Hematology

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Etiology and pathogenesis

Chronic myelogenous leukemia and related myeloproliferative entities are regarded as neoplastic diseases [4]. Many of the morphologic stigmata of neoplasia arising from other tissues occur in CML [4]: immature and abnormal cells varying in size and shape, with large nuclei, prominent nucleoli, an increased number of mitotic figures. and chromosomes anomalies. Abnormalities can be demonstrated that involve nucleoli, nucleosomes, Golgi bodies. endoplasmic reticulum, and mitochondria [5]. In CML, about 90 percent of patients have a unique abnormality, the Ph' (Philadelphia) chromosome in which part of the long arm of chromosome 22 has been translocated, usually to chromosome 9 (see below).

Clues to the etiology of CML are not evident in most patients, although antecedent causes have been identified [6]. These relate to the virtually pathognomonic Ph' chromosome, which may be produced by irradiation and possibly other agents which damage hemopoietic cells [4,7]. When multiple leukemogenic factors operate, each one may potentiate the risk of all the others [8]. Evidence indicates that CML develops with or following the appearance in the marrow of an abnormal stem cell from which a new clone proliferates. The latter has selective growth advantages and in the course of time, after many cell generations, suppresses or replaces normal marrow progenitors.

RADIATION LEUKEMOGENESIS

The acute inflammatory effect of irradiation on the conjunctiva and skin was recognized within a few months after W. K. von Rontgen discovered x-rays in November 1895 and the more chronic. destructive effect of x-rays and radium on blood cells and their precursors in humans was well documented during the first decade of this century [9,10]. Early hematologic changes appeared to be reversible. but after a certain amount of exposure, they became permanent.

Reports of leukemia developing in physicians and others who had been exposed to radiation for some period appeared. and then large-scale surveys showed that the overall incidence of leukemia in physicians was 1.7 times that of the general population [11]. This increase was the result of a high rate among radiologists, in whom the incidence of leukemia was 9 times that of other practitioners [12–14]. In physicians, the excessive mortality from leukemia occurred within the first 5 years of their exposure to radiation [15]. The incidence of leukemia among radiologists has fallen in recent years coincident with the use of better-shielded radiation apparatus and the more systematic use of monitoring devices (4.14).

The exposure of Japanese in Hiroshima and Nagasaki to the atomic bomb explosions in 1945 provided a unique demonstration of the leukemogenic effects of a single dose of radiation [16–20] After a latent period of about 3 years the annual incidence of leukemia in the survivors gradually increased to a maximum some 7 years after the explosion and then began to tall. Fourteen years after the explosion. the rate still exceeded the national average. The risk for those nearest the hypocenter, who received the greatest irradiation, was about 50 times that of persons who were in the nonirradiated periphery [18,19]. For a high-level single-dose exposure. the increased incidence of leukemia was approximately linear with dose, but the effect of smaller amounts of irradiation was less predictable [20]. In almost all instances the leukemia was acute or chronic myelogenous or an atypical variant, such as myelofibrosis, the types prone to occur in the Japanese people. The incidence of leukemia in the offspring of persons exposed to atomic bomb irradiation was not increased [21], and there was no demonstrable increase in mutation rate [22].

The leukemogenic effects of therapeutic irradiation in humans have been documented most clearly by careful studies of a large group of patients with ankylosing spondylitis treated by radiotherapy in Great Britain [23–25]. After a latent period, which again averaged about 6 years, the incidence of leukemia increased to become nearly 13 times that of the general population. The leukemia was chronic myelogenous in almost every instance. While the incidence of leukemia may be slightlv increased in ankylosing spondylitis itself, the exposure to radiation seemed to be the factor of major importance [26,27]. The risks of radiation therapy given for thymic enlargement in infancy [28–30], chronic infections [4,31], and carcinomas [4,32]; of ^{131}I administration for hyperthyroidism [33]; and of diagnostic x-ray procedures during pregnancy [34,35] are less but statistically significant [4].

An increased incidence of leukemia following irradiation has been observed in many animal species [36–39], including rodents, beagles, and miniature swine. but its pathogenesis has been studied in greatest detail in mice. In certain strains, leukemia is increased from 7 to as much as 30 percent by irradiation. Irradiation leukemogenesis in mice involves many modifying factors, such as direct and indirect cellular effects, the kinetics ot cell division. organ specificity, hormone influences, and the activation of occult viral infection. all of which have been reviewed extensively [4,40–42].

CHEMICAL LEUKEMOCENS

Despite the scientific importance of ionizing radiation as an etiologic factor in CML. not more than 1 person in 15 or 20 who develop the disease has had unusual exposure to any form of radiation or to the solvents. drugs. and chemicals discussed below. Identification of chemical leukemogens has been difficult, since our society offers a plethora of candidates. Any chemical capable of damaging hemopoietic stem cells is potentially leukemogenic.

The only chemical that has been clearly identified as one that increases the incidence of myelogenous leukemia in humans is benzene in heaw occupational exposure [43–45]. The development of mvelogenous leu-

kemias [45] and persistent chromosome abnormalities in exposed persons known to have had neutropenia [46] is especially significant The leukemogenic importance of other widely dismbuted chemicals, such as sedatives, solvents, antibiotics. analgesics. and insecticides, that mav produce adverse hemopoietic reactions is still uncertain.

CYTOGENETICS

Improved methods for studying human metaphase cells [47] have led to remarkable advances in knowledge of chromosome abnormalities in the leukemias. Short-term culture of marrow cells with colchicine treatment showed that aneuploidy and morphologic abnormalities of chromosomes occurred in some patients with acute leukemia [47,48]. The application of this method to blood leukocytes led to the recognition of the minute abnormal Ph¹ chromsome. which had been overiooked earlier in preparations made from cultured marrow [49–531.

The description of the Ph¹ chromosome, a member of the G group (number 22) missing approximately half its longer arm, was a notable advance in the understanding of CML. It is present in about 90 percent of patients with typical disease manifestations and was usually absent in other myeloproliferative variants [53–56]. Studies of marrow using a direct method that required no culture confirmed its specificity for the hemopoietic cells in CML [52,53]. The granulocytic. megakaryocytic, and erythroid cells had the Ph¹ chromosome. but the lymphocytes and fibroblasts had normal chromosomes [52]. When one of a pair of identical twins developed CML, the abnormal chromosome was present in only the affected member [57–59]. The Ph¹ chromosome thus was an acquired or induced abnormality and was found to persist in precursors during remissions of the disease and in the abnormal myeloblasts when CML became acute [60,61].

Ionizing radiation was shown to produce a number of chromosome abnormalities, including the Ph¹ chromosome in occasional cells in normal persons [7,24,60]. Those who developed CML following irradiation usually had the Ph¹ chromosome [60].

In the early 1970s, DNA-binding fluorescent agents and Giemsa-stain banding were developed to study human chromosome structure [61,62]. The Ph¹ chromosome was confirmed as being derived from chromosome 22, which had lost the distal half of its long arm [63]. With the new techniques, the Ph¹ chromosome could be distinguished from the trisomy 21 chromosome anomaly involved in Down's syndrome [@]. Study of chromosome 22 showed that it was the chromosome uniquely involved in patients with CML, and that its distribution in cells supported the unicellular (clonal) nature of the disease [65]. The Ph¹ chromosome was shown to represent a translocation and not a deletion [66]. The displaced fragment of chromosome 22 most frequently became attached to chromosome 9, but occasionally to other chromosomes [66–72]. Using the chromosome nomenclature in which the short arm of a chromosome is designated p and the long arm q, the Ph¹ chromosome in CML is designated t(9+;22q–) [73–74]. In 5 percent of patients with Ph¹-positive CML, unusual or complex translocations involve recipient chromosomes other than number 9 or rearrangements, including multiple chromosomes, chromosome breaks, or chromatin loss [70–76]. The clinical features of the disease in these patients and their response to treatment, course, and survival are about the same as in those with the standard Ph¹ translocation. The crucial event in the pathogenesis of CML appears to be the abbreviation of chromosome 22.

When CML undergoes exacerbation or becomes acute, the Ph¹ chromosome persists, but in about 80 percent of patients, additional chromosome rearrangements, additions, or deletions develop. The most common of these are (1) duplication of the Ph¹ chromosome, (2) an extra chromosome 8, or (3) isochromosomes for the long arm of number 17 (17q) [70–76].

While about 90 percent of patients with CML have the Ph¹ chromosome when the disease is first discovered, a few patients develop the anomaly later. Rarely, a mixture of abnormal and normal cell lines persists indefinitely. Patients who are Phi-negative tend to have atypical disease. Their clinical course is usually more acute and their response to therapy less satisfactory, but some seem to have an unusually chronic form of the disease [77–78].

The cytogenetic findings suggested that CML is a monoclonal disease. i.e., that it arises from a single cell. Confirmatory evidence was obtained from studies of women with CML who also were heterozygotes for the X-linked glucose-&phosphate dehydrogenase (Gd-PD) enzyme [79]. If the CML cells were unicellular in origin, they should contain only one of the two G-6-PD enzymes, while if their origin was multicellular. both isoenzymes should be present [80]. Three Negro women with typical CML, one untreated and one undergoing busulfan therapy, who were heterozygous for the common isoenzyme of G-6-PD were selected for study and enzyme assays of their granulocytes, red cells, and fibroblasts from skin biopsies carried out. Only one isoenzyme (type A) was demonstrable in erythrocyte and granulocyte preparations, while fibroblasts from cell cultures in each patient contained both A and B isoenzymes.

Leukemic granulocytes containing only one isoenzyme were found in additional patients [81–83], and a single isoenzyme was found also in platelets and monocyte-macrophage cells cultured from the blood of patients with CML [83]. Heterogeneity occurred in some patients with more acute disease variants [84].

PATHOGENESIS

In 1971, hematologic remissions lasting several months were reported to occur in about 30 percent of patients with CML in blast cell transformation following treatment with vincristine and prednisone, the drugs considered most effective in the treatment of acute lymphoblastic leukemia [85]. Further studies showed that