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Irradiation for progressive paraparesis in ß-thalassemia intermedia

JONATHAN J. WILSON,* MD; MARION E. HILL,† MD, FRCP[C]; JOHN H. CROOKSTON,‡ MD, PH D, FRCP[C]

Spinal cord compression secondary to extramedullary hematopoiesis is rare in patients with thalassemia.[1-5] We describe the successful treatment of such a patient with irradiation and "hypertransfusion".

Case report

The patient was born in Canada in 1952 of Italian parents. Both parents had β-thalassemia minor; of their five children, two had β-thalassemia intermedia. The patient was found to have β-thalassemia in infancy. After 5 years of regular blood transfusions (approximately two units per month) he had a splenectomy and required no further transfusions to maintain a hemoglobin concentration of between 7 and 8 g/dl. In 1971 a cholecystectomy for pigment stones was complicated by an episode of acute renal failure requiring hemodialysis on one occasion. In October 1976 he started receiving intramuscular injections of deferoxamine mesylate (Desferal), 1 g/d, 6 days a week, because of evidence of iron overload (cardiomegaly with a normal electrocardiogram, hepatomegaly with mildly abnormal results of liver function tests, and an increase in the 24-hour urinary excretion of iron from 1.0 to 13.2 mg after the intramuscular injection of 1 g of deferoxamine). There was no evidence of endocrine dysfunction. He had attained normal developmental milestones. He continued to receive the injections until November 1977, when he moved to another city. He was a nonsmoker and a "social drinker", and was taking no medication other than folic acid, 5 mg/d.

In March 1978 he was admitted to hospital with a 5-month history of progressive paresthesia and weakness of his trunk and legs.

Five months earlier interscapular pain that was increased by bending or walking had begun; it had gradually increased in frequency until it was constant. During the next 2 months he noticed persistent numbness below the costal margins bilaterally, extending into both legs and accompanied by increasing leg weakness. He had difficulty climbing stairs and rising from a squatting position; his toes dragged when he walked. In the 2 months before admission he had urgency of bowel movements but no urinary symptoms.

When admitted to hospital he was thin, with prominent cheekbones. There was increased dusky brown pigmentation of his skin. The sclerae were moderately icteric and the conjunctivae were pale. There were no enlarged lymph nodes. The lungs were clear. The cardiac apex was felt 3 cm lateral to the midclavicular line in the fifth intercostal space. A grade 3/6 systolic ejection murmur was heard along the left sternal border. The

From the department of medicine, Toronto General Hospital

*Resident in hematology
†Staff neurologist and associate professor of medicine, University of Toronto
‡Staff hematologist and professor of medicine and pathology, University of Toronto

Reprint requests to: Dr. John H. Crookston, Department of laboratory hematology, Toronto General Hospital, 101 College St., Toronto, Ont. M5G 1L7

smooth liver edge was palpable 7 cm below the right costal margin; the liver spanned 17 cm. The genitalia were normal. Rectal tone, mental state and cranial nerve function were normal.

He had a flaccid weakness of his legs that was worse on the left side and proximally. Pinprick and thermal testing demonstrated sensation at the level of the fifth thoracic vertebra, and there was vertebral tenderness at this level. Vibration sense was decreased up to the iliac crests bilaterally; position sense and sensation of light touch were normal. The tendon reflexes in the legs were hyperactive on the right and normal on the left, and there was an extensor plantar response bilaterally; abdominal reflexes were absent. Cerebellar testing gave normal results and the Romberg test gave a negative result.

The blood hemoglobin concentration was 8.2 g/dl, the corrected leukocyte count 17.6 $\times$ 10^9/l, the platelet count 700 $\times$ 10^9/l and the reticulocyte count 7%. A peripheral blood film showed 500 erythroblasts per 100 leukocytes and postsplenectomy changes, including thrombocytosis. Hemoglobin electrophoresis (on cellulose acetate at pH 8.4) showed hemoglobin A (26.6%), A_2 (6.4%) and F (67.0%). The following levels of serum constituents were noted: glucose (with the patient fasting) 4.2 mmol/l (76 mg/dl), creatinine 62 μmol/l (0.7 mg/dl), total bilirubin 173 μmol/l (10.1 mg/dl) (conjugated 17.1 μmol/l [1.0 mg/dl]), glutamic oxaloacetic transaminase (SGOT) 95 IU/l, alkaline phosphatase 121 IU/l, albumin 4.3 g/dl and globulin 5 g/dl. Urinalysis showed 2+ protein and no bilirubin. A 24-hour urine collection contained 1.9 g of protein; the creatinine clearance was 102 ml/min. The serum iron level was 41.6 μmol/l (232 μg/dl) and the iron binding capacity 45.1 μmol/l (252 μg/dl), with 92% saturation. Hepatitis B surface antigen was not detected in the serum. A liver biopsy showed marked iron overload and moderate portal fibrosis.

An electrocardiogram was consistent with left ventricular hypertrophy. A one-dimensional echocardiogram showed an enlarged left ventricle with normal function; the right ventricle and left atrium were also dilated. There was no evidence of pericardial effusion. Roentgenograms showed severe osteoporosis of the cervical, thoracic and lumbosacral vertebrae, posterior and left superior mediastinal soft tissue densities and multiple densities projecting laterally adjacent to both right and left ribs. Mediastinal tomograms showed lobulated widening of the right and left mediastinal soft tissues, consistent with extramedullary hematopoiesis. A bone marrow scan with technetium 99m sulfur colloid showed increased uptake in all areas of the red marrow, but did not reveal the paraspinal masses.

The patient was treated with radiation to the thoracic spine (1500 rad in 5 days) and was given six units of packed cells in 48 hours. Five days later his neurologic function had improved, and a further 2 days later he had only mild weakness of his trunk and hip flexors bilaterally. There was no sensory impairment except for decreased vibration sense below his knees. The reflexes were unchanged.

His recovery was complicated by a fever, thought to be virus-induced, associated with intravascular lysis. His serum contained anti-HI, an autohemagglutinin that reacted in vitro most strongly at low temperatures; it was weakly active (titre 2) at 34°C. It was not detectable a year later.

The patient was discharged in April 1978. Six weeks later weakness of his lower limbs and numbness up to his nipples developed, along with interscapular pain that increased with coughing. He was readmitted to hospital.

There was no significant change from 6 weeks earlier in the radiologic findings. A myelogram showed a long thoracic extradural filling defect with tapering ends, consistent with extramedullary hematopoiesis (Fig. 1). His condition improved with bed rest: the numbness and weakness of his legs disappeared, but slight back pain persisted. Neurologic examination has yielded normal findings since July 1978.

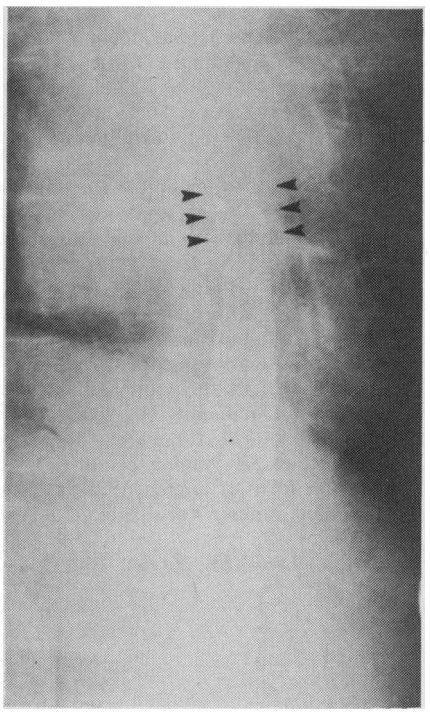

FIG. 1A—Lateral-view myelogram with patient's head down, showing narrowing of contrast column (arrowheads), with almost complete obstruction. The compression is both anterior and posterior, suggesting a circumferential extradural mass.

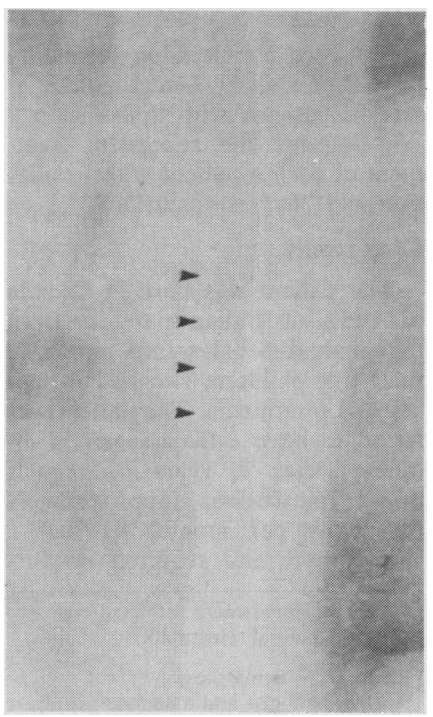

FIG. 1B—Anteroposterior-view myelogram with patient's head down, showing gradual attenuation of contrast column over several segments (arrowheads), with almost complete obstruction. The diffuse extradural mass appears to be predominantly right-sided.

Since June 1978 he has been given regular blood transfusions (four units of packed red cells every 4 weeks) to keep his hemoglobin level above 10 g/dl and thus suppress the extramedullary hematopoiesis. In November 1978 he was assessed at the National Institutes of Health in Bethesda, Maryland, where computer-assisted tomography showed paraspinal extramedullary hematopoiesis. He entered a clinical trial of iron chelation therapy in which deferoxamine, 1.5 g/d over 12 hours, 5 days each week, was self-administered subcutaneously. With this treatment his urinary iron excretion has averaged 25 mg/d.

His skin colour has become lighter, his exercise tolerance has increased, his liver span has decreased from 17 to 13 cm and the proportion of erythroblasts in the peripheral blood has decreased from 500 to 100 per 100 leukocytes. The pertinent serum constituents have the following levels: glucose (with the patient fasting) 4.8 mmol/l (86 mg/dl), total bilirubin 46 μmol/l (2.7 mg/dl), SGOT 70 IU/l, alkaline phosphatase 114 IU/l, albumin 5.0 g/dl, globulin 3.6 g/dl, serum iron 38.3 μmol/l (214 μg/dl) and total iron-binding capacity 40.6 μmol/l (227 μg/dl), with 94% saturation.

His persistent proteinuria was investigated by means of a renal biopsy in October 1979. The specimen showed mild mesangial hypercellularity and sclerosis, with iron deposition in the distal tubules. Immunofluorescence microscopy showed mesangial deposits of IgM, IgA and the C3 component of complement.

Discussion

In this patient the anemia was less severe than is usual in classic β-thalassemia major; the phenotype is described as β-thalassemia intermedia. It is assumed that the β-thalassemia genes he inherited together contribute more β-globin than is usual in homozygous β-thalassemia.

When his paraparesis developed in March 1978 the many possible causes of spinal cord compression were considered. These included intrathoracic meningocele, vascular anomalies, paraspinal abscess, metastatic malignant disease, lymphoma and myeloma. There was no evidence at that time, or subsequently, to support any of these alternative diagnoses.

Spinal cord compression secondary to extramedullary hematopoiesis is an unusual complication of β-thalassemia major and β-thalassemia intermedia.[1-5] In the present case the diagnosis was based on the clinical presentation and the radiologic findings. However, since a biopsy of the spinal mass was not done, proof of the diagnosis was not obtained. A bone marrow scan did not show the lesion. Studies with ^{59}Fe or ^{52}Fe, which are reported to be superior in delineating the extent of extramedullary hematopoiesis,[6] were not done, nor was indium chloride used.[3] Unfortunately the lesion was not diagnosed myelographically until the second admission to hospital. Subsequently computer-assisted tomography showed paraspinal extramedullary hematopoiesis.

The possible ways of managing extramedullary hematopoiesis, as summarized by Stahl, Ellinger and Baringer,[4] include no treatment, irradiation, laminectomy, and laminectomy plus irradiation. Irradiation alone has been successfully used to treat one patient with thalassemia intermedia[1] and another with myelofibrosis.[7] Fessas and Loukipoulos[8] stated that symptomatic paravertebral erythropoiesis is an indication for local irradiation. Our patient illustrates the success of irradiation without recourse to laminectomy.

The value of "hypertransfusion" in the treatment of homozygous β-thalassemia is now recognized.[9] Regular blood transfusion, by keeping the patient's hemoglobin concentration nearly normal, suppresses erythropoiesis (medullary and extramedullary). The present case illustrates the value of regular transfusion in the long-term management of spinal cord compression secondary to extramedullary hematopoiesis.

Iron overload in our patient was attributed in part to the blood transfusions given in childhood, but more to increased intestinal absorp-

tion of iron associated with anemia due to ineffective erythropoiesis.[10] The value of iron chelation therapy in patients with anemia and iron overload is the subject of a recent extensive review.[11]

The cause of the renal lesions in our patient is unknown. The lesions may be related to his cirrhosis; an association between cirrhosis and glomerulonephritis has been reported.[12]

We are indebted to Dr. R.C. Holgate for his assistance in interpreting the radiologic findings.

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BOOK REVIEWS

Exercise Electrocardiography. Practical Approach. Edited by Edward K. Chung. 354 pp. Illust. The Williams & Wilkins Company, Baltimore; the Macmillan Company of Canada Limited, Toronto, 1979. $39.95. ISBN 0-683-01569-9

This book will be helpful to cardiologists, internists, residents, nurses and technicians who supervise exercise tests or interpret their results. After a look at the history of exercise testing and at Master's two-step test the book focuses on the technical aspects and potential risks of exercise electrocardiography, reviewing the indications, contraindications and precautions.

The interpretation of the exercise electrocardiogram (ECG) is well described and abundantly illustrated. An interesting chapter deals with the effects of drugs and metabolic abnormalities on the results of the test. Exercise electrocardiography for children is also discussed.

There is a chapter on myocardial perfusion imaging with thallium 201 and its correlations with exercise electrocardiography and coronary angiography. Stress scintiscanning may be helpful when the interpretation of a stress ECG is equivocal because of ECG abnormalities at rest. Studying perfusion scintiscans obtained with the subject at rest and after stress may help differentiate reversible ischemia from irreversible infarction. However, this section is not entirely up to date.

The value of exercise electrocardiography in screening asymptomatic subjects for latent coronary artery disease is reassessed; an abnormal response in those already at high risk for coronary artery disease can be indicative. But the predictive value of an abnormal response is directly related to the prevalence of disease in the subject's population group. A biostatistical section demonstrates this new concept and may prevent the indiscriminate use of stress testing in asymptomatic young people.

Some medicolegal considerations conclude the book: it is good practice to obtain written informed consent before conducting a stress test.

The book contains a good index, precise summaries after each chapter and an extensive reference list. It deserves a place in all exercise laboratories and in the library of all cardiologists.

Paolo E. Puddu, MD
André Pasternac, MD, FACC
Institut de cardiologie de Montréal
Montreal, PQ

Heart Disease in Infants and Children. Edited by Gerald Graham and Ettor Rossi. Translated from Herzkrankheiten im Sauglingsalter. 495 pp. Illust. Edward Arnold (Publishers) Ltd., London; Gage Educational Publishing Limited, Toronto, 1980. $124.95. ISBN 0-7131-4345-2

The 31 authors of this comprehensive review textbook on pediatric cardiology, with the exception of two Americans, practise their specialty in Europe. The editors are well known among pediatric car-