A 39-year-old lady presented with bloody diarrhea for 6 weeks, and pedal edema, abdominal distension and reduced urine output for 3 days. Six weeks back she developed predominantly watery stools with blood and mucus, large volume, 10-12 times/day. She also had mild predominantly non-colicky abdominal pain. Three days prior to hospitalization she developed increased pain, abdominal distension, bilateral pedal edema and decreased urine output. She had taken some NSAIDs for headache prior to the onset of this illness. There was associated anorexia and weight loss, but no joint pains, fever or rashes.

She underwent colonoscopy and CT abdomen elsewhere. Colonoscopy showed multiple ulcers; she was treated there with a diagnosis of ulcerative colitis. Subsequently she was diagnosed to have toxic megacolon and referred to us.

Six years back she had bleeding per-rectum, was diagnosed to have hemorrhoids, and was treated with ayurvedic medication, with good response. She was a housewife, with two children, and had no addictions.

On examination, she looked sick and had a puffy face. She was well oriented, afebrile and dehydrated. Her pulse rate was 130 per minute, blood pressure 80/60 mmHg and respiratory rate 45/ min. She was pale and had bilateral pitting pedal edema. Jugular venous pressure was not raised. She had a distended and tense abdomen with no tenderness, rigidity or guarding. Bowel loops were palpable with sluggish bowel sounds and minimal free fluid. The rectum was empty on examination and there was no bloody stool. The other systems were normal.

**Table: Investigations**

<table>
<thead>
<tr>
<th></th>
<th>June 12, 2005</th>
<th>June 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>15.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Leukocytes (/cmm)</td>
<td>13,000</td>
<td>48,000</td>
</tr>
<tr>
<td>N/L/E/M</td>
<td>73/20/4/3</td>
<td>94/4/1/1</td>
</tr>
<tr>
<td>Platelets</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Na/K (mEq/L)</td>
<td>130/2.5</td>
<td>137/3.6</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>Sugar (mg/dL)</td>
<td>68</td>
<td>-</td>
</tr>
<tr>
<td>PTI (%)</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>APTT (C 30-40)</td>
<td>47</td>
<td>58</td>
</tr>
<tr>
<td>PT (C 10)</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>pH</td>
<td>7.46</td>
<td>7.34</td>
</tr>
<tr>
<td>PO_2(mmHg)</td>
<td>59</td>
<td>47-60</td>
</tr>
<tr>
<td>PCO_2(mmHg)</td>
<td>28</td>
<td>29-40</td>
</tr>
<tr>
<td>SaO_2 (%)</td>
<td>92</td>
<td>81-89</td>
</tr>
<tr>
<td>HCO_3 (mmHg)</td>
<td>19</td>
<td>15-21</td>
</tr>
<tr>
<td>Base excess</td>
<td>-3</td>
<td>-5.9</td>
</tr>
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</table>

CPK MB was 96.5 IU/L (normal <25). Ascitic fluid had protein 850 mg/dL, sugar 76 mg/dL, leukocyte count 400 per dL (polymorphs 95%, lymphocytes 5%). Blood culture was sterile. EKG showed heart rate of 100 per minute with junctional rhythm and low voltage, with depression of ST waves that reversed on intravenous K+ infusion. Terminally she developed ventricular tachycardia.

**Radiology (Kang)**

*Chest X-ray* taken 10 days prior to admission was normal. On the day of admission it showed endotracheal tube *in situ*; there was a dense homogenous opacity in the left lower zone silhouetting the left hemi-diaphragm and cardiac border and obscuring the left costophrenic angle, suggestive of pleural effusion. In addition, there was a hazy opacity in both lower zones suggestive of consolidation. On the day of demise X-ray showed homogenous dense opacities with air bronchogram in both lungs (left > right), suggestive of ARDS.

*X-ray abdomen* (erect and supine films) showed dilated (predominantly air-filled) large and small bowel loops. The transverse colon was grossly distended and measured 6 cm, suggestive of toxic megacolon. There was mild irregularity along the wall of the hepatic flexure and the sigmoid loop, which could be due to submucosal edema or gross mucosal destruction with mucosal islands. No air was seen in the biliary tree or under the diaphragm.

**USG abdomen:** Liver was enlarged and measured 17.5 cm with increased echotexture. Hepatic veins were normal and portal vein measured 15.5 mm. Intrahepatic biliary radicals were not dilated. Gall bladder wall was of normal thickness and there was biliary sludge. There were ascites. Kidneys and spleen were normal. Significant dilatation of bowel loops was noted. There was bilateral pleural effusion.

**Contrast-enhanced CT scan** 4 days prior to admission showed mildly enlarged liver and diffuse decreased attenuation, consistent with fatty infiltration. No focal lesion was seen. Biliary radicles, and hepatic and portal veins are normal. Spleen, gall bladder, pancreas and both kidneys were normal. Aorta, inferior vena cava, and superior mesenteric artery and vein were normal. There was diffuse, circumferential, smooth mural thickening of 5-10 mm involving the cecum and ascending and descending colon, with submucosal hypodensity (Fig 1). Mucosal irregularity was seen in the ascending colon. Mural thickening was seen in the transverse colon and rectum. There was no soft tissue stranding, intramural air or pneumoperitoneum. The transverse colon was grossly distended. The jejunal loops were collapsed. There was mild dilatation of the distal small bowel loops. There was no significant retroperitoneal or mesenteric lymphadenopa-
Ulcerative Crohn's colitis
TB
Amebic Ischemic

<table>
<thead>
<tr>
<th>Age</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Severity</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6-week course</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No fever</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>No response to treatment</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bowel wall l cm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>No fistula</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>No stricture</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Diffuse involvement</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No lymphadenopathy</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

The other chronic colitis that could be considered are cytomegalovirus (CMV) colitis, strongyloidosis and Yersinia infection.

If she had idiopathic ulcerative colitis (IUC), I will discuss the possible reasons for such severe acute disease.1-5

i) A severe first attack may be seen in 5%-10% of cases. They more commonly present with pancolitis, and require a more vigilant management. Earlier this was associated with a high mortality of 37%, which has gone down to 2% in the post-steroid era. A third of these patients would undergo colectomy within the first year.

ii) Toxic megacolon can complicate 5% of cases with severe IUC. It can be triggered by hypokalemia, NSAIDs use, colonoscopy, infection with CMV, ameba or C. difficile, and indiscriminate use of opiates.

iii) Superadded CMV infection. This is usually seen in immunosuppressed individuals. CMV colitis per se can also mimic IUC. It can precipitate toxic megacolon in a patient with IUC, can exacerbate the disease process, can rarely be the initiating factor for the first episode, both conditions can co-exist, and it can be the cause for disease refractoriness.

Fifteen percent of patients with IUC infected with CMV will develop toxic dilatation. Two-thirds of these will require colectomy, with a mortality of 44%. Specific treatment for CMV improves the outcome of IUC; up to 50%-100% of cases improve with ganciclovir, thereby avoiding colectomy.

There are a few prevalence studies from India.6,7,8 A study from Lucknow revealed an incidence of 16%, more often in females, with pancolitis, active disease and azathioprine use. A study from our own center showed presence of IgM antibody in 34% of cases (against 4.7% in normal subjects) and IgG in 90% (against 97%). Thirty percent of...
Vaiphei

patients had either only serology or tissue positivity.

The infection can result in severe refractory colitis in 19%-44% of patients and active non-refractory colitis in 0.5%-5%. In 5%-27% of patients post-colectomy infection supervenes. CMV DNA was demonstrable in these patients in 81% of colonic tissue (against 29% in normal subjects).

iv) Other infections superadded. Amebic infection is uncommon and usually responds well to metronidazole. Shigella / Salmonella / E. coli are quite common but are unlikely to last 6 weeks. C. difficile infection is likely, but the patient had received many antibiotics without any respite right from the onset of the acute attack.

Other complications that she had terminally were

- pedal edema, pleural effusion and ascites, which could be explained by hypoalbuminemia;
- ascites with high neutrophil count, which could be explained by septicemia with no evidence of hollow organ perforation;
- hepatomegaly, which could be due to fatty liver as the result of malnutrition or drugs like steroids;
- septicemia, shock and disseminated intravascular coagulation;
- terminal breathing difficulty, which could be due to ARDS, which was evident on X-ray.

The terminal events were ventricular arrhythmias due hypotension, acidosis and dysselectromenia, and possibly myocardial ischemia as indicated by raised CPK-MB value, or a remote possibility of CMV myocarditis.

My final clinical diagnosis is

- Ulcerative colitis, severe refractory, with toxic megacolon, with a possibility of superadded CMV infection
- Septicemia-related peritonitis, shock, DIC and ARDS
- Non-alcoholic fatty liver disease
- Hypokalemia and dysarrhythmias
- Myocardial ischemia

Open house forum

Gupta: The X-ray pictures are not very characteristic for ARDS. The first X-ray had evidence of pleural effusion. Sudden appearance of white lung in the second X-ray with significant drop in hemoglobin level could also suggest pulmonary hemorrhage. Dr. Usha attributed the bilateral pleural effusion to hypoalbuminemia. How common would pericardial effusion be in such a setting? In a patient with evidence of polyserositis in the form of ascites, bilateral pleural and pericardial effusions, one of the most likely diagnosis would tuberculosis.

Singh: The patient had clinical symptoms characteristic for ulcerative colitis. But the rectum was apparently spared both on radiology and colonoscopy. With the presence of pulmonary symptoms, a more likely diagnosis would be intestinal and pulmonary tuberculosis.

Chairman: The details of the colonoscopy findings are not available to us as it was done elsewhere.

Jain: In a young lady who has multisystem involvement including the heart, vasculitis is an important possible diagnosis, though she had predominant large bowel involvement. Secondly, an infective colitis remains possible as she also had neutrophilic leukocytosis. Shigella is well known to cause infective colitis and even myocarditis.

Talwar: Clinically there was no evidence to suggest myocarditis. Raised CPK could be of non-cardiac origin. The changes seen on EKG could be metabolic. The patient apparently had multisystem involvement including, possibly, toxic megacolon. The mild pericardial effusion could be part of a systemic condition resulting in effusion in all the serous cavities. CMV myocarditis is usually seen in post-transplant or other immune-compromised states.

Thapa: The picture in Shigella colitis has changed totally due to availability of various broad-spectrum antibiotics, though some strains are developing drug resistance. In the mid-1980s when shigellosis was treated with co-trimoxazole, some cases would be complicated by dilatation of the colon associated with perforation. This patient was receiving treatment even before she was admitted with us, but she failed to respond. Hence, infection with resistant strains of Shigella would be a possibility.

Jha: A co-existing renal problem needs to be excluded. We do not know whether there was renal protein loss as well. I would like to consider a possibility of amyloidosis. We have seen amyloid involving both the kidney and the GI tract. Obviously, for the rapid downhill course, we have to keep open a possibility of superadded infection by organisms like cytomegalovirus. In GI CMV infection, it is well known that extra-intestinal involvement is less frequent. When dealing with a case with multi-system involvement, we cannot dismiss systemic vasculitis as an important differential diagnosis.
Dutta: GI tract amyloidosis usually involves the small intestine, and the patient presents with watery diarrhea. Bloody diarrhea would be odd. Ulcerative colitis is an extremely protein-depleted condition that can result in severe hypoalbuminemia. Vasculitic ulcer is painful. Our patient had mild pain towards the terminal part of her illness. Shigella colitis usually produces acute bloody diarrhea, but sometimes can have a protracted course. This patient had received selenium and it is unusual for shigellosis not to respond. Shigellosis would have systemic inflammatory response with fever right at its outset. With regards to immune-compromised state for developing CMV infection, she was indeed malnourished and hypoalbuminemic and was receiving steroids and cyclosporine and probably other drugs the details of which we do not know.

Rana: Superadded CMV infection in IUC is usually seen with long-term steroid therapy rather than in patients presenting with acute symptoms. It is also one of the causative agents for the development of toxic colitis in IUC. This patient also received NSAIDs, which are known to precipitate toxic megacolon.

Pathology protocol (Vaiphei)

A partial autopsy was carried out without examination of the brain. She had generalized edema and excessive yellow-colored fluid in both pleural (240 mL on either side) and peritoneal (500 mL) cavities.

Colon and rectum: There was diffuse dilatation involving mainly the proximal half, with diffuse serosal discoloration and adhesion of the pericolic fat. A large sac-like outpouching was present in the ascending colon and another near the splenic flexure, with a kink in the gut wall. The kink was apparently the result of shelf-like infolding of reduplicated colonic wall with serosal adhesion, which possibly had resulted in partial obstruction and segmental dilatation. The colonic wall corresponding to these two areas was thickened as a result of fibrosis and marked adhesion of the surrounding fat. The mucosa was diffusely ulcerated, with many discolored pseudopolyps (Fig 2). The cecum and proximal ascending colon had granular and congested mucosa. The ileo-cecal valve and terminal ileum were not involved. Appendix was thickened with mucosal discoloration and ulceration.

On microscopy, there were characteristic changes of acute-on-chronic colitis (Fig 3) in the areas where the mucosa was preserved as well as in the pseudopolyps. There was diffuse deep mucosal ulceration covered by fibrino-purulent exudate. The ulcers were deep, involving the muscularis propria, with extensive smooth muscle degeneration. Beneath the exudates, the ulcer beds were composed of granulation tissue with prominent capillaries and marked endothelial cell proliferation. The latter resulted in complete occlusion of the vascular lumen. These changes were also seen deep in the muscularis pro-
The ulcer beds were composed of sheets of epithelioid histiocytes; many of the cells were markedly enlarged (Fig 4). The granulation tissue of the ulcer bed also contained many plump oval or spindle-shaped stromal cells with bizarre nuclei. Amidst the lymphocytes and plasma cells were a few multinucleated giant cells (Fig 4). All these cells had abundant deeply eosinophilic to amphophilic vacuolated cytoplasm with faintly basophilic multiple globular bodies. There was no definite intranuclear or intracytoplasmic inclusion. Large areas of submucosal and subserosal fibrosis were also noted. The pseudopolyps and the granular mucosa showed changes of acute-on-chronic colitis. Ziehl-Nielsen stain for acid-fast bacilli was negative.

Immunostaining using anti-CMV showed strong positivity of the epithelioid and conventional size histiocytes, endothelial cells and proliferating plump fibroblasts. Transmission electron microscopy of the colonic ulcer showed many intracytoplasmic crystalline bodies and intranuclear large globular inclusions (Fig 5) with malformed viral capsids. Sections from the appendix showed similar changes with less intensity.

Small intestine showed only mild congestion. Stomach showed erosions and features of chronic gastritis. Esophagus showed submucosal hemorrhage.

Liver weighed 1400 g and was enlarged, bile stained and firm. Histology revealed diffuse micro- and macrovesicular fatty change. Portal tracts appeared round with variable amount of chronic inflammatory cell infiltration (pericholangitis). Some portal tracts showed evidence of bridging fibrosis and focal spillage of inflammatory cells into the hepatic lobules. Intrahepatic bile ducts of different sizes showed thickening of the wall by collagenization, some of which had characteristic onion-skin appearance of the collagen fibers (Fig 6). In a few of these bile ducts, the lining epithelium showed mucinous metaplasia and positive alcian blue staining. There was marked kupffer cell hyperplasia with evidence of hemophagocytosis. There was also intra-hepatic and intracanalicular cholestasis.

Lungs weighed 800 g; there was patchy consolidation, more in the lower lobes. Microscopy showed diffuse intraalveolar edema, hemorrhages, early bronchopneumonia and patchy hyaline membrane formation.

Spleen weighed 130 g and there was depletion of the red pulp. There was prominence of the splenic sinusoidal macrophages showing evidence of hemophagocytosis. The enlarged mesenteric lymph nodes showed sinus histiocytosis with evidence of hemophagocytosis.

Bone marrow was normo- to hypercellular with erythroid cell hypercellular.

Kidneys weighed 230 g together. There were a few subcapsular cortical scars. Microscopy showed vacuolization of tubular lining.

The rest of the organs were essentially normal.

Final autopsy diagnosis

Idiopathic ulcerative colitis with
- CMV colitis, CMV appendicitis and toxic megacolon
- Primary sclerosing cholangitis, biliary mucinous metaplasia and fatty liver
- Diffuse alveolar injury and early bronchopneumonia
- Chronic gastritis and erosion
- Hemophagocytosis
Open house forum

Mishra: PCR carried out using postmortem tissue from the colonic mucosa was positive for CMV DNA.

Jain: I would like to know the sequence of events in the two disease conditions.

Vaiphei: CMV infection is not synonymous with CMV disease, but can result in long-standing after-effects. It usually infects endothelial cells, besides many other types of cells. The cytomegalic and proliferating endothelial cells cause occlusion of the blood vessels, resulting in vascular compromise and ischemia. This could result in fibrosis, with partial or total change in the disease course.

Chairman: Since it is not easy to confirm the diagnosis of CMV colitis in such a situation, would empiric treatment be appropriate?

Dhiman: This patient had changes of sclerosing cholangitis. Pericholangitis is an early pathological event. Taking into account the biliary pathology, the disease appears to be long standing rather than of recent onset.

Chugh: In our experience with renal transplant, one has to differentiate between CMV disease and CMV infection. This patient obviously had CMV disease. In such a case, one should screen for HIV infection.

Dutta: With increasing recognition of CMV disease, patients with ulcerative colitis refractory to steroid and antibiotics, with acute severe colitis and toxic megacolon, should be tested for CMV infection and treated appropriately. Colectomy may be avoided in them. IgM serology is not very useful. Demonstration of the virus in tissue by immunohistochemistry or PCR is useful.

The features of CMV infection have been well described recently.9

References
7. Udawat H, Dutta U, Vaiphei K, Singh K. To study factors responsible for acute exacerbation of idiopathic ulcerative colitis with special reference to role of infection. Thesis submitted in partial fulfillment of DM (Gastroenterology) to Post Graduate Institute of Medical Education and Research, Chandigarh.

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This case was discussed in the staff clinico-pathological forum of the Institute. Usha Dutta, Associate Professor, Department of Gastroenterology, presented and discussed the clinical protocol; Mandeep Kang, Assistant Professor, Department of Radiodiagnosis, the radiology; and Kim Vaiphei, Additional Professor, Department of Histopathology, the pathology. Vinay Sakhuja, Professor and Head, Department of Nephrology chaired the forum. The case was admitted in the Emergency ward under the care of Emergency Medical services. Kim Vaiphei compiled and edited the protocol. Affiliations of other participants in the forum: D Gupta, Additional Professor, Department of Pulmonary Medicine; V Singh, Additional Professor, Department of Hepatology; S Jain, Professor, Department of Internal Medicine; K K Talwar, Professor and Head, Department of Cardiology; B R Thapa, Professor, Department of Paediatric Gastroenterology; V Jha, Additional Professor, Department of Nephrology; S Rana, Pool Officer, Department of Gastroenterology; B Mishra, Associate Professor, Department of Virology; R K Dhiman, Additional Professor, Department of Hepatology; K S Chugh, Emeritus Professor, Department of Nephrology.