with Takayasu arteritis, therefore morbidity and mortality are high[28]. Adjunctive methotrexate treatment can reduce the relapse rate and cumulative dose of prednisone exposure, but only to a limited extent[29]. Tocilizumab seems more effective on the basis of a few open-label studies and a small randomized controlled trial of 30 newly-diagnosed or relapsing patients with GCA, in which 85% of patients achieved sustained

Table 1 | **Common gastrointestinal manifestations of systemic vasculitides**

Vasculitis	Common gastrointestinal manifestations and frequency
Large-vessel vasculitides	
Takayasu arteritis	• Abdominal bruits (14%)[8] • Diffuse, long-segment gastrointestinal tract ischaemia (4%)[8]
Giant cell arteritis	• Elevated alkaline phosphatase level (50%)[26] • Slightly elevated transaminase level (10–40%)[24,26] • Mesenteric ischaemia (12 cases)[21]
Medium-sized vessel vasculitides	
Polyarteritis nodosa	• Abdominal pain (up to 95%)[34,35,66] • Narrow, tapered arteries and/or saccular or fusiform microaneurysms in renal, hepatic and mesenteric arteries[59]
Kawasaki disease	Gallbladder mucocele (5–20%)[56]
Small-vessel vasculitides	
ANCA-associated vasculitis	• Mucosal ulcerations, patchy intestinal infarction, ischaemia, perforations or occlusion (20–50%)[35] • GPA and EGPA: granulomatous ulcerations of large bowel (can mimic IBD)[35] • GPA: pancreatic granulomatous lesion (can mimic cancer on imaging)[66]
IgA vasculitis (Henoch–Schönlein purpura)	• Mucosal purpura (20–50%) with gastrointestinal bleed[83,85] • Bowel wall oedema, infarct, perforations or intussusception (3–5%)[83,85]
Cryoglobulinaemic vasculitis	• Intestinal ischaemia (80% of patients with gastrointestinal manifestations)[35,66,96] • Acute cholecystitis, pancreatitis (7% of patients with gastrointestinal manifestations)[96]
Behçet's disease	• Ileocaecal ulcers (round-shaped, focal distribution) • Budd–Chiari syndrome (1.3–3.2%)[105]

ANCA, antineutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis.

remission at 1 year and 80% could stop glucocorticoid treatment[30]. A larger study (GiACTA), with final results expected in early 2017, evaluated subcutaneous tocilizumab for 12 months in patients with GCA, as a first-line treatment or for relapsers[31]. Abatacept has also been investigated with interesting results. According to the preliminary analysis, a slight but significantly ($P = 0.049$) lower relapse-free survival at 12 months was found with abatacept (same doses as for Takayasu arteritis) compared with placebo[32].

Medium-sized vessel vasculitides

Polyarteritis nodosa

Polyarteritis nodosa is a medium-sized muscular artery vasculitis. One hallmark of polyarteritis nodosa is the existence of narrow, tapered arteries along with saccular or fusiform microaneurysms on conventional abdominal arteriography, CT or magnetic resonance angiographies. These features occur in up to 85% of patients with polyarteritis nodosa, predominantly in the mesenteric, renal and/or hepatic arteries, often at the branching points of those vessels[1,33–36]. Whereas polyarteritis nodosa included HBV-associated polyarteritis nodosa in the 1994 Chapel Hill nomenclature, polyarteritis nodosa now only refers to a disease not related to any known infectious agents, whereas HBV-associated polyarteritis nodosa is now named HBV-associated vasculitis[1]. Patients with HBV-associated vasculitis should be screened for cryoglobulin, as a few cases of HBV-associated cryoglobulinaemic vasculitis have been reported[37], although this manifestation is more common in HCV infection than HBV infection.

Epidemiology. In parallel with the decreased prevalence of HBV infection (the major cause of previous polyarteritis nodosa cases) following widespread vaccination and improved blood transfusion policies, the incidence of polyarteritis nodosa has also decreased[38]. Annual incidence of polyarteritis nodosa was 0–8 cases per million in European countries and Australia in the early 2000s, but was up to 77 cases per million in HBV-endemic Alaskan native populations in 1980–1990 (REFS 39,40). Polyarteritis nodosa is most common in men in their mid-50s[33].

Gastrointestinal features. Gastrointestinal involvement is more frequent in HBV-associated vasculitis than non-HBV polyarteritis nodosa[1,3,35]. Severe gastrointestinal involvement (bleeding, perforations, infarction and/or pancreatitis) during the first year after HBV-associated vasculitis onset is associated with a higher mortality than in non-HBV polyarteritis nodosa[41].

Abdominal pain, nonspecific and variable in intensity, is present in 35–95% of patients with polyarteritis nodosa[34,42]. This pain is thought to be secondary to transmural necrotizing inflammation of the mesenteric vessels, leading to bowel ischaemia, most commonly in the small bowel[2]. Other symptoms include nausea, vomiting, diarrhoea, haematochezia, melaena and haematemesis. Gastrointestinal or intra-abdominal bleeding can result from mucosal ischaemic ulcerations, bowel infarctions, perforations or intraperitoneal rupture of hepatic, splenic and/or renal (micro)aneurysms[2]. Ulcers are found in 5–6% of patients with polyarteritis nodosa, mainly in the jejunum[2,35].

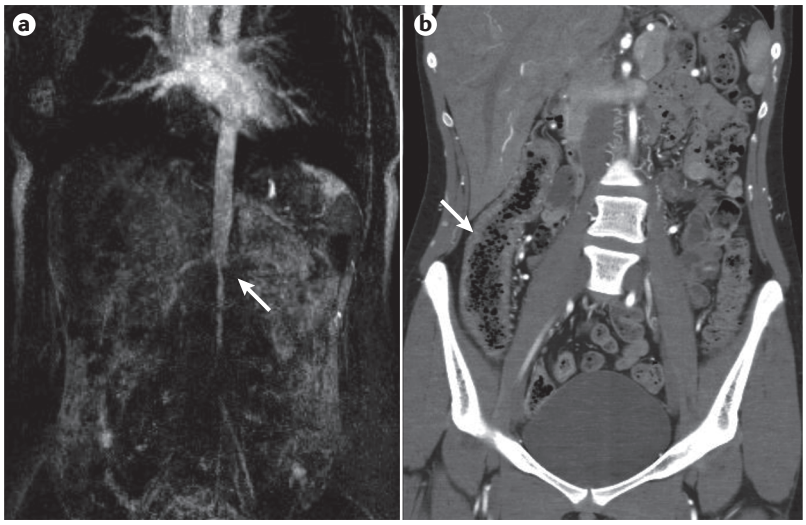

Figure 1 | **Chronic ischaemic colitis in a female patient with Takayasu arteritis.** **a** | Magnetic resonance angiogram of the aorta and abdominal branches showing severe narrowing of the infrarenal aorta (thin white arrow) with complete occlusion just distal to the origin of the inferior mesenteric artery. Absent right and middle colic arteries with collateral vessels running alongside the right colon. **b** | CT of the abdomen identifies moderate thickening of the ascending (large white arrow) and transverse colon.

Interestingly, the acute hepatitis is usually mild in patients with HBV-associated polyarteritis nodosa, but fibrosis might still develop later on[33,35,42]. Segmental liver or spleen infarcts and occlusion of the hepatic veins (Budd–Chiari syndrome) have also been reported, owing to the hepatosplenic vessel involvement[2,43].

Management. The 5-year survival for patients with polyarteritis nodosa exceeds 80%[33,42]. The FFS can be used to guide treatment of non-HBV polyarteritis nodosa[3]. For severe forms (FFS ≥1), including severe gastrointestinal manifestations, cyclophosphamide (2 mg/kg body weight per day orally, or 7.5–15.0 mg/kg body weight in intravenous pulses on days 1, 15 and 29, then every 3–4 weeks for a maximum of 6 months) and high-dose glucocorticoids (prednisone-equivalent 1 mg/kg body weight per day, possibly preceded by daily intravenous pulses of 7.5–15.0 mg/kg body weight methylprednisolone for 1–3 days, followed by a gradual taper) are recommended for induction, followed by azathioprine (2 mg/kg body weight per day) or methotrexate (20–25 mg per week) for maintenance[33,44]. For patients with nonsevere forms (FFS = 0), glucocorticoids alone achieve sustained remission in 50% of patients[45]. The systematic addition of azathioprine to glucocorticoids as first-line treatment failed to reduce treatment failure or relapse rates[46]. An immunosuppressant other than azathioprine might achieve better results but, for now, these are only added for nonsevere polyarteritis nodosa that fails to respond to glucocorticoids alone or for severe polyarteritis nodosa.

The treatment of HBV-associated vasculitis relies on antiviral drugs (such as lamivudine, 100 mg per day) or newer agents such as entecavir (0.5 mg per day), tenofovir (300 mg per day), adefovir dipivoxil (10 mg per day) or telbivudine (600 mg per day). For severe disease or to more rapidly control the clinical manifestations, the drugs are combined with a short course of glucocorticoids (prednisone-equivalent 0.5–1.0 mg/kg body weight per day, with a rapid tapering regimen over 1–2 months) and plasma exchange[38,42,47,48].

Kawasaki disease

Kawasaki disease is a mucocutaneous lymph node syndrome associated with medium-artery involvement, possibly including the coronary arteries[1].

Epidemiology. Kawasaki disease is mostly seen in young children, with >80% of cases in children 6 months to 4 years old. This disease is more prevalent in Asian populations, especially in Japan, where the annual incidence rate in 2012 was 265 cases per 100,000 children <5 years old[49]. In North America, Australia and Europe, the incidence is 4–25 cases per 100,000 children <5 years old[50]. Adults are exceptionally affected, most often with incomplete forms of the disease[51,52].

Gastrointestinal features. In a series of 198 children with Kawasaki disease, 61% had gastrointestinal symptoms (abdominal pain, nausea and vomiting) 10 days before the Kawasaki disease diagnosis[53]. In another cohort of 219 children with Kawasaki disease, 10 (4.6%) presented with more severe abdominal symptoms: nine had an acute abdomen (gallbladder mucocele (hydrops), paralytic ileus, appendicular vasculitis and/or haemorrhagic duodenitis)[54]. Interestingly, coronary aneurysms developed in half of the children (compared with 20–25% usually) despite early administration of intravenous immunoglobulins[54]. Gallbladder mucocele has been reported in 5–20% in another series, occurring usually within the first 2 weeks of the illness, possibly secondary to vasculitis of the gallbladder wall[55].

In the largest series of 43 adult patients with Kawasaki disease, 56% had gastrointestinal symptoms, with abdominal pain and jaundice being the most common manifestations[51].

Management. Standard treatment consists of aspirin and intravenous immunoglobulins (2 g/kg body weight), which reduces the risk of coronary artery aneurysms from 20–25% to 2–4%[56]. Patients who do not respond to this initial therapy (~10%) should receive repeat intravenous immunoglobulin infusion[57]. Although the effect of glucocorticoids on coronary artery abnormalities is as yet uncertain, it has been recommended in children with refractory disease[57]. Other rescue therapies to consider include infliximab, IL-1 antagonists (anakinra), plasma exchange and cyclophosphamide, as illustrated by a few case reports[57,58].

ANCA-associated small-vessel vasculitides

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are necrotizing vasculitides that predominantly affect small vessels (capillaries, venules, arterioles and small arteries), with few or no immune deposits[1,59,60]. However, AAV might involve medium-sized arteries as well. Very few cases with angiographic imaging of visceral vessels in AAV have been published;

those that are published usually do not reveal microaneurysms, at least not as large and numerous as in polyarteritis nodosa[59,60].

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (GPA) commonly involves the upper and lower respiratory tracts and kidneys[1]. GPA is typically associated with anti-proteinase 3 ANCA.

Epidemiology. The global annual incidence of GPA is estimated at 2–15 cases per million, with the lowest incidence reported in Japan[61]. The global prevalence is 23–160 cases per million[61]. The disease is rare in non-white individuals and peaks at 55–65 years old.

Gastrointestinal features. Gastrointestinal symptoms are observed in 5–11% of patients with GPA[35,62,63]. Autopsy studies identified histopathological evidence of gastrointestinal vasculitis in up to 24% of cases[62].

Any part of the gastrointestinal tract can be involved but the small intestine and large bowel are most common; symptoms range from transient abdominal pain and ulcerations (oral, oesophageal and peptic ulcers) to bloody diarrhoea and intestinal perforations[35,63]. Gastrointestinal imaging findings are usually nonspecific, ranging from multifocal or diffuse bowel-wall thickening to mesenteric vascular engorgement and ascites[59]. Endoscopic studies can reveal ulcerations, sometimes described as granulomatous, and ischaemic changes. Compared with Crohn's disease, ulcers seen in GPA are more typically shallow and transversely oriented, but the distinction can be challenging and cases of associated Crohn's disease (or ulcerative colitis) and GPA (or other AAV) have been reported[11,62,64,65]. Perendoscopic biopsies of oesophagus or stomach are rarely contributive to diagnosis. Biopsies of colon ulcers might have a slightly increased sensitivity (~30–40%) if deep and submucosal[66]. Such deep biopsies have a high risk of perforation in patients with vasculitis, and are therefore rarely safely feasible[35].

Granulomatous cholecystitis, granulomatous pancreatic mass and liver granulomas, which can initially be suspicious for malignancy on imaging, have also been reported in GPA, as have spleen or liver infarcts or haemorrhage[67].

Microscopic polyangiitis

In microscopic polyangiitis, granulomatous inflammation is absent[1] and ANCAs are more often directed against myeloperoxidase.

Epidemiology. The annual incidence of microscopic polyangiitis is 1–10 cases per million, with a prevalence of 9–94 cases per million[61]. In contrast to GPA, microscopic polyangiitis is more common in Asian populations.

Gastrointestinal features. Gastrointestinal involvement has been reported in 5–30% of patients with microscopic polyangiitis, with symptoms ranging from abdominal pain, nausea, vomiting and diarrhoea to, rarely, colonic ischaemic ulcers, peritonitis and bowel perforations[35,66,68].

EGPA

Most patients with EGPA have late-onset asthma and eosinophilia, which are not sufficient to make the diagnosis, and vasculitic manifestations such as skin purpura or mononeuritis multiplex[1,69]. Only 30–40% of patients have detectable serum ANCAs, usually against myeloperoxidase[70,71]. Cardiac involvement, more common in ANCA-negative patients, is the main mortality risk factor[70,71].

Epidemiology. The annual incidence is 0.8–2.8 cases per million and prevalence is 7–22 cases per million[61]. The mean age at diagnosis is 34–54 years[72].

Gastrointestinal features. Gastrointestinal symptoms are seen in 30–50% of patients, are nonspecific and include abdominal pain (91%), diarrhoea (45%), melaena or haematochezia (19–36%), nausea and vomiting (18%) and surgical abdomens (6–36%)[35,70,71]. Mesenteric artery vasculitis is the most common explanation for these manifestations and can lead to bowel infarction and perforations, particularly in the small intestine. Gastrointestinal tract mucosal infiltration by eosinophils can also cause pain, motility disorders, obstructive symptoms and diarrhoea, as seen in eosinophilic oesophagitis, gastritis or colitis. Granulomatous and eosinophilic mucosal ulcerations have been described as potential sources of bleeding in the stomach, duodenum, jejunum and/or, more rarely, the colon, as have acalculous cholecystitis, omental nodules and haematomas[35]. The coexistence of EGPA and IBD has been reported[11].

Management of AAV

Severe gastrointestinal involvement in microscopic polyangiitis and EGPA (bleeding, perforation, pancreatitis, laparotomy) is associated with poor outcome[44,73]. Patients with severe gastrointestinal manifestations must promptly receive glucocorticoids combined with another potent immunosuppressant such as cyclophosphamide (2 mg/kg body weight per day orally, or 7.5–15.0 mg/kg body weight intravenous pulses on days 1, 15 and 29, then every 3 weeks for a maximum of 6–9 pulses total). All patients with GPA should receive a combination of glucocorticoids and another immunosuppressant, regardless of severe gastrointestinal manifestations. Whereas the median survival of patients with untreated GPA was 5 months before the introduction of cyclophosphamide and glucocorticoids, the 5-year survival of patients with AAV has now improved to 80%[74,75]. Rituximab (375 mg/m^2 body area, weekly for 4 consecutive weeks), a chimeric CD20 B-cell-targeting antibody, is an alternative to cyclophosphamide in ANCA-positive patients with systemic GPA or severe microscopic polyangiitis[76]. In EGPA, preliminary studies on mepolizumab, an anti-IL-5 monoclonal biologic agent, have yielded promising results[77]. A randomized controlled study is ongoing[78], and others will start that might provide some evidence of its effect on gastrointestinal features. In addition to urgent medical therapy, surgery is sometimes required. Once sustained remission is achieved, different treatment approaches are used for maintenance as relapses are common in AAV[69,79–82].

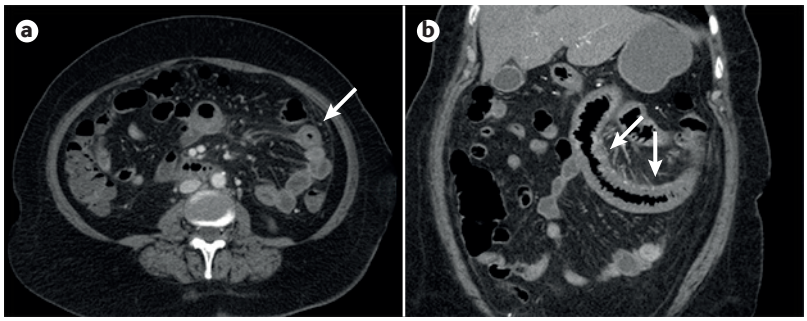

Figure 2 | **Jejunitis in a female patient with IgA vasculitis.** Horizontal (part **a**) and coronal (part **b**) CT view of the abdomen demonstrates mural thickening of a long segment of the proximal jejunum (white arrows) with mild mesenteric fat stranding and mesenteric vascular engorgement.

Other small-vessel vasculitides

Immune-complex small-vessel vasculitides are characterized by vessel wall inflammation with deposits of immunoglobulins and/or complement[1].

IgA vasculitis

Epidemiology. IgA vasculitis (also known as Henoch–Schönlein purpura) can develop at any age but is most common in children between 3–10 years old[83]. The incidence is 2–3 cases per 100,000 children and 0.1–1.8 cases per 100,000 adults[83]. The male:female ratio is 1.5:1.0 and no ethnic predominance exists, but the disease is rare in black populations[83,84].

Gastrointestinal features. Overall, 50–75% of patients with IgA vasculitis have gastrointestinal manifestations[85]. Abdominal pain is the presenting symptom in up to 20% of patients; it is colicky in nature, often periumbilical and worse after meals[85]. Gastrointestinal bleeding related to mucosal and submucosal vasculitis occurs in 18–52% of patients[85]. The duodenum is most commonly involved, followed by the descending colon. Endoscopic findings can reveal petechial lesions, diffuse mucosal redness and haemorrhagic erosions[86]. Oesophageal involvement is rare and can present with ulcers, strictures or severe oesophagitis[2]. The extent of associated skin purpura to the upper extremities is associated with risk of gastrointestinal bleeding[87].

Most gastrointestinal manifestations are self-limited, but 3–5% of patients show bowel wall oedema (visible on abdominal CT) (FIG. 2), infarcts, necrosis, perforations or intussusception[2,85]. Other rare manifestations include protein-losing enteropathy, pancreatitis, cholecystitis and appendicitis[2]. Hepatobiliary involvement was noted in 1.8% of 225 children with IgA vasculitis, who had right upper-quadrant pain (80%), elevated circulating transaminase levels (75%), hepatomegaly on ultrasonography (75%) and gallbladder wall thickening (25%)[88].

Management. IgA vasculitis is usually benign and self-resolving in a few weeks[83]. Recurrence is more common in patients with renal involvement[84]. Sufficiently powered, randomized controlled trials on gastrointestinal manifestations of IgA vasculitis are lacking and would be difficult to conduct due to the rarity of the condition. Glucocorticoids should be used for patients with abdominal manifestations. In severe cases, the addition of cyclophosphamide might yield more adverse effects and no clear benefit[89]. Mycophenolate mofetil or rituximab can help achieve remission in some patients who do not respond well to glucocorticoids[90,91]. Overall, 5–12% of patients require laparotomies because of intussusception, bowel perforations and/or severe bleeding[2].

Cryoglobulinaemic vasculitis

Cryoglobulins are circulating immunoglobulins that precipitate at temperatures below 37 °C and dissolve on rewarming. Three subtypes of cryoglobulins have been described: type I refers to a single monoclonal immunoglobulin, usually in relation with an underlying lymphoproliferative disorder; type II is composed of both polyclonal IgG and monoclonal immunoglobulin; and type III are polyclonal immunoglobulins. Cryoglobulins are difficult to detect owing to technical temperature constraints. In a patient with possible cryoglobulinaemia, a low C4 complement fraction (with normal C3 fraction) and a positive rheumatoid factor would strongly suggest the presence of cryoglobulins, leading to a repeat screening test. Cryoglobulinaemic vasculitis is mainly observed with type II and III cryoglobulins and can affect the skin, kidneys and/or peripheral nerves[1].

Epidemiology. Cryoglobulinaemic vasculitis is most common in patients in their mid-50s, with a male:female ratio of 3:1 (REF. 92). HCV infection is the main cause of mixed cryoglobulinaemia in up to 98% of cases[93]. Up to 50% of patients with HCV infection have circulating cryoglobulins, but vasculitis develops in only 5–10% of these patients[94]. Other causes of cryoglobulinaemia and cryoglobulinaemic vasculitis include HBV and HIV infection, autoimmune disorders such as Sjögren syndrome and lymphoma[95,96].

Gastrointestinal features. Gastrointestinal involvement in cryoglobulinaemic vasculitis is rare but often catastrophic[97]. Gastrointestinal symptoms range from abdominal pain and bloody stools to intestinal perforations, intestinal ischaemia, acute cholecystitis and pancreatitis.

Liver involvement is observed in up to 60% of HCV-infected patients with cryoglobulinaemic vasculitis, with 25% showing progression to cirrhosis[92]. Hepatocellular carcinoma is seen less frequently in HCV-infected patients with cryoglobulinaemic vasculitis than in those without[92,98]. Severe gastrointestinal manifestations are associated with a poor prognosis in both HCV-related and non-HCV cryoglobulinaemic vasculitis[98,99].

Management. Treatment is guided by the underlying disorder (for example, HCV infection or lymphoma) and cryoglobulinaemic vasculitis severity. New antiviral therapies are the cornerstone of treatment for virus-associated cryoglobulinaemic vasculitis[93,100]. Rituximab (375 mg/m^2 body area, weekly for 4 consecutive weeks) can also be used with antiviral agents to induce remission in patients with severe disease, including gastrointestinal manifestations[96,101,102]. Glucocorticoids might be useful in

non-HCV cryoglobulinaemic vasculitis, or transiently in HCV-associated cryoglobulinaemic vasculitis.

Variable-vessel vasculitides

Vessels of any size in the venous and arterial circulation can be affected in variable-vessel vasculitides, which include Behçet's disease and Cogan syndrome (only rare cases of mesenteric vasculitis have reported in patients with the latter)[103].

Behçet's disease

Behçet's disease is characterized by recurrent oral and/or genital aphthous ulcers and can be complicated by cutaneous, ocular, articular, gastrointestinal, thrombotic and/or CNS inflammatory lesions[1].

Epidemiology. Behçet's disease is most common in Asia and Mediterranean regions[1]. The prevalence in Turkey is 80–420 cases per 100,000, 13.5–85 cases per 100,000 in Asian countries, and 0.12–0.64 cases per 100,000 in Western countries[104]. The male:female ratio varies by region, with males most commonly affected in Mediterranean and Asian countries, and females in the USA and Northern Europe[105].

Gastrointestinal features. Reported frequencies of gastrointestinal involvement in Behçet's disease varied between 2.8% of patients in a Turkish series, 32% in Taiwan, 37–43% in the USA and 50–60% in Japan[105,106]. Clinical symptoms vary from anorexia, vomiting, dyspepsia, diarrhoea, melaena and abdominal pain to perforations requiring surgical intervention.

Two forms of intestinal Behçet's disease can be distinguished: mucosal ulcers from neutrophilic infiltrates that can mimic IBD[107], and intestinal ischaemia and infarction due to large-vessel vasculitis (especially the mesenteric vessels)[108]. Any part of the gastrointestinal tract can be involved, most commonly the terminal ileum and ileocaecal junction[64,109]. Oesophageal ulcers are most often found in the inferior part of the oesophagus. Oesophageal varices have also been reported in patients with occluded vena cava[110]. Gastric involvement includes ulcers and pyloric stenosis[111]. In the colon, three types of ulcers have been described: volcano, geographic and aphthous[64]. Volcano ulcers have the highest risk of perforation, especially in patients <25 years old[112]. Rectal and/or anal involvement is rare[105].

Budd–Chiari syndrome affects 1.3–3.2% of patients with Behçet's disease, especially young males[105]. The extent of the thrombus within the inferior vena cava is a major determinant of survival (complete diffuse occlusion is associated with a mean survival of 10 months)[113].

Management. Colchicine is the cornerstone treatment for oral and genital ulcers, but other agents are often required for gastrointestinal manifestations, such as glucocorticoids, sulfasalazine, azathioprine or, for more severe cases, cyclophosphamide or eventually anti-TNF agents, such as infliximab (5–10 mg/kg body weight per infusion at days 1 and 15, then monthly initially) or adalimumab (subcutaneously, 40 mg every 2 weeks)[105,114,115]. Surgery can be required for perforations, fistulas or obstruction[116]. The rate of disease recurrence at the site of anastomosis is high[117].

The use of anticoagulation therapy for Behçet's disease-related venous thrombosis remains debated, but a potent immunosuppressive treatment is mandatory.

Vasculitis with systemic diseases

Systemic lupus erythematosus

Gastrointestinal manifestations are common in patients with systemic lupus erythematosus (SLE). Most manifestations are due to adverse reactions to medications and infections[118]. Gastrointestinal manifestations directly attributable to SLE affect 1.3–27.5% of patients[119–121]. The prevalence of vasculitis in SLE is 11–36% of patients, and is mainly cutaneous[119]. Mesenteric vasculitis prevalence is less, at 0.2–9.7%[120,121], predominantly affecting the superior mesenteric artery, resulting in ischaemia of the ileum and jejunum[119] with risk of perforations and haemorrhage. CT findings include prominence of mesenteric vessels with a palisade pattern (comb sign), with focal or diffuse dilated bowel loops, ascites and bowel wall thickening with a double halo or target sign appearance[122]. Thrombosis of the mesenteric vessels can also occur without vasculitis, usually causing more focal or limited ischaemic areas[123]. Involvement of the duodenum would be more suggestive of vasculitis than thrombosis. Hepatic arteritis is rare but has been reported in autopsy studies[124].

Treatment of SLE-associated mesenteric vasculitis includes high-dose glucocorticoids and complete bowel rest. Cyclophosphamide is added when other major organs are involved (for example, CNS or glomerulonephritis) or in case of intestinal necrosis or persistent abdominal pain despite glucocorticoids. Remission is achieved in 85% of patients, and the relapse rate is 23% at 1 year, but lower in patients on glucocorticoids and cyclophosphamide[122]. Prompt surgical intervention is required in patients with large intestinal necrosis or perforation. Mortality is up to 50% in patients with perforations[120].

Rheumatoid vasculitis

Rheumatoid vasculitis can develop in patients with long-standing (usually 10–15 years) erosive rheumatoid arthritis[125]. However, with the use of biologic agents, its prevalence has decreased by 30–50% since 2000, down to 1–5% of patients with rheumatoid arthritis[126].

Rheumatoid vasculitis usually involves vessels of small and medium size and is associated with poor prognosis: mortality is ~25% at 5 years[127]. Cutaneous vasculitis and vasculitic neuropathy are the most common clinical manifestations. In all, 10–38% of patients with rheumatoid vasculitis have gastrointestinal involvement[125], which can result in ischaemic ulcers, perforations and segmental or extensive bowel infarction. Similar to SLE, glucocorticoids and cyclophosphamide are commonly used to treat severe rheumatoid vasculitis.

Single-organ vasculitis

Isolated, gastrointestinal single-organ vasculitis (SOV) has been reported in the oesophagus, stomach, omentum, small and large intestines, appendix, gallbladder

Box 1 | **Vasculitis mimickers**

- Infection (for example, endocarditis)
- Atherosclerosis and atheroembolic disease
- Thromboembolic disorders (cardiac myxoma, cardiac thrombus, endocarditis, mycotic aneurysm, others)
- Antiphospholipid syndrome
- Fibromuscular dysplasia
- Superior mesenteric artery syndrome
- Segmental arterial mediolysis
- IgG4-related disease
- Hypereosinophilic syndrome
- Thromboangiitis obliterans
- Malignant atrophic papulosis
- (Epithelioid) angiosarcoma
- Intravascular large B-cell lymphoma
- Ehlers–Danlos type IV
- Erdheim–Chester disease
- Marfan syndrome
- Adenosine deaminase 2 deficiency

IgG4, immunoglobulin G4.

and pancreas[128,129]. Patients with gastrointestinal SOV often present with an acute abdomen (two-thirds of patients as compared with one-third of patients who have systemic vasculitides with gastrointestinal involvement), which might represent a diagnostic bias as most SOV diagnoses are indeed established based on histological findings after the required surgery[2,128–130].

With the exception of small bowel and large intestine involvement, most reported gastrointestinal SOVs resolve after surgical excision without immunosuppressive therapy[129]. The progression to, or subsequent development of, systemic vasculitis seems uncommon, and has been reported in 0–25% of patients with gastrointestinal tract involvement at 5 years[129,130]. A systematic diagnostic work-up is still required to look for extra-gastrointestinal findings suggestive of systemic vasculitis, which should include at least a study of serum inflammatory markers (such as C-reactive protein), creatinine and urine sediment analysis, search for ANCAs and antinuclear antibodies, HBV and HCV serology and chest enterography.

Gastrointestinal vasculitis mimickers

Besides gastrointestinal infections, the main conditions that can mimic vasculitis with gastrointestinal involvement are listed in BOX 1 (REFS 131–133). Mesenteric ischaemia has multiple possible causes, most frequently atherosclerosis. IBD can mimic AAV or Behçet's disease and is occasionally associated with vasculitis[11]. Whether eosinophilic oesophagitis, gastritis and colitis fall within the pathogenic spectrum of hypereosinophilic syndrome or EGPA remains unclear[69]. IgG4-related disease can cause various gastrointestinal manifestations, including aortitis and periaortitis with possible involvement of gastrointestinal arterial branches of the aorta, or enterocolic lymphocytic phlebitis[134].

Thromboangiitis obliterans affects the small and medium-sized arteries and veins of the extremities. On pathology, a highly cellular inflammatory thrombus can be observed, but blood vessel walls are relatively spared compared with those seen in patients with vasculitis[135,136]. Thromboangiitis obliterans has a high prevalence in the Middle East, Asia and the Far East[137] and is most common in young male smokers[137]. Patients most often present with subacute ischaemic claudication of the extremities, with frequent development of ulcerations[135]. Gastrointestinal involvement is rare but has a poor prognosis[138]. Mesenteric involvement with small bowel ischaemia can occur at any time and, in some instances, can even be the sole manifestation of the disease[139]. Coeliac, gastric or other visceral arteries can also be involved[138]. Chronic and intermittent abdominal pain with weight loss has been described[138]. On angiography, multiple vascular occlusions with tortuous collateralization can typically be seen[139]. Vasodilators, possibly including prostacyclin analogue infusions, are usually used and smoking cessation is mandatory. Immunosuppressants are not useful with this disease[140]. Amputation is sometimes unavoidable[141] and, in gastrointestinal thromboangiitis obliterans, emergency laparotomy is often needed to resect ischaemic bowel segments and carries a high perioperative mortality (~30%)[138]. In chronic cases, bypass surgery might be required.

In patients with known vasculitis, some gastrointestinal complications of treatments can be challenging and difficult to differentiate from a disease flare. These complications include stress and/or glucocorticoid-induced gastritis, oesophagitis and ulcers, or infections such as herpes virus, cytomegalovirus, *Candida*, other parasites or bacteria. Endoscopy with brushing and/or biopsies are essential for making the correct diagnosis and in guiding treatment.

Conclusions

The spectrum of gastrointestinal manifestations in systemic vasculitides is broad and symptoms are usually poorly specific. As abdominal pain can be an early sign of ischaemic perforations, physicians should always be wary and monitor their patients with known systemic vasculitis closely if they start complaining of unusual gastrointestinal symptoms. The diagnosis of vasculitis can be also very challenging in patients with isolated gastrointestinal manifestations, because systemic vasculitis can present first with isolated gastrointestinal symptoms, and single-organ vasculitis can remain limited to the gastrointestinal tract. Once a diagnosis of vasculitis and vasculitis-related gastrointestinal manifestations is established, adapted treatments must be initiated promptly, which usually include immunosuppressants and sometimes urgent abdominal or vascular surgery. The medical and surgical facets of the treatment must be tightly combined and should not excessively delay each other. Morbidity and mortality associated with severe gastrointestinal manifestations remain high. Effective management of vasculitis and gastrointestinal manifestations requires close collaboration between medical and surgical specialists.

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