Chronic Myelocytic Leukemia with Two Philadelphia Chromosomes and Prominent Peripheral Lymphadenopathy

By Charles P. Duvall, Paul P. Carbone, William R. Bell, Jacqueline Whang, J. H. Tjio and Seymour Perry

A MINOR DEGREE OF LYMPHADENOPATHY occurs in relatively few cases of patients with chronic myelocytic leukemia (CML).1 Marked lymph node enlargement may occur late in the course of the disease, usually with the development of the myeloblast crisis, and may be considered a poor prognostic sign.2,3 Rarely, the clinical and histopathologic picture can mimic lymphoma.4 Recently, Kiossoglou, Mitus and Dameshek reported a patient with “significant” lymphadenopathy with two Philadelphia (Ph') chromosomes.5 In reports of cytogenetic studies in CML there is no mention made of lymphadenopathy of marked degree in those patients with 2 Ph' chromosomes.6-8 Three adult patients with chronic myelocytic leukemia, marked peripheral lymphadenopathy, and two Ph' chromosomes are described in this report. It is noteworthy that all 3 patients had the double Ph' chromosome in cytogenetic preparations and 2 of the 3 had significant adenopathy before blastic crisis occurred.

MATERIALS AND METHODS

The 3 patients all had typical leukocytosis, granulocytic hyperplasia of the bone marrow, splenomegaly, and a low leukocyte alkaline phosphatase. Bone marrow aspirates for cytogenetics were studied by the direct method of Tjio and Whang.9 Cultures of peripheral blood for karyotype analysis were made employing the technic of Moorhead and co-workers.10 Leukocyte alkaline phosphatase was determined by the biochemical method of Peacock and co-workers.11 Leukocyte kinetics were studied on 3 occasions in patient R.H. after intravenous injection of 50 μc./Kg, tritiated thymidine of specific activity 1.9 C./mM* and measurement of radioactivity in serial blood samples. Leukocytes were separated by dextran sedimentation,12 and a liquid scintillation technic was employed for sample counting.13

CASE STUDIES

Patient R. H. (04-60-21). This 21-year-old clerk consulted his physician because of leg pain in January 1960. Physical findings included pallor and splenomegaly, but there was no lymphadenopathy (Fig. 1). A diagnosis of CML was made and splenic irradiation...
and busulfan therapy were given. In May of 1963 relapse occurred and the patient was treated with hydroxyurea until March 1965.

In February 1965 the patient noted increasing weakness and abdominal pain. The spleen was palpable 4 cm. below the left costal edge. Discrete, tender, enlarged lymph nodes measuring 2-5 cm. in diameter were present in all node groups. Marked tonsillar hypertrophy was noted. Three bone marrow aspirates over a 2-month period revealed granulocytic hyperplasia with 20, 5 and 5 myeloblasts per 100 cells, respectively. The peripheral blood leukocyte count was 17,000/cu. mm. with 38 segmented neutrophils, 4 bands, 40 myelocytes, 1 myeloblast. 11 lymphocytes, 2 basophils, and 4 monocytes per 100 cells. Toxoplasma and heterophil titers were within normal limits. Six-mercaptopurine was substituted for the hydroxyurea and adenopathy abated for 2 months.

In May, confluent nodes measuring 7 x 7 cm. were noted in the anterior triangle of the neck and large nodes were present in other node groups. Biopsy of the neck nodes on June 2. 1965, revealed myeloblastic infiltration. while the bone marrow still showed granulocytic hyperplasia. Six-mercaptopurine was increased in dosage without effect. Between August 13, 1965, and September 14, 1965, radiation therapy was given, 400 r to the abdomen and 1000 r to neck, groin, and iliac fossa bilaterally. There was marked subjective and objective improvement.

In early October 1965 the patient developed fever, and after appropriate studies a diagnosis of blastic crisis was made. The leukocyte count was 23,900/cu. mm. with 54 myeloblasts/100 cells; over half of the marrow cells were blasts. The patient developed E. coli septicemia and died 24 hours after admission.

At autopsy there was generalized peripheral node enlargement with matted nodes measuring up to 3 x 3 cm. In the perihilar and periarterial areas adenopathy was also marked. The spleen weighed 1850 Gm. Microscopic sections showed that all viscera and nodes had heterogenous leukemic infiltrates with areas of predominant myeloblastic involvement and others with some evidence of maturation.
CASE II
E. B. 05-41-11
MYELOID INFILTRATION OF NODES

Biopsy

Nodes
Spleen

6-MP

Biopsy

OH Urea

CA. Busulfan

Marrow:
Hyperplasia 
Ph' chromo-
some
% Blast

1964 1965

Jan Feb Mar Apr May June July Aug Sep Oct Nov Dec Jan Feb Mar Apr May June July

x10^9/mm^3

M

WBC

Absolute blasts

Abbr: OH Urea: Hydroxyurea.
6-MP: 6-mercaptopurine.
CA.: Cytosine arabinoside

Fig. 2.—Clinical course, patient E. B.

Patient E. B. (05-41-11). This 51-year-old laborer developed symptoms of anemia and congestive heart failure in December 1963 (Fig. 2). One month later CML was diagnosed and at that time generalized lymph node enlargement was present with nodes measuring up to 2-4 cm. in diameter. Biopsy of a right supraclavicular node showed a diffuse myeloid infiltration with cells representing all stages of maturation.

The patient responded to treatment with busulfan but resistance developed in October, 1964. During relapse in mid-December 1964 exquisitely tender lymph node enlargement developed suddenly during a 12-hour period. The nodes grew in size to confluent masses measuring 6 x 12 cm. There was no evidence for blast transformation. Cytosine arabinoside therapy was partially effective but the nodes did not completely disappear until 6-mercaptopurine was given in March 1965. Adenopathy did not recur and, during the last 3 months of life, the major clinical problems were thrombocytopenia, hyperuricemia, and monarticular hemarthrosis. There never was evidence of blast transformation of the disease as judged clinically and by bone marrow and blood smears. On July 25, 1965, the patient experienced dyspnea and severe precordial pain and died unexpectedly at home. Autopsy permission was not obtained.

Patient R. D. (05-57-81). This 34-year-old housewife was found to have CML during evaluation of menometrorrhagia in July 1963 (Fig. 3). Therapy was refused until May 1964, at which time increased fatigability, ecchymoses, and an enlarging right cervical mass developed. Splenomegaly and generalized adenopathy were present with nodes measuring up to 4 cm. in diameter. A 2.5 x 3.0 cm. cauliflower-like mass filled the right tonsillar fossa and on biopsy revealed leukemic infiltration with immature cells...
of the myeloid series. The leukocyte count was 149,000/cu.mm, with 3 blasts/100 cells. Splenic and right cervical irradiation resulted in only a partial response, and busulfan therapy was added. In July 1964 the bone marrow showed numerous nests of myeloblasts and the peripheral blood differential count was 54 blasts/100 cells. Adenopathy and hepatosplenomegaly returned. Between July and September, combined chemotherapy with prednisone, vincristine, methotrexate, and 6-mercaptopurine was administered and a complete remission was achieved and then maintained with 6-mercaptopurine. In January 1965 relapse occurred and adenopathy returned. Axillary node biopsy on January 14, 1965, revealed myeloblastic infiltration. Despite retreatment the patient died January 26, 1965, with hyperpyrexia and acute pulmonary insufficiency. Autopsy was not permitted.

**RESULTS**

**Histopathology**

In each case biopsied tissue was greyish tan in color and of rubbery consistency. In patient R. H. the nodal architecture was completely effaced and the normal lymph node elements were totally replaced by fairly uniform and very immature cells of the myeloid series. Randomly interspersed between the neoplastic cells were numerous phagocytic histiocytes producing a starry-sky appearance similar to that seen in the undifferentiated lymphoma. Scattered eosinophilic and segmented neutrophilic granulocytes were especially noted in and around vascular channels but were seen in smaller numbers in other areas as well. Giemsa-stained touch preparations confirmed the identity of the
neoplastic elements as myeloid cells with a preponderance of myeloblasts (Fig. 4). It should be noted that this lymph node involvement antedated the development of blastic transformation in the marrow and peripheral blood by at least 4 months (probably 7 months).

In patient E. B. adenopathy was present at the time of diagnosis and again 1 year later, some 7 months prior to death. The initial node enlargement was caused by leukemic infiltration with cells of the myeloid series in all stages of maturation. Megakaryocytes were noted but areas of erythropoiesis were not seen. This patient never developed a blastic change.

The third patient, R. D., developed lymph node and tonsillar enlargement 1½ months before the diagnosis of blastic crisis and 8 months before death. The tonsil was infiltrated with large round cells with irregular large nuclei and prominent nucleoli. These cells were also thought to be myeloblasts and were smaller than reticulum cells. Similar histopathologic changes were seen in a lymph node biopsied at the time of terminal relapse.

Chromosome Studies

Table 1 lists the results of chromosome studies carried out on bone marrow, lymph node, and blood cultures. As can be observed in all 3 patients, 98–110 per cent of the marrow metaphases contained the Ph1 chromosome. In addition, all had a hyperdiploid cell line with 2 Ph1 chromosomes. The 2 cell lines were present in all the marrow and lymph node samples as well as 24-hour cultures of the peripheral blood.

Patient R. H. had 2 cell lines on April 16, 1963, one with 46 chromosomes including one Ph1 chromosome, and the other with 47 chromosomes with 5
CML WITH 2 PH¹ CHROMOSOMES AND LYMPHADENOPATHY

Fig. 5.—Metaphase of bone marrow cell and the karyotype of patient (R. H.) with 47 chromosomes, including 2 Ph¹.

chromosomes in group 21-22 of which 2 were Ph¹ (Fig. 5). The subsequent marrow samples had only the 47 chromosome cell line with 2 Ph¹ chromosomes. On October 15, 1963, peripheral blood cultures were done in triplicate and harvested after 1, 2, and 3 days of growth. The cultures harvested after 1 and 2 days had only cells with 47 chromosomes with 2 Ph¹ chromosomes. After 3 days of incubation only cells with normal karyotypes were seen. The lymph node
<table>
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<th>Specimen</th>
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<th>Total %</th>
<th>Bone Marrow</th>
<th>Clinical Status</th>
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<td>Ph&lt;sup&gt;1&lt;/sup&gt; 46 45 44</td>
<td>% Ph&lt;sup&gt;1&lt;/sup&gt;</td>
<td>% Hyper- 2 Ph&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>1 47 50 51 52 53 54</td>
<td>100% 18%</td>
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<td>Granulocytic hyperplasia</td>
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<td></td>
<td>Ph&lt;sup&gt;1&lt;/sup&gt; 46 45 44</td>
<td>% Ph&lt;sup&gt;1&lt;/sup&gt;</td>
<td>% Hyper- 2 Ph&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>10/8/63</td>
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<td>113</td>
<td>113</td>
<td>100% 100%</td>
<td>Remission</td>
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<tr>
<td>10/15/63</td>
<td>Blood&lt;sub&gt;1&lt;/sub&gt;d</td>
<td>34</td>
<td>34</td>
<td>100% 100%</td>
<td>Remission</td>
</tr>
<tr>
<td>10/15/63</td>
<td>Blood&lt;sub&gt;2&lt;/sub&gt;d</td>
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<td>111</td>
<td>100% 10%</td>
<td>Remission</td>
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<tr>
<td>10/15/63</td>
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<td>105</td>
<td>0% 0%</td>
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<td>84</td>
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<td>Adenopathy</td>
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<tr>
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<td></td>
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<td>% Ph&lt;sup&gt;1&lt;/sup&gt;</td>
<td>% Hyper- 2 Ph&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>100</td>
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<td>100</td>
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<td>Erythroid</td>
<td>Myeloblast</td>
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<td>----------------</td>
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<td>Granulocytic</td>
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<td>4/28/64</td>
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<td>70  1 29</td>
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<td>Marked</td>
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<td>68  4 30</td>
<td>98%  30%</td>
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<td></td>
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<td>74  4</td>
<td>78%  4%</td>
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<td>25</td>
<td>50%  0%</td>
<td>Hypoplasia</td>
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<td>91  7</td>
<td>98%  7%</td>
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<tr>
<td>9/4/64</td>
<td>Bone marrow</td>
<td>65  34  1</td>
<td>100%  35%</td>
<td>Erythroid</td>
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<tr>
<td>1/11/65</td>
<td>Bone marrow</td>
<td>28  1 69</td>
<td>99%  71%</td>
<td></td>
<td>30%</td>
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Fig. 6.—Metaphase of a bone marrow cell and its karyotype of patient E. B. with 47 chromosomes, including 2 Ph1.
CML WITH 2 PH\(^1\) CHROMOSOMES AND LYMPHADENOPATHY

was also studied with the direct technic and showed one cell with a normal karyotype and 99 cells with 47 chromosomes containing 2 Ph\(^1\) chromosomes.

In 3-day peripheral blood and bone marrow cultures taken on March 25, 1965, a number of cells were observed with gross chromosomal aberrations which may have been due to drug treatment. In the 3-day blood culture 5 of 100 randomly screened metaphases had fragments and a single cell had a dicentric chromosome. The marrow sample had extensive fragmentation in 20 per cent of metaphases.

There were 2 marrow samples from patient E. B. studied 1 year apart. Both revealed cells with 47 chromosomes and 2 Ph\(^1\) chromosomes (Fig. 6). The first sample was of poor quality and only 4 cells could be analyzed.

Patient R. D. consistently had 2 distinct cell lines: one cell line was pseudodiploid with one Ph\(^1\), and the other was a hyperdiploid line with 52 chromosomes containing 2 Ph\(^1\). The hyperdiploid cell line had the following 6 additional chromosomes in excess: one in group 4–5, three in group 6–12, and one each in groups 19–20 and 21–22 (Fig. 7). The ratio of the pseudodiploid to hyperdiploid line was variable but had no apparent relationship to the clinical status of disease. However, just before death the incidence of the hyperdiploid line increased to 71 per cent of 98 metaphases analyzed. Peripheral blood cultures were also studied at the same time as the first marrow sample. The 1-day culture had 2 per cent normal diploid cells, 68 per cent pseudodiploid with one Ph\(^1\), and 30 per cent with 52 chromosomes including 2 Ph\(^1\). In the 2- and 3-day cultures the incidence of the hyperdiploid cells decreased to 4 per cent and zero, respectively.

**Leukokinetic Studies**

Studies were performed on all 3 patients but only those done in R. H. have bearing on the role of the enlarged lymph nodes. In normal subjects following an intravenous injection of tritiated thymidine, there is a 5-day lag before the progeny of cells in DNA synthesis at the time of pulse labeling divide, mature, and are released into the circulation. In acute leukemia and CML there is a loss of such orderly maturation and release as reflected in the early appearance of labeled cells.\(^{13}\)

The first curve (Fig. 8) was obtained at a time when peripheral adenopathy was maximal and few blasts were present in the peripheral blood. Following radiation therapy of all enlarged nodes (curve 2) the degree of leukocyte labeling in the first 24 hours was markedly decreased and the peak of specific activity in the second day was smaller in magnitude. At the time of terminal blastic crisis there was reversal to the earlier pattern of release of labeled cells.

**DISCUSSION**

Joseph, Zarafonetis and Durant\(^4\) have recently reviewed several cases of "lymphoma" complicating CML. To their 2 cases could be added one of Frank and Isaac\(^4\) and one reported by Serra.\(^5\) Peripheral lymph node enlargement was prominent in less than half of the patients. In 3 patients blastic crisis was
Fig. 7.—Metaphase of a bone marrow cell and its karyotype of patient R. D. with 52 chromosomes and 2 Ph1. There are 3 additional chromosomes in group 6–12, and one each in groups 4–5, 19–20, and 21–22.
well documented while in most, data are not adequate for appraisal of this point. R. H. is the first patient reported to have the Philadelphia chromosome abnormality documented in tumor tissue which might otherwise have been interpreted as an undifferentiated lymphoma. Touch preparations showed that the undifferentiated cells were actually myeloblasts.

In patient E. B. the marked node enlargement was clearly due to leukemic infiltration, and blastic crisis never developed. R. D. had myeloblastic infiltration of tonsil and, undoubtedly nodes, which began prior to the clinical diagnosis of blastic crisis.

**Chromosome Abnormality**

Two Philadelphia chromosomes have been observed in a single cell line by several authors, but lymphadenopathy was mentioned only in two instances. There was no suggestion of adenopathy as marked as that seen in the 3 patients described in this report.

Of 133 patients with CML followed at the National Cancer Institute on whom chromosome studies are routinely performed, 87 per cent were found to have the Ph\(^1\) chromosome; only 4 of these had a hyperdiploid line with 2 Ph\(^1\) chromosomes. One patient not included in this report is a 10-year-old boy without adenopathy who had a single Ph\(^1\) chromosome at the onset of disease and a hyperdiploid "double" Ph\(^1\) cell line in up to 25 per cent of marrow cells in 2 of 3 subsequent studies. He died in blastic crisis but never developed
lymph node enlargement. As in the other 3 patients in this report, there was no clear relationship between the fluctuation of the proportion of "double" Ph1 positive cells and the status of disease. In one patient blastic crisis did not develop and another patient lived 2½ years following the documentation of 2 Ph1 chromosomes. The tendency for the proportion of cells with 2 Ph1 chromosomes to increase with the duration of disease suggests that the second Ph1 chromosome is an acquired abnormality.

Although 2 Ph1 chromosomes usually are found in hyperdiploid cells, Kiosoglou and co-workers noted 2 Ph1 chromosomes in diploid and even hypodiploid cell lines. In one patient trisomy of chromosomes 21-22 was thought to be present but the extra chromosome may have been the extra Ph1 in view of its slightly smaller size apparent in the published report. In our patients the cells with 2 Ph1 chromosomes invariably had three normal-appearing chromosomes of chromosomes 21-22. Such a finding might suggest origin of the second Ph1 chromosome through nondisjunction during anaphase of a Ph1 positive cell. However, the morphology of these Ph1 chromosomes was different (Figs. 5-7) and no corresponding Ph1 negative cells were found which were monosomic for the 21-22 chromosomes. Another possibility could be translocation combined with non-separation during anaphase of the Ph1 daughter chromosome.

Leukokinetic Studies

Data using the liquid scintillation counting technic indicated an early abnormal release of labeled cells at a time when there were insignificant numbers of circulating myeloblasts. Radiation therapy to involved nodal areas considerably altered this early portion of the kinetic curve. This suggests a change in the manner of release of labeled cells from blast-packed nodes and implies that these neoplastic areas contributed in major fashion to the kinetic pattern of circulating labeled cells. Reversion to the original "early release" kinetic pattern was noted at the time of terminal myeloblastic crisis as judged by comparison of the first 24 hours of the 3 curves. Analysis of the autoradiographs, now in progress, may help in the evaluation of these data.

In certain patients, leukemic infiltrates of nodes may be associated with a poor prognosis because of the more malignant and less-differentiated nature of the cells involved. Malignant cells from the marrow may reside and grow in extramedullary sites and from there perhaps return to invade the marrow and peripheral blood. There is evidence both from leukokinetic data and from effective marrow grafts following intravenous infusion of homologous marrow or leukocytes that leukocytes can return to the marrow. On the other hand, stem cells in the nodes or other sites could conceivably be subjected to a similar leukemogenic stimulus. Evidence in support of this possibility might be the discovery of the Philadelphia chromosome in lymph node or other tissue replaced by malignant cells indistinguishable from reticulum or lymphosarcoma cells on touch preparation.
Summary

1. Three adults with CML, 2 Ph1 chromosomes, and marked peripheral lymphadenopathy are described.
2. In each instance node enlargement was thought to be due to leukemic infiltration rather than a supervenient lymphomatous process.
3. Marked adenopathy is an unfavorable prognostic sign in CML, particularly if caused by myeloblastic infiltration. Such infiltration can precede myeloblastic involvement of the peripheral blood and bone marrow.
4. Karyotype analysis and touch preparations of extramedullary tumor tissue in CML will aid in accurate diagnosis and may help to answer more basic questions regarding the pathogenesis of this malignancy.

Summario in Interlingua

1. Es describite 3 patientes adulte con chronic leucemia myelocytic, 2 chromosomas Ph1, e marcate lymphadenopathia peripheric.
2. In cata-un de iste casos, il esseva opinate que le allargamento del nodos lymphatic esseva le effecto de infiltration leucemic plus tosto que evidentia de un superveniente processo lymphomatose.
3. Adenopathia de grado marcate es un adverse signo prognostic in chronic leucemia myelocytic, particularmente si illo es causate per infiltration myeloblastic. Tal infiltration pote preceder le affection myeloblastic del sanguine peripheric e del medulla ossee.
4. Le analyse caryotypic e preparatos de contacto de tissu tumoric extramedullari in chronic leucemia myelocytic va esser de valor in le accurate diagnose e pote esser de adjuta in clarificar questiones plus fundamental relative al pathogenese de iste malignitate.

Acknowledgments

We are grateful to Dr. Gregory O'Conor and to Dr. George Brecher for their extremely helpful advice and criticism.

References

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