

CORRESPONDENCE

Chronic Hepatitis C Virus and Gastric MALT Lymphoma

To the Editor:

Cases of lymphocytic monoclonal B-cell proliferation such as non-Hodgkin's lymphomas have been reported in chronically hepatitis C virus (HCV)-infected patients. Lymphomas of the mucosa-associated lymphoid tissue (MALT) type are due to monoclonal proliferation of B cells showing characteristic histopathological features of MALT. Luppi et al¹ recently reported an unexpectedly high prevalence of HCV infection in a series of patients with low-grade lymphomas of the MALT type in various body sites. This study showed the presence of both anti-HCV antibodies and HCV-RNA in the serum of 8 of 16 MALT lymphoma patients (50%).¹ In another study, Pioltelli et al² also observed a high prevalence of HCV infection in low-grade lymphomas of the MALT type (36.4%), although they did not mention the number of cases examined.

The aim of the present study was to assess the prevalence of HCV infection in a well-characterized series of 46 patients with gastric MALT lymphoma. Of the 46 patients, 25 had a low-grade lymphoma (14 women, 11 men, mean age 54.2 years, range 30 to 75) and 21 had a high-grade lymphoma (8 women, 13 men, mean age 56.3 years, range 23 to 85). *Helicobacter pylori* infection was demonstrated by serological and/or histological tests in 37 of 46 patients (80.4%). One hundred sixty-five patients with gastroduodenal disease were recruited to compose the control group. There were 84 patients with duodenal ulcer, 43 with gastric ulcer, and 38 with dyspepsia. The two groups were comparable in terms of the sex ratio, age, prevalence of *H pylori*, risk factors for HCV infection (previous parenteral exposure to blood products, intravenous drug misuse, nosocomial exposure), and geographical origin. Diagnosis of gastric MALT lymphoma was based on gastric biopsy specimens evaluated according to Isaacson's classification³ and by immunophenotypic analysis of surface T- and B-lymphocyte markers. Anti-HCV antibodies were determined by third-generation enzyme-linked immunosorbent assay and confirmed by third-generation recombinant immunoblot assay (RIBA) in all patients (Ortho Clinical Systems, Raritan, NJ). There was no significant difference between the prevalence of HCV infection in the MALT lymphoma group and the control group: among the patients with gastric MALT lymphoma, only 1 had anti-HCV antibodies (2.2%), compared with 4 in the control group (2.4%) (not significant). The only MALT patient who tested anti-HCV Ab-positive was also positive for *H pylori* and belonged to the low-grade MALT lymphoma group.

Thus, we found no higher prevalence of HCV infection among patients with gastric MALT lymphoma than in a control group composed of subjects with a gastroduodenal disease similarly related to *H pylori* infection, with the same risk factors for hepatitis C and deriving from the same geographical region. Our data contrast with those of the Italian teams^{1,2} and are more in keeping with those of the American and British teams,^{4,5} who did not specifically study gastric MALT lymphoma but found no evidence of a relationship between HCV infection and non-Hodgkin's lymphoma.

To our knowledge, this is the first study to evaluate the prevalence of HCV infection in a large, well-characterized series of patients with gastric lymphomas of the MALT type. Our results indicate that there is no link between HCV infection and gastric MALT lymphoma in France.

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REFERENCES

1. Luppi M, Longo G, Grazia Ferrari M, Ferrara L, Marasca R, Barozzi P, Morselli M, Emilia G, Torelli G: Additional neoplasms and HCV infection in low-grade lymphoma of MALT type. *Br J Haematol* 94:363, 1996
2. Pioltelli P, Zehender G, Monti G, Monteverde A, Galli M: HCV and non-Hodgkin lymphoma. *Lancet* 347:624, 1996 (letter)
3. Isaacson PG, Norton AJ: Extranodal lymphomas: Malignant lymphoma of the gastrointestinal tract, in *Extranodal Lymphomas*. Edinburgh, UK, Churchill Livingstone, 1994, p 15
4. King PD, Wilkes JD, Herten CM: Non-Hodgkin's lymphoma in the USA is not associated with hepatitis C infection. *Gastroenterology* 112:1304a, 1997 (abstr)
5. Hanley J, Jarvis L, Simmonds P, Parker A, Ludlam C: HCV and non-Hodgkin lymphoma. *Lancet* 347:1339, 1996 (letter)

Congenital Erythropoietin-Dependent Erythrocytosis Responsive to Theophylline Treatment

To the Editor:

In a recent article in *BLOOD*, Sergeeva et al¹ describe a secondary form of congenital polycythemia that appears to be particularly frequent in Chuvasia, a region in the central part of European Russia. This erythrocytosis is transmitted as an autosomal recessive trait and generally becomes clinically manifest in the second decade of life. Because these individuals have elevated erythropoietin (Epo) levels with no abnormality in hemoglobin (Hb) dissociation curve or red blood cell 2,3-diphosphoglycerate, Sergeeva and coworkers¹ conclude that the excessive Epo production likely reflects an abnormal oxygen sensing mechanism.

We studied a 17-year-old girl with a history of intermittent headache and progressive appearance of plethora. One year before admission a

blood cell count showed Hb 19.4 g/dL, hematocrit 65.6%, red blood cell $7.65 \times 10^{12}/L$, white blood cell $4.15 \times 10^9/L$, and platelet $130 \times 10^9/L$. Her parents and a sister had normal blood counts. Spleen size was normal and arterial saturation was 96.6%. Serum Epo (sEpo) was increased (107 mU/mL), and there was no evidence of in vitro spontaneous burst-forming unit-erythroid growth from peripheral blood. Because Hb increased to over 20 g/dL, in the months preceding admission to our department the patient underwent regular phlebotomies to maintain levels around 16 g/dL.

We first excluded abnormalities in oxygen unloading of hemoglobin by measuring Hb P₅₀ using the Hemox-Analyzer (TCS Medical Products Division, Southampton, PA). The oxyhemoglobin dissociation curve was normal and P₅₀ was 24.5 mmHg (normal values range from 23 to 27.5 mm Hg).

Serum Epo was determined using venous blood sampled without anticoagulant by means of an enzyme-linked immunosorbent assay (ELISA) (CLINIGEN, Amgen Diagnostic, Thousand Oaks, CA); values in normal reference individuals range from 6 to 20 mU/mL. Serum transferrin receptor (sTfR), the level of which provides an estimate of erythroid marrow activity,² was also measured by an ELISA (CLINIGEN); values in normal reference individuals range from 1.47 to 3.4 mg/L.

Basal sEpo was 204 mU/mL with a Hb level of 16.6 g/dL, a value 10 times the upper normal limit. At the same time sTfR was 9.7 mg/L, ie, four times the mean normal level. It should be noted that in this case the elevated sTfR level was likely a result of both increased erythroid marrow activity and iron deficient erythropoiesis. In fact, transferrin saturation was 11%, and defective iron supply to erythropoiesis increases both the expression of transferrin receptors on erythroid cells and sTfR level.² In any case, the above findings indicated an inappropriately elevated endogenous Epo production with secondary expansion of erythroid marrow activity. Computed tomography scans of the chest and the abdomen, ultrasonography of the abdomen, and magnetic resonance imaging of the brain excluded Epo-producing tumors and/or renal disorders. In addition, sEpo appeared to be normally influenced by oxygen-mediated feedback (107 mU/mL at a Hb level of 19.4 g/dL v 204 mU/mL at 16.6 g/dL).

We therefore concluded for a congenital form of polycythemia, transmitted with an autosomal recessive pattern of inheritance and caused by an upregulated oxygen sensing mechanism.³ This condition appears to be very similar to the Chuvash polycythemia.¹

To further investigate the regulation of Epo production, we evaluated whether Epo synthesis was normally modulated by adenosine as a second messenger. Adenosine receptor antagonists like theophylline, in fact, attenuate the production of Epo in both normal subjects and patients with erythrocytosis after renal transplantation.^{4,5} We therefore tested the effect of theophylline on sEpo and sTfR levels. The patient was given intravenous theophylline, 240 mg two times a day for 2 days; subsequently she took a long-acting preparation of theophylline (7 mg per kg of body weight per day). The time course of sEpo and sTfR under theophylline treatment is reported in Fig 1. There was a definite decrease in both endogenous erythropoietin production and erythroid marrow activity within a few days, although after 11 days values remained still elevated. Treatment was continued with oral administration of theophylline. Hb level declined to about 15 g/dL and remained stable around this value for several months.

In conclusion, we suggest to evaluate the effect of theophylline on endogenous Epo production in Chuvash polycythemia. This may allow to gain a deeper insight into the pathophysiology of this disorder and to try a potentially useful therapeutic tool.

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REFERENCES

1. Sergeeva A, Gordeuk VR, Tokarev YN, Sokol L, Prchal JF, Prchal JT: Congenital polycythemia in Chuvasia. *Blood* 89:2148, 1997
2. Cazzola M, Beguin Y: New tools for clinical evaluation of erythropoiesis and iron status in man. *Br J Haematol* 80:278, 1992

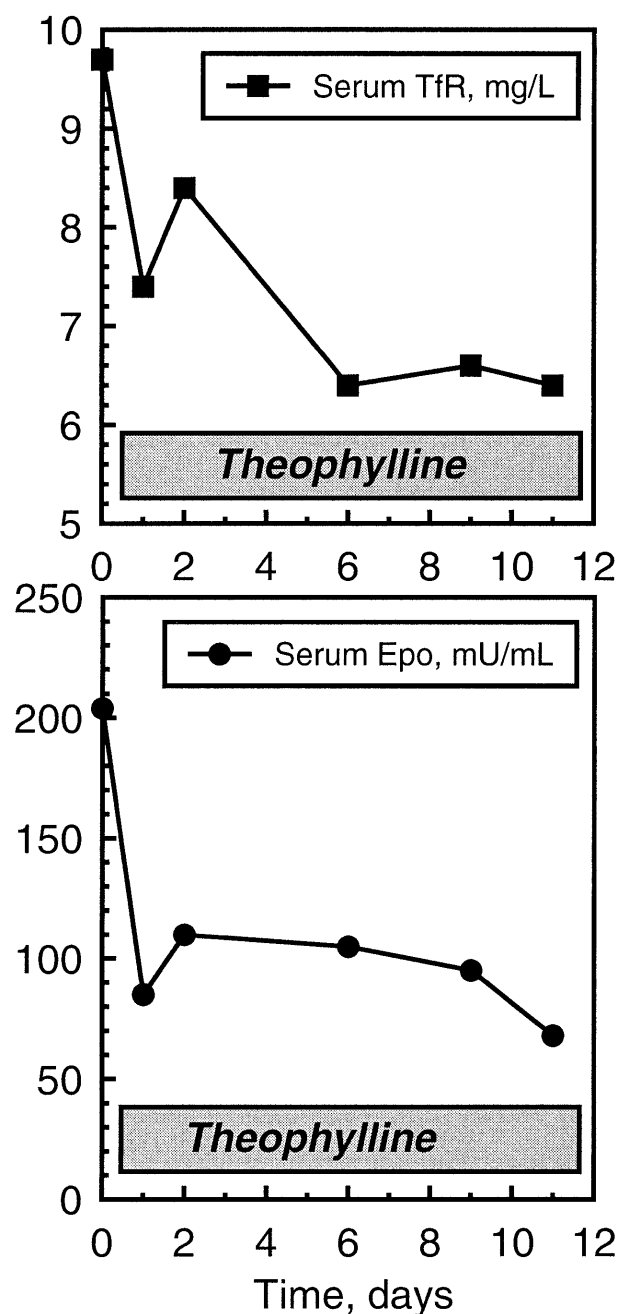


Fig 1. Effects of theophylline on serum Epo and serum transferrin receptor (TfR) in the 17-year-old girl with erythropoietin-dependent erythrocytosis. Theophylline was given intravenously in the first 2 days and then orally (see text for details).

3. Whitcomb WH, Peschle C, Moore M, Nitschke R, Adamson JW: Congenital erythrocytosis: A new form associated with erythropoietin-dependent mechanism. *Br J Haematol* 44:17, 1980

4. Bakris GL, Sauter ER, Hussey JL, Fisher JW, Gaber AO, Winsett R: Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 323:86, 1990

5. Barosi G: Control of erythropoietin production in man. *Haematologica* 78:77, 1993