HLA-A*3303 and *3301 predispose patients to persistent hepatitis B infection

To the Editor,

Host and viral factors influence the clinical expression and behavior of hepatitis B virus (HBV) infection. HLA is a critical genetic factor that determines individual variations of immune response and the HLA genotype of an individual may influence the progression of HBV infection [1].

Many different HLA alleles have been shown to play roles in HBV infection [2] but this relationship is not universal on the basis of the investigated population. DRB1*13 and HLA DRB1*11/*12 are consistently associated with viral clearance and viral persistence of HBV infection respectively in major populations [3]. In contrast HLA DRB1*11/*12 alleles are associated with HBV clearance in Chinese [4] and HLA DRB1*13 is reported as a susceptibility gene for chronic HBV infection in the Turkish population [5]. HLA-A*3303 and DRB1*0701 were associated with HBV chronicity among Korean people [6]. Thursz et al [7] reported that DRB1*1301 was less frequent in children with persistent infection than in those with transient infection. In a series of patients with chronic hepatitis B and acute hepatitis B it was further confirmed that HLA-DRB1*1301 and -DRB1*1302 alleles were associated with the clearance of HBV infection and protected people against chronic hepatitis B [8].

We investigated HLA-A and DRB1 alleles in patients with persistent HBV infection compared to subjects who had spontaneously recovered from HBV infection. To complete the findings of this study we performed another survey in certain HLA alleles that were significantly related to the outcome of HBV infection. This study determined predominant subtypes of HLA-A*33 and HLA-DRB1*13 alleles which were associated with HBV infection outcomes. Ninety-four HBV infected patients were enrolled in this study. The study groups were: 30 patients recovered from HBV infection, 31 inactive healthy carriers, and 33 chronic hepatitis B patients. The 33 CHB patients and 31 inactive healthy carriers formed one group together (persistent group) and were compared with the recovered group.

HLA-A and DRB1 alleles were first analyzed by using low resolution PCR sequence-specific-primer (PCR-SSP) and then we used a high resolution PCR-SSP method for subtyping HLA-A*33 and DRB1*13 alleles which were significantly related to the outcome of the HBV infection. The frequency of the A*33 allele in the persistent group was higher than in the recovered group (9.37% vs. 0%, $p < 0.008$) and subtyping showed HLA-A*3303 and HLA-A*3301 in 75% (allele frequency: 7.3) and 25% (allele frequency: 2.34) of persistent HBV infected cases, respectively. The frequency of DRB1*13 allele was lower in the persistent group than in the recovered group (3.13% vs. 11.67%, $P < 0.03$, OR = 0.22, 95%CI 0.06-0.82), and HLA- DRB1*1301 and HLA-DRB1*1303 were found in 66.7% (allele frequency: 4.89) and 33.3% (allele frequency: 3.45) of cases, respectively. HLA-A*3303 and DRB1*1301 were the predominant subtypes of HLA-A*33 and DRB1*13 at the high resolution PCR-SSP method.

In our investigation, the frequency of DRB1*1301 allele was lower in the persistent group than in the recovered group which was in accordance with other studies [7, 8]. Our results indicated that the frequency of HLA-A*3303 allele was higher in the persistent group than the recovered group, which was consistent with findings of Hwang et al [6].

In conclusion, the host HLA polymorphism is an important factor to determine the outcome of HBV infection. HLA-A*3303 and DRB1*1301 were the predominant allelic subtypes related to HBV infection outcomes in our study.

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Severe autoimmune hemolytic anemia complicated with liver decompensation and invasive aspergillosis in a patient with chronic hepatitis C during treatment with peg-interferon-a and ribavirin

To the editor,

A 60 year old female patient was admitted to our department with signs and symptoms of hepatic encephalopathy. She had a history of chronic hepatitis C genotype 1a diagnosed in 1994 and a possible source of HCV transmission by blood transfusion in a) 1967 when she underwent splenectomy for hereditary spherocytosis and b) 1987 when she underwent hysterectomy for benign uterus fibromyoma. She was treated with standard IFN-a for one year with no significant side effects but without virological response. A liver biopsy at the end of 2006 showed a high necro-inflammatory activity and stage 3-4 fibrosis. She had a high viral load (HCVRNA $7x10^5$ UI/ml), so in January 2007 she was retreated with PegIFN-a2a and ribavirin. During therapy she experienced a progressive hematocrit (Ht) and hemoglobin (Hb) reduction and on July 2007 treatment was stopped.

Despite treatment discontinuation, the patient showed a further reduction of Hb and she was diagnosed with autoimmune haemolytic anemia in a Haematology Department. Laboratory tests: Hb 8.3g/dl, total bilirubin 3.2 mg/dl, unconjugated bilirubin 2.6 mg/dl, a positive Coombs test (IgG3, C3d also for panagglutinant irregular antibodies on eluate), high lactic deydrogenase (LDH) and hemoglobinuria. The patient was treated with high doses of corticosteroids (150 mg/day) and within 15 days all parameters returned almost to normal levels. Corticosteroids were progressively tapered and she was discharged with methylprednisone (16 mg, 2x3 per day). She was re-admitted 17 days later with uncontrolled diabetes mellitus and within 3 days the patient deteriorated. At that time, she was referred to our department with signs of liver function deterioration, ascites and hepatic encephalopathy stage III probably precipitated by the high doses of prednisone. Laboratory tests were as follows: WBC 9,470 103/µl, neutrophils 88.8%, Ht 44%, Hb 15.5g/dl, 2-3% reticulocytes and few spherocytes in blood smear, both direct and indirect Coombs positive, INR 1.62, AST 154 UI/L, ALT 294 UI/L, normal creatinine, glucose 192 mg/dL, ALP 185 IU/L, GGT 1,315 U/L, total bilirubin 7.1 mg/dl, unconjugated bilirubin 3.2 mg/dl, albumin 2.57 g/dl, respiratory alkalosis and mild hypoxemia. The chest X-ray showed left pleural effusion. She received i.v. fluids, lactulose and neomycin, and insulin for diabetes. The dose of methylcortisone (64mg/day) was decreased by 25% every 4 days. There was an immediate improvement of her clinical condition and hepatic function and the patient came out of hepatic encephalopathy. She was then treated with diuretics (furosemide and spironolactone). At that time subclinical hypothyroidism was diagnosed and she was treated with thyrormone.

In October '07, the patient suddenly presented with tachypnea, hypoxia and cough without fever. The chest CT revealed diffuse infiltrates in the right upper lobe, lingual and the middle lobe as well as in the left lower lobe, atelectasia in the right middle lobe and pleural effusion in the left hemithorax. After a week the patient experienced very intense pleurodynia and cough. The chest high resolution CT (HRCT) revealed diffuse alveolar infiltrates and nodules in the right upper, middle and low lobes and the lingula with a crescent of air surrounding nodules indicative of cavitation (Fig. 1). Aspergillus fumigatus was detected in sputum cultures (Fig. 2), IgG and IgM antibodies for aspergillus were positive and invasive aspergillosis was diagnosed. The patient was treated with vorticonazole (6

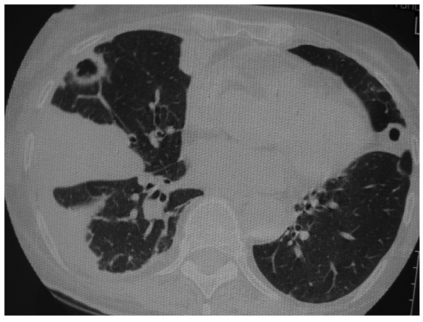

Fig 1. Chest HRCT (15/10/07) with diffuse alveolar infiltrates and nodules in the right upper, middle and low lobes and the lingula with cavitations.

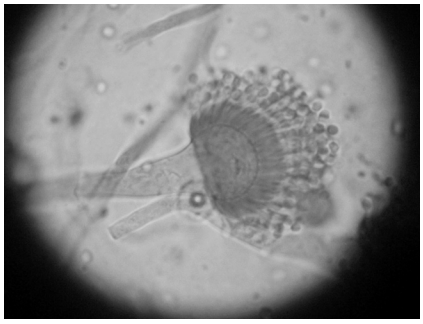

Fig 2. Aspergillus fumigatus isolated in sputum cultures.

mg/Kg) and caspofungin 50 mg IV which resulted in a spectacular improvement. HRCT on 29/10/07 showed the disappearance of some of the alveolar infiltrates, a substantial decrease of the pleural effusion and disappearance of most cavities. Two weeks later she was discharged on treatment with vorticonazole 200 mg/day, diuretics and thyrormone 0.1mg (0.5t).

During follow-up, insulin treatment for diabetes was stopped on 05/12/07 with normal glycemia thereafter. Vorticonazole, methylprednisone, diuretics and thyrormone were also stopped in the following weeks. One year after the evolution of autoimmune haemolytic anemia, the patient has no other problems except chronic hepatitis C with a high viral load, for which treatment can not be resumed.

PegIFN alfa in combination with ribavirin represents the most effective therapy for chronic hepatitis C although it is associated with various side effects [1]. Autoimmune haemolytic anemia in patients with chronic viral hepatitis treated with standard IFN-a or combination therapy with Peg-IFN and ribavirin occurs rarely and most of the cases, unlike our patient, had preexisting autoimmune disorders [2-4]. Severe haemolytic anemia and hypothyroidism occurred 5 months after initiation of treatment and she had to be treated with high doses of corticosteroids. Immunosuppression led to uncontrolled diabetes mellitus and life threatening invasive aspergillosis, for which she was successfully treated. Invasive aspergillosis is a rapidly progressive, often fatal infection (mortality 30-45%) that occurs in patients severely immunosuppressed, therefore prevention and rapid institution of therapy may be lifesaving [5].

In favor of the role of PEG-IFNa, with a known prolonged half-life, in the induction of haemolytic anemia, is the fact that the patient had a previous course of standard IFN-a 12 years ago without any adverse events. Furthermore, this case demonstrates that in patients without pre-existing immunological abnormalities, PEG- IFN-a can de novo induce autoimmune disorders that might be life threatening.

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Familial Mediterranean Fever coexisting with celiac disease: is there a link with long-term colchicine treatment?

To the Editor,

Familial Mediterranean Fever (FMF) is an inflammatory disease with an autosomal recessive inheritance caused by mutations in the gene MEFV encoding for pyrin [1]. FMF is clinically characterized by recurrent and self-limited attacks of fever, severe abdominal pain, polyserositis, and arthritis [1]. Colchicine is known to be effective in suppressing the episodes in more than 90% of the patients. FMF and celiac disease (CD) may share genetic and epigenetic factors as well as certain clinical features [2]. However, in the light of recent data [3], the association between FMF and CD remains controversial. Here we describe the case of a female patient with FMF under long-term colchicine treatment who presented with severe diarrhea due to gluten-related enteropathy.

A 23-year-old Turkish woman was admitted to our clinic with severe diarrhea and weight loss of more than 20 kg in five months. Eleven years ago, she was diagnosed as FMF after self-limited attacks of abdominal pain and fever. The patient was homozygous for the M694V mutation of the pyrin gene. She was started on 1.5 mg of colchicine daily and symptoms subsided. Colchicine therapy was interrupted only during her two pregnancies. While she was receiving colchicine 1.5 mg/day after her second pregnancy, the patient began to experience worsening diarrhea. On examination, she was pale, very uncomfortable, and cachectic weighing 36 kg. She was hospitalized for further investigation. Although the patient had no history of colchicine intolerance, the therapy was discontinued during hospitalization. Laboratory investigations showed iron deficiency anemia. Antibodies to gliadin, endomysium, and tissue transglutaminase were positive and had high titers (1/320, 1/320, 1/160, respectively). The patient was positive for the HLA DQ2 allele. A small bowel biopsy demonstrated villous atrophy. Contrast-enhanced CT scan showed benign mesenteric

lymph nodes and intestinal lymphoma was excluded. A gluten-free diet was started and the patient had noticeable clinical improvement within two weeks. Colchicine therapy was then restarted and no intolerance was evident at follow-up.

Familial Mediterranean Fever and CD share some clinical features and have common inflammatory mechanisms. Patients with both conditions have been rarely described [2]. In adults, intestinal damage in the course of CD might lead to colchicine intolerance in FMF [4]. Concerning this it is known that approximately 20% of FMF patients may show colchicine intolerance as manifested by 1-10 soft or watery stools/day [2]. However, the presence of significant malabsorption and weight loss in our patient did not support the presence of simple intolerance to colchicine. We thus speculate that our patient may represent a rare case of coexisting FMF and CD. It is worth noting that our patient was treated with colchicine for more than 10 years before presenting mainly with gastrointestinal symptoms. It is reasonable to hypothesize that long-term cholchicine treatment may have intensified the severity of malabsorption in our patient with underlying CD [4]. Although in a recent study among pediatric patients no association between FMF and CD was found [3], we believe that our case might further stimulate research on the interrelationship between these two conditions.

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An unusual cause of upper gastrointestinal obstruction in an adult: annnular pancreas

To the Editor,

A 49-year-old female presented with a six-week history of early satiety and vomiting, occurring shortly after food ingestion, resulting in 7 kg weight loss. No significant past medical history was reported. Gastroduodenoscopy revealed significant food retention in a dilated stomach and duodenal bulb with stenosis of the second descending part of the duodenum and only a pediatric endoscope could pass the stenosis. Double contrast barium radiography showed an obstructed duodenum with convexity to the left. Proximal to the obstruction a dilated duodenal bulb and stomach was found: classically known as “double bubble” sign (Fig. 1) [1]. Abdominal computed tomography revealed a mass surrounding the duodenum. Additional angulated MR imaging showed a ring of tissue surrounding the duodenum, which was iso-intense with pancreatic tissue, thus leading to the diagnosis of annular pancreas (Fig. 2).

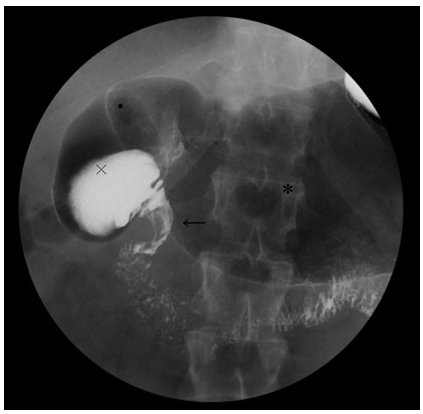

Fig 1. Conventional stomach investigation; showing ‘double bubble’ sign. * = stomach, × = duodenum, • = pyloric channel. Arrow shows duodenal convexity to the left.

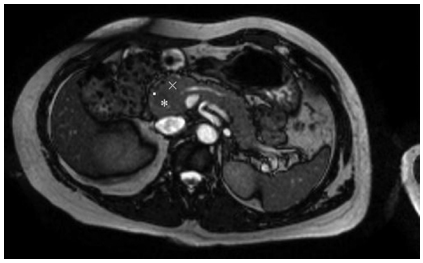

Fig 2. MR, B-FFE, Angulated; showing annular pancreas. *=duodenum, ×=pancreatic head, • = annular pancreas.

The patient underwent explorative surgery of the second part of the duodenum, showing a very narrow ring of normal-looking pancreatic tissue encircling the duodenum, thus confirming the diagnosis. Subsequently, a Roux-Y-gastrojejunostomy was made and the postoperative course was uneventful.

Annular pancreas is a congenital anomaly with a prevalence of one in 2,000 persons, where a band of pancreatic tissue encircles the duodenum, due to an embryological migration fault [2]. There are two peaks of presentation, first in infancy (52%) and second in the fourth decade of life (48%). In middle aged patients with symptoms of upper gastrointestinal obstruction the most likely differential diagnosis involves carcinoma of the duodenum or pancreas, intramural haematoma of the duodenum and postbulbar peptic ulcer. Annular pancreas is a rare cause of these symptoms. However, annular pancreas can also present with peptic ulcer (26-48%) and pancreatitis (15-30%) [3].

Some patients will live without ever getting symptoms, thus explaining the incidence of 1 in 7,000 persons found in obduction [4].

In most cases the initial investigation will be a gastroduodenoscopy, which usually shows concentric narrowing and prestenotic dilatation. Additional conventional plain abdominal film may show the double bubble sign. In upper gastrointestinal double contrast studies the presence of a smooth, annular filling defect, concentric, luminal dilation and reverse peristalsis proximal of the obstruction, are classic signs for an obstructive annular pancreas. CT can visualize the annular pancreas, but it is of less value because of the minor soft-tissue contrast compared to MRI [3]. ERCP and MRCP are useful, because they both are able to demonstrate Santorini's duct encircling the duodenum. In experienced hands, endoscopic ultrasonography can also be very valuable in the diagnostic process [5].

In adult patients the proper treatment is surgical, either a gastrojejunostomy, when there is obstruction, or a pancreaticoduodenectomy, in chronic pancreatitis. Although it is not necessary to explore the pancreatic head preoperatively for a Roux-Y-procedure, it can be used to confirm the diagnosis. However, in our opinion, diagnostic imaging is able to present the diagnosis preoperatively to the surgeon.

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Cystic hepatic metastasis from gastrointestinal stromal tumor prior to imatinib mimicking a liver abscess

To the Editor,

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors specific to the gastrointestinal tract, generally defined as c-kit (CD117)-positive tumors with a characteristic set of histologic features. Cystic liver metastases are described with tumors of pancreas, ovary, colorectal, carcinoid and cervical [1]. Targeted therapy with imatinib can inhibit c-kit and thereby aberrant tumoral proliferation. Imatinib can induce shrinkage and cystic changes in hepatic lesions [2].

We present the second case of cystic hepatic metastases from GIST prior to imatinib therapy presenting as a liver abscess [3].

A 50-year old man presented with right hypochondrium pain, moderate to high grade fever associated with anorexia of 3 days duration. He was febrile, had tachycardia, liver palpable 6cm below right costal margin and tenderness over right hypochondrium. His investigation showed a hemoglobin of 10.8g/dl, total leukocyte count of 23,500/mm3 with polymorphs 87.5%, lymphocytes 6.5%, erythrocyte sedimentation rate of 70 mm in 1st hour, albumin of 3.0 gm/dl, serum AST 87U/L, ALT 97U/L and alkaline phosphatase of 570U/L. He had normal platelet count, blood sugar, serum urea, creatinine, electrolytes, bilirubin, alpha fetoprotein, chest and abdominal X-ray. Amoebic serology was negative. Ultrasound of the abdomen showed a 12x9 cm thick smooth walled hypoechoic area with dense echoes in left liver lobe. An ''anchovy sauce-like'' fluid was aspirated from the liver cyst. He was started on metronidazole and ceftriaxone with suspicion of an amoebic abscess. Contrast enhanced computed tomography (CECT) showed an enlarged liver with a large irregular marginated hypodense lesion in the left lobe, circumferential wall thickening of stomach fundus and multiple enlarged perigastric lymph nodes (Fig. 1). The density of hepatic metastasis was 20HU. He responded to antibiotics. Fine-needle aspiration cytology from wall of cyst showed atypical cells . Oesophagogastroduodenoscopy showed ulcerated polypoidal lesion in gastric fundus >5cm in diameter. Biopsy demonstrated a mesenchymal tumor (Fig. 2) positive for CD117, desmin, CD34, focal positive for S100 and smooth muscle actin. A diagnosis of GIST with smooth muscle and focal neural differentiation was made. He was started on imatinib mesylate 400mg twice a day. On follow-up at 6 months, the liver lesion had decreased to 5x2 cm and the gastric lesion to 2cm. Imatinib is being continued for another 6 months.

GISTs most commonly occur in the stomach (60%) and jejunum and ileum (30%) and rarely as apparently primary extraintestinal tumours in the vicinity of the gastrointestinal tract. GISTs occur predominantly in middle-aged and older persons at a median age of 50-60 years [4].

Gastric GISTs $\leq$ 11cm and $\leq$ 5 mitoses per 50 HPFs have a low risk for metastasis whereas those with >5 per 50 HPFs and >5cm in diameter have a high risk for metastasis. Gastric GISTs can be divided into histologic subgroups including 4 spindle cell (70%) and 4 epitheliod variants (30 %). About 10-30% of GISTs are malignant and show intraabdominal spread [5]. In a series of 31 patients with GISTs, 32% of the patients had liver metastasis on CT and MRI, liver metastases were hypervascular in 92% of patients and rapidly became cystic following therapy with imatinib mesylate [6].

Mucinous types of adenocarcinoma such as colorectal, ovarian or pancreatic result in cystic liver metastasis by

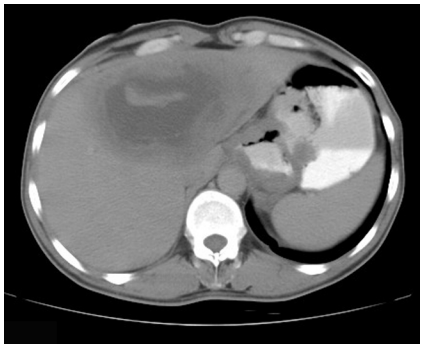

Fig 1. Contrast enhanced computed tomography (CECT) of the abdomen shows circumferential thickening of fundus, lesser curvature with irregular outer margins and multiple enlarged perigastric lymph nodes.

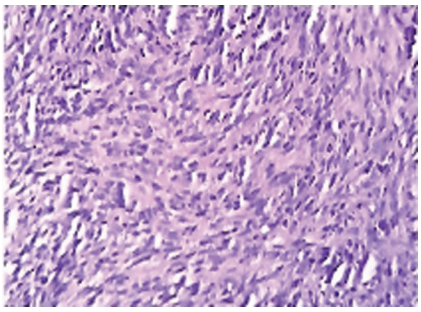

Fig 2. Biopsy from gastric lesion shows spindle shaped cells.

accumulation of mucin or serous fluid produced by the tumour. Some have areas of cystic degeneration due to ischemic necrosis and infarction of the tumour mass, while others are cystic without undergoing liquefactive necrosis. Hepatic metastasis that are predominantly cystic are uncommon and were identified in only 14 of 390 cases of all hepatic metastases studied at one institution by CT scanning [7]. The appearance of polycystic liver disease on CT scan usually does not represent malignancy. Major differential considerations include benign hepatic cysts, abscesses and chronic hematoma. Furthermore, in countries with a high prevalence of amebiasis, the amebic abscess must be evaluated. Obviously, a definitive diagnosis can only be made using pathology and/or percutaneous aspiration of cystic lesions, as was done in our patient.

In conclusion, cystic liver metastasis of GIST may mimic a liver abscess and be present prior to imatinib treatment.

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Atypical presentation of a kidney tumor

To the Editor,

A 25 year old female presented with abdominal distension which had progressively increased over a period of 3 years. However, she had no history of associated abdominal pain, vomiting, constipation, bleeding per rectum or jaundice. Her general physical examination revealed an emaciated and rundown status. Local examination revealed a protuberant abdomen with everted umbilicus. Palpation found a huge firm to hard swelling almost occupying whole of the abdomen including flanks. The margins of the swelling were well felt, surface was smooth and mobility was reduced. We could not elicit any shifting dullness or fluid thrill. The swelling as such was dull on percussion and examination per rectum did not reveal any abnormality. All baseline investigations were normal except for a low hemoglobin (10.6g/dl). Ultrasonography of the abdomen showed a left kidney in the left iliac fossa with an impression of a huge splenic mass. Abdominal CECT visualized a large mass with variable attenuation almost filling up the entire abdomen with left bulge of the lesion compressing the surrounding bowels towards the right side (Fig. 1).

The right kidney was normal but the left kidney was pushed inferiorly with a rotational deformity due to the mass effect of the lesion. No lymphadenopathy or ascites were found on CECT. Laparotomy revealed a retroperitoneal tumor (50 x 40 cm) firm in consistency and fleshy on cut section, well encapsulated, arising from the upper pole of the malrotated and unascended left pelvic kidney (Fig. 2).

The sigmoid colon was adherent to the tumor anteriorly. The liver, gallbladder, stomach and small gut were normal but grossly compressed by the tumor bulk. No lymphadenopathy was found. Complete resection of tumor inclusive of upper pole of pelvic kidney was performed. We also fixed the pelvic kidney by a left sided nephropexy. The excised specimen weighed 10 kilograms. Histopathology revealed an angiofibroma of the kidney. Post operative and follow up period were uneventful.

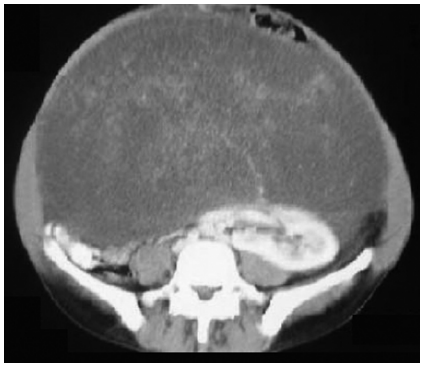

Fig 1. CT picture of massive tumor of kidney.

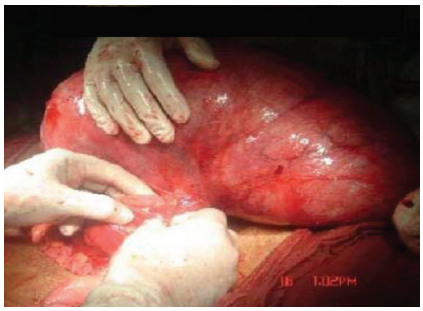

Fig 2. Intraoperative photograph of lesion.

Angiofibromas (AFs) have been usually reported from skin and nasopharynx. In literature it is usual to come across references of tuberous sclerosis rather than isolated references of AFs of kidney. Tuberous sclerosis is a complex disorder of hamartoma formation in many organs, particularly in the skin, brain, eye, kidney and heart. The characteristic skin lesions are AFs, the shagreen patch, periungal fibromas and "ash leaf" white macules. Treatment of AF has previously included electrocoagulation, electrodessication and curettage, derm-abrasion, excision, cryosurgery, and oral 13-cis retinoic acid. Both argon and CO_2 lasers have been used in isolated cases to treat AF [1]. Also, it is now known that benign neoplasms of patients with tuberous sclerosis are highly angiogenic (vascular) especially the lesions from brain, kidney and skin [2]. Eble et al [3] reported 5 cases (epithelioid angiomyolipoma of the kidney) with a prominent component of epitheloid smooth muscle cells that occurred in patients from 20 to 48 years of age. The tumors often posed problems in diagnosis, particularly with regard to distinction from renal cell carcinoma. Two of the patients had tuberous sclerosis. Two patients with more than 5 years follow up are alive and well. Obvious elements of typical angiomyolipoma were present in two tumors. The other contained only scattered, thick-walled blood vessels or a few fat cells suggestive of typical angiomyolipoma.

An angiofibroma arising from the upper pole of an unascended kidney with such a massive size (10 kg) may probably be the first case reported in the literature.

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Health-related quality of life in chronic liver diseases: issues and controversies

To the Editor,

I read with great interest the paper by *Svirlith et al* which analysed the quality of life in chronic viral liver diseases [1]. It is already well-known that these diseases are invalidating and lead to the impairment of the quality of life [2].

Currently there is a shift in focus from structure and process to outcomes, and from specific clinical outcomes to generic outcomes. The patients and the medical community are more interested in evidence that the health care system produces patients who feel better and who are confident in their health. This concept is known as the health-related quality of life (HRQOL) and it is an important aspect of the natural history of the disease and an important means of assessing the results of therapeutic interventions.

In order to assess quality of life, the authors used the SF-12 Questionnaire, a previously validated questionnaire. Their results showed a reduced quality of life compared to a healthy population, no significant differences between B and C chronic viral hepatitis, and evidenced worse scores in liver cirrhosis compared to hepatitis.

In 2003, we also assessed, for the first time in Romania, the quality of life in chronic viral hepatitis, using the SF-36. This instrument is based on a core set of generic health measures that have proved useful in determining the quality of life in different diseases and in measuring the benefits of treatments where the higher scores indicated better health [3].

Our results have some similarities to those obtained by Svirlith et al, but there are also some important differences [4]. First of all, we found significant differences between the two groups (chronic viral hepatitis and healthy controls) for every domain of the quality of life questionnaire. We also looked for a correlation between the level of patients' transaminases and the scores they obtained in this quality of life questionnaire, but statistical analysis did not find any significant correlation. The main differences between our results and those reported by Svirlith et al are that we found that scores in patients with HBV were significantly better in certain items (general health, social functioning, mental health) than in patients with HCV, data consistent with the previous report of Foster et al [5].

It is now clear that the measurement of HRQOL in

chronic diseases is an increasingly important factor in clinical research, but also in every-day patient care. It represents a major achievement in the management of these patients.

Of course further studies are needed to evaluate several issues of HRQOL in chronic liver diseases: influence of viral load and antiviral treatment on HRQOL; analysis of risk factors and disease variables to establish the way they affect HRQOL (direct, or through distress?); possibility for the predictive factors of HRQOL to predict other significant outcomes, such as resource utilization, or treatment response.

At this moment, we cannot talk about a tradition in measuring HRQOL in chronic liver diseases. There is a need to develop more disease-specific instruments for chronic liver diseases and more useful instruments in order to get valuable information on how the patients feel about their disease and how it influences their life. This will help us to focus better on interventional methods that would reduce the impact of chronic liver diseases on HRQOL.

An efficient approach would be to facilitate collaboration among investigators to develop a cross-cultural validation of existing instruments. In this way, we can work together towards a better understanding of the impact of chronic liver diseases on HRQOL.

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Reply,

We appreciate the interest and comments from Cristina Pojoga on our manuscript regarding the quality of life in patients with chronic viral liver disease. In this work we reported our preliminary results concerning the well-being of these patients in comparison with a healthy population as assessed by the SF 12 questionnaire. In the analysis of the quality of life in these two groups, we found significant differences between the lower scores for both components (physical and mental) in patients with chronic viral diseases vs. controls. Similar results were reported by other authors using different questionnaires including the study of Pojoga et al [1]. The main dissimilarity between our results was the influence of C and B viruses on the HRQOL scores. Searching the literature we observed controversies in relation to this issue: some authors reported no difference in quality of life between chronic C and B patients but others did [1-4]. Generally, the difference was found in lower total scores or in particular domains reflecting mental or physical health in patients with chronic C infection in comparison to B infection, mostly associated with depression, fatigue or decrease of neuropsychological functions.

Continuing our investigation in this field, my co-author Sladjana Pavic (working on a doctoral thesis, personal communication) used the SF 36 questionnaire and a liver disease-specific questionnaire (CLDQ) to measure the quality of life in 100 patients with chronic hepatitis C, 30 with chronic hepatitis B, 30 with non-viral chronic liver disease, and 50 healthy controls. The SF 36 scores did not differ in the total score between chronic C and chronic B hepatitis patients ($p=0.062$), although a substantial impairment was found in some domains in chronic C hepatitis patients: physical function and activity, bodily pain and emotional function. Similar results were obtained with CLDQ, no difference in total scores ($p=0.627$) nor in any domain were found between chronic B and chronic C hepatitis patients. Additionally, total score ($p< 0.001$) and all domains of SF 36 were significantly improved in patients with viral C liver cirrhosis six months after stopping combination therapy (peginterferon alfa plus ribavirin) who achieved sustained viral response. Non-cirrhotic patients did not show any difference in the total score ($p=0.434$), except in some domains.

We agree that an efficient approach would facilitate collaboration among researchers in order to better understanding the impact of chronic liver diseases on the patients' well-being.

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