CASE REPORT

A 59-year-old Chinese man with no significant past medical history presented with a two-week history of diffuse abdominal pain, watery stools, and loss of weight of 2 kg. His pain acutely worsened on the day of presentation and was associated with a fever of 38°C. Physical examination revealed a distended abdomen with left paraumbilical and left iliac fossa tenderness and guarding. A computed tomography (CT) scan of the abdomen and pelvis showed pneumoperitoneum with large bowel loops dilated up to 6 cm (Figure 1). His total white blood cell count was 27.7 × 10^9/L, and he had metabolic acidosis. He underwent an emergency exploratory laparotomy for colonic perforation on the same night. Intraoperatively, there was a perforation of the proximal descending colon just distal to the splenic flexure. The proximal colon was dilated and ischemic. We performed a subtotal colectomy with ileorectal anastomosis and created a defunctioning ileostomy.

Postoperatively, the patient recovered uneventfully, but presented two months later with a purpuric rash over bilateral lower limbs and left second toe gangrene. He also complained of left hand and left leg weakness which was worsening over the last two weeks. Physical examination revealed duskiness of the fingers and toes with left second toe gangrene but his peripheral pulses were strong. The patient also had a left foot drop and a left wrist drop with wasting of the intrinsic hand muscles. Laboratory investigations showed acute kidney injury with proteinuria.

The clinical picture of ischemic colitis, vasculitic rash, digital infarcts, and mononeuritis multiplex was initially suggestive of systemic vasculitis. However, careful review of the resected colonic specimen did not reveal any histological evidence of vasculitis. The specimen was fixed in formalin and embedded in paraffin. After embedding, 3-µm paraffin sections were prepared with a microtome and stained with hematoxylin and eosin (H&E). No significant inflammatory infiltrate was seen in the blood vessel walls. Some of the mesenteric blood vessels showed focal fibroblastic infiltration within fibrin thrombi (Figure 2). In other parts of the mesentery, the blood vessels had narrowed lumina with asymmetric fibrointimal proliferation (Figure 3), which are features suggestive of an organized thrombus. Vascular...
thrombosis, at various stages of organization, raises the possibility of a prothrombotic phenomenon that has led to pauci-inflammatory vascular occlusion, causing mesenteric ischemia.

Autoimmune serologies (including anti-nuclear antibody, anti-double stranded DNA, anti-extractable nuclear antigen profile, anti-neutrophilic cytoplasmic auto-antibodies, and rheumatoid factor), serum and urine protein and immunofixation electrophoresis, viral serologies (including hepatitis B and C, HIV, and Epstein–Barr virus), malignancy screen (with a CT scan of the neck, thorax, abdomen, and pelvis), and evaluation for hypercoagulable states were all negative. The patient’s serum sample was then incubated at 4°C for 72 hours which showed precipitates at the bottom of the test tube after one centrifugation. These re-dissolved when warmed to room temperature suggesting the presence of cryoglobulins. The type of cryoglobulin was not identified. He was diagnosed to have cryoglobulinemia with hyperviscosity syndrome, and was referred to the rheumatologist and hematologist for further management. Bone marrow aspiration and trephine biopsy were subsequently performed and these showed focal involvement by low grade B-cell lymphoma. The patient was started on plasma exchange and received systemic corticosteroids and rituximab. Unfortunately, he eventually succumbed to a nosocomial pneumonia and passed away four months after his initial presentation.

**DISCUSSION**

Cryoglobulinemia refers to the presence of circulating immunoglobulins called cryoglobulins in the serum. These immunoglobulins precipitate at low temperatures and dissolve upon rewarming. This disease mainly causes vasculitis in small- to medium-sized blood vessels and manifests clinically with rash, arthralgia, neuropathy, and proteinuria [1]. Cryoglobulins are classified into three types by Brouet et al. [2, 3]. Type I cryoglobulins are single monoclonal immunoglobulins related to underlying B-cell lymphoproliferative disorders. Types II and III are often referred to as mixed cryoglobulinemias and consist of monoclonal and polyclonal immunoglobulins (Ig). They are often related to autoimmune diseases or chronic infections, such as hepatitis C (Table 1). In patients with clinical symptoms suggestive of vasculitis, diagnosis of cryoglobulinemia is confirmed by the presence of cryoglobulins in serum maintained at 4°C for at least 7 days, which subsequently dissolve

<table>
<thead>
<tr>
<th>Type</th>
<th>I</th>
<th>II</th>
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<tr>
<td>Frequency</td>
<td>25–30%</td>
<td>25%</td>
<td>50%</td>
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<tr>
<td>Clonality</td>
<td>Monoclonal</td>
<td>Monoclonal + polyclonal</td>
<td>Polyclonal</td>
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<tr>
<td>Immunoglobulin classes</td>
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<td>Monoclonal IgM + polyclonal IgG (rarely IgA)</td>
<td>Polyclonal IgM + polyclonal IgG (or IgA)</td>
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<td>Associated diseases</td>
<td>B-cell lymphoproliferative disorders</td>
<td>Autoimmune disorders, chronic infections</td>
<td>Autoimmune disorders, chronic infections</td>
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Modified from Guili et al. [3].

*Abbreviation:* Ig: Immunoglobulin.
when heated to 37°C [4]. The disease manifestation is variable, ranging from mild clinical symptoms (purpura, arthralgia) to severe, life-threatening complications (glomerulonephritis, pulmonary and gastrointestinal involvement). Gastrointestinal involvement is rare in cryoglobulinemia. In one study, only 5 out of 443 patients with cryoglobulinemia developed gastrointestinal involvement [5]. Patients above 65 years old, with pulmonary, gastrointestinal, or renal complications, have higher risk of mortality [6]. High quality, evidence-based treatment for cryoglobulinemia is limited but management generally involves a combination of rituximab, corticosteroids, plasma exchange, and treatment of the underlying etiology [7].

CONCLUSION

Cryoglobulinemic vasculitis is a rare cause of ischemic bowel. It should be suspected in patients with concomitant signs of systemic vasculitis, such as vasculitis rash, digital gangrene, and mononeuritis multiplex, especially if no other causes of ischemic bowel are apparent during surgery. Management is complex and will always require multidisciplinary care.

Keywords: Cryoglobulinemia, Ischemic colitis, Vasculitis

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.
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