The Changing Clinical Picture of Tropical Sprue

Norman Maldonado*

RESUMEN
El esprue tropical es un padecimiento endémico en Puerto Rico, algunas islas del Caribe y el Sur de Asia. Se caracteriza por diarrea, pérdida del apetito y de peso y anemia. En años recientes la incidencia de esprue tropical ha disminuido y su cuadro clínico es distinto. El suplemento de cereales y harinas con ácido fólico y las campañas para consumir ácido fólico para la prevención de defectos del tubo neural en las mujeres y para disminuir la hiperhomocisteinemia, han enmascarado el cuadro clínico del esprue tropical. El padecimiento puede presentarse sin anemia significativa y con concentraciones normales de ácido fólico, pero bajas de vitamina B₁₂. La anemia perniciosa es hematológicamente indistinguible del esprue tropical. Se comunican ocho casos de pacientes con esprue tropical.

Palabras clave: esprue tropical, ácido fólico, defectos del tubo neural, hiperhomocisteinemia.

ABSTRACT
Tropical sprue is an endemic condition in Puerto Rico, some Caribbean islands and Southeast Asia. It is characterized by diarrhea, poor appetite, weight loss and anemia. In recent years the incidence of tropical sprue has declined and the clinical picture is different. The supplementation of cereals and flours with folic acid for the prevention of neural tube defects in the newborns and to decrease hyperhomocysteinuria has disguised the clinical picture of tropical sprue. The condition can be seen without significant anemia with normal folic acid but low vitamin B₁₂ levels. The pernicious anemia which is indistinguishable from tropical sprue hematologically. We are reporting eight patients with tropical sprue who had normal or high folic acid levels but low or high vitamin B₁₂ levels.

Key words: Tropical sprue, folic acid, neural tube defects, hyperhomocysteinuria.

Tropical Sprue is a condition characterized by intestinal malabsorption, which in its chronic state leads to megaloblastic anemia. Dietary findings of folic acid and also vitamin B₁₂ deficiency have been frequent findings. D-xylose absorption has been a most effective test to screen for the condition. Jejunal biopsies have shown abnormalities characterized by atrophy of the villae and a lymphocytic infiltrate. An infectious cause has been advocated since the early days, when Ashford who described the condition in Puerto Rico, suspected Monilia psylosis as the etiologic agent.¹²

Many attempts to find the cause of this condition were made. In 1958 French and collaborators showed improvement in seven British patients with tetracycline and chloramphenicol. Half of more seriously ill patients also improved. In 1961 Sheehy and Perez Santiago also confirmed these patients in two week trials.³ Long term therapy was proven effective by Guerra and collaborators in Puerto Rico and also by Klipstein in New York with expatriates from the tropics.⁴ In 1969 we reported the success of poorly absorbed sulfonamides in the treatment of tropical sprue and subsequently compared it with tetracycline.⁵

In 1973 Klipstein and Corcino working in our laboratory were able to prove the infectious nature of the condition. Enterotoxigenic Gramnegative bacteria especially Enterobacter cloacae were grown from jejunal aspirates.⁶ The blind loop test was positive and the bacteria produced alcohol. Another aspect of the study was the evaluation of the nutritional status and intestinal function of a rural population in Puerto Rico.⁷ The findings showed that 25% of the normal asymptomatic population had one or more
abnormal absorption test. The most sensitive was vitamin B\textsubscript{12} malabsorption.

The incidence of tropical sprue has definitely decreased in Puerto Rico. One can speculate on the many factors which contribute to the decrease in incidence including improved sanitary conditions, safer water, less fried food and less lard used in cooking. We can not ignore the frequent use of multivitamins, the enrichment of all cereals with folic acid, the campaign for all women after age 10 to take at least 400 mcg of folic acid daily and also the frequent use of antibiotics for all kinds of serious but also minor infections.

I am reporting on the change in the clinical picture and laboratory findings in eight patients seen recently.

**CASE REPORTS**

**Case 1.** S.H. This 65 years old physicians wife complained of poor appetite, tired easily and 20 pounds weight loss with no diarrhea or abdominal symptoms. She had distaste for milk and meats. The physical examination was normal. The CBC showed hemoglobin 13 g, WBC 4,300, platelets 260,000 and MCV of 96 μ\textsubscript{3}.The folic acid was >40 ng /mL and vitamin B\textsubscript{12} levels were 1,094 pg/mL. A small bowel series was abnormal with segmentation and flocculation of the barium. The xylose absorption was 0.8 gm in 5 h (normal >1.2 g). The patient was given tetracycline 250 mg qid for one month and then bid. Folic acid 1 mg was also given. In 3 months she had improved from her symptoms and the xylose absorption was 2.4 g in 5 h.

**Case 2.** P.R. This 68 years old man, retired professor was referred because he had dropped his hemoglobin to 13.4 g/dL and had an MCV of 101 μ\textsubscript{3}. He had loose stools. The physical examination was normal. The LDH was elevated. A bone marrow was 2+ megaloblastic. The serum folate was >40 ng/mL; vitamin B\textsubscript{12} was 89 pg/mL. Xylose absorption was 0.7 g in 5 hours. He was given oral folic acid and IM vitamin B\textsubscript{12}. She improved her symptoms and her appetite in two weeks. She was treated with tetracycline 250 mg qid for one month and then twice daily for five months. She gained 30 pounds and the hemoglobin became normal. The MCV became normal in three months.

**Case 4.** AR. This 60 years old woman and hospital worker developed dizziness and was found with anemia of 9.9 g/dL, MCV 108μ\textsubscript{3}. Normal WBC and elevated platelets of 500,000/mL. She had lost 20 pounds in the past year and had occasional diarrhea. She had mild glossitis and evidence of weight loss on physical examination.

The bone marrow was megaloblastic. Serum folate was 7 ng/mL; vitamin B\textsubscript{12} was 89 pg/mL. Small bowel series showed a very rapid transit time. Parietal cell antibodies were positive and intrinsic factor antibodies were negative. Xylose absorption was 0.7 g in 5 hours. She was given oral folic acid and IM vitamin B\textsubscript{12}. She improved her symptoms and her appetite in two weeks. She was treated with tetracycline 250 mg qid for one month and then twice daily for five months. She gained 30 pounds and the hemoglobin became normal. The MCV became normal in three months.

**Case 5.** LM. This 80 years old woman began loosing weight and feeling weak. She was seen by her physician and referred to a hematologist. She was found with macrocytic anemia. She had a bone marrow done, flow cytometry and cytogenetic studies which were inconclusive. The patient had lost 50 pounds and was weak and had no appetite. Had a history of colitis but denied diarrhea. She came to the emergency room at teachers' hospital and was admitted with hemoglobin of 6.8 g/dL with a diagnosis of symptomatic anemia. The MCV was 102 μ\textsubscript{3}, WBC 5,120 with a normal differential count and platelets 287,000. She was seen by another hematologist who diagnosed a macrocytic anemia. Serum folate level was 17.2 ng/mL, vitamin B\textsubscript{12} level was <60 pg/mL, ferritin was 120 ng/mL. The LDH was 870 m/L' (normal 100-200). She
was transfused two units of packed RBC and started on oral folic acid and vitamin B₁₂ IM, then orally. She was discharged with the diagnosis of symptomatic anemia. The patient did not gain weight and came for an opinion. She had neurological deficit in the lower extremities with a positive Romberg test and unstable gait.

The hemoglobin rose to 13 g/dL with normal indices, but she did not gain weight and felt weak. A xylose absorption test was 1.0 g/5 hours. Parietal cell and intrinsic factor antibodies were done and were positive. She was considered to have pernicious anemia and probable coexistent malabsorption.

She was started on vitamin B₁₂ IM weekly and then monthly. She gained weight and was feeling better with improvement of the neurologic picture.

**Case 6.** LAR. This 72 year old physician was having diarrhea on and off for four years. He began loosing weight and lost his appetite 4 months prior to the evaluation. On physical examination there were no abnormal findings. Hemoglobin was 12 g/dL with normal WBC, platelet count and indices. The serum folate was elevated and the vitamin B₁₂ was over 1,000 pg/mL. Upper and lower endoscopies were normal. A 5 g xylose absorption was .4 g in 5 hours. He was started on tetracycline 250 mg qid for one month and then 250 mg bid. In one week the diarrhea stopped and the appetite and well being returned. His hemoglobin increased and the xylose was 1.0 g in 5 hours and he gained 10 pounds.

**Case 7.** AR. This 72 years old patient had chronic renal disease and had a renal transplant 7 years prior to his visit. He did well post p.o. but began loosing weight up to 40 pounds. He had diarrhea and anemia. He was referred for evaluation after receiving oral iron and vitamin B₁₂ injections. The Hgb was 12.3 g/dL. The MCV was 108 M³. A folate level was over 13.7 ng/mL and the vitamin B₁₂ was not done. Xylose absorption was low 0.2 g/5 hour and the serum creatinine was 0.9 mg/dL. He was started on tetracycline 250 mg Bid. In a short time the diarrhea stopped and he felt better. The xylose rose to normal 1.2 g/5 hours in 6 months. The hemoglobin remained at 12.7 g/dL. He did not gain weight.

**Case 8.** ER. This 65 years old protestant minister came with a history of loose stools and early satiety. He was found with anemia and had lost 24 pounds. He was on a coffee enema regime daily by his naturopathic doctor. He had a Hgb of 8.7 g/dL. The MCV was 123 M³. The bone marrow was megaloblastic. Serum folate was 14.5 ng/mL and vitamin B₁₂ was low at 115 pg/mL. Xylose absorption was low at 0.2 g/5 hours. Parietal cell and intrinsic factor antibodies were negative. Therapy with tetracycline, and vitamin B₁₂ was started. He had a good response and hemoglobin rose to 14.7 g/dL. He gained 18 pounds. The xylose became normal at 1.2 gm/dL and he was asymptomatic when last seen.

**DISCUSSION**

Tropical sprue has been an endemic disease in Puerto Rico. Dr. William Crosby in his Ashford Lecture proposed the theory that the high mortality of the Puerto Ricans who had hookworm infestation and anemia was due to the coexistence of the parasitic infestation and tropical sprue. The infectious etiology proposed by Ashford eventually was proven, but not caused by *Monilia psyllosis* but by an abnormal gram negative flora. The ultimate confirmation was the cultures of the enterotoxigenic bacteria and the cure with the treatment of oral antibiotics and unabsorbable sulfonamides.

The changes in public health, economic conditions, frequent use of broad spectrum antibiotics for all sorts of infections, supplementation of diets with multivitamins and food with folic acid supplementations have been factors that have changed the clinical picture of tropical malabsorption.

The patients with tropical sprue now have fewer diarrheas, and anemia seems to be less prominent. Folic acid levels in seven of our eight patients were normal which is contrary to the classical picture where folic acid deficiency was characteristic in the clinically manifestation of the disease. The low vitamin B₁₂ levels were found in five of the eight patients measured. Two patients were on vitamin B₁₂ therapy when seen and had high levels. Vitamin B₁₂ is known to be stored in the liver and that it takes 4 years to deplete the body when absorption is stopped in patients without malabsorption. In tropical sprue vitamin B₁₂ is lost in the stools due to the enterohepatic circulation. The changes in the intestine include the whole intestine especially the small bowel and affect the distal ileum where B₁₂ is absorbed. In the studies done by Klipstein and Corcino in the rural population of Bayamon the most frequent abnormality detected was B₁₂ malabsorption. In our patients treated with antibiotics and poorly absorbed
sulfonamides the vitamin B\textsubscript{12} levels began to normalize before the folic acid did.

Pernicious anemia still exists and has to be considered in every patient with megaloblastic anemia. A normal xylose excludes tropical sprue. A positive parietal cell and most specific intrinsic factor antibodies suggest the disease is pernicious anemia which can be confirmed by the Schilling test which is difficult to obtain these days. Parietal cell and particularly intrinsic factor antibodies are diagnostic of the condition. Both conditions sprue and pernicious anemia rarely can coexist in endemic areas. It is very important to make the distinction, because pernicious anemia patients have to be treated with parenteral B\textsubscript{12} for the rest of their lives and tropical sprue treatment can be stopped when the absorption is normal. The practice of gun shot therapy is not recommended. Blood transfusion is rarely needed. A growing numbers of young physicians and others, who studied abroad where topical sprue is not seen, frequently miss the diagnosis or have not heard of the condition. Tropical sprue still exists in Puerto Rico, in some tropical Caribbean Islands and Asian countries, so it should be kept in mind when the patient has macrocytic anemia, chronic diarrhea and weight loss. Multivitamin therapy can mask the underlying malabsorption which can persist. Xylose absorption is an excellent screening test, but the renal function must be normal.

REFERENCES