major problems in CHILDHOOD CANCER

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MAJOR PROBLEMS IN CHILDHOOD CANCER

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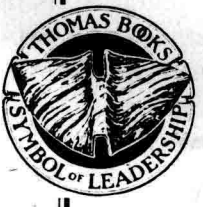

CHARLES C THOMAS · PUBLISHER
Springfield · Illinois · U.S.A.

Published and Distributed Throughout the World by
CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

ISBN 0-398-02713-7
Library of Congress Catalog Card Number: 72-88466

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Printed in the United States of America
N-1

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FOREWORD

ONE OUT OF EVERY SIX DEATHS in children under the age of fourteen years is due to cancer. Malignancy is *the* leading cause of death from disease in the childhood years. As the practicing pediatrician or general physician finds more and more of infectious disease states yielding to immunization procedures or antimicrobial therapy, the early diagnosis of malignancy becomes a relatively more frequent problem than it has in the past. Accordingly, he must become more sensitive to the great variety of clinical expressions of cancer in the younger individual.

Only a few short years ago, the practicing physician usually deliberately chose to avoid this area of medicine. The outlook for children with cancer was almost uniformly hopeless and the physician found that his involvement with these pathetic patients was so depressing that he was only too glad to refer their total care to the hematologist or oncologist at the nearest medical center. Care was frequently fragmented between the surgeon, radiotherapist and hematologist with no one formulating an organized plan of care or maintaining communication with the primary physician. The latter frequently lost track of the patient or when the family did turn to him for advice or counsel, he was unaware of the current status of the patient or his therapy.

New drugs, new approaches and the combination of various modalities of therapy have led to a marked improvement in the prognosis in a number of types of childhood malignancies. This improvement, in many cases, is predicated on the close cooperation between the hematologist-oncologist, the radiotherapist and the surgeon. The participation of the primary physician in this cooperative effort becomes increasingly important. Not only may he be called upon to administer various aspects of the patients' chemotherapy and to recognize possible side effects, but he must

also be able to communicate with the family, discussing the child's condition, care and prognosis, as well as providing the personal support so important for any family faced with a catastrophic illness.

Close participation of the pediatrician or generalist in the care of these children necessitates a fairly comprehensive knowledge of current techniques in the diagnosis, therapy and prognosis of the various types of malignancies. Unfortunately, this information is not readily available; many of the current texts are outdated, and review articles are scattered throughout the medical literature. Drs. Pochedly and Necheles have gathered together contfibutions from a number of clinicians active in this field into a monograph which encompasses the more common forms of childhood cancer. Included is a review of immunotherapy which, although without immediate clinical utility, may well represent the most dramatic prospect for the eventual control of cancer.

For most affected children, cancer is still a fatal disease. However, the increasing numbers of children with acute leukemia, Hodgkin's disease, or Wilms' tumor who survive for five years or longer with no evidence of disease provide the basis for realistic hope for the eventual control of most varieties of malignant disease. Even now, the application of present knowledge in this field can improve the life of practically every patient.

SYDNEY S. GELLIS

PREFACE

KNOWLEDGE IN THE FIELD of childhood cancer has grown at an ever-increasing rate in the past twenty years. The impetus has been successful therapy, with surgery, x-ray therapy and chemotherapy. Progress in many other areas of pediatrics has kept pace and has enabled the pediatrician to build a meaningful interest in the child with cancer and to participate importantly in therapy.

The material contained in the various chapters was selected on the basis of its clinical relevance and its value to the practitioner. The chapters are clinically oriented and are not intended to be comprehensive reviews of the topics discussed.

The editors are very grateful to the many contributors for their diligence in preparing the various chapters and for meeting a reasonable time schedule. The editors are also grateful to Dr. Guilio D'Angio, of Memorial Hospital for Cancer and Allied Diseases, for reviewing the chapter on Wilms' tumor, and to Dr. E. Omer Burgert, of Mayo Clinic, for reviewing the chapter on bone tumors.

CARL POCHEDLY
THOMAS F. NECHELES

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Chapter 1

ACUTE LEUKEMIA

JANET CUTTNER

ACUTE LEUKEMIA is the commonest of the childhood malignancies, accounting for approximately 50 percent of the deaths from childhood cancer in the United States from 1950 to 1959.[1] This is a disease of unknown etiology characterized by infiltration of primitive white cells, mainly blasts, into the marrow and peripheral blood. It generally terminates months to years after onset with the death of the child. In the past two decades important gains, attributable to intensive research in many different disciplines, have brought about an increase in the survival time of afflicted children. Considerable progress has been made in the field of chemotherapy, but the disease remains fatal in the great majority of affected children. Of prime importance in helping to extend the life span of leukemic children is the necessity of recognizing complications early so that supportive care can be given.

ETIOLOGY

The etiology of leukemia is unknown. Many investigators believe that this disease is caused by an infectious agent. There have been several reports of so-called leukemic clusters, in which an unusually high incidence of leukemia has been reported within a relatively small area.[2,3] Of those who consider an infectious etiology for leukemia, most believe the infectious agent to be a virus. There are diseases in chickens, mice and cats which resemble the human leukemias and which are definitely known to be caused by viruses.[4-6]

Note: This study was aided in part by United States Public Health Service Grants number CA 04457, CA 08866 and CA 11816 from the National Cancer Institute and from the Albert A. List, Frederick Machlin and Anna Ruth Lowenberg funds.

Electron microscopic studies on human acute leukemia patients have been reported to show virus-like particles similar to those found to induce the animal leukemias.[7] There are other factors which may point to a viral etiology: one is the presence of the Australia antigen and another is the finding of RNA-dependent DNA polymerases. The Australian antigen, which originally was found in the blood of an Australian patient with hepatitis, has also been found in many patients with acute leukemia. The Australian antigen has also been found in patients with Down's syndrome in which there is an increased incidence of both leukemia and hepatitis.[8,9] More recently Temin[10] and Baltimore[11] reported an RNA-dependent DNA polymerase in several RNA oncogenic viruses. In addition, an RNA-dependent polymerase analogous to that of RNA tumor viruses was found in the lymphoblasts of patients with acute lymphocytic leukemia.[12] RNA-dependent DNA polymerases have subsequently been found in the blood of patients with acute myelocytic leukemia.[13] It remains to be determined whether this enzyme is of viral origin.

The relationship of genetics to leukemia is uncertain. Families have been reported in which there appears to be an unusually high incidence of leukemia and lymphoma.[14-16] Chromosome abnormalities have been reported in several cases of acute leukemia.[17,18] However there is doubt as to their etiological significance. The only consistent chromosome abnormality is that of trisomy[21] found in Down's syndrome.[19,20] These children definitely have an increased incidence of acute leukemia. Bloom's syndrome, which is inherited through an autosomal recessive gene, shows an increased susceptibility to acute leukemia.[21] The apparent association of acute leukemia with a variety of chromosomal disorders suggests that genetic mechanisms may form part of the causal chain of leukemogenesis in a small proportion of cases.[22] Ionizing radiation is known to be associated with both an increased incidence of leukemia and an increase in chromosome breaks.[23,24] It may well be that in order for leukemia to be expressed several etiologic factors have to be present. Thus, certain children may have inherited, or acquired through exposure to radiation, an increased susceptibility to a leukemogenic virus. In

one study the association of four factors was noted: mother's irradiation before conception, *in utero* irradiation of the child, previous history of reproductive wastage and the occurrence of viral disease in children less than four years of age. They found that any one of these factors alone was not associated with an increased incidence of leukemia but that the association of three of the four factors resulted in an increased incidence of leukemia.[25]

SYMPTOMS

The commonest symptoms observed in a leukemic child are those related to infection or bleeding. A persistent or recurrent fever with infection is often the reason the mother brings her child to the physician. The mother may observe that her child appears unusually tired. She may note that her child has developed many ecchymoses which cannot be accounted for by trauma. Joint pains resembling those seen in acute rheumatic fever can occasionally be a presenting symptom. Headache, nausea and vomiting are often present when there is involvement of the central nervous system. Proptosis can be seen as the presenting symptom in children with acute myeloblastic leukemia who initially have localized involvement, a so-called chloroma.

PHYSICAL FINDINGS

Upon examination, pallor especially of the mucous membranes is apparent. Scattered petechiae and ecchymoses are evidence of easy bruisability. Generalized lymphadenopathy varying from pea size to several centimeters in diameter frequently are found. Bone tenderness may be present. The child may develop respiratory stridor due to greatly enlarged cervical and mediastinal lymph nodes.[26] The liver and spleen are usually enlarged. Gingival hypertrophy is unusual in children but it is seen in monomyeloblastic leukemia. Cranial nerve paralysis may be seen in children with central nervous system involvement. Enlargement of the testicles may also be present.

LABORATORY FINDINGS

The diagnosis of acute leukemia usually is easily made after a complete blood count and bone marrow examination. One finds

evidence of anemia in the low hemoglobin, red cell count and hematocrit. The platelet count is usually low and the white blood count may be decreased, normal or elevated. The diagnosis is made on the stained peripheral blood smear and bone marrow examination by the presence of large numbers of blasts. In children the commonest type of leukemia is acute lymphoblastic leukemia, where mainly lymphoblasts and lymphocytes are found in the marrow and the peripheral blood. The other type of leukemia which is seen, though not nearly as frequently, is acute myeloblastic leukemia. Here one sees predominantly myeloblasts and promyelocytes in the peripheral blood and bone marrow. Some of the myeloblasts contain bright red rods (Auer rods) in their cytoplasm, which are diagnostic of acute myeloblastic leukemia. Even less common are acute progranulocytic leukemia, acute monocytic leukemia and erythroleukemia.

Hyperuricemia is seen very frequently and is associated with either an elevated white blood count or hepatosplenomegaly, or both, with a concomittant increase in purine catabolism.[27] Since uric acid is the end product of nucleoprotein degradation, large quantities may be produced and may lead to uric acid nephropathy. This is especially likely to occur when the child is undergoing chemotherapy because of the great increase in cell catabolism. This danger has virtually been eliminated through the prophylactic use of allopurinol (Zyloprim®), a xanthine oxidase inhibitor which interferes with the final conversion of oxypurine by effectively blocking the conversion of hypoxanthine and xanthine to uric acid.[28]

Hypercalcemia is an uncommon complication. It is usually associated with roentgenographic evidence of bone disease.[29] Most often this complication appears coincidently with bone marrow relapse but has occasionally preceded actual bone marrow relapse by a few weeks. The hypercalcemia responds to the treatment of the leukemia; however, temporary alleviation of symptoms may also be obtained by the administration of corticosteroids or sodium sulfate.

Serum muramidase (lysozyme) is a hydrolytic enzyme commonly found in the lysosomes of granulocytes and monocytes. Its

chief value lies in the differentiation of acute lymphocytic leukemia from acute myelocytic leukemia and acute monomyelocytic leukemia. There have been many papers corroborating the fact that the serum muramidase is elevated consistently in acute monocytic leukemia, acute monomyelocytic leukemia and many cases of acute myelocytic leukemia.[30,31] In acute lymphocytic leukemia the serum muramidase level has been found to be normal or low. It may prove of value in following patients with monomyelocytic leukemia as there is evidence that the serum muramidase will rise before there is evidence of peripheral blood relapse.[32]

It is well known that children with chronic myelogenous leukemia have a very elevated *fetal hemoglobin*.[33] The reason for this elevation is unknown. Perhaps this is an abortive effort to respond to the anemia or represents dyserythropoiesis secondary to the leukemic process. Elevated fetal hemoglobin levels have also been found in children with acute leukemia.[34]

Disseminated intravascular coagulation may play an important role in the bleeding diathesis which many of these patients have.[35] Coagulation studies will usually show a hypofibrinogenemia, a prolonged prothrombin time, prolonged partial thromboplastin time, and thrombocytopenia. The most definitive test is the finding of fibrin split-products in the patient's blood. Intravenous heparin administration has proved helpful for the immediate treatment of defibrination, however, one must also treat the underlying cause, namely the leukemia.

Immunoglobulin levels performed at the time of diagnosis of children with leukemia have been found to be within normal limits.[36] After the institution of chemotherapy, however, a temporary decrease in IgG levels has been noted. With each change in chemotherapy there has been a greater reduction in IgG levels with a gradual return to normal values. A significantly greater depression was found in those patients who were no longer able to respond to therapy There have been a few case reports of children with acute leukemia who develop a monoclonal spike in the serum protein electrophoresis.[37-39] In most of these cases the abnormal immunoglobulin has been IgG. We observed a child of seven years of age with acute lymphoblastic leukemia who was found to

have a monoclonal gammapathy due to IgG (Fig. 1-1). He was in remission for eighteen months when first studied because of frequent infections. When he relapsed several months later the IgG spike disappeared.

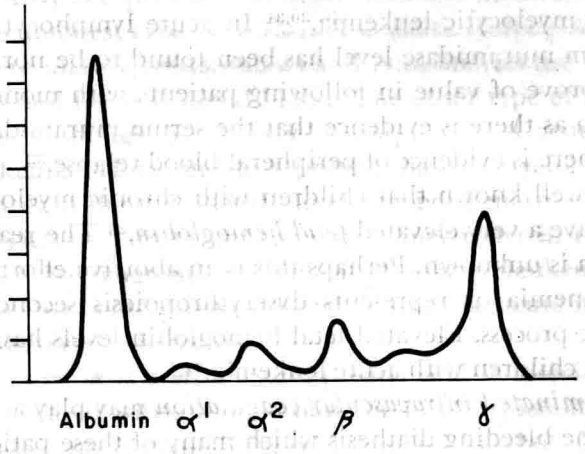

Figure 1-1. Serum protein electrophoresis showing an M spike in the region of gamma-globulin. Immunoelectrophoresis showed this to consist of IgG, type kappa.

COMPLICATIONS

Infection is the chief fatal complication in patients with acute leukemia, presumably due to the absolute granulocytopenia and lymphopenia which these patients have.[40,41] The incidence of infections can be correlated with the degree of granulocytopenia. The critical level of granulocytopenia is 1,500/mm^3. Above this level there is no further decrease in the incidence of infection.[42] At any given level of granulocyte count and lymphocyte count, the frequency of infectious episodes is greater during relapse than with the same count during remission. There is evidence that circulating granulocytes are functionally impaired, since the leukocytes of children with acute leukemia have decreased bacteriocidal activity.[43] It has also been shown that granulocytes from patients with acute leukemia are not mobilized well.[44]