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To the editor:

Hepatitis C virus infection in patients with non-Hodgkin lymphoma in Thailand

The role of hepatitis C virus (HCV) in the pathogenesis of non-Hodgkin lymphoma (NHL) is controversial.[1-3] Germanidis et al[4] recently reported in *Blood* the lack of association of HCV infection and NHL in France, where HCV infection is not common. This is in contrast to the reported high prevalence of HCV infection in patients with NHL (9% to 35%) in Italy[5] and North America,[6] where HCV infection in normal population is quite frequent (1% to 5%). These results lead to speculation that HCV infection may be associated with NHL only in areas where HCV is highly prevalent.

Thailand has had an increasing incidence of NHL in recent years.[7] It also has a high prevalence of HCV infection, averaging 1% to 5% in the general population.[8-9] The aim of our study was therefore to determine whether high prevalence of HCV infection exists in our Thai patients with NHL. Ninety-eight patients with intermediate- to high-grade NHL and 32 patients with low-grade NHL seen at Siriraj Hospital were screened for HCV using Cobas Core anti-HCV indirect EIA assay (Roche, Basel, Switzerland) after informed consent. NHL was classified according to working formulation. The Table shows the prevalence of anti-HCV antibody according to NHL subtype. The overall prevalence of HCV antibody in Thai NHL patients was 2.3%. All patients were HIV-negative and not previously transfused. Only 3 out of 130 cases were HCV-positive including 2 patients with diffuse large-cell lymphoma and 1 patient with follicular mixed small- and large-cell lymphoma. The route of HCV infection in the first 2 patients with intermediate-grade NHL was not clear because no history of blood transfusion or drug abuse could be elicited. The route of viral acquisition in the third patient with low-grade NHL, however, is quite unique because he developed hepatitis after a cut injury occurred while he was performing a surgical procedure in North America. He received interferon treatment for hepatitis and subsequently cleared the virus several years prior to the diagnosis of NHL. PCR for 8 HCV genotypes did not reveal HCV RNA at the time of diagnosis of NHL in Thailand. Whether HCV infection led to the development of NHL in this third patient is unknown. Our overall results, however, do not support the existence of a significant relationship between HCV infection and NHL in Thailand.

NHL in Thailand has a different distribution of histologic subtypes than does the West, with a lower prevalence of low-grade B-cell NHL (averaging 10%).[7,10] Whether this may account for the overall low prevalence of HCV infection in NHL in our country is not known. Source and genotype of HCV may play an important role. The predominant HCV genotypes in Thailand appeared to be different from those found in the West.[11-12]

In conclusion, although HCV infection is common in Thailand, the majority of Thai NHL patients do not carry the HCV antibody. HCV infection is unlikely to play a major role in the pathogenesis of NHL in Thailand, where HCV infection is highly prevalent.

Table. Histology of NHL and prevalence of anti-HCV antibody in Thai patients

Histology	n	% HCV-positive
Intermediate to high-grade NHL (including follicular large cell, diffuse small-cleaved cell, diffuse mixed small and large cell, diffuse large cell, immunoblastic, lymphoblastic, small noncleaved cell)	98	2
Low-grade NHL (Including small lymphocytic cell, small lymphocytic cell with plasmacytoid features, follicular small-cleaved cell, follicular mixed small and large cell)	32	3.1
Total	130	2.3

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To the editor:

Fucose supplementation in leukocyte adhesion deficiency type II

We read with great interest the report by Marquardt et al[1] regarding the beneficial effect of fucose supplementation in a patient with leukocyte adhesion deficiency type II (LAD II). Not only was improvement noted in neutrophil adhesion function, but also the patient's developmental delay was reduced. It should be noted that fucose treatment was started when the child was already more than 1 year of age.

From the time of our initial report of LAD II,[2] we have discovered another 2 infants, a male and a female, affected by LAD II. They were both of Arabic origin, the parents were close relatives, and they live in the same area as the previous ones.

No evidence of consanguinity between the families is present. Their birth length and weight was normal for gestational age. Both children presented with febrile illnesses, and a complete blood count showed a very high leukocyte count (above 40 000 cells/mm^{3}). CD15a was not expressed on leukocyte surfaces, and the children had the Bombay blood group phenotype. CD18, CD11a, and CD11b were expressed normally, and the diagnosis of LAD II was made. Because no anti-H antibodies were detected, we decided to start fucose supplementation at the age of 4 weeks, after obtaining informed consent from the parents. As no data regarding fucose administration in humans is currently available, we estimated that around 200 mg/kg per day may achieve the desired normal blood fucose level.[3] A loading dose of 5-gram fucose (Pfanctiehl, IL) was given orally to patient 1 (in 4 divided doses). A day later a marked decrease in the leukocyte count was noted (Figure). Hypoglycemia developed, and the dose was decreased to 2.5 g, followed by an increase in leukocyte count to 80 000/mm^{3}. Although the baseline of blood-free fucose was less than 50% of normal (Figure), repeated fucose measurements showed very high levels while the child was on therapy, which were comparable to those obtained by Marquardt et al[1] using a high dose of fucose. Fucose concentration in samples was determined using both gas chromatographs coupled with mass spectrometry and the enzymatic assay with fucose dehydrogenase.[3-4]

Urine fucose levels in the patient while on therapy were 10 times higher (1.2 μmol/L) than in control (25-110 μmol/L). Still, no decrease in leukocyte count was observed, and CD15a expression was not detected on leukocyte surfaces.

After a month, the dose of fucose was decreased to 1 g/d and was continued for up to 12 months. Unfortunately no change in leukocytes counts or CD15a expression was noted, and her psychomotor retardation continue to deteriorate. Her weight, length, and head circumference were all below the third percentile for age. The same unfavorable results were seen in the male infant with LAD II, with whom therapy also started at age 1 month.

How can one explain the different results of fucose supplementation in our 2 patients and Marquardt et al's patient? The widespread lack of L-fucose on several different glycoconjugates seems to exclude any impairment of fucosyl-transferase activities and to
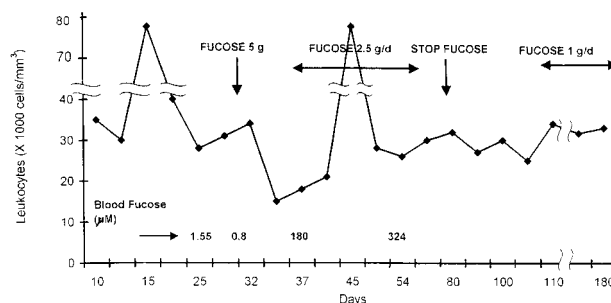
Leukocyte count during fucose administration in an infant with LAD II.

favor a general defect in L-fucose metabolism. Lymphocytes from 1 of our patients display a significant reduction of GDP-D-mannose-4,6 dehydratase (GMD) activity, even though no qualitative or quantitative defects are observed for this enzyme, thus suggesting the presence of inhibitory mechanisms.[5] Recently, Lubke et al[6] found that the activity of this enzyme was normal in their LAD II patient, but a defect in the import of GDP fucose into Golgi-enriched vesicles was found. A decreased import of GDP-L-fucose into the Golgi-enriched vesicles was also observed in our patient (Tonetti, unpublished results), and the consequent increase in the cytosolic concentration of GDP-L-fucose, which is a very good noncompetitive feedback inhibitor for GMD, can explain the defect in the enzymatic activity observed. Our in vitro studies on cells from the LAD II patient indicated that administration of L-fucose is able to restore the expression of fucosylated antigens on the cell membrane.[7] But the concentrations used in vitro were many times higher than those achievable in vivo. In Marquardt et al's patient, fucose administration was able to correct not only the expression of various glycoproteins on the cell surface but even some of the neurological defects,[1] while in our 2 patients no effect was observed.

We believe, therefore, that although the phenotype of LAD II in our 4 Arabic patients is very similar to the Turkish patient reported by Marquardt et al, the biochemical defect is somehow different. It is clear that the increased fucose delivery to the cell through the scavenger pathway is enough to overcome the Golgi-uptake defect in Marquardt et al's patient. Still, in our patients the specific defect in fucose import by the Golgi apparatus seems more profound and could not be overcome by increasing fucose delivery to the cell, at least at the concentrations that can be obtained in vivo. In order to clarify this very interesting issue, complementation studies using cells from the different patients should be performed in order to find the primary molecular genetic defect.

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