High concentration of lactic dehydrogenase in small volumes of ascites

To the Editor,

During routine computed tomography and magnetic resonance imaging studies, small volumes of ascites may be detected in patients without liver cirrhosis or gross peritoneal dissemination of cancer. Additionally, transvaginal ultrasonography of the Douglas pouch makes sampling of peritoneal ascites technically easy. It is often necessary to sample the ascites to rule out peritoneal carcinomatosis (exudative ascites - EA). In addition, certain disorders such as liver failure can result in transudative ascites (TA).

Various methods of analysis of ascites fluid are available to distinguish exudative and transudative ascites. Cytological examination of ascites fluid is specific but has a high false-negative rate [1]. In addition, cytologic analysis requires considerable time and is not widely available. Therefore, we investigated other conventional parameters for analyzing ascites fluid including levels of total protein (TP), lactic dehydrogenase (LDH) or total cholesterol (T-cho). The presence of small amounts of physiological ascites can be seen in healthy men and women [2]. However, no studies have reported on the levels of these values in physiological ascites. Therefore, the purpose of this study was to determine if measurements of TP, LDH, and T-cho could be used to differentiate among exudative, transudative, and physiological ascites.

Transudative ascites from 8 patients with hepatic failure and EA from 9 patients with peritoneal carcinomatosis were obtained by a percutaneous approach or paracentesis. Physiological ascites (PA) were obtained from 9 patients with early gastric cancer (final pathology T1NO, no patients with peritoneal recurrence during follow up periods after operation) upon entry into the abdomen for surgical exploration. Note that these patients did not have any evidence of gross peritoneal dissemination of their cancer nor did they have any pain or symptoms. Laboratory values of TP, LDH, and T-cho in the ascites fluid from transudative, exudative and physiological samples were measured. As shown in Fig.1, TP and T-cho levels in physiological ascites were similar to levels in malignant ascites. However, LDH levels were 104 ± 41 (TA), 322 ± 78 (EA), and 2612 ± 498 (PA) U/l. LDH level of physiological ascites was approximately eight times higher than that of exudative ascites. The usefulness of measuring LDH, T-cho, and TP in ascitic fluid for differentiation of exudative and transudative ascites has been reported [1, 3]. According to the criteria in previous reports, sensitivity and specificity for LDH are 90-85% and 89-79% (cut off value 200-130 U/l), for T-cho 90-87% and 82-67% (45-31mg/dl), and for TP 90-83% and 75-68% (2.8-2.5 g/dl), respectively (Fig. 1). However, our results show that patients with PA were classified as having EA according to the traditional parameters. The reason why PA has such high levels of LDH is not clear.

![Fig. 1. Levels of total protein (TP), total cholesterol (T-cho) and lactic dehydrogenase (LDH) in ascites. TA: Transudative ascites, EA: exudative ascites, PA: Physiological ascites. Data represent the means ± SEM. Comparisons among multiple groups were performed with ANOVA. P values less than 0.05 were considered to be significant.](image)

The major limitation of this study is the use of patients with early stage cancer with small volumes of ascites which may not be representative of true PA. Nonetheless, with the ability of advanced imaging techniques to detect increasingly small volumes of ascites, the limitations of using traditional laboratory parameters in differentiating types of ascites must be recognized.
Hepatic myelolipoma

To the Editor,

A 76-year-old male was admitted to the Emergency Department with symptoms related to a urinary tract infection. Past medical history included benign prostatic hyperplasia. Abdominal and pelvic ultrasound examinations revealed mild enlargement of the liver with diffuse fatty infiltration. There was a single echogenic lesion measuring 3.2 cm in the VIIIth segment of the right liver. There was no definite vascularity of the lesion on Doppler investigation. CT scan with oral and I.V. contrast confirmed the presence of a hepatic lesion with a heterogeneous enhancement (Fig. 1). An ultrasound guided biopsy was performed. The biopsy showed adipose tissue tumour (Fig. 2) with large bone marrow elements (inset). No obvious malignancy was seen. The overall appearance was compatible with the diagnosis of a hepatic myelolipoma.

Myelolipomas are rare tumours of mature fat and bone marrow elements. They are more commonly encountered in the adrenal glands and rarely in extra-adrenal sites. A review of the literature revealed occasional cases reported in the spleen, mediastinum, testis and liver [1-3]. They are quite rare in young patients and are most often encountered in patients older than 40 years of age. Small tumours tend to be asymptomatic and are often detected as incidental findings during radiologic studies, or during surgery for some unrelated disease, or at autopsy. Large tumours tend to be symptomatic and may rupture and cause massive hemorrhage. Adrenal myelolipoma can be associated with hormonally active neoplasms such as adrenal cortical adenomas, pheochromocytoma, and Conn’s syndrome [4, 5]. To date, no known association has been described in the literature with hepatic myelolipoma. The fatty component of a myelolipoma is macroscopic in most patients and is diagnostic when discovered on cross-sectional imaging. The preferred imaging modality is CT, which shows focal fatty density within the mass. MRI also accurately depicts both microscopic and macroscopic fat using chemical shift imaging and explicit fat saturation technique, respectively. Some myelolipomas may have a larger amount of hematopoietic tissue and no recognizable fat, making them impossible to distinguish from non fatty tumours on CT or MRI examination. Gross pathological appearance is that of a fatty lesion with grayish-red appearance.

The histogenesis of these lesions is not clear, but theories include metaplastic changes or emboli from bone marrow, or embryonic rests of hematopoietic tissue [3]. Only one case of myelolipoma has been studied by cytogenetics, revealing (3;21)(q25;p11) translocation suggesting a neoplastic process [3]. The differential diagnosis of this rare hepatic lesion include: angiomyolipoma, adenoma, lipoma and liposarcoma. Therefore, a biopsy is required for accurate diagnosis, and subsequent management. Small asymptomatic lesions can be treated conservatively with follow up. There has been no malignant transformation of myeloid element reported in the literature.

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Application of non-invasive tests of fibrosis by gastroenterologists and hepatologists

To the Editor,

Non-invasive methods to assess stage of liver fibrosis have been widely validated in patients with chronic hepatitis C (HCV). The two main systems which have been most extensively evaluated are the serum biomarker based FibroTest (FT), and sonographic liver stiffness measurement by the FibroScan (FS) [1-4]. These tests are extensively applied in clinical practice in many countries [5]. Although non-invasive methods have been evaluated in Israel with compatible accuracy rates [6, 7], they are still not reimbursed.

We evaluated the application of non-invasive methods for HCV patients among gastroenterologists/hepatologists in Israel. Gastroenterologists/hepatologists attending the annual meeting of the Israeli Association for the Study of the Liver were requested to complete a questionnaire. The questionnaire was intended to assess the physician’s experience in clinical practice, the clinical exposure to liver diseases in general and to HCV patients in particular, the mode of pre-treatment assessment of liver damage/fibrosis of HCV patients and the application of liver biopsy versus non-invasive methods mainly FT and FS.

Seventy-two gastroenterologists/hepatologists completed the questionnaire. Over two-thirds of the responding physicians had clinical experience of 10 years or more. Approximately one quarter of the physicians were in the field of liver diseases, and about a third of these consulted more than 10 HCV patients per month. Liver biopsy was performed by 57 (79%) physicians either universally 24 (33%) or in selected patients 33 (46%). Non-invasive measures were used by 23 (32%) physicians, 8 (11%) as the only modality and the rest in conjunction with liver biopsy. Twenty physicians used FT, 9 FS, while 6 used both methods. We did not find difference in the application of non-invasive tests between the more experienced and the younger gastroenterologists/hepatologists probably due to small numbers.

In conclusion, most gastroenterologists/hepatologists in Israel still use liver biopsy as the main method to assess fibrosis in hepatitis C patients. One third use non-invasive measures mainly FT either alone or in conjunction with biopsy. The possible causes for conservative implementation of non-invasive tests include: perceived limitations of accuracy in the eyes of many, especially experienced gastroenterologists/hepatologists that rely on liver biopsy which holds the merits of time and experience. Limited availability of these tests in Israel, and last but certainly not least the issue of reimbursement of non-invasive tests by the HMOs. Refinement of these techniques along with legislative changes may popularize these tests.

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An unusual cause of Budd-Chiari syndrome: paroxysmal nocturnal hemoglobinuria

To the Editor,

I read with interest the case report “Budd-Chiari syndrome secondary to polycythemia vera” in the September 2009 issue of JGLD [1]. We agree that the causes and most effective therapy of the Budd-Chiari syndrome (BCS) represent a challenge. A few points in the management of BCS can be added with this case of rare associated hematological abnormality.

A 30-year old female patient presented with fluctuating, non-cholestatic jaundice with intermittent cola-colored urine, anasarca for 11 years and abdominal distension preceded by...
severe right upper quadrant abdominal pain for 6 months. On examination she had pallor, icterus, lower limb edema, firm enlarged liver and free fluid in the abdomen. She had had blood transfusion for anemia. She had two living children and a history of a death of a pre-term child. She presented with hemoglobin 4.1 g/dl, hematocrit 12%, platelets 1.25x10⁵ /mm³, ESR - 62mm/1 hour, bilirubinemia 3.6 mg/dl with direct fraction of 1.5mg/dl, AST 148 UI/L, ALT 38 UI/L, serum protein 6.9 g/dl, albumin 2.8 g/dl, PT prolonged by 4 seconds, lactate dehydrogenase raised 4-fold, serum urea 90.6 mg/dl and creatinine 2.6 mg/dl. The hepatitis viral markers, ANA, APLA were negative; ceruloplasmin and iron studies were normal.

Doppler ultrasound showed a heterogeneous texture of liver, hypertrophy of the caudate lobe, non-visualisation of the right hepatic vein, periporal collaterals, splenomegaly and moderate ascites (Fig. 1). Abdominal contrast enhanced CT showed in addition small curvilinear vessels seen in the periphery of the liver representing collateral flow (Fig. 2). Upper digestive endoscopy was normal, ascitic fluid showed a cell count of 100/mm³ lymphocyte 100%, protein 3 g/dl with a high SAAG. Urine and plasma hemoglobin were raised, hemoglobin electrophoresis, bone marrow, osmotic fragility test, glucose-6 phosphate dehydrogenase were normal and Coombs test was negative. Her flow cytometry showed leucocytes CD55 cells 88.22%, CD59 cells 94.25%, diagnostic for paroxysmal nocturnal hemoglobinuria (PNH).

The patient was managed with albumin, prednisolone (30mg/day) and anticoagulants. She had cirrhosis on liver biopsy, was advised a salt-restricted diet, high protein diet, therapy with diuretics and UDCA. At 6 months follow-up, she had a rise in hemoglobin to 8.4 g/dl on prednisolone 10mg/day with INR 2.5-3 on acetrom 4 mg/day.

This case demonstrates a rare cause of BCS preceding the disease by many years. Paroxysmal nocturnal hemoglobinuria is an acquired clonal disease characterized by hemolytic anemia, venous thrombosis and deficient hematopoesis present in 0-1.6% of patients with BCS [2]. Venous thrombosis affecting 39% at one time or another is less common in Asian patients [3]. The diagnosis is often delayed because of lack of suspicion of the disease and attributing elevation of LDH to a liver disease. Marrow transplantation should be considered in patients with either marrow hypoplasia or thrombosis in the early course of the disease [4]. Liver transplantation is contraindicated due to a potentially fatal generalized disease [5].

Paroxysmal nocturnal hemoglobinuria should be suspected in any patient with hypoplastic anemia or intravascular hemolysis. The presence of venous thrombosis demands rapid intervention before the opportunity for curative treatment is lost.

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Budd Chiari syndrome and V617F/JAK 2 mutation linked with the myeloproliferative disorders

To the Editor,

We read with great interest the case report published in the September issue of JGLD by Buzas et al regarding Budd
Chiari syndrome secondary to polycythemia vera in a young patient diagnosed at 3 month post-partum (1).

In our Institute we diagnosed and treated 20 patients with Budd Chiari syndrome in the last five years (2004–2009). The diagnosis was based on the demonstration of the obstructed hepatic venous outflow tract by Doppler ultrasound, triphasic CT scan and/or MRI. Fourteen patients had myeloproliferative disorders diagnosed by the identification of a somatic mutation (V617F) in the Janus tyrosine kinase-2 (JAK2) gene in myeloid cells. V617F/JAK2 was found in 80% and 50% of patients with polycythemia vera or essential thrombocythemia and idiopathic myelofibrosis, respectively.

Three patients were positive for anticardiolipid antibodies and lupus anticoagulant and consequently were diagnosed with antiphospholipid syndrome; the last three patients were identified with factor V Leiden mutation. In the majority of Budd Chiari syndrome patients, factor V Leiden is associated with other risk factors for thrombosis, as is expected from its relatively weak thrombogenic potential. Factor V Leiden mutation is present in the majority of cases of pregnancy and oral contraceptive related cases of hepatic vein thrombosis. All three patients took oral contraceptives.

The risk of recurrence required the use of therapeutic anticoagulation in our patients, combined with a low-dose of antiplatelet agents.

Eleven of the 14 patients, with myeloproliferative disorders received hydroxyurea and the other three were treated with interferon alpha 2a. In two patients with Budd Chiari syndrome uncontrolled by medical therapy mesocaval shunt was performed

TIPS was performed in two patients, one with refractory ascites and the other with repeated uncontrolled variceal bleeding episodes. In one patient with segmentary inferior vena cava thrombosis, the severe compression was managed with stenting after the surgery. Two patients died of progressive liver failure during the follow-up period. Liver transplantation is the final therapeutic option in patients with suboptimal clinical results of pharmacological or interventional therapy; it is also the case in point where procedures have failed.

Contrasting with a high degree of heterogeneity in etiology, presentation and level of hepatic venous outflow block, it is notable that all the prognostic information appears to be accounted for by the components of the MELD score or the Child-Pugh score. However, these markers are poor predictors of the outcome in an individual patient.

In our experience, Budd Chiari remains a rare diagnosis even in a referral center for liver transplantation.

At this time, two of the 20 patients diagnosed and follow-up in our center are awaiting liver transplantation, for progressive liver failure associated with uncontrolled bleeding from eso-gastric varices in one case and re-occlusion of postoperative segmentary inferior vena cava in the other.

Two recent retrospective analyses of the outcome in transplanted patients have shown 5 year survival rates reaching 80%. This considerable improvement in survival expectancy has been obtained together with a good quality of life due to the complete resolution of clinical signs and symptoms and quasi-normalization of liver function tests.

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Diagnosing functional abdominal disorders: evaluations are mandatory in those with warning symptoms

To the Editor,

I read with interest the paper by Khoshkrood-Mansoori B et al on irritable bowel syndrome (IBS) published in a recent issue of the journal [1]. I am surprised by the high incidence of bloody stools (10% overall, 17% male and 9% female) among their patients with IBS. This is perhaps not surprising considering that gastrointestinal infections are common in developing countries and post-infectious IBS is now being increasingly recognized [2]. However, I am more surprised by the high incidence of weight loss among their patients (17% overall, 37% in male and 14% in female). There was no mention whether the patients with bloody stool and weight loss had any colon evaluations. Both these symptoms are warning symptoms that require evaluations before a diagnosis of IBS can be confidently made. This is regardless of the patients’ age, as significant pathologies can be present.

We recently encountered the case of an 18 year old girl who was referred from the surgical department for evaluation of intermittent lower abdominal pain. This was associated
with mild bleeding per rectum that was attributed to hemorrhoids diagnosed on proctoscopy. There were no other warning symptoms or any family history of cancers. She was managed with regular antispasmodic, bowel sedatives and fibers. Her symptoms improved but she continued to have intermittent exacerbations. However, as her symptoms persisted after 6 weeks of therapy, a sigmoidoscopy was arranged and surprisingly, a stenosing recto-sigmoid tumour detected. Biopsies confirmed mucinous adenocarcinoma. Computed tomography scan staging showed localized disease and she proceeded to surgery. Resected specimen showed signet ring mucinous adenocarcinoma with three out of eight lymph nodes positive, consistent with Duke’s C staging. She later completed 12 cycles of adjuvant chemotherapy and has remained well on follow-up.

Our case, although uncommon highlights that colorectal cancer can occur in young patients with symptoms resembling those of functional abdominal disorders. Just like in many other countries, young colorectal cancer accounts for a proportion of the overall number and 18.4% of our patients with colorectal cancers were younger than the age of 45 [3]. Similarly young colorectal cancer is also not uncommon in Iran [4-6]. In another study, significant lesions were found in 30.5% of young patients with minimal bleeding per rectum [7]. Given the mean age of their patients of 38.7±17.1 years, it is possible that a few may have significant pathology especially those with warning symptoms [1]. Therefore it is important to evaluate any patients with warning symptoms even those with symptoms consistent with functional abdominal disorders.

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