The Sinus Node in Chronic Granulocytic Leukemia

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A 65-year-old white man with chronic granulocytic leukemia manifested a variety of worsening atrial rhythm disturbances during his progressive clinical deterioration over a one-year period. At autopsy, leukemic infiltration involving the sinus node was evident. It is tempting to assume a cause and effect relationship from these findings. Unexplained abnormalities in cardiac rhythm in patients with leukemia should alert the clinician to the possibility of involvement of the heart by cellular infiltrate or hemorrhage. Such knowledge might help curtail the morbidity of these patients, for sometimes the arrhythmia may be amenable to local, palliative treatment.

Cardiac involvement in leukemia may be more prevalent than is apparent. Javier et al† report a 30 percent incidence of involvement of the heart in 20 of their 66 autopsied cases of leukemia. They estimate the incidence of metastases to the heart to be 29 percent based on a review of 423 cases accumulated from previous reports. Leukemic stigmata may be manifest in various ways: pericarditis, with or without effusion; congestive heart failure; myocardial infarction; and various electrocardiographic manifestations, such as premature atrial and/or ventricular beats, ST-T changes, axis deviations; and heart block. An interesting report of heart block due to involvement of the interventricular septum has been reported by Dresdale et al.1

The following report of arrhythmia in a patient with chronic granulocytic leukemia is of interest, since leukemic involvement of the sinus node was demonstrated, and this was correlated with the clinical and electrocardiographic abnormalities.

Case Report

A 65-year-old retired payroll clerk was referred by his physician to the Hematology Clinic on March 20, 1964 for evaluation of unexplained high white blood cell count (32,000/mm³). The patient complained of lack of energy for one and a half years and vague abdominal distress for about two months. He had recently lost ten pounds in weight. Past history, family history and systemic review were noncontributory.

On physical examination, the significant findings were an enlarged liver palpable three fingerbreadths below the right costal margin and a few bilateral basilar subcrepitant rales. No abnormalities were present on examination of the heart. The blood pressure was 180/80 and the pulse rate was regular at 80 per minute.

Laboratory studies showed hemoglobin 12.0 grams/100 ml, and white blood cell count 33,750/mm³. The platelet count was 317,500/mm³. A peripheral blood smear showed: 1 myeloblast, 3 promyelocytes, 8 myelocytes, 9 metamyelocytes, 12 bands, 45 segmented neutrophils, and 1 erythroblast. Red cells were normochromic and platelets were adequate. The sternal bone marrow revealed intense hypercellularity with a slightly increased M:E ratio of 4.4:1. Megakaryocytes were also increased. Chest x-ray film showed a chronic pulmonary change pronounced in both lung bases consistent with pulmonary fibrosis. The cardiovascular silhouette was within upper limits of normal.

A diagnosis of chronic granulocytic leukemia was made and the patient was treated with busulfan. Initially there was gratifying clinical response, and the busulfan was discontinued after a month. However, in July of 1964, progressive weakness and liver enlargement were noted. The hemoglobin was 11.2 grams/100 ml and the white blood cell count 60,000/mm³. Busulfan was re instituted, with resultant improvement in symptoms and decrease in the white blood cell count to 30,000/mm³ by August, 1964. An occasional premature beat was noted at this time.

Three months later further progression of the leukemic process was evidenced by a rising peripheral white blood cell count, progressive splenomegaly, and a clearly leukemic bone marrow aspirate, characterized by marked hyperplasia of myeloid elements with a maturation arrest in the progranulocyte stage. Although the heart size was normal, without signs of congestive heart failure, the cardiac rhythm was noted to be irregular with frequent premature beats.

By January, 1965, the patient had developed intractable musculoskeletal pain and further weight loss. The heart size was still normal. However, the electrocardiogram showed frequent atrial premature beats, many of them blocked, and some premature ventricular contractions with a short run of atrial tachycardia (Fig 1A).

Despite intensification of treatment, the next three months were marked by further deterioration with the onset of exertional dyspnea, profound weakness and progressive splenomegaly. Atrial rhythm disturbances were repeatedly noted. Terminally, the patient was digitalized in an attempt to control a chaotie atrial tachyarrhythmia, but he failed to show improvement (Fig 1B), and expired on April 9, 1965.

Postmortem findings were typical of chronic granulocytic leukemia. The liver and spleen were predominantly involved weighing 3340 gm and 1370 gm respectively. Microscopically, a diffuse myelocytic infiltration was present. Only the cardiac findings are described in detail. The heart weighed 460 gm. It was reddish brown in color and of firm consistency. The pericardium was normal. Considerable subepicardial fat was present. The most striking finding was the presence of numerous patchy white areas surrounded by petechial hemorrhages in the wall of the right atrium. On section, it proved to have extended through the atrial muscle. The right ventricle measured 0.7 cm and the left ventricle 1.8 cm in width. The interventricular and interatrial septa were intact. The valves were normal. No gross infarcts or scarring were evident in the myocardium. The coronary arteries

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The progressive nature of the atrial irregularities in rhythm during the last four months of illness are illustrated: (A) On January 8, atrial premature beats, some conducted, some blocked, with a short run of atrial tachycardia are noted. On February 17, the premature atrial beat superimposed on the T wave of the 3rd QRS-T complex is blocked, following which there is an atrial escape beat ("sick sinus node"). On April 7, the initial part of the tracing suggests atrial flutter with Wenkebach type of conduction followed by atrial bigeminy. (B) On February 17, a run of nodal tachycardia is seen. On March 3, there is a more orderly rhythm with few atrial prematurets. On April 7, the rhythm is chaotic (multifocal atrial tachycardia).

The microscopic findings in the heart were striking, showing heavy infiltration of the sinus node by leukemic cells (Fig 2).

Comment: This case depicts the downhill course over a year of a patient with chronic granulocytic leukemia in whom atrial arrhythmias were repeatedly documented. Serial electrocardiography showed definite progression in the atrial chaos with increase in the white blood cell count and worsening of his condition. In January, 1965, frequent atrial premature contractions with runs of atrial tachycardia were noted (Fig 1A). In February, an episode of nodal tachycardia occurred (Fig 1B). In March, the rhythm was more orderly, but terminally, in April, the rhythm was chaotic, coincident with very high peripheral leukocytes (102,000/mm³), as well as marked anemia, high fever, and infection.

DISCUSSION

Abnormal function of the heart in leukemia is not surprising considering the serious nature of the illness. Various factors, such as anemia, fever, hypoxia, electrolyte abnormalities, and the presence of coincidental heart disease may be operative. However, the incidence of leukemic infiltration of the heart is not insignificant, variously estimated to be from 34 percent to 44 percent. Recently, Javier et al noted a 30 percent incidence of cardiac involvement on autopsy of 86 patients who died from all forms of leukemia between 1934 and 1963. Only eight had gross evidence of involvement by leukemia; most often it was a microscopic finding. Pathologically, this was characterized by focal infiltrates and hemorrhages. No mention was made of sinus node infiltration.

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FIGURE 1. The progressive nature of the atrial irregularities in rhythm during the last four months of illness are illustrated: (A) On January 8, atrial premature beats, some conducted, some blocked, with a short run of atrial tachycardia are noted. On February 17, the premature atrial beat superimposed on the T wave of the 3rd QRS-T complex is blocked, following which there is an atrial escape beat ("sick sinus node"). On April 7, the initial part of the tracing suggests atrial flutter with Wenkebach type of conduction followed by atrial bigeminy. (B) On February 17, a run of nodal tachycardia is seen. On March 3, there is a more orderly rhythm with few atrial prematurets. On April 7, the rhythm is chaotic (multifocal atrial tachycardia).

FIGURE 2. In A the sinus node of the patient is outlined by four arrows. The broader portion of the node (toward the free right atrial wall) is heavily infiltrated by leukemic cells (×52). In B a higher magnification of the leukemic infiltrate of the sinus node is shown (×1275).
filtration by leukemia, as in our case. Of 119 patients with leukemia in 500 consecutive autopsies reviewed by Bisel et al, 44 percent had evidence of cardiac involvement. Seven (35 percent) of their 20 patients with chronic granulocytic leukemia had cardiac involvement. Roberts et al noted the slightly more frequent presence of hemorrhages (54 percent) than infiltrates in 420 autopsies on patients who died of acute leukemia. They noted that cardiac abnormalities were probably being overshadowed by the clinical manifestations resulting from leukemic involvement in other organs.

Sometimes the cardiac manifestations may predominate, leading to errors in diagnosis. Wintrobe and Mitchell describe two such cases. One patient was treated for "heart disease" due to paroxysmal atrial tachycardia for several months before granulocytic leukemia was diagnosed. The other was a patient diagnosed as having gallbladder and coronary disease. Only at autopsy was it realized that he had granulocytic chloroma with widespread infiltration. Of additional interest is a case reported by Wendkos of massive pericardial effusion in a patient with lymphocytic leukemia which was mistaken for tuberculous pericardial effusion.

In other instances, an abnormal electrocardiogram is the only indicator of the presence of heart disease. Aronson and Leroy in a study correlating the electrocardiogram with clinical and autopsy findings in eight patients with leukemia, noted several electrocardiographic abnormalities, including sinus tachycardia, axis deviation, premature beats and heart block.

In the present report, the only evidence of cardiac involvement was repeated atrial arrhythmias, progressively worsening with the disease. That these were due to a "sick sinus node" is suggested by the autopsy findings of a marked infiltration of the sinus node by leukemic cells. This knowledge can be of more than theoretic interest because disturbing symptoms due to cardiac arrhythmias may sometimes be amenable to local treatment such as radiotherapy.

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Hypocalcemia, Hypomagnesemia and Hypokalemia during Chemotherapy of Pulmonary Tuberculosis*

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Marked hypocalcemia hypomagnesemia, tetany, hypokalemia alkalosis and hypophosphatemia developed during conventional dose viomycin-pyrazinamide treatment of pulmonary tuberculosis in a middle-aged man. Recovery of renal potassium conservation required nine weeks, but serum calcium and magnesium normalized after three weeks of replacement therapy.

A patient without clinical evidence of liver disease or malabsorption developed profound hypocalcemia, hypomagnesemia, tetany and hypokalemia during conventional dose antituberculosis treatment with viomycin and pyrazinamide (ZPA).

CASE REPORT

This 58-year-old man presented with cough and weakness of ten days' duration. Twenty years prior to admission the patient developed right upper lobe pulmonary tuberculosis which was treated with right phrenic nerve crush and a ten-month course of intramuscular streptomycin. Fifteen years prior to admission cavitation was noted in the involved lobe and the patient underwent right upper lobectomy followed by a year's course of isoniazid (INH) and para-aminosalicylic acid (PAS). He was followed regularly in a chest clinic.

One month before admission the patient developed symptoms of an upper respiratory infection and ten days before admission he noted shortness of breath, weakness, anorexia and some nausea and vomiting.

The patient had a 15-year history of rheumatoid arthritis which had required joint surgery. He admitted consuming a half-pint of vodka weekly.

On physical examination the patient was a thin white man who appeared chronically ill. His blood pressure was 100/70 mm Hg, heart rate 100 per minute and regular, respiratory rate 20 per minute and oral temperature 99.6°F. Skin turgor

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