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LETTERS TO THE EDITOR

ARE BLOOD DONORS AN ADEQUATE CONTROL GROUP TO ASCERTAIN HCV PREVALENCE IN NON-HODGKIN'S LYMPHOMA PATIENTS

To the Editor,

We have read with interest the paper of Kuniyoshi *et al.* on hepatitis B or C infections and non-Hodgkin's lymphoma (NHL) recently published in the Journal.[1]

Of the 348 patients with NHL, 8.1% of cases were hepatitis C virus (HCV) positive and 6.9% were hepatitis B virus (HBV) positive. In male NHL patients, the rate of HCV infection was significantly higher than in an age- and sex-matched population of blood donors in the same area.[1]

Consequently, the authors concluded that the high prevalence of HCV or HBV infection in the study population provides epidemiologic evidence that HCV and HBV infection may be involved in the development of a subgroup of NHL in males.

We would like to focus on the HCV prevalence rate data because this is a critical issue and to clarify the existing relationship between HCV infection and NHL.

In fact, the epidemiologic studies conducted so far are rather contradictory: studies conducted in southern Europe have reported a high prevalence (9–37%) of HCV infection in patients with B cell NHL, whereas those performed in western Europe and in Canada have failed to confirm this association.[2]

Whether these controversial data reflect virologic differences in genotypes and/or ethnogeographic disparities or weakness in the statistical power of the studies remains a matter of debate.

We would like to draw your attention to the possibility that an inadequate choice of control population may represent a serious bias.

The study of Kuniyoshi *et al.* has been performed on NHL patients diagnosed in the district of Fukuoka.[1] A previously published prevalence study on the general population conducted in the same geographic district reported a 2% prevalence rate of HCV infection among 14 341 subjects, with a definite age prevalence curve:[3] HCV infection rate ranged from 0.4% in the under-29 age group to 12% in the over-70 age group.

In the paper of Kuniyoshi *et al.*,[1] the blood donor control group showed only a 0.75% crude prevalence rate with a much lower increase in HCV infection rate with age (higher value 1.99% in the 50–64 years age group) and ignores individuals in the over 65 age group, an age group to which more than 45% of the NHL patients belong.

It is well known that the prevalence of HCV infection among subjects representative of the entire population is higher than that found among blood donors.[4] By using age-specific prevalence data, at least three distinct transmission patterns can be identified. In countries such as Japan or Italy, most infections are found among older people, a fact that is consistent with the risk for HCV infection being greater in the distant past.[5] Seventy-five percent of NHL patients in the report of Kuniyoshi *et al.*[1] are older than 50 years and all HCV-positive NHL patients fell into this group, a picture very similar to that reported by Hayashi *et al.*[3] in the general population. If the comparison had been made with the latter control group, no significant differences would have been found between controls and the study population.

Non-Hodgkin's lymphomas are diseases of the elderly; therefore, it should be taken into account that a cohort effect could have been highlighted in the study of Kunyioshi *et al.* The higher prevalence of HCV infection found by Kuniyoshi *et al.* in male NHL is intriguing and not easy to explain. It cannot be ruled out that HCV can play a role in the development of a selected type of NHL.[6] However, we think that this issue needs to be addressed with a well-designed prospective study on a Poisson study cohort and a properly chosen control population, which must be truly representative of HCV prevalence in the general population.

Moreover, people with cancer are often referred to highly specialized centers far away from where the live. As a consequence of the wide variations of HCV prevalence rate in different geographic areas,[4,5] even within the same country, the place of birth, as well as residence, of affected people rather than the hospital where NHL has been diagnosed should be considered.

In conclusion, we believe that the choice of blood donors as a control group, as well as the comparison of non-age-adjusted prevalence rates are crucial biases that may explain, at least in part, the conflicting results on HCV prevalence in NHL in studies performed in countries with high HCV infection rate.

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Emilio Iannitto* Stefano De Cantis†
Sonia Cirrincione* Emanuele Ammatuna*
Rosa Di Trapani* Gerlando Quintini*
Antonio Carroccio‡ Gugliemo Mariani*
**Department of Oncology, Hematology and Bone marrow Transplant Unit,*
†*Department of Social Statistic,*
‡*Department of Internal Medicine, University of Palermom, Italy*

A CASE OF HEMOLYTIC UREMIC SYNDROME AND WHOLE SPLENIC INFARCTION SECONDARY TO ACUTE PANCREATITIS

To the Editor,

Hemolytic uremic syndrome (HUS) and whole splenic infarction are relatively rare complications of acute pancreatitis. Herein, we report on a 58-year-old Japanese man with acute pancreatitis complicated with both manifestations. To our knowledge, such a case has not been reported previously.

The patient was admitted to Sumitomo Hospital complaining of severe epigastric pain after drinking alcohol on 7 September 2001. He had been a heavy alcohol drinker for more than 30 years. His past history was unremarkable. His consciousness was clear and his temperature was 38.5°C. Physical examination revealed only epigastric tenderness. Laboratory data were as follows: hemoglobin (Hb) 15.5 g/dL, white blood cell (WBC) 10 100 /μL, platelets 145 000 /μL, amylase 1313 U/L, bilirubin 1.0 mg/dL, lactate dehydrogenase (LDH) 896 U/L and creatinine 1.0 g/dL. Liver enzymes were slightly elevated. Abdominal ultrasound and computed tomography (CT) showed swelling of the pancreas and fluid accumulation in the anterior parapancreatic space (Fig. 1a). A diagnosis of acute pancreatitis was made and the usual treatment initiated. On the third day, the abdominal pain gradually subsided and the serum amylase level decreased to 824 U/L, while the patient was icteric and acute renal failure developed. The Hb was 8.3 g/dL, WBC count 9600 /μL, platelet count 14 000 /μL, LDH 1701 U/L, bilirubin 5.7 mg/dL, creatinine 3.2 g/dL and the blood film was typical of microangiopathic hemolytic anemia, showing the presence of fragmented red blood cells. The serum haptoglobin level decreased to 29 mg/dL (normal 45–320 mg/dL). The prothrombin time (PT) was normal, the international normalized ratio (INR) was 0.92, the partial thromboplastine time (PTT) was 33.6/33.2 s, fibrinogen was 599 mg/dL and the concentration of fibrinogen degradation products (FDP) and the D-dimer test were at the upper limits of normal. We

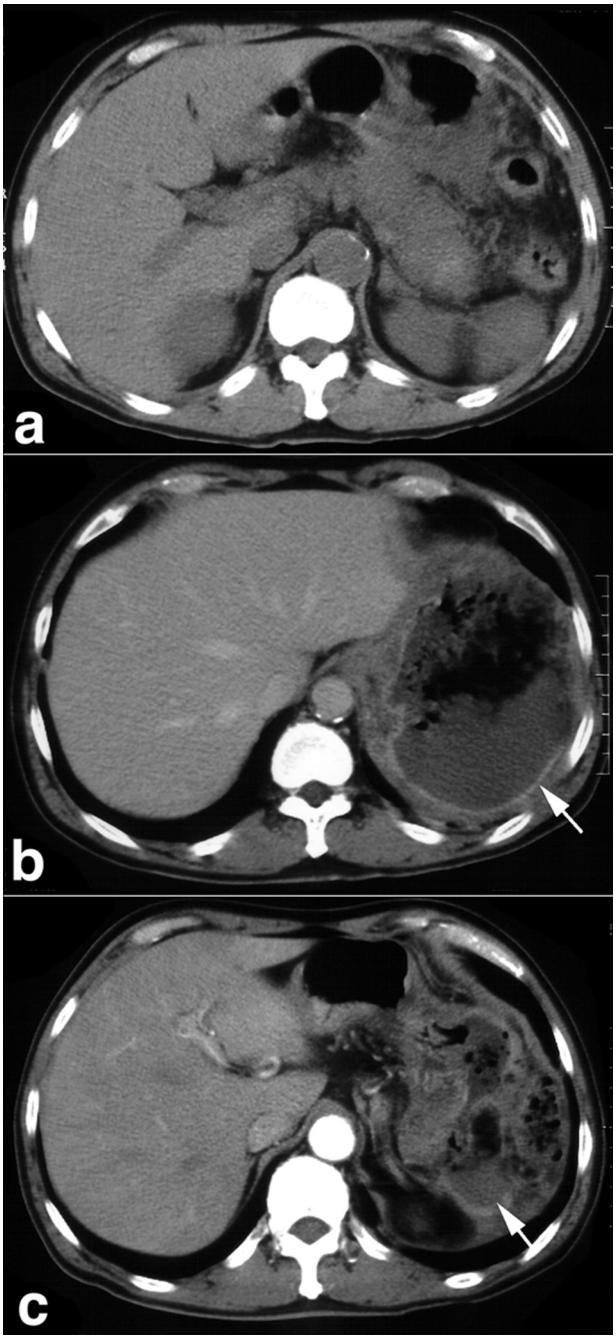

Figure 1 (a) Abdominal computed tomography (CT) of the patient on admission revealed swelling of the pancreas and fluid accumulation in the anterior parapancreatic space. (b) Abdominal enhanced CT on the 29th day. The spleen was not enhanced in the least (arrow), which showed whole splenic infarction. (c) Abdominal enhanced CT on the 57th day showed a quite atrophic spleen (arrow) that could not be differentiated from the stomach.

believed that the patient was suffering from HUS and fresh frozen plasma (total 16 units) was given and a hemodialysis program was started. After this, the Hb slowly rose, the fragmented red cells decreased and the platelet counts were normalized on the 9th day. The serum creatinine level was elevated to 6.2 mg/dL on the 11th day, from which time renal function improved and recovered to within the normal range on the 26th day.

On the 29th day, while the patient recovered from the pancreatitis and HUS, he complained of sudden left upper quadrant pain. Abdominal enhanced CT revealed whole splenic infarction (Fig. 1b). Two days after onset, his temperature rose to 38.8°C. Conservative management, including administration of antibiotics, was initiated and the pain and fever subsided. No complications, such as active bleeding or abscess formation, were found. Although a follow-up abdominal CT at 4 weeks after onset revealed a quite atrophic spleen that could not be differentiated from the stomach (Fig. 1c), the patient was asymptomatic and discharged.

Hemolytic uremic syndrome is a rare complication of acute pancreatitis. Although solitary, multiple or massive splenic infarction is sometimes found in patients with pancreatitis, whole infarction is relatively rare. We have reported a case of acute pancreatitis accompanied by both rare manifestations. In a review of English literature, such a case has not been reported previously.

Disseminated intravascular coagulation (DIC) is a common complication of acute pancreatitis. Patients with severe DIC reveal marked thrombocytopenia, anemia and variable renal involvement, as found in the present case, while these patients are always expected to have prolonged PT and/or PTT. However, in the present case, from the results of normal PT, PTT, FDP and D-dimer test, we diagnosed the patient as suffering from HUS although a renal biopsy was not performed.

Pathophysiologic mechanisms of HUS secondary to acute pancreatitis are not clearly established. A variety of proteases and cytokines, such as interleukin-1 and tumor necrosis factor-α, released during acute pancreatitis can directly and/or indirectly damage the endothelium and promote platelet aggregation, which may lead to HUS. The apparent reversibility of renal insufficiency following treatment with plasmapheresis, fresh frozen plasma infusions and hemodialysis has often been reported in patients with HUS secondary to acute pancreatitis.[1–3] In the present case, the renal function of the patient recovered to normal within 24 days after starting treatment for HUS. The reason for the reversibility is unclear because renal biopsies have not been performed in most cases, including the present case. One possible explanation is that the pathology involving the kidneys may be glomerular rather than the more severe arteriolar-type thrombotic microangiopathy in many cases of HUS secondary to pancreatitis, which may lead to a good prognosis.[4]

Splenic infarction is seen in 5–7% of cases of acute pancreatitis and is usually of the partial type. Rypens *et al.*[5] reported that whole infarction was not found in 14 cases of splenic infarction secondary to acute pancreatitis. In addition, most cases of splenic infarction have been reported to heal spontaneously and primary conservative management may be proposed.[5] In the present case, conservative treatment was initiated and led to a good outcome because the patient had a stable hemodynamic condition.

In the present case, an association between HUS and whole splenic infarction is unclear. Two possible explanations can be given. One is that the two complications may have occurred independently. It has been reported that thrombus and dissection of pseudocyst may cause splenic infarction. On the basis of no evidence of pancreatic pseudocyst in our patient, whole splenic infarction may have been caused by the complete obstruction of the splenic artery by a thrombus due to intrinsic damage to the vessel intima after inflammation. The other possible explanation is that the thrombus raised on the basis of HUS may have completely obliterated the splenic artery, resulting in whole splenic infarction. We favor the former explanation because the infarction occurred after the patient had recovered completely from HUS and because no clinical signs of a thrombus were found in any other organs.

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Takeshi Minami
Mitsunori Saito
Takahiro Yamamoto
Shinya Kondo
Osikazu Ohmori
Shyuji Kanayama
Department of Gastroenterology
Sumitomo Hospital, Osaka, Japan