

## Gelatin tannate for treating acute gastroenteritis

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In their review of gelatin tannate (GT) Ruszczyński *et al* [1] extensively explain tannic acid (TA) activity and they may give the impression that TA is responsible for the mechanism of action of GT and also responsible for the possible adverse effects of the product. Various *in vivo* studies have demonstrated that GT is a stable complex not dissociated in the small intestine. Therefore any reference to the TA, in this case, is not justified.

L. Bueno has presented at the 21st UEG Week 2013 in Berlin [2] a review of the *in vitro* studies regarding the mechanism of action of GT and the results of his own *in vivo* investigations confirming that there is no dissociation of GT.

Indeed, the *in vivo* studies performed to confirm the mechanical film forming activity of the stable complex between gelatin and TA have been done by Bueno *et al* in the prestigious center of INRA in Toulouse. The results of the study showed that 6 h after LPS injection, both jejunal TJ permeability and MPO activity were dramatically increased in rats. Oral pretreatment with GT reduced the jejunal increase of permeability by 78.1%, whereas gelatin as well as TA did not affect it. The conclusion was that only the stable complex between gelatin and TA has the potential to form a biofilm and to offer the activity of GT [2].

The conclusions of *in vitro* and *in vivo* testing are that GT acts by mechanical protection of the mucosa and that the therapeutic activity of GT is linked exclusively to its undissociated form, the only one present at the intestinal level [2].

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Conflict of Interest: This letter was written by the medical director of Novintethical Pharma Sagl

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## Authors' reply

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We appreciate Dr. Rupérez's comment that the potential mechanism of action of gelatin tannate is linked exclusively to its undissociated form. We feel it is an important addition to our manuscript. However, to judge this mechanism in more detail, we are looking forward to reading a full publication by Bueno *et al*.

Regardless of the mechanism of action of gelatin tannate, our conclusions remain valid. Currently, there is no evidence to support the use of gelatin tannate for treating acute gastroenteritis in children and only sparse evidence to support the use of gelatin tannate in adults.

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## Adult celiac disease: delayed onset or delayed diagnosis?

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Our understanding of celiac disease (CD) has increased enormously over the years and many facts have been elucidated [1,2] but still the explanation for the variations noted in age at onset of disease and disease manifestations remain unsettled. The marked variation between the two types of CD (childhood vs. adult CD) is intriguing as both types share a common genetic background and environmental trigger i.e. dietary gluten. We aimed to evaluate whether symptoms in patients with adult CD actually begin at adult age (delayed onset of disease) or symptoms actually begin during childhood but are missed or get ignored in the early years of life (delayed diagnosis).

The study was based on 'recall' of symptoms during childhood i.e. <14 years of age. The ascertainment of symptoms suggestive of CD was assessed by a questionnaire based survey conducted between January 2009 to December 2012. A comprehensive questionnaire aimed at identifying symptoms suggestive of CD was developed and it included

3 domains, intestinal symptoms (chronic diarrhea, failure to thrive, malnutrition/malabsorbtion), extraintestinal features (anemia, short stature, thyroid disease, failure to gain weight/height, unexplained chronic liver disease, epilepsy, insulin dependent diabetes mellitus) and treatment history (medical attention sought for intestinal and/or extraintestinal symptoms mentioned above). In addition, age at menarche was enquired in female patients.

Of a total of 445 patients with adult CD who reported in the outpatient department, 370 (83.1%) consented for participation. The mean age of the patients with adult CD was  $33.36 \pm 10.82$  years; 143 being males. The clinical presentation in these patients has been intestinal in 261 (70.5%) and extraintestinal in 109 (29.5%). Of these 370 patients who returned the questionnaire, 134 (36.2%; 42 males) admitted having experienced symptoms suggestive of CD during childhood. Of these 134 patients only 54 (40.3%) of them visited doctors seeking medical attention for these symptoms. Recall symptoms reported are shown in Table 1. Of a total of 227 females, 198 (87.2%) were able to recall their age at menarche, the average age being  $14.9 \pm 1.8$  years. Of those 139 females who had no recall symptoms during childhood, 120 (86.3%) recalled their age at menarche, the mean age being  $14.45 \pm 2.7$  years.

Our study reveals that almost one third of patients with adult CD had symptoms suggestive of CD even during their childhood. Intestinal symptoms such as diarrhea and painful abdomen were more frequently recalled than extraintestinal symptoms. However, only 40% of patients reporting recall symptoms actually sort medical advice. Reasons for not seeking medical help in childhood could be milder severity of symptoms, intermittent nature of symptoms or the subtlety of extraintestinal manifestations.

The mean age at menarche in northern Indian females is reported as  $13.2 \pm 1.09$  years [3]. Age at menarche was delayed in patients with CD irrespective of presence or absence of recall symptoms ( $14.9 \pm 1.8$  vs.  $13.2 \pm 1.09$ ;  $14.45 \pm 2.7$  vs.  $13.2 \pm 1.09$ ,  $P < 0.0001$ ). Delayed menarche points towards undiagnosed CD. Although the symptoms included in the questionnaire are non-specific and non-diagnostic for onset of CD in childhood, however these could be indicative of possible

onset of the disease from childhood. In conclusion, adult CD may actually be a case of delayed diagnosis rather than delayed onset of disease, at least in some patients.

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## ***Helicobacter pylori* infection and liver cirrhosis: possible association with hepatic encephalopathy and/or post-hepatic encephalopathy cognitive impairment in patients with portal hypertension**

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In their retrospective series, Sathar *et al* [1] concluded that there is significant association between *Helicobacter pylori* infection (*Hp-I*) and portal hypertensive gastropathy (PHG) in cirrhotic patients, also related to PHG severity, thereby necessitating *Hp* eradication.

Apart from PHG, hepatic encephalopathy (HE) is another complication of portal hypertension that remains a major cause of morbidity in cirrhotic patients [2]. HE encompasses a spectrum of neuropsychiatric disorders related to liver failure and the mechanisms responsible for the neurological alterations in HE begin to emerge [3].

Hepatitis B (HBV) and C (HCV) infections are among the commonest causes of liver cirrhosis worldwide; *Hp-I* is strongly associated with HBV- and HCV-related cirrhosis in Europe; *Hp-I* is more common in cirrhotic patients with HE than in those without [4]; HE is not a fully reversible

**Table 1** Recall symptoms/disease reported by adult celiac disease during childhood

Symptom/disease	n (%)
Diarrhea	58 (43.3)
Abdominal discomfort	70 (52.2)
Failure to gain height/weight	32 (23.9)
Known anemia	48 (35.8)
Chronic liver disease	6 (4.4)
Seizure disorder	2 (1.4)
Type I diabetes mellitus	2 (1.4)
Hypothyroidism	1 (0.7)

condition and the mechanism behind the lack of reversibility of the neurocognitive status despite the resolution of mental status changes is unclear [5]; and cognitive dysfunction is a factor associated with falls in cirrhotic patients, though further studies are warranted to address the mechanisms implicated in this predisposition and to design preventive strategies [5]. In this regard, *Hp*-I has been frequently detected in cognitive impairment and Alzheimer's disease (AD) [6] and we found that *Hp* eradication may positively influence AD manifestations at five-year clinical endpoints [7], thereby supporting a role for this common infection in the pathobiology of the disease.

*Hp* may be involved in the pathophysiology of both HE and post-HE persistent cognitive impairment by several mechanisms [7], including the release of proinflammatory/vasoactive substances, involved, through blood-brain-barrier disruption, in a number of vascular disorders including AD, which can lead to long-term neurologic deficits [4,5]. It is therefore important to know if the authors have considered the association between *Hp*-I, HE and/or post-HE cognitive impairment in their cirrhotic patients.

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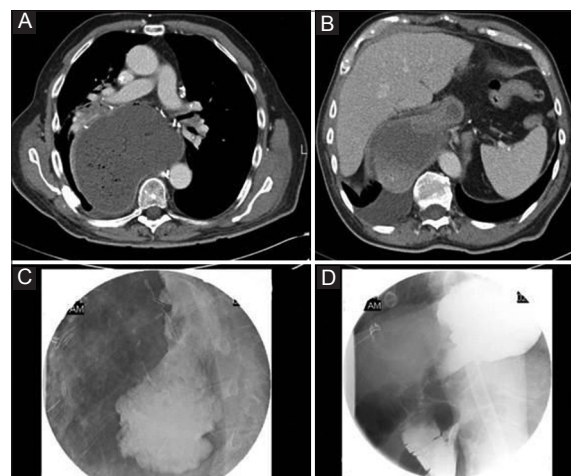
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## Stent placement for delayed conduit obstruction at hiatus after esophagectomy

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We report a case of a 62-year-old male who presented with shortness of breath after having undergone a modified McKeown esophagectomy 6 months after induction chemotherapy for cT3N1 adenocarcinoma of the distal esophagus. A chest computed tomography demonstrated a dilated gastric conduit with evidence of hiatal obstruction and aspiration pneumonia (Fig. 1A). Patient was subsequently intubated for respiratory distress, but eventually extubated three days later. Barium esophagram revealed a dilated gastric conduit with poor emptying (Fig. 1B). Patient underwent endoscopic evaluation revealing a dilated conduit with extensive food and gastric debris. The pylorus was found to be widely patent. However at the level of the hiatus just proximal to the pylorus, there was evidence of obstruction with passage of gastric contents impeded by redundant gastric conduit that formed a shelf at the hiatus with a resulting valve-like effect. A 10 cm × 18 mm Alimaxx™ stent was then placed across the area obstructed by the flap to just proximal to the pylorus (Fig. 1C). The area of obstruction was effectively opened with clearance of gastric content immediately evident. The patient subsequently underwent a barium swallow the succeeding day showing passage of contrast into the duodenum across the hiatus (Fig. 1D). The patient was started on clears and then was eventually discharged tolerating a soft solid diet. The patient remains free of obstructive symptoms for the past 12 months.



**Figure 1** (A) Chest computed tomography illustrating dilated gastric conduit with obstruction at level of hiatus. (B) Barium esophagram demonstrating a dilated gastric conduit with virtually no emptying of contrast into the duodenum. (C) Endoscopic view with stent across area of obstruction at hiatus. (D) Barium esophagram now demonstrating emptying of contrast into the duodenum across the stent

Previous studies have reported an incidence for delayed gastric emptying post-esophagectomy of up to 50% [1-4]. Vagotomy, torsion of the stomach, size and compression of conduit and lack of accompanying drainage have been implicated in delayed gastric emptying. Patients who undergo intrathoracic anastomosis are more prone to gastric emptying problems from a redundant conduit as seen in our patient [5]. Our case report demonstrates that a fully covered stent is an effective treatment for delayed obstruction due to a redundant gastric conduit. The stent effectively relieves the obstruction so that regurgitation and aspiration pneumonia are avoided. The stent is also well tolerated by the patient and can be left in place for extended periods of time.

In conclusion, our case report demonstrates the use of a stent to treat delayed gastric conduit obstruction after esophagectomy due to a redundant conduit.

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## Intra-abdominal desmoplastic small round cell tumor

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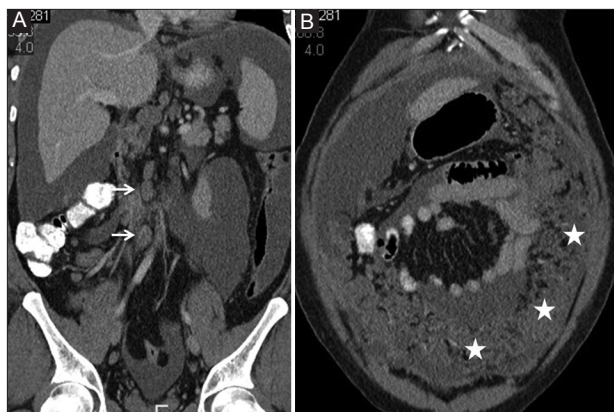
A 30-year-old Syrian male presented with complaints of dull aching abdominal pain for 2 weeks associated with progressive abdominal distension. On examination he had abdominal shifting dullness. Routine investigations were normal, ultrasound scan revealed moderate ascites. Ascitic tap showed viscous straw-colored fluid with high protein (4.2 g/dL) and albumin (3.9 g/dL) levels, low serum ascites albumin gradient (SAAG) (1.0 g/dL) and high total leukocyte count (8950/mm<sup>3</sup>, predominantly lymphocytic). Evaluation for tuberculosis and tumor markers (carcinoembryonic antigen, CA19-9,  $\alpha$ -fetoprotein) were non-contributory. His ascitic fluid cytology showed abnormal cells suspicious of malignancy.

Computed tomography (CT) of abdomen showed ascites, omental cakes and retroperitoneal lymph nodes (hypodense nodes measuring up to 3.0 cm) (Fig. 1). CT-guided biopsy of retroperitoneal lymph nodes and omental cakes showed dense infiltration of small round blue cells (Fig. 2) in clusters and stained positive for desmin, AE1/AE3 and EMA with Ki-67 of 60%. A diagnosis of a rare neoplasm, intra-abdominal desmoplastic small round cell tumor (IDSRCT) was established. With diffuse intra-abdominal spread and progressive disease, he was started on IE/VAC (ifosfamide, etoposide)/(vincristine, doxorubicin and cyclophosphamide) chemotherapy (alternating cycles three weekly). He received 4 cycles of chemotherapy with initial clinical and radiological response. Unfortunately, the patient started to deteriorate thereafter with symptomatic right pleural effusion. A repeat positron emission tomography scan showed right-sided pleural effusion, reappearance of ascites, peritoneal caking and increase in size of mesenteric and retroperitoneal lymph nodes. He was started on second-line chemotherapy with docetaxel and gemcitabine. However, he developed refractory sepsis and multiple organ dysfunction after the 1<sup>st</sup> cycle of second line chemotherapy and succumbed to illness.

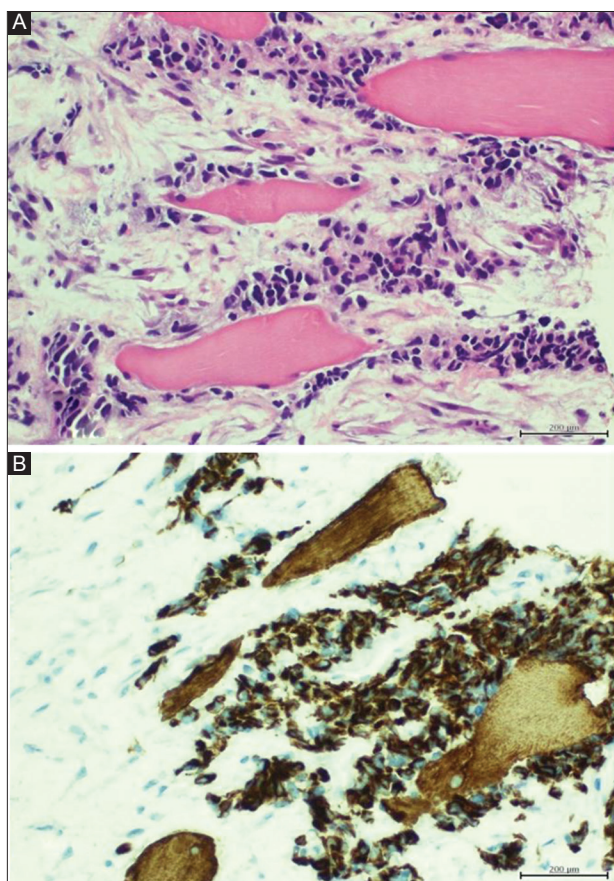
IDSRCT is a rare neoplasm with mean age of diagnosis 22 years (range 6-49), and male to female ratio 4:1 [1]. The tumor typically develops in the abdominal cavity, invading the omentum with multiple nodular deposits in peritoneum, diaphragm, splenic hilum, mesentery of small and large bowel. Clinically, patients remain asymptomatic for a variable period and then present with symptoms of abdominal pain and/or distension, constipation, vomiting, and weight loss. Ultrasound, CT scan or magnetic resonance imaging demonstrate lesions of varying size (from millimeter sized lesions to large confluent nodules). Histopathologically it is characterized by small round cells that have a positive reaction to immunostaining for epithelium, myogenic cells and neurogenic cells. Chromosomal translocation t11,22 is identified in this tumor. In most cases, they present with metastatic disease, resection is incomplete and chemotherapy is only temporarily effective, median survival ranging between 17-25 months [1]. Other small round cell tumors include embryonal rhabdomyosarcoma, small cell carcinoma, mesothelioma and Ewing's sarcoma.

Despite polychemotherapy, whole abdominal radiation and debulking surgery results are mostly suboptimal. Hyperthermic intraperitoneal chemotherapy after tumor debulking, postoperative intensity modulated radiotherapy, treatment





**Figure 1** Computed tomography (CT) scan of abdomen. Coronal CT contrast images (A, B) show massive ascites, diffuse soft tissue thickening of omental (star), and retroperitoneal and mesenteric lymphadenopathy (white arrow)



**Figure 2** Immunohistopathological appearance of omental deposits. (A) Microscopic examination revealed undifferentiated small cell tumor dissecting between muscle bundles (Hematoxylin and Eosin  $\times 400$ ). (B) Immunohistochemical stain using antibody against Desmin shows characteristic perinuclear staining of the tumor cells (Desmin  $\times 400$ )

of hepatic metastases with [90Y] Yttrium microsphere liver embolization have been tried in adjuvant settings [2]. There

are rare reports of IDSRCT and only one report of the same presenting with ascites [3]. We wish to emphasize that while evaluating low SAAG ascites, rare malignancies like IDSRCT need to be considered.

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## Hepatic artery aneurysm: a rare case of obstructive jaundice with severe hemobilia

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Hepatic artery aneurysms (HAA) account for nearly one fifth of all visceral artery aneurysms [1]. The incidence of hepatic artery aneurysm has been on the rise due to the increasing numbers of imaging studies and hepatobiliary procedures being performed. The classical presentation of Quincke's triad, comprising abdominal pain, obstructive jaundice and hemobilia, has been reported in only one third of the cases [2]. While the vast majority of cases remain asymptomatic, those which present clinically are the ones which rupture, which have an estimated mortality of 40% [3].

A 73-year-old lady, with no significant comorbidities, presented with complaints of right upper quadrant dull aching abdominal pain and progressively increasing jaundice associated with pruritus of 3 months duration,

with an episode of melena 2 weeks back. On evaluation she had deep icterus, hepatomegaly and hepatic bruit. Her liver function tests showed total bilirubin/direct bilirubin: 22.9/17.3 mg%; aspartate aminotransferase/alanine aminotransferase: 386/380 U/L; and alkaline phosphatase: 821 IU/L. Her hemogram, renal function tests, urine routine and electrolytes were within normal limits. Viral markers for hepatotropic viruses were negative. Contrast-enhanced computed tomography of the abdomen with angiogram demonstrated aneurysmal dilatation of common hepatic artery (Fig. 1). The proximal fusiform dilatation measured  $12.7 \times 52.6 \times 13.3$  mm. The distal saccular aneurysm measured  $57.4 \times 53.6 \times 50.3$  mm with a rind of thrombus within. There was marked narrowing of the common bile duct at this region with moderate bilateral intrahepatic biliary radicle dilatation.

On the second day of admission, she developed high-grade fever with chills and rigors with neutrophilic leukocytosis. A side viewing endoscopy was performed which revealed blood spurting from the ampulla of Vater with multiple blood clots. Endoscopic retrograde cholangiogram with biliary stenting was deferred in view of active hemobilia and the patient was planned for immediate surgical repair. On the same day she developed massive hematemesis and succumbed to the illness.

Notwithstanding the rarity, HAA is reported to be the second commonest visceral artery aneurysm second to splenic artery aneurysm. In the past, mycotic aneurysms accounted for most HAAs but atherosclerosis has emerged as the most common cause in the present era. Less frequent causes are polyarteritis nodosa, tuberculosis, Marfan syndrome and diagnostic instrumentation [4,5].

No definite risk factors have been established which predict the tendency for HAA rupture, but non-atherosclerotic origin and multiple lesions have been cited as potential risk factors [3]. Once HAA ruptures, the patient manifests hemobilia, which may range from mild to severe [6]. The

therapeutic options available include coil embolization of the aneurysm, stenting across the main trunk and embolization of the common hepatic artery or open surgical repair with reconstruction [7,8].

In conclusion, HAAs are an extremely rare cause of obstructive jaundice and hemobilia. Symptomatic HAAs are associated with a poor prognosis if the diagnosis is delayed. We also believe that HAAs which present with an index bleed, as in our case, warrants urgent management strategies, as they rupture in no time, resulting in fatal hemobilia.

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Conflict of Interest: None

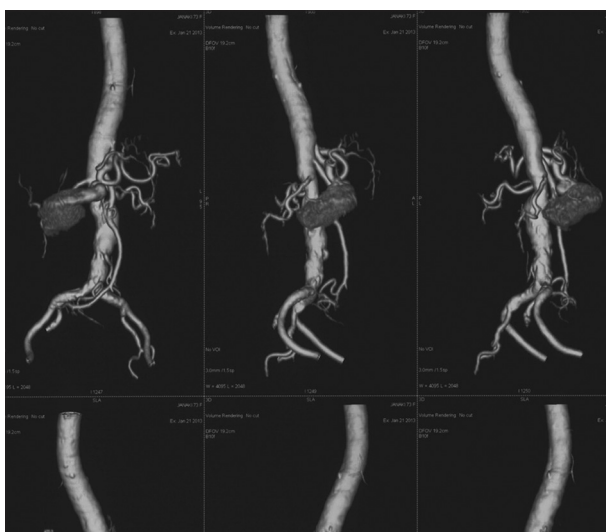
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## Acalculous cholecystitis with multiple organ failure and disseminated intravascular coagulation in a patient with adult onset Still's disease

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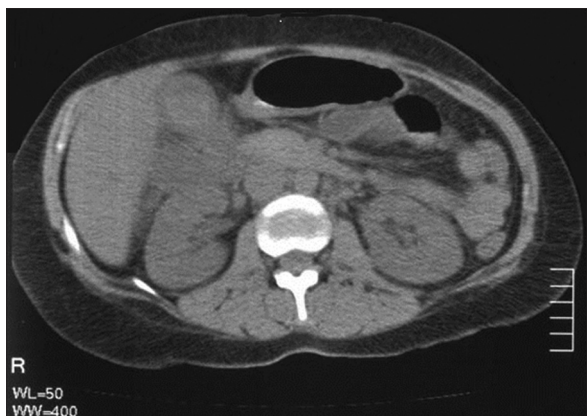
**Figure 1** Computed tomography angiogram demonstrating common hepatic artery aneurysm

Acute acalculous cholecystitis usually occurs in critically ill patients. Herein, we describe a young female patient on prednisone and anakinra therapy due to adult onset Still's disease who presented to the hospital with shock and multiple organ failure.

A 28-year-old female patient presented to the emergency department with fever and vomiting, a temperature of 40°C, with no peripheral pulse, difficulty communicating and abdominal pain with severe and diffuse tenderness. Her systolic blood pressure was 50 mmHg and intravenous fluids were rigorously administered together with antimicrobial chemotherapy with ciprofloxacin, meropenem and metronidazole. The patient was referred for abdominal ultrasound that was normal and for abdominal CT scan, which revealed the presence of acalculous cholecystitis (Fig. 1).

From her medical history, the patient had adult onset Still's disease and had been receiving prednisone 10 mg/d and anakinra daily. Laboratory findings together with the clinical presentation of the patient were compatible with shock with multiple organ failure and disseminated intravascular coagulation. The patient received fresh frozen plasma and was referred for laparoscopic cholecystectomy. On histopathology, chronic cholecystitis with signs of acute inflammation with invasion of many neutrophils was present. Her clinical signs gradually improved and she was stabilized. Defervescence occurred and the patient recovered, but five days afterwards, she experienced a temperature of 38.3°C without any abdominal pain and with negative blood cultures. After consultation with rheumatologists, she was administered prednisone and naproxen with complete resolution of fever.

Acalculous cholecystitis accounts for 5-15% of cases of cholecystitis and has usually a more severe presentation and worse prognosis than calculous cholecystitis. It occurs predominantly in critically ill patients and has a high morbidity and mortality rate [1]. Its pathophysiology remains largely unknown, but it is suggested that ischemia and prolonged hypoperfusion of the gallbladder play an important role in its pathogenesis [2]. It is commonly seen secondary to sepsis, trauma, burns, diabetes mellitus, vasculitis, prolonged fasting or the prolonged use of total parenteral nutrition and generally any critical illness [1-3].



**Figure 1** Abdominal CT scan depicting an enlarged gallbladder with edema, findings suggestive of acute cholecystitis

Acalculous cholecystitis has been reported as a very rare manifestation of systemic lupus erythematosus either alone or in combination with rheumatoid arthritis or Sjögren's syndrome [4-6]. Vasculitides and connective tissue disorders are well-known factors predisposing to acalculous cholecystitis. It is noteworthy that in connective tissue disorders and vasculitides, acalculous cholecystitis is usually a manifestation of the disease itself and not the result of immunosuppression [7]. In some cases of vasculitis- or connective tissue disorder-related acute acalculous cholecystitis, surgical intervention was usually preferred over enhanced doses of corticosteroids. Others administered high-dose corticosteroids and immunosuppressive agents instead of surgery, with fine results. Of course, the role of antimicrobial chemotherapy cannot be overlooked.

To our knowledge, acute acalculous cholecystitis has only been reported once in adult onset Still's disease to date [8]. The presence of acute acalculous cholecystitis in the context of Still's disease must not be overlooked as the administration of corticosteroids, non-steroid anti-inflammatory drugs or immunomodulatory agents could be beneficial. Another possibility is that surgery could be substituted by corticosteroids or immunomodulatory therapy.

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