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Hematopoietic Malignancies and Related Disorders Among Benzene-Exposed Workers in China

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Although the relationship between benzene and acute nonlymphocytic leukemia (ANLL) is well established, most of the analytic cohort investigations examining the relationship between benzene and hematologic neoplasms have evaluated only death certificates to validate diagnoses. In a follow-up study of 74,828 benzene-exposed and 35,805 non-exposed workers in China, pathology reports, medical records, and/or histopathologic material were reviewed for all patients with hematopoietic malignancies to ensure correct classification and to provide clinicopathologic descriptions. Eighty-two patients with hematopoietic neoplasms and related disorders were identified among benzene-exposed workers, including 32 cases of acute leukemia, 7—myelodysplastic syndrome (MDS), 9—chronic granulocytic leukemia (CGL), 20—malignant lymphoma or related disorder (ML), 9—aplastic anemia, and 5 others. Among the comparison group, 13 hematologic malignancies were observed, including 6 patients with acute leukemia, 2—CGL, 3—ML, and 2 others. The hematopathologic characteristics of the benzene-exposed ANLL cases resembled those following chemotherapy or radiotherapy. ANLL in workers exposed to benzene may represent a distinct clinicopathologic entity, with characteristics similar to treatment-related ANLL, including a preceding preleukemic phase in some patients. Results in our series, one of the largest to date, also indicate that a greater diversity of hematologic neoplasms is evident among benzene-exposed workers than previously described.

KEY WORDS: Benzene leukemia dysplasia

INTRODUCTION

The International Agency for Research on Cancer (IARC) concluded in the early 1980s that there was sufficient evidence that benzene could cause acute myelogenous leukemia (AML).[1] At that time, the major studies implicating benzene in the occurrence of AML were two US cohort mortality investigations,[2,3] a clinical series drawn from Turkish shoe and leather manufacturing workers,[4,5] and case-control studies in France, Sweden and the US.[6-9] Worldwide sources of exposure to benzene include its widespread use in industry and its presence in cigarette smoke, gasoline, and automobile exhaust,[1] thus potentially exposing a large population to its carcinogenic risks. Since the IARC report, investigators have also raised concerns about possible associations of benzene with non-

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Hodgkin's lymphoma,[10] multiple myeloma,[11] and other hematopoietic malignancies.[12] Clarification of the role of benzene exposure in the etiology of various hematopoietic malignancies requires accurate classification. However, most of the investigations examining the relationship between benzene and hematologic neoplasms have evaluated only death certificates, with very few studies reviewing medical record or histologic data to provide detailed clinicopathologic descriptions and ensure correct categorization.[4,6,13,14] Thus, a major objective of a recent epidemiologic study among a large number of benzene-exposed (and non-exposed) workers in China was to obtain medical record data and histopathologic specimens for patients with hematopoietic malignancies to enable classification according to recently published criteria and to identify unusual clinical and pathologic features.

SUBJECTS AND METHODS

A retrospective cohort study of incident cases of hematopoietic neoplasms and related disorders was conducted among 74,828 benzene-exposed workers employed between January 1, 1972 and December 31, 1987 in 672 factories in 12 Chinese cities (Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Guangzhou, Nanchang and Kaifeng).[15] A concurrent comparison group consisted of 35,805 workers not occupationally exposed to benzene who were employed during the same period in 109 factories in the 12 cities. Careful review of factory records identified eligible exposed and unexposed persons. Data abstracted from these files included name, job title and information describing the types of work units and dates employed.

Since the factories usually provide all health care for current and retired workers, follow-up of benzene-exposed and unexposed subjects through December 31, 1987 was carried out utilizing factory occupational and medical records to ascertain hematopoietic malignancies and related disorders, vital status, and, for those deceased, cause of death. Additional means of follow-up were utilized for a small number of subjects who had left the factories prior to retirement. For workers reported to have developed hematologic neoplasms and related disorders, pertinent histopathologic material, pathology reports and medical records were requested for confirmation. Clinical, laboratory and pathology data for all patients were abstracted onto standardized forms by physician investigators who were not aware of the exposure status of the subjects, nor of the numbers of exposed and non-exposed cases. All slides were reviewed systematically using structured, detailed abstract forms to objectively characterize hematopoiesis. Evaluation of the peripheral blood smear included review of polymorphonuclear (PMN) leukocytes for hypersegmentation, hyposegmentation (the pseudo-Pelger-Huet anomaly), hypogranularity, abnormal granules and the presence of vacuolization. Platelet size and granularity and red blood cell shape, size and general morphology were also noted. Eosinophilia was defined as an absolute count of more than 450 cells/uL; basophilia was defined as an absolute count of more than 200 cells/uL.[16]

Hematologic parameters recorded for bone marrow aspirates included the following: the estimated erythrocyte:granulocyte ratio, per cent blasts and morphologic changes. Evidence of dyserythropoiesis included the presence of ringed sideroblasts, multinuclearity, karyorrhexis, nuclear fragmentation, abnormal nuclear shape, impaired hemoglobinization, megaloblastoid changes or other nuclear or cytoplasmic abnormalities. Dysgranulopoiesis was characterized as for the peripheral blood smear. Dysmegakaryopoietic features included the presence of micromegakaryotes, large mononuclear forms, multiple small nuclei, or giant or abnormal granules. The upper limit of the normal range for marrow basophils was defined as 0.2 per cent of total nucleated cells (TNC), and for eosinophils, 6.2 per cent of TNC.[17]

Diagnoses were assigned after evaluation of all available clinical, laboratory and pathologic data without knowledge of the patient's benzene exposure status. Published criteria were utilized to classify myelodysplastic syndrome (MDS),[18] acute nonlymphocytic leukemia (ANLL),[19-21] acute lymphoblastic leukemia (ALL),[19] and non-Hodgkin's lymphoma (NHL).[22] Since study objectives did not include quality control of the previously assigned Chinese diagnoses, which derived from a variety of sources, a systematic comparison of these diagnoses with the results of the current review was not undertaken.

RESULTS

Eighty-two hematopoietic malignancies and related disorders were documented among benzene-exposed workers, with 13 such cases identified among the non-exposed comparison group. Frequencies of the major diagnostic categories of hematologic neoplasms in

benzene-exposed and non-exposed subjects are summarized in Table 1. Diagnoses confirmed by review of pathology reports and medical records for 51 benzene-exposed subjects included acute leukemia (17 patients [pts]), MDS (2 pts), chronic granulocytic leukemia (CGL) (5 pts), malignant lymphoma or related malignancy (ML) (16 pts), aplastic anemia (8 pts) and 3 other disorders. For an additional 31 benzene-exposed subjects, diagnoses based on evaluation of histopathologic material included 9 cases of ANLL; 5 acute leukemias which could not be classified further; 5 MDS; 4 CGL; 4 ML; 1 ALL; and 1 aplastic anemia (Tables 2–5). Findings in an additional patient were considered compatible with malignant histiocytosis and those in another subject were thought consistent with some type of toxic bone marrow effect.

Diagnoses confirmed by review of histopathologic material for the non-exposed comparison group included ANLL-M2 (1 pt), multiple myeloma (1 pt) and lymphoproliferative disorder (1 pt). Evaluation of medical records and pathology reports for 10 additional patients indicated diagnoses of acute leukemia (5 pts), CGL (2 pt), NHL (2 pt) and 1 leukemia, not otherwise specified. Diagnoses observed among only benzene-exposed cases included aplastic anemia and MDS (Table 1).

Preliminary analyses indicate that the age- and sex-adjusted relative risk of all confirmed lymphohematopoietic disorders in exposed versus unexposed workers is 3.4 (95% confidence interval: 1.9–6.1). The results of future analyses (which will evaluate risk by industry, occupational category, level of benzene exposure and type of hematologic malignancy) will be reported separately. Available clinicopathologic data for 31 of the benzene-exposed cases are presented below by diagnostic subgroup; data for patients 32–34, who were not exposed to benzene, are summarized in Tables 2–4.

Table 1 Frequency of major diagnostic groups of all hematopoietic malignancies and related disorders among benzene-exposed and non-exposed workers

Diagnosis	*Number of cases (%)**	
	Exposed workers	*Non-exposed workers*
Aplastic anemia	9 (11%)	0
Acute leukemia	32 (39%)	6 (46%)
Myelodysplastic syndrome	7 (9%)	0
Chronic granulocytic leukemia	9 (11%)	2 (15%)
Malignant lymphoma and related disorders	20 (24%)	3 (23%)
Other	5† (6%)	2‡ (15%)
Total	82	13

*Numbers may not sum to 100 due to rounding error.

†Includes diagnoses of agranulocytosis (2), multiple myeloma (1), leukemia, not otherwise specified (NOS) (1), and toxic effect (1).

‡Includes diagnoses of multiple myeloma (1) and leukemia, NOS (l).

ANLL Histopathologic data were evaluated for 5 men and 4 women with ANLL (Table 2); patients typically presented with anemia and thrombocytopenia, with white blood cell counts ranging from 1,200 to 16,800 per uL (Table 3). Dyspoiesis was common (Tables 4 and 5). Three cases of ANLL-M2 and four of ANLL-M3 were included in the histopathologic review. In two patients (numbers 4 and 9), subtyping of ANLL was not possible. The leukemic bone marrow of Patient 4 was thought consistent with either ANLL-M2 or ANLL-M4. Review of bone marrow for Patient 9 revealed peroxidase-positive blasts, which demonstrated prominent nucleoli and a moderate amount of cytoplasm, some with granules. This patient was thought to have either a myelomonocytic or monocytic leukemia. An unusual increase in small, atypical basophils or mast cells was also noted in this patient, who had a prior diagnosis of chronic benzene poisoning.

Acute leukemia, not otherwise specified (AL, NOS) In five persons with acute leukemia, the cell type could not be established after review of histopathology, without the availability of additional cytochemical stains. Data available for two of these cases suggested blastic transformations of antecedent myeloproliferative disorders: Patient 10 presented with hepatosplenomegaly; basophilia and large platelets were among the features noted on the peripheral blood smear. Bone marrow examination revealed approximately 35 per cent blasts and right-shifted granulopoiesis with numerous PMNs, many of which were hypogranular. The peripheral blood smear for Patient 11 showed dacrocytes, basophilia and large platelets, many in aggregates, features consistent with the prior diagnosis of CGL noted in the medical record. Dysplasia was evident in peripheral blood and bone marrow, with undifferentiated blasts comprising approximately 30–35% of marrow cellularity. Other characteristics supporting the underlying diagnosis of CGL included bone marrow basophilia and available laboratory values (Table 3) which included a low leukocyte alkaline phosphatase (LAP) score.

More than 90% of marrow cellularity in Patient 12 consisted of blasts, which did not stain with peroxidase according to an accompanying report. The sig-

Table 2 Clinical presentation of 34 patients with hematopoietic malignancies and related disorders*

Patient no.	*Age/Sex (yr)*	*Symptoms/Signs*	*Physical examination*		*LN*	*Diagnosis*
			HM	*SM*		
1	40/M	lower limb ulceration, ecchymoses, petechiae	–	–	+	ANLL-M2
2	45/F	vertigo, weakness, palpitations	–	–	–	ANLL-M2
3	24/M	fever	–	–	–	ANLL-M2
4	25/M	fever, malaise	–	–	–	ANLL-M2 or M4
5	43/M	sternal tenderness, gingival infiltration	–	–	+	ANLL-M3, microgranular
6	47/F	petechiae, sternal tenderness, gingival bleeding, ecchymoses	–	–	–	ANLL-M3
7	23/M	N/A	N/A	N/A	N/A	ANLL-M3
8	43/F	petechiae, ecchymoses	–	–	–	ANLL-M3
9†	53/F	fever. malaise, vertigo, pallor, dyspnea, mucosal ulceration	–	–	–	ANLL-M4 or M5
10	70/M	bronchitis	+	+	–	AL, NOS
11	64/M	N/A	N/A	N/A	N/A	AL, NOS
12	42/M	sternal tenderness, ecchymoses	+	–	+	AL, NOS
13	42/M	N/A	–	–	–	AL, NOS
14	42/M	fever	+	–	+	AL, NOS
15	53/M	N/A	–	–	–	RA
16†	48/F	lower limb ulceration	–	N/A	+	CMML
17	30/F	N/A	–	–	–	RAEBT
18	41/F	N/A	N/A	N/A	N/A	MDS, NOS
19†	40/M	fever, joint pain	+	–	–	MDS, NOS
20	28/F	petechiae	+	+	+	CGL
21	62/M	abdominal mass, malaise, weight loss	+	+	–	CGL
22	30/M	N/A	–	–	–	CGL, atypical
23	N/A	N/A	N/A	N/A	N/A	CGL
24	20/M	fever, malaise vertigo	+	+	–	NHL (possible)
25	41/F	malnutrition, pallor	–	–	+	NHL
26	40/M	fever	–	–	+	NHL
27	34/M	fever	+	+	+	NHL
28	23/M	sternal tenderness, gingival pain	+	+	+	ALL
29	45/M	gingival bleeding, petechiae	+	N/A	N/A	Aplastic Anemia
30	58/M	fever, malaise	–	–	+	Malignant Histiocytosis (possible)
31‡	33/M	weakness, vertigo	+	+	–	Toxic effect
32	49/M	epistaxis, malaise, weight loss	–	–	+	ANLL-M2
33	52/M	chest wall mass	–	–	–	Multiple Myeloma
34	54/M	N/A	N/A	N/A	N/A	LPD

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; HM: hepatomegaly; LN: lymphadenopathy; LPD: lymphoproliferative disorder; MDS: myelodysplastic syndrome; N/A: not ascertained; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; RA: refractory anemia; RAEBT: refractory anemia with excess blasts in transformation; SM: splenomegaly; +: present; –: absent.

*This table is limited to those patients for whom histopathologic materials were reviewed (Tables 3–5). Patients 1–31 were occupationally exposed to benzene.

†Patient had been previously diagnosed with chronic benzene poisoning.

‡Available data preceded the reviewed bone marrow aspirate by 10 years.

nificant variation in blast size together with the presence of cytoplasmic granules and budding seemed suggestive of a megakaryocytic lineage. However, in the absence of immunohistochemical stains to evaluate a possible diagnosis of acute megakaryocytic leukemia (ANLL-M7),[21] this patient was also considered to have AL, NOS.

An unusual feature of increased lymphocytes with large cytoplasmic granules was present in both the peripheral blood smear and marrow aspirate of Patient 13. Otherwise, findings in this patient were consistent with AL, NOS (Table 4).

MDS Myelodysplastic syndromes were evident in five subjects based upon review of histopathologic material. Findings in Patient 15 included bone marrow hypocellularity, with markedly dyserythropoietic features, including multinuclearity, megaloblastoid changes, and abnormal nuclear shape; the general

Table 3 Laboratory data and peripheral blood morphologic findings in patients* with hematopoietic malignancies and related disorders†

Patient no.	*Hemoglobin (g/dl)*	*WBC ($x10^3$/uL)*	*% blasts*	*Platelets ($x10^3$/uL)*	*Peripheral blood morphologic findings*	*Diagnosis*
1	8.6	16.8	20	N/A	pseudo-Pelger-Huet PMNS, Auer rods, thrombocytopenia	ANLL-M2
2	4.4	4.4	0	105	N/A	ANLL-M2
4	3.0	13.7	0	N/A	anisocytosis, poikilocytosis, pseudo Pelger-Huet PMNs, pancytopenia, type II blasts	ANLL-M2 or M4
5	7.0	1.6	20	15	thrombocytopenia, hypogranular promyelocytes or monocytic cells	ANLL-M3, microgranular
6	8.8	1.2	10	66	N/A	ANLL-M3
8	5.2	3.1	0	40	N/A	ANLL-M3
9‡	4.6	3.4	38	10	N/A	ANLL-M4 or M5
10	8.0	15.2	23	56	polychromasia, NRBCs, hypersegmented, hyposegmented and hypogranular PMNs, large platelets, basophilia	AL, NOS
11§	N/A	84.6¶	4	350	dacrocytes, left-shifted granulopoiesis, large platelets, basophilia	AL, NOS
12	5.9	2.9	50	10	N/A	AL, NOS
13	14.7	2.3	0	86	oval macrocytes, neutropenia, thrombocytopenia, immature lymphoid cells with granules	AL, NOS
14	8.0	17.5	0	0.7	N/A	AL, NOS
15	4.0	1.8	0	16	N/A	RA
16‡	6.5	36.2	2	17	oval macrocytes, target cells, megaloblastic and megaloblastoid NRBCs, hypogranular PMNs, giant bands, basophilia, thrombocytopenia	CMML
17	8.1	4.6	N/A	36	N/A	RAEBT
19‡	10.0	4.7	0	50	N/A	MDS, NOS
20‖	7.0	198.0**	2	134	hypogranular PMNs and myelocytes, rodent nuclei, basophilia, eosinophilia	CGL
21	10.0	121.6	3	242	oval macrocytes, target cells, NRBCs, basophilia	CGL
22	7.0	32.8††	0	300	left-shifted granulopoiesis, no basophilia nor eosinophilia	CGL, atypical
23	N/A	N/A	N/A	N/A	left-shifted granulopoiesis with mild basophilia	CGL
24	8.4	2.6	0	37	N/A	NHL (possible)
25	8.5	16.8	0	N/A	N/A	NHL
26	11.0	8.3	0	210	N/A	NHL
27‡‡	7.0	5.5	0	N/A	N/A	NHL
28	9.5	23.0	96	51	oval macrocytes, thrombocytopenia	ALL
29	4.0	2.2	0	26	N/A	Aplastic Anemia
30	11.5	4.4	0	100	pancytopenia, large atypical monocytoid cells present	Malignant Histiocytosis (possible)
31§§	8.0	220.0¶¶	0	406	N/A	Toxic effect
32	6.0	4.9	64	N/A	anisocytosis, poikilocytosis, numerous Auer rods	ANLL-M2
33	5.5	2.9	0	76	rouleaux	Multiple Myeloma

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; N/A: not available; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; NRBC: nucleated red blood cells; PMN: polymorphonuclear leukocyte; RA: refractory anemia; RAEBT: refractory anemia with excess blasts in transformation; WBC: white blood cell.

*Neither laboratory data nor peripheral blood smears were available for patient nos. 3, 7, 18, and 34.

†Patients 1–31 were occupationally exposed to benzene.

‡Patient had been previously diagnosed with chronic benzene poisoning.

§Laboratory values preceded the reviewed peripheral blood and bone marrow specimens by 3 years.

¶WBC differential: 22% PMN, 33% bands, 8% metamyelocytes, 6% myelocytes, 5% promyelocytes, 4% blasts, 7% basophils, 4% eosinophils, 11% lymphocytes.

‖Patient was Philadelphia-chromosome positive.

**WBC differential: 27% PMN, 18% bands, 13% metamyelocytes, 25% myelocytes, 5% promyelocytes, 2% blasts, 4% eosinophils, 4% basophils, 2% lymphocytes.

††WBC differential: 49% PMN, 11% bands, 7.5% metamyelocytes, 20.5% myelocytes, 5% promyelocytes, 5% lymphocytes, 2% other.

‡‡Laboratory values were obtained approximately 1 month after lymph node biopsy.

§§Laboratory values preceded the reviewed bone marrow aspirate by 10 years.

¶¶WBC differential: 40% PMNs, 20% bands, 15% metamyelocytes, 25% promyelocytes.

Table 4 Bone marrow features in patients* with hematopoietic malignancies and related disorders††

Patient no.	*E:G*	*Cellularity/Dyspoiesis*			*% blasts*	*Comments*	*Diagnosis*
		Erythrocytes	*Granulocytes*	*Megakaryocytes*			
1	1:50	Decr/+	Incr/–	Decr/–	60	peroxidase stain: positive	ANLL-M2
2	1:30	Decr/+	Incr/–	Decr/†	30–35	—	ANLL-M2
3	1:10	Decr/–	Incr/–	Decr/†	40	—	ANLL-M2
4	1:100	Decr/†	Incr/–	Decr/†	40	numerous immature cells, either monocytes or granulocytes	ANLL-M2 or M4
5	1:20	NI/–	Incr/–	Decr/†	60	—	ANLL-M3, microgranular
6	1:20	Decr/+	Incr/–	Decr/†	—	hypergranular promyelocytes: 90%	ANLL-M3
7	1:15	Decr/+	Incr/–	Decr/†	—	hypergranular promyelocytes: 90%	ANLL-M3
8	50:1	Decr/+	Incr/+	Decr/–	—	hypergranular and hypogranular promyelocytes: 90%	ANLL-M3
9‡	1:100	Decr/+	Incr/+	Decr/†	80	increase in basophils or mast cells (5%), which are dysplastic; increase in monocytes; peroxidase stain: positive	ANLL-M4 or M5
10	1:8	Decr/+	Incr/+	Decr/†	35	preceding MPD	AL, NOS
11	1:100	Decr/+	Incr/–	Decr/+	30–35	undifferentiated blasts; preceding CGL	AL, NOS
12	§	§	Decr/–	Decr/–	90	blasts demonstrate cytoplasmic budding and granules	AL, NOS
13	1:1	N/A	N/A	N/A	see comment	immature lymphoid-like cells (some with granules): 90%	AL, NOS
14	1:50	Decr/–	Incr/–	Decr/†	90	—	AL, NOS
15	3:1	Incr/+	Decr/–	Decr/†	<5	significant dyserythropoiesis: marked granulocytic hypoplasia	Refractory Anemia
16‡	1:6	NI/+	Incr/+	Decr/+	5–10	incr. basophils: l–2%. incr. monocytes: 20–25%	CMML
17	1:3	Incr‖/+	Incr/+	Decr/†	5–10	Auer rods noted	RAEBT
18	5:2	Incr¶/+	Decr/+	Decr/†	<5	—	MDS, NOS
19‡	N/A	N/A	N/A	N/A	N/A	pseudo-Pelger-Huet PMNs	MDS, NOS
21	1:15	NI/+	Incr/+	NI/–	<5	low LAP score, slight increase in basophils	CGL
22	1:10	NI/+	Incr/+	NI/–	<5	no basophilia nor eosinophilia, low LAP score	CGL, atypical
23	1:5	NI/+	Incr/–	NI/–	<5	eosinophilia: 5% basophilia: <1%	CGL
24	1:1	Incr¶/+	Decr/+	NI/+	<5	increase in granular lymphocytes; hemophagocytosis	NHL (possible)
28	5:1	NI/–	Decr/†	Decr/†	90%	no Auer rods	ALL
29	10:1	Incr**/+	Decr/†	Decr/†	<5	megaloblastoid RBCs	Aplastic Anemia
30	1:2	NI/+	Decr/–	Decr/†	<5	—	Malignant Histiocytosis (possible)
31	1:18	NI/+	Incr/–	NI/–	<5	eosinophils: 5–8%; extensive dyserythropoiesis	Toxic effect
32	1:100	Decr/–	Incr/–	Decr/†	70	numerous Auer rods	ANLL-M2
33	1:3	Decr/–	Decr/–	NI/–	<5	myeloma cells: 50%	Multiple Myeloma
34	1:10	Decr/–	Decr/–	Decr/†	<5	lymphocytes: 50–60%	LPD

Abbreviations: AL: acute leukemia; ALL: acute lymphoblastic leukemia; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocytic leukemia; CMML: chronic myelomonocytic leukemia; Decr: decreased; E:G: erythrocyte: granulcyte ratio; Incr: increased; LAP: leukocyte alkaline phosphatase; LPD: lymphoproliferative disorder; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorder; N/A: not ascertained; NHL: non-Hodgkin's lymphoma; N0S: not otherwise specified; PMN: polymorphonuclear leukocyte; RAEBT: refractory anemia with excess blasts in transformation; RBC: red blood cell; +: present; –: absent.

*Bone-marrow was not available for review in Pt. 22. Lymph node biopsies (Pts. 25, 26, and 27) are not included in the table.

†† Patients 1–31 were occupationally exposed to benzene.

†Dyspoiesis could not be assessed since so few cells were available.

‡Patient had been previously diagnosed with chronic benzene poisoning.

§No erythroblasts were identified on the slide.

‖ Erythoblasts: 30%

¶Erythroblasts: 60%

**Erythroblasts: 80%

Table 5 Summary of dysplastic morphologic findings in the peripheral blood or bone marrow of benzene-exposed workers with hematopoietic malignancies and related disorders*

Morphologic finding	*Diagnostic category (no. of patients)*								
	ANLL (9)	*AL. NOS (4)*	*MDS (5)*	*CCL (4)*	*NHL (possible) (1)*	*ALL (1)*	*AA (1)*	*MH (possible) (1)*	*Toxic effect (1)*
Dyserythropoiesis (all types)	6	3	5	3	1	0	1	1	1
Multinuclearity	0	0	2	1	1	0	0	0	1
Impaired hemoglobinization	5	2	3	1	1	0	1	1	1
Abnormal nuclear shape	0	0	3	0	0	0	0	0	1
Megaloblastoid changes	3	0	4	2	1	0	1	0	1
Dysgranulopoiesis (all types)	5	1	4	3	1	1	0	0	0
Hypersegmented PMNs	0	1	0	0	0	0	0	0	0
Hypogranulation	1	1	2	1	0	0	0	0	0
Pseudo-Pelger-Huet anomaly	2	0	3	0	1	0	0	0	0
Dysmegakaryocytopoiesis (Micromegakaryocytes)	0	1	0	0	1	0	0	0	0

Abbreviations: AA: aplastic anemia; ALL: acute lymphoblastic leukemia; AL, NOS: acute leukemia, not otherwise specified; ANLL: acute non-lymphocytic leukemia; CGL: chronic granulocyti c leukemia; MDS: myelodysplastic syndrome; MH: malignant histiocytosis; NHL: non-Hodgkin's lymphoma.

*This table is limited to benzene-exposed subjects (patient numbers 1–31). Specimens from Patient 13 were not evaluable for dysplasia. The 3 subjects for whom lymph node biopsies were reviewed are not included in this table.

morphology of the red cells was dimorphic. Features of this case were consistent with refractory anemia (RA).

The findings in Patient 16, who had a prior diagnosis of chronic benzene poisoning, were most consistent with chronic myelomonocytic leukemia (CMML). Peripheral blood smear features included oval macrocytes, megaloblastoid nucleated red blood cells (NRBCs), hypogranular PMNs and monocytosis. Bone marrow demonstrated megaloblastoid dyserythropoiesis and giant bands and metamyelocytes, as well as an increase in monocytes (20–25%). Excess numbers of both peripheral blood and marrow basophils were also apparent. Information about the size of the spleen on physical examination was not available, and cytogenetic studies and a LAP score had not been performed to exclude a diagnosis of CGL. However, the extensive dyspoiesis evident on both the peripheral smear and the bone marrow, together with the increase in marrow monocytes, seemed to favor a diagnosis of CMML.

Although a marrow smear from Patient 17 contained only 5–10% blasts, the presence of Auer rods, together with other findings, met criteria for a diagnosis of refractory anemia with excess blasts in transformation (RAEBT). Dyserythropoiesis in this subject consisted of abnormal nuclear shape, megaloblastoid changes, and impaired hemoglobinization. Hypogranular PMNs and the pseudo-Pelger-Huet anomaly were also evident.

For 2 of the cases, the MDS could not be subclassified further. Dyspoietic features in Patient 18 included megaloblastoid, multinucleated red cells, impaired hemoglobinization, and hypogranular and pseudo-Pelger-Huet granulocytes. Patient 19, who had a prior history of chronic benzene poisoning, was considered to have a possible MDS, based on the peripheral blood counts, presence of pseudo-Pelget-Huet cells on the reviewed slide, and a bone marrow report which noted 4 per cent blasts. Unfortunately, the available marrow aspirate was of poor quality.

CGL Four cases of CGL are summarized in Tables 2–5. Although a bone marrow aspirate was not available for examination in Patient 20, clinical findings and laboratory studies (which included the presence of the Philadelphia chromosome) were consistent with the diagnosis of CGL indicated in the medical record. Patient 21 presented with hepatosplenomegaly, a high white blood cell (WBC) count with basophilia and a LAP score of 8. Peripheral blood and bone marrow findings, which were consistent with CGL, also included dyspoiesis. Patient 22 had a medical record diagnosis of CGL. Given his peripheral blood counts, myelocyte bulge, LAP score of 6, and striking granulocytic hyperplasia on the marrow aspirate, we maintained CGL as the study diagnosis. However, in

the absence of basophilia, we considered this to be an atypical variant.

Malignant lymphoma Patient 24 presented with constitutional symptoms, hepatosplenomegaly and pancytopenia. Marrow review revealed hemophagocytosis, multinucleated and megaloblastoid dyserythropoiesis, slight impairment of hemoglobinization, pseudo-Pelger-Huet PMNs, hyposegmented eosinophils, eosinophils with pseudopodic and micromegakaryocytes. Several very large cells with cytoplasmic granules, possibly suggestive of malignant T-lymphocytes, were also present. Although this patient may have had an unusual peripheral T-cell lymphoma,[23] in the absence of additional immunohistochemical stains, only a diagnosis of possible non-Hodgkin's lymphoma (NHL) could be assigned.

Evaluation of lymph node biopsies disclosed three cases of NHL. Two patients (25 and 26) were both considered to have malignant lymphoma, diffuse mixed small and large cell, based on samples of tonsillar tissue and a cervical lymph node, respectively. Patient 27 was thought to have diffuse large cell lymphoma based on review of a supraclavicular lymph node biopsy

Other diagnoses Bone marrow from Patient 28 generally demonstrated characteristic findings of ALL. The hypoplastic bone marrow of Patient 29, which was consistent with aplastic anemia, demonstrated impaired hemoglobinization and megaloblastoid dyserythropoiesis; the peripheral blood WBC differential was remarkable for a mild relative lymphocytosis (47%).

Patient 30, who presented with fever, malaise, lymphadenopathy and pancytopenia, had a medical record diagnosis of malignant histiocytosis. Although special stains to confirm this cell lineage were not available for our review, both the peripheral blood and marrow smears showed large, erythrophagocytic, monocytoid cells suggestive of malignant histiocytes. Therefore, since the patient's clinical and pathologic features were consistent with the medical record diagnosis, we maintained it for study classification. Dyspoietic changes observed for this case included slightly impaired hemoglobinization.

Patient 31, a 33 year old man, had been exposed to benzene for approximately 11 years at the time the specimen described in Table 3 was obtained. This marrow aspirate demonstrated marked dyserythropoiesis, including multinuclearity, megaloblastoid changes, abnormal nuclear shape and cytoplasmic vacuolization. These changes were thought most consistent with some type of toxic bone marrow effect, with further hematologic classification not possible.

DISCUSSION

The present report represents one of the largest series of benzene-related hematopoietic malignancies, identified from a cohort study, in which diagnoses were confirmed by review of pathology reports, medical records, and/or histopathologic material and in which individual clinicopathologic descriptions are provided.[4,6,13,14] Important findings include the observation that the hematopathologic features of ANLL associated with benzene exposure resemble those following chemotherapy or radiotherapy, and documentation of diagnoses of MDS. Taken together, these observations suggest that benzene-related ANLL may represent a distinct clinicopathologic entity and perhaps display a preleukemic phase in some patients, as does therapy-related ANLL.

Another new finding in our study is the greater diversity of hematologic malignancies than usually reported with benzene exposure, perhaps due in part to the sizable number of subjects in a variety of occupational settings. In previous investigations of cancer risk among various groups of benzene-exposed workers, excesses of several forms of hematopoietic malignancies have been described, but only AML and aplastic anemia appear to be consistently increased.[1] Results have, otherwise, varied considerably between studies. For example, preleukemia and acute erythroleukemia were especially common among Turkish workers with chronic benzene poisoning,[24] and erythroleukemia was also noted among Italian workers exposed to benzene.[25] In the Paris region, CGL and CLL accounted for 26 and 16%, respectively, of all leukemias associated with benzene exposure.[6] In addition, elevated risks for multiple myeloma, although based on only four cases, were reported among benzene-exposed workers in the US.[26] Reasons for the variation in the distribution of hematopoietic malignancies between studies may include the presence of concomitant exposures in the workplace, the duration and/or level of benzene exposure, or dissimilarities in case ascertainment and reporting. Furthermore, differences in genetic or other susceptibility factors in the at-risk populations may also affect the distribution of malignancies which are observed. For instance, although CLL was not seen among benzene-exposed

workers in our cohort and only one case of multiple myeloma was evident, population-based incidence data for China indicate that rates for these malignancies are very low.[27,28] Similarly, acute erythroleukemia, also rare in our series, comprises only 5% of ANLL in China.[27] Otherwise, the spectrum of hematopoietic disorders in our series includes many of the conditions reported in prior studies of benzene-exposed workers. Clinicopathologic features of the benzene-exposed cases are discussed below by diagnostic subgroup and compared with observations in prior reports.

ANLL Although the presenting signs and symptoms of the benzene-exposed patients with ANLL typical of acute leukemia occurring de novo,[29] many of the hematologic features resembled those reported in leukemias secondary to chemotherapy or radiotherapy.[30] Characteristics typical of t-ANLL which were observed in our patients included the presence of dysmyelopoietic changes,[30-33] the common occurrence of anemia and thrombocytopenia,[30-32] and increased bone marrow cellularity.[30,31,33] Basophilia, which has been reported in t-ANLL,[30,34] was evident in 2 of 3 patients with a prior history of chronic benzene poisoning, although other clinicopathologic series of benzene-induced leukemias have not noted increased numbers of basophils.[4,13,14] Also, basophilia does not seem to be a typical feature of chronic benzene toxicity.[35]

Treatment-related leukemias, which may demonstrate a preleukemic phase,[30-33] are generally considered distinct clinicopathologic entities with characteristic non-random cytogenetic changes.[30,36,37] Morphologic and hematologic similarities between our benzene-exposed cases and t-ANLL suggest an overlap in pathogenesis, perhaps including damage to marrow stem cells and to extra-medullary mediators of carcinogenesis. One of the metabolic products of benzene postulated to be leukemogenic includes trans-trans-muconaldehyde, which shares functional similarities with alkylating agents.[38] Non-random abnormalities of chromosomes 5 and 7 have been reported among patients with ANLL and past occupational exposure to either solvents or petroleum products[39,40] and subjects with t-ANLL following alkylating agent therapy.[36] More recently, Faglioli *et al.*[41] noted that the clinicopathologic features of ANLL following exposure to organic solvents also resembled those seen in t-ANLL. Another metabolize of benzene, hydroquinone, may inhibit the production of interleukin-1, a cytokine necessary for hematopoiesis.[42] These and other potential mechanisms of benzene hematotoxicity and carcinogenicity were recently reviewed by Cox.[43]

Acute promyelocytic leukemia has been reported infrequently in benzene-exposed groups[4] as well as in t-ANLL.[30-33] Although ANLL-M3 occurred in at least 4 patients in this series, its general representation among the subtypes of ANLL was similar to its distribution in *de novo* ANLL in China.[27]

MDS The occasional reports of preleukemia in association with benzene exposure[4,14] have only rarely included descriptions of dysplasia, such as megaloblastoid dyserythropoiesis.[4] To our knowledge, diagnoses of MDS *per se* have not been previously reported in benzene-exposed workers, perhaps due in part to the relatively recent recognition of some of these disorders.[18] Among benzene-exposed workers in general, reports of dyspoiesis have usually been limited to the rare occurrence of the pseudo-Pelger-Huet anomaly.[35,44] To date, dysplastic findings have not been observed in pancytopenic patients with chronic exposure to benzene.[45]

It is likely that, with increasing appreciation of various types of hematologic dyspoiesis, MDS may be recognized more often among benzene-exposed subjects, enabling further characterization of the dysplastic features associated with benzene toxicity. Correlations between specific cytologic and cytogenetic aberrations might aid in understanding the genetic basis of morphologic dysplasia, as suggested by the possible association reported between pseudo-Pelger-Huet anomaly and monosomy 17.[46] A study of the natural history of benzene-related MDS, including its possible progression to acute leukemia as reported in t-ANLL,[30-33] should help elucidate mechanisms of leukemogenesis.

CGL Although secondary CGL has been reported following chemotherapy,[47] it is mainly considered to be radiogenic.[48] Other clinicopathologic series of benzene-exposed workers have found variable proportions of CGL among reported hematopoietic malignancies.[6,14] Among all benzene-exposed workers in our cohort, CGL accounted for approximately 11% of hematologic malignancies. The four patients with CGL included in our histopathologic review generally showed features characteristic of that diagnosis,[49] as reported in other benzene-exposed workers with this disorder.[6,14] However, dysplastic changes were noted in all cases, and two subjects (numbers 20 and 22) were relatively young at diagnosis, given that CGL typically does not show a sharp increase in incidence

until after age 50.[27] The absence of basophilia in the latter patient was unusual, but has been noted in atypical CGL.[50]

Malignant lymphoma Although lymphoma and related disorders (ML) accounted for approximately 24% of the hematopoietic malignancies among benzene-exposed patients in our series, to date there have been only scattered clinicopathologic reports of ML in benzene-exposed workers, as summarized recently by Aksoy.[12] Most of these descriptions have utilized older classification systems, thus limiting comparisons with our cases. It is noteworthy that two of the four cases of NHL among benzene-exposed patients in this series for whom slides were reviewed represent one subtype of lymphoma as classified by the Working Formulation, although this could represent a chance observation, given the small numbers. Further investigations including immunohistochemical studies as well as histopathologic review should help to clarify the relationship of NHL subtypes to benzene exposure.

Other diagnoses There have been occasional clinicopathologic descriptions of ALL in benzene-exposed workers.[4,6,14,51] Leukocyte counts (median: 4,200/uL; range 1,700–39,000/uL) cited in these reports tend to be somewhat lower than in de novo ALL,[52] but the cases seem otherwise typical. Clinicopathologic features of our patient were also similar to those of de novo ALL.[52]

Although the association between benzene exposure and pancytopenia or aplastic anemia (AA) is well established,[1] there is considerable variability in bone marrow cellularity among pancytopenic patients, even when clinical and other hematologic features are similar.[45] Although benzene-related AA is frequently accompanied by an absolute lymphopenia,[45] a mild relative lymphocytosis was noted in the patient for whom histopathologic material was reviewed. Dyserythropoiesis was minimal in this subject, in accordance with previous reports of benzene-related AA.[45]

The marked degree of toxic changes observed in erythropoietic cells in Patient 31 seems to have not been previously reported among benzene-exposed workers. Cytoplasmic vacuolization of erythroid (n = 1) or myeloid cells (n = 2) was noted on bone marrow examination in 3 apparently asymptomatic benzene-exposed workers with peripheral blood cytopenias, all of whom also demonstrated maturation arrests in the myeloid series.[35] Similarly, cytoplasmic vacuolization has been reported in the bone marrow of benzene-intoxicated rats.[53]

Marrow eosinophilia was also evident in Patient 31. Proportions of eosinophilic leukocytes greater than 8 per cent were noted in the peripheral blood of 6 of 217 benzene-exposed workers in one series,[35] and in 2 of 30 women with chronic benzene poisoning reported by Smith.[54] Relative or absolute numbers of eosinophils were not increased in the peripheral blood or bone marrow of the three patients in our series with prior diagnoses of chronic benzene poisoning.

Rapidly expanding knowledge of the importance of oncogenes in hematologic malignancies,[55] the application of molecular genetic techniques to hematology,[56] and characterization of the importance of the bone marrow stromal environment hold promise for identifying potential similarities, as well as differences, in the mechanisms of action of known leukemogens, such as benzene, radiation, and chemotherapy. It is hoped that the results of this clinicopathologic evaluation of hematologic neoplasms among benzene-exposed workers will encourage further incidence studies to clarify risks by subtype in the general population and in occupational cohorts with excessive hematopoietic malignancies. In addition, cytogenetic and molecular studies of benzene-related leukemias, along with corresponding studies of t-ANLL, should deepen our insights into the underlying mechanisms of leukemogenesis.

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