CHILDHOOD LEUKEMIC HEART DISEASE

A Study of 116 Hearts of Children Dying of Leukemia

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SUMMARY

One hundred sixteen hearts of children dying with leukemia during the 5-year period of 1962 to 1967 were examined at necropsy. Forty-four per cent of the patients had at least one focus of leukemic infiltration, a slightly higher incidence than previously reported. The evidence suggests that peripheral leukocyte count, type of leukemia, and length of survival are factors that influence cardiac infiltration. Increased survival time due to improved therapy may explain the increase in percentage of hearts with leukemic infiltration. Electrocardiographic patterns, in general, were found, as previously reported, to be nonspecific for leukemic myocardial infiltration.

Cardiac hypertrophy of significant degree was found in 33 of 99 hearts evaluated for this aspect. Anemia, intrinsic to leukemia, is proposed as the principal factor responsible for this hypertrophy inasmuch as all possible alternate mechanisms were excluded and since previous clinical as well as experimental animal studies clearly have shown that chronic anemia frequently results in cardiac hypertrophy regardless of the etiology of the anemia.

Additional Indexing Words:
Cardiac hypertrophy
Anemia

CARDIAC INFILTRATION by tumor cells in children with leukemia may be masked by the myriad manifestations of the disease and is usually an incidental autopsy discovery. Several pathological studies of heart disease secondary to leukemia in adults have been reported. Leukemic infiltration of the heart was observed in 34% of 123 cases in one series and in 30% of 66 cases in another, but only 20 patients in the former group and 1 patient in the latter group were under 20 years of age at death. An autopsy survey extending over 11 years (1954 through 1964) by Roberts and his associates included approximately 240 patients with acute leukemia who succumbed before their twentieth birthdays, and 180 who were older than 20 years of age. However, no distinction was made between findings of the children in the group and those in the adults, although the response to therapy for malignancy in adults varies from the response observed in children suffering from the same neoplasm, and consequently the course of disease in adults with leukemia differs from that of children. In addition to these differences, recent therapeutic advances have markedly altered the natural history of the disease and extended the survival time of children with leukemia.

Several children with leukemia in this institution manifested signs and symptoms of cardiac complications. Postmortem findings in

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some of these children were noted to be at variance with reports in the few recorded series. Because of this, a survey was made of the clinical and pathological aspects of cardiac involvement of all children with leukemia who were autopsied at this hospital during a 5-year period (1962-1967) to determine (1) the incidence of cardiac leukemic infiltration; (2) the incidence of cardiac hypertrophy; and (3) the correlation of macroscopic and microscopic findings with clinical features such as anemia, peripheral leukocyte counts, duration of disease, and type of leukemia.

Case Material

One hundred sixteen hearts of children with leukemia who were necropsied between June 14, 1962, and March 2, 1967, were reviewed. All except two patients had received antileukemic treatment. Their ages ranged from 6 months to 18 years. Sixty-nine were male and 47 were female. There were three cases of chronic myelocytic leukemia; all others were acute leukemias. The latter included 14 patients with lymphosarcoma whose disease converted to acute lymphocytic leukemia. These were classified as acute lymphocytic leukemia. Classification of the various types is shown in Table 1.

Clinical Data

Analysis of recorded hemoglobin concentrations revealed that 66 patients had a nadir hemoglobin below 7.0% sometime during the 6-month period before death, and 39 patients had hemoglobin values below 7.0% in the period extending from 4 weeks to 1 week ante mortem; 35 had this value during the last week of life. A similar analysis of the highest peripheral leukocyte counts showed that 19 patients had a count of 100,000 cells/mm³ or greater during the period extending from 6 months to 4 weeks ante mortem and 31 had such counts during the terminal month of life.

Thirty-two patients had clinical evidence of congestive heart failure. Sixteen were noted to have had precordial systolic murmurs characteristic of anemia. Eight-five patients had one or more electrocardiograms (ECG). Electrocardiographic changes occurring with electrolyte imbalance, digitalization, and pleuroperticarditis were not included in the analysis. Forty-three of the 85 patients had electrocardiographic changes that showed mainly nonspecific changes (T-wave flattening in the limb leads and left precordial leads, ST-segment changes) with the exception of 18 tracings that satisfied the diagnostic criteria for left ventricular hypertrophy and

two patients who had changes compatible with anterolateral myocardial injury (fig. 1).

Further clinical correlations are precluded because cardiac complications, such as congestive heart failure, were noted terminally when the patients were toxic (many had terminal sepsis) and were without immunological defense. To relate, therefore, the cardiovascular manifestations to a single factor, such as anemia or leukemic myocardial infiltration, would be an oversimplification.

Pathologic Findings

Postmortem examination of the hearts revealed the principal macroscopic changes to be cardiomegaly, pericardial effusion, and myocardial hemorrhages. The hearts were weighed after having been opened and emptied of blood. The presence or absence of enlargement (hypertrophy) was determined according to weight. Seventeen cases were not included in this particular evaluation because of insufficient data, such as weight having been obtained without first opening the heart or because of the presence of presumably unrelated disease such as endocardial fibroelastosis. Analysis of gross heart weights showed that 33 of 99 examined had weights

Figure 1

Electrocardiogram of a 14-year-old boy with terminal leukemia who had severe chest pain 24 hours before death. ST-segment elevation is apparent in leads I, aVL, and V₅ through V₆ and ST depression is present in leads III, aVR, and V₁.
greater than 2 standard deviations above the mean according to the tables of normal heart weights of children presented by Schulz and Giordano.8 Pericardial fluid of 15 or more milliliters was found in 19 cases (16%). One patient (with multiple myocardial hemorrhages) had a pericardial effusion of 150 ml and 2 additional patients had effusions of 100 ml. Hemorrhage, usually subepicardial or subendocardial, was noted in 19 cases.

In all patients a single section extending from the endocardium to the epicardium was taken routinely through the posterior wall including the left ventricle, an area of the lower left atrium, and the mitral valve. Other histologic sections were taken from areas in which there were significant gross findings. Principal histologic changes consisted of myocardial leukemic infiltration, myofiber damage of varying severity, and intramyocardial hemorrhages. The areas involved and the type of damage by leukemic infiltration are indicated in table 1. Infiltration, in most cases, involved multiple areas and was minimal to moderate. Dense infiltration was found in only three cases with visceral pericardial involvement and two patients had extensive endocardial penetration. The parietal pericardium was not included in this survey since it is not an intrinsic component of the heart. Some infiltration was present in 51 cases (44%) in the visceral pericardium, myocardium, or endocardium. A significantly higher incidence of cardiac infiltration was found in acute myelocytic leukemia than in acute lymphocytic leukemia \( (P < 0.05) \). This difference was manifested as myocardial infiltration rather than pericardial or endocardial infiltration.

Multiple myocardial hemorrhagic infarctions were noted in one patient who had acute myelocytic leukemia (fig. 2). These were secondary to leukemic plugging of the intramyocardial vessels as well as to subendothelial and perivascular leukemic infiltration (fig. 3). Extensive infiltration of the subendocardial conduction system was found in a case of erythroleukemia. Generalized subendocardial involvement, including the valves, was present in a case of acute monomyelocytic leukemia.

Damage to myofibers was evident histologically in 17 cases (15%). This damage included shrinkage, pyknosis, and loss of myofiber nuclei in addition to shrinkage and vacuolization of myofibers. One patient with acute lymphocytic leukemia was thought to have had cardiac infiltration clinically and was given radiation to the heart area. Microscopic examination at necropsy revealed shrinkage and loss of many myocardial fibers (fig. 4). One patient with acute lymphocytic leukemia who had clinical evidence of heart failure had myofiber atrophy, slight pericardial infiltration, and endocardial fibroelastosis.

**Clinicopathological Correlations**

Figures 5 and 6 show the relation between the highest recorded peripheral leukocyte counts and the incidence of cardiac leukemic infiltration. Figure 5 shows the distribution of the highest...
leukocyte count in the period extending from 4 weeks to 1 week ante mortem in patients in whom cardiac infiltration was found at necropsy as compared to those in whom no cardiac infiltration was noted. Of those patients without cardiac infiltration, 55% had a peripheral leukocyte count of less than 10,000/mm³ during this time. However, 30% of those with cardiac infiltration also had similar peripheral blood findings at this time. Furthermore, no essential difference between presence or absence of heart infiltration occurred in patients with peripheral blood leukocyte cell counts up to 50,000/mm³ during this period. The significant increase in cardiac infiltration correlated with a peripheral leukocyte count of 50,000/mm³ or greater during the final month of life (P < 0.05). No difference was found between patients with peripheral counts between 50,000 and 100,000 cells/mm³ and those with counts greater than this. During the last week of life the significant increase in cardiac infiltration occurred when the peripheral leukocyte count was greater than 100,000 cells/mm³ (P < 0.01).

Of 33 patients with cardiac hypertrophy, 31 had hemoglobin values available for analysis. Of these 31, one patient survived only 1 week after the diagnosis of leukemia was established, but the nadir hemoglobin was below 7 g%. Three of the 31 lived from 1 to 5 weeks after diagnosis and two of these three were found to have had at least one hemoglobin level below 7 g% during this period. The remaining 27 patients lived from 6 weeks to 4 years after diagnosis; 25 of these were found to have had one or more hemoglobin levels less than 7 g% during the period extending from 6 months to 4 weeks ante mortem and 16 of these 25 also had had hemoglobin levels less than 7 g% during the last 4 weeks of life.

Discussion

The 44% incidence of myocardial leukemic infiltration in this series is greater than the
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34% reported by Kirshbaum and Preuss in 1943 and the reported 37% by Roberts and associates in 1968. The latter series extended over the 11-year period, 1954 through 1964. It is probable that the progressive increase in mean survival time of patients with acute leukemia, through improved antileukemic therapy, accounts for the progressively greater incidence of leukemic infiltration noted in various organ systems in the more recent reports. Therefore, it is not surprising that this also holds true for the increasing incidence of cardiac leukemic involvement.

Roberts and co-workers did not describe any difference in percentage of cardiac infiltration between lymphocytic and myelocytic leukemia although variation in patterns, as well as incidence of infiltration of various organ systems by different types of leukemia, regularly occur. For example, acute lymphocytic leukemia more frequently involves the gastrointestinal tract but is limited to the mucosal and submucosal areas without infiltration of the muscularis, a feature not shared by acute myelocytic leukemia. It has been reported that monocytic and acute lymphocytic leukemias more commonly involve the pulmonary parenchyma than does the acute myelocytic type. Infiltration of the larynx has been shown to occur more extensively in acute myelo-locytic than in acute lymphocytic leukemia.

Leukemic cellular involvement of the heart has been described as occurring often, particularly in stem-cell and acute leukemia, and Saphir stated that infiltration of the myocardium occurs more frequently with myelocytic than with lymphocytic leukemia. The higher incidence of infiltration in patients with acute myelocytic as compared with acute lymphocytic leukemia in the present series is readily apparent from the data presented in table 1.

As observed by Bierman and associates, a direct relation should be expected between the number of circulating leukemic cells and the extent of leukemic involvement of body tissues. Such a relation has been clearly established as the mechanism of cerebral hemorrhage in which there is elevation of circulating leukemic cells during the so-called "blast crisis." Although the onset of leukemic infiltration of the heart is necessarily unknown until clinical complications occur or necropsy is performed, the presence or absence of cardiac infiltration by leukemic cells is directly related to the level of circulating leukemic cells, as demonstrated in figures 6 and 7. It is apparent from the findings in this study that the type of leukemia and the level of circulating leukemic cells are both important determinants of leukemic cardiac involvement, and there is a greater likelihood of multiple episodes of abnormally high counts of circulating leukemic cells occurring as survival time increases. Hence, a third factor, time, influences the incidence, but not necessarily the extent of cardiac infiltration. Of the three factors, cell type, cell count, and survival time, that influence cardiac infiltration, the last factor may have more bearing upon percentage of hearts with involvement than in influencing the extent of cardiac involvement in a particular case. For example, extensive cardiac leukemic infiltration can be observed in patients who have had a disease of short clinical duration.

Survival time is also probably an important determinant of the cardiac effect due to anemia because the duration of anemia is also roughly proportional to survival time. Cardiac hypertrophy has been produced in rats and

Figure 6

Comparison of leukocyte counts with respect to infiltration in the week prior to death.

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Survival time is also probably an important determinant of the cardiac effect due to anemia because the duration of anemia is also roughly proportional to survival time. Cardiac hypertrophy has been produced in rats and
dogs by experimentally induced anemia.\textsuperscript{15, 16} Hemoglobin levels below 8 g\% and of 3 months' duration produce cardiac hypertrophy in man as a direct result of anemia per se, and this effect is not related to age, sex, or etiology of the anemia.\textsuperscript{17} However, cardiac hypertrophy was not found to be a significant feature in one reported necropsy series of leukemia,\textsuperscript{5} and the authors indicated that cardiac hypertrophy, had not, to their knowledge, been reported in patients with acute leukemia in the absence of underlying heart disease. It is well known that anemia is a recurrent problem in acute leukemia, so that if anemia can result in cardiac hypertrophy, as has been reported in experimental animals, as well as in man, at least some patients with acute leukemia might be expected to demonstrate cardiac hypertrophy. One third of the hearts evaluated in this series had weights greater than 2 standard deviations above the mean weight for their age. This indicates that a significant percentage of our patients did have cardiac hypertrophy which most likely is attributable to anemia associated with their leukemia. Steroid therapy has been considered by Amromin\textsuperscript{18} in the genesis of cardiac hypertrophy. However, its role, in this series, is not completely understood in the absence of elevated blood pressures.

Extensive myocardial interstitial infiltration, suspected clinically in a few cases, very probably was the cause of myocardial fibrosis with the observed loss of muscle fibers. Intramural cardiac hemorrhages, secondary to clotting defects including thrombocytopenia, most frequently observed beneath the endocardium of the left ventricle, cannot be excluded as contributing to permanent myocardial morphological changes in some instances, and it is also conceivable that some myocardial damage may be related to the end-arterial plugging in consumptive coagulopathy, a phenomenon observed in leukemia. Other factors to be considered are radiation to the heart\textsuperscript{19, 20} and antileukemic chemotherapy, although the exact role of these agents in this series is unknown.

Myocardial damage of sufficient severity to be apparent by light microscopy, for example, fibrosis and subsequent ischemic conditions, may all be assumed to be contributory factors to cardiac dilatation and hypertrophy with the consequent reduction of cardiac reserve, setting the stage for potential cardiac failure. Extensive myocardial infiltration will, at least temporarily, cause an increase in heart size. Hypervolemia, incidental to intravenous fluids, has also been suggested as a cause of cardiac dilatation by Roberts and associates.\textsuperscript{5} Other factors to be considered are the nutritional status and serum electrolyte status of the terminal patients.

Electrocardiographic (ECG) findings vary widely in patients with leukemia,\textsuperscript{21} and our observations confirm this. Electrocardiographic findings are related to the particular cardiac complications of the disease (infiltration and anemia) or to aspects of treatment (digitalis, electrolyte imbalance). Cardiac hypertrophy, documented in a significant number of the cases in this study, was reflected by confirmatory ECG changes. Evaluation of the ECG may be helpful in locating areas of extensive intramyocardial hemorrhage or infiltration if these factors produce ischemia, injury, or death of myofibers, and the changes observed are then similar to those observed in acute myocardial infarction.

It has been noted for a long period of time that severely anemic patients had ECGs that showed markedly increased QRS voltage, particularly in the precordial leads. It has been shown subsequently by Hugenholtz and associates\textsuperscript{22} that anemia is associated with increased precordial voltage. This increase in precordial voltage has been related to the decreased specific resistivity of anemic intracardiac blood, an effect originally described by Brody.\textsuperscript{23} Therefore, increased QRS voltage suggesting ventricular hypertrophy in patients with leukemia may be related to the anemia per se rather than to ventricular hypertrophy or may be related to both.

References

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