Regression of Cardiac Insufficiency After Ambulatory Intravenous Deferoxamine in Thalassemia Major

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A case of severe cardiac failure due to iron overload in a patient with β-thalassemia major is reported. The patient was successfully treated with high-dose ambulatory intravenous deferoxamine (desferoxamine). This type of chelation appears to be a valuable alternative to subcutaneous deferoxamine administration in the presence of severe iron overload.

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Patients with Cooley's anemia suffer from transfusional iron overload. Parenchymal accumulation of iron may lead to cirrhosis of the liver, endocrine organ insufficiency, and congestive cardiomyopathy.1 Iron chelation with nightly subcutaneous (sc) infusions of deferoxamine (DFO) has been shown to delay or reverse some of these complications (eg, fibrosis of the liver and cardiac toxic effects),4 however, the efficacy of this painful and cumbersome therapy is often questioned because compliance is poor, and the amount of daily sc DFO that can be injected is limited.5 Higher doses of DFO can be given intravenously (IV). The negative iron balance (ie, in urine and stools) is proportional to the degree of iron overload and to the dose of DFO administered.15

The case of a young adult with β-thalassemia major and severe congestive heart failure due to iron overload is reported. With intensive medical treatment, including IV DFO followed by ambulatory IV chelation, marked improvement of cardiac function was observed.

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CASE REPORT

In an Italian boy born in October 1970, β-thalassemia major was diagnosed at the age of 6 months. Splenectomy was performed when he was 10 years old, and sc chelation was started 2 years later. In 1987, hypogonadism was diagnosed and treated with monthly injections of testosterone. In March 1989, diabetes mellitus occurred following substitution of somatotropin (human growth hormone; Norditropin). At that time, an echocardiogram showed left ventricular enlargement; however, the shortening fraction of the left ventricle was 37 percent (normal >30) (Table 1, Fig 1A). Two months later, the patient presented with signs of myocardial insufficiency. He was started on therapy with digitalis, furosemide, and enalapril. Nevertheless, cardiac failure occurred, and the patient was referred to our hospital in November 1989.

On admission, the patient's height and weight were 2.5 SD below the mean for his age. He appeared cyanotic and perspiring, with stage 3 to 4 cardiac insufficiency according to the criteria of the New York Heart Association. Decreased heart sounds and a gallop were present, along with hepatojugular reflex; the span of the liver was 16 cm, and there was peripheral edema. The chest x-ray film showed a cardiothoracic ratio of 0.65 and pulmonary congestion. Microvoltage was noticed on the ECG; 24-h Holter monitoring revealed numerous episodes of supraventricular arrhythmias and ventricular tachycardia. The echocardiogram displayed dilatation of all cardiac cavities and severe ventricular dysfunction, with a shortening fraction of the left ventricle of 12 percent (Fig 1B). Cardiac output was estimated with the Doppler method at 1.4 L/min/m² (normal, 3.5 to 4 L/min/m²). Laboratory data revealed the following levels: hemoglobin, 138 g/L; blood glucose, 10.5 mmol/L; creatinine, 86 μmol/L; calcium, 2.32 mmol/L; ferritin, 4,875 ng/mL (normal, 13 to 230 ng/mL). Hepatic function tests showed moderately elevated serum aminotransferase activity (119 U/L) and total bilirubin concentration (24 μmol/L) but normal alkaline phosphatase level. Prothrombin time was prolonged to 16 s (normal, 11 to 13 s). A computed tomographic (CT) scan of the liver without contrast showed an elevated tissue density of 85 Hounsfield units (normal, 55 to 75 Hounsfield units).

The treatment for cardiac insufficiency was adjusted, and therapy with amiodarone was added for the management of arrhythmias. Intravenous deferoxamine methane sulfonate (Desferal) was administered continuously through an implanted catheter (Groshong Port; Cath-Tech) at a dose of 100 mg/kg/day, seven days per week. Urinary iron excretion during therapy varied widely (mean, 1.48 ± 0.9 mg/kg/day [SD]); stool iron excretion was not measured. Under this intensive medical treatment the patient's general condition improved, and he was discharged to his home after 2 months on therapy with digitalis, furosemide, enalapril, amiodarone, and insulin (0.5 U/kg/day).

<table>
<thead>
<tr>
<th>Data*</th>
<th>sc DFO</th>
<th>iv DFO</th>
<th>Normal Value (Range)†</th>
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<tr>
<td></td>
<td>3/89</td>
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<td>Mean Vcf, circumferences/s</td>
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<td>0.65</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*LADₐ, Left atrial dimension (atrial diastole); LVDₐ, left ventricular diameter (diastolic); RVDₐ, right ventricular diameter (diastolic); IVSₐ, interventricular septum (diastolic); Ao STI, aortic systolic time interval; SFLV, shortening fraction of left ventricle; and Vcf, velocity of circumferential shortening.

†Values related to body surface area according to our laboratory and Meyer.16

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Therapy with DFO was continued IV (18 g over 4.5 days every week for 16 months). This treatment was regularly followed by the patient except during vacations. The infusion was run continuously at a constant rate of 0.93 ml/h from a 100-ml cassette connected to a portable pump (Cadd 1; Pharmacia Nu Tech). The DFO was soluble in distilled water up to a concentration of 20 percent at 22°C or 37°C and was stable for 7 days. Over this period the patient was transfused with 75 units of packed red blood cells (14,250 ml or 213 ml/kg/yr) to maintain the hemoglobin concentration over 120 g/L.

Cardiac function improved after 7 months of treatment, as seen on echocardiographic assessments (Table 1). One year after regular IV chelation, therapy with diuretics, enalapril, and finally digoxin could be progressively and successfully stopped. At that time an electro-oculogram revealed a low Arden ratio of 1.6, compared to values of 1.84 to 2.15 obtained before IV chelation was begun (normal >1.8). Two electroretinograms done 3 months apart showed a lowering in the flicker response at 44 Hz (from 72μV to 45μV; normal >45μV). The patient was asymptomatic; nevertheless, the weekly dose of DFO was lowered to 50 mg/kg/day, given as a 4-day continuous IV infusion; subsequent electrophysiologic tests of visual function returned to normal.

After 17 months of IV chelation, the serum ferritin level had fallen to 1,780 ng/ml, results of hepatic function tests had normalized, and the density of the liver on CT scan had returned to a normal value (66 Hounsfield units). The echocardiogram showed improved left ventricular function, although the shortening fraction of the left ventricle remained subnormal (28 percent) (Fig 1C). Occasional arrhythmias were recorded and justified further antiarrhythmic treatment. No improvement of diabetes or growth rate were noted.

No audiologic toxic effects of DFO were observed on periodic audiograms. Unfortunately, thrombosis of the superior vena cava was diagnosed after 16 months of therapy. The catheter was pulled after successful fibrinolysis with recombinant tissue plasminogen activator (Actilase). Thereafter, DFO was continued sc, with periodic hospitalization for high-dose IV chelation.

**Discussion**

Long-term blood transfusions in patients with thalassemia suppress endogenous erythropoiesis and associated dysmorphic bone marrow expansion but are responsible for toxic iron overload. Manifestations of endocrinopathies, cirrhosis of the liver, and cardiac dysfunction occur in the first two decades, and studies in the 1970s showed that patients with thalassemia dying from heart failure most often did so in the year following the diagnosis of cardiomyopathy. Life expectancy of patients with thalassemia has improved over the past years, with a 94.4 percent survival at 15 years for patients born between 1970 and 1974. Cardiac disease remains the major cause of death (60 percent). The DFO combines with both parenchymal and reticuloendothelial iron to produce ferrioxamine, which is excreted in the urine and stool. The balance between urinary and stool iron excretion may be influenced by the iron load, by the dose and route of administration of DFO, and by the rate of erythropoiesis. Iron chelation and, more specifically, regular sc DFO therapy in compliant patients has been shown to delay the development of heart disease.

This 19-year-old patient had advanced secondary hemochromatosis with multiple organ dysfunctions. He was referred to our hospital with sudden and rapidly progressive heart failure that was probably worsened by arrhythmias. Continuous high-dose IV chelation dramatically reversed cardiac insufficiency to stage 2 in the classification of the New York Heart Association; however, arrhythmogenic areas, probably due to scars secondary to chronic iron toxicity, have developed and continued to cause ventricular tachycardia. Thus, only inotropic and diuretic medications could be stopped after 1 year of IV chelation, but antiarrhythmic therapy remained necessary. The patient's daily activities returned to normal. Results of hepatic function tests normalized after 2 months. No change in endocrine functions (diabetes or sexual hormones) were observed, in spite of the fact that a rise of testosterone level after continuous IV DFO has been reported by others. The continuous IV infusion was well tolerated by the patient.

With current reliable portable pumps, outpatient IV chelation with up to a 20 percent DFO concentration can be considered relatively safe. During DFO therapy, significant modifications in the electro-oculogram and electroretinogram were observed while the patient was asymptomatic; DFO was thought to be responsible for the retinal toxic effects, which fortunately disappeared with lower dose of DFO. Careful ophthalmologic monitoring and sensorineural hearing loss screening are mandatory in patients undergoing DFO chelation, since neurotoxic effects have been found even in patients treated with standard doses of DFO. Electrophysiologic testing should be recommended as a screening method in an attempt to detect early retinal dysfunction before decreased visual acuity, color vision abnormalities, and night blindness occur. Another com-
plication of this treatment was associated with the presence of a permanent central catheter. Superior vena caval thrombosis is a known complication of central venous catheters, since up to 40 percent of these are associated with a central vein thrombosis. In patients with thalassemia major, increased thromboxane production was recently reported. This hypercoagulable state secondary to platelet activation may represent an additional risk factor.

The development of a safe oral iron chelator has been the focus of intense investigation in the last few years. Although clinical trials have yielded encouraging results, the superiority to DFO and its lack of toxicity have not yet been demonstrated with such regimens. Ambulatory IV DFO may thus represent, for the time being, an alternative treatment to SC chelation in patients with severe iron overload. In these cases, high doses of DFO can be administered with improvement of cardiac function. Intrageneric complications of this invasive treatment may be important, but they appear to be balanced by remarkable benefits for the patients. To minimize the frequency of thrombosis associated with central catheters in this high-risk population, the routine use of platelet inhibitors or anticoagulation (or both) should be studied.

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REFERENCES

Ectopic Intrapulmonary Thyroid*

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An 83-year-old woman underwent resection of a pulmonary tumor. Histologic examination of the tumor demonstrated thyroid follicles without evidence of malignancy or teratomatous elements. Developmental anomaly may account for the ectopic intrapulmonary thyroid, which, to our knowledge, has not been reported in the literature.

(Chest 1993; 103:1278-79)

Ectopic thyroid tissue occurs mainly along the course of the thyroglossal duct. We present a case of an ectopic thyroid in the lung without evidence of a primary thyroid gland tumor. To our knowledge, this is the first report of an ectopic intrapulmonary thyroid.

CASE REPORT

An 83-year-old woman was admitted to our hospital for the evaluation of a solitary nodule in the right lung. She had no history of thyroid disease or malignancy, and the thyroid gland was not enlarged on palpation. A chest roentgenogram showed a solitary nodule in the right lower lobe of the lung (Fig 1). Comparison with a previous roentgenogram showed that the nodule had enlarged over the past two years.

The nodule was excised surgically. At operation, a 2.5×2.0×2.0-cm tumor was found lying within the lower lobe of the lung and was enclosed in a thin fibrous capsule. The cut surface had a brownish red color, resembling a normal thyroid gland.

Histologic examination showed thyroid follicles of various sizes filled with colloid (Fig 2). Psammoma bodies or papillary proliferation of the follicular epithelium was absent. The colloid was intensely stained by periodic acid-Schiff stain. The epithelium of the follicles was composed of cuboidal cells without nuclear atypia or hyperchromatism. Serial step sections failed to reveal any elements of a teratoma.

Routine immunoperoxidase staining using polyclonal antibodies against thyroglobulin and calcitonin (DAKO, Kyoto, Japan) showed a strongly positive reaction for thyroglobulin within the epithelial cells and the colloid of the follicles (Fig 3), but was negative for calcitonin.

Examination after the operation showed that hormonal blood levels were within normal limits and a radionuclide thyroid scan with technetium 99m pertechnetate was entirely normal. The postoperative course was uneventful.

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Ectopic Intrapulmonary Thyroid (Bando et al)