The Familial Occurrence of Polycythemia Vera: Report of a Father and Son, With Consideration of the Possible Etiologic Role of Exposure to Organic Solvents, Including Tetrachloroethylene

By William D. Ratnoff and Ronald E. Gress

The occurrence of polycythemia vera (PV) have been described since Nichamin's initial report in 1907. Earlier cases have been reviewed by several authors, who presented new cases and accepted as authentic only a few of those previously recorded.2-5

We shall present two cases that are unique in that PV occurred in successive generations.

CASE REPORTS

Case 1

Patient 1 was a Jewish executive who was 53 yr old when PV was recognized in 1955. His father and mother, a half-brother and half-sister, and two of his three children were known to have PV or any other blood disorder. He directed a firm that distributed industrial organic solvents. Although he did not handle solvents himself, there was often spillage of the agents in the plant. He had been exposed occasionally to the vapors of several volatile hydrocarbons, especially Stoddard solvent. He had had no known exposure to benzene.

The evolution of PV was documented by a succession of routine blood studies (Table 1). For several years, he had noted pruriitus after bathing. In 1955, he developed spots before the eyes, dull headaches, and later burning, itching, and redness of the eyes.

On admission to The Johns Hopkins Hospital in 1955, he appeared phtheoric, with suffusion of the eyes, redness of the pharynx, and distention of the retinal veins. The spleen was palpable. Hematocrit was 61%, white cell count 17,800, and platelet count 294,000. The gradually increasing hematocrit, splenomegaly, and leukocytosis suggested the diagnosis of PV.

Within 4 days, 2150 ml of blood was withdrawn; the hematocrit declined to 49%, and the symptoms subsided. Thereafter, the hematocrit was maintained at about 45% by venesection. By 1965, the liver had enlarged and the spleen had extended to the umbilicus and to the right of midline. Hematocrit had declined to 35%, with white cell count 24,500 and platelet count 272,000. Biopsied marrow was hypocellular, but chromosomal studies were normal. The anemia did not respond to treatment with iron, and the disease was thought to have transformed into myelofibrosis and myeloid metaplasia. Anemia became more severe in subsequent years, with hematocrit values as low as 27%. Leukocytosis persisted, and a few myelocytes appeared in the blood. In 1975, the patient was treated briefly with oxymethalone without response. In 1978, at age 75, the patient had persistent anemia but needed only an occasional blood transfusion. White cell count remained elevated, and differential count showed a few myelocytes and nucleated red cells.

The patient, an only child, has two children (Table 2, Fig. 1). One son, age 46, is well with a hematocrit of 43% in 1977. His younger son is described as case 2.

Case 2

Patient 2 was a 44-yr-old chemical salesmen when he was recognized to have PV in 1977. For 22 yr, he had worked in his father's chemical supply firm, in a division that distributed tetrachloroethylene to dry-cleaning plants. His responsibilities included checking for leaks of the chemical by measuring its atmospheric concentration in clients plants. When searching for leaks, the patient had been exposed transiently to concentrations between 50 and 1000 ppm, which made him feel giddy and “high”; the concentration often exceeded the maximum exposure limit set by Federal Occupational Safety and Health Act of 300 ppm for 5 min out of any 3 hr. He had had negligible exposure to other vapors, including benzene.

Before the onset of illness, the patient was known to have had a normal hematocrit; in 1960, it was 48% and in 1965, 44%.

The patient's complexion had been ruddy for at least 20 yr; the redness increased during the year before admission. Pruritus after bathing and burning of the eyes had troubled him for 2 yr. The patient's internist found that the hematocrit was 71%, and made a tentative diagnosis of PV.

On admission to The Johns Hopkins Hospital in 1977, he appeared phtheoric and sunburnt, with suffusion of the eyes, redness of the pharynx, distention of the retinal veins, blanching erythema of the face and hands, and dusky cyanosis of the lips. The spleen was palpable. Hematocrit was 73%, white cell count 17,500 with 15% bands, and platelet count 302,000. Red cell volume was 590 ml or 72.7 ml/kg (normal: 25–35), with a normal plasma volume (2727 ml). Arterial oxygen saturation and serum vitamin B12 concentration were normal. Biopsied marrow was hypercellular with increased numbers of all marrow elements as well as a mild increase in reticulocyte fibers. Cyto genetic studies were not done. Electrocoagulation of the hemoglobin and hemoglobin oxygen affinity were normal.

Within 8 days, 3250 ml of blood was withdrawn, and the hematocrit fell to 59%. The patient appeared much less phtheoric, and the symptoms regressed, although they did not subside completely. Thereafter, the hematocrit was maintained at about 47% by venesection.

In 1979, the spleen extended 4 cm below the left costal margin; white cell count was 26,000 with 12% bands, 64% neutrophils, 13%
lymphocytes, 9% monocytes, and 2% basophils; platelet count was 616,000. These data confirmed the diagnosis of PV.

His two sons, ages 17 and 19, are both in excellent health. The hematocrit of the older son was 43%.

**DISCUSSION**

**Familial/Genetic**

Evaluation of reports of familial PV is complicated by the difficulty of separating PV from secondary forms of polycythemia. In 1968, the Polycythemia Vera Study Group (PVSG) defined diagnostic criteria for selecting patients for prospective investigation:7 (1) the total red cell volume must be elevated in the face of normal total plasma volume and normal arterial oxygen saturation; (2) splenomegaly or any two of these findings must be present: leukocytosis, thrombocytosis, elevated leukocyte alkaline phosphatase score, or elevated serum vitamin B12 concentration. These criteria enable us to make positive diagnoses of PV in both the father and son.

Many of the reported cases of familial PV do not supply sufficient information to evaluate whether they fulfill PVSG criteria. Some are tantalizing: for example, Bernstein described a 56-yr-old man with splenomegaly and elevated hemoglobin and red cell count whose 23-yr-old son had had elevated red cell counts for over a year. Wieland alleged the occurrence of PV in three generations and presented evidence for PV in siblings in both second and third generations.

Only the cases of Lawrence and Goetsch, Levin and his associates, and Manoharan and Garson appear to fulfill current-day criteria for diagnosis of familial polycythemia vera. In each instance, the affected individuals were siblings (Table 2, Fig. 1). Additionally, Erf described five related individuals, two of them brothers, who were said to have PV, but insufficient data were reported to evaluate the diagnosis. In the cases presented here, PV affected two generations, father and son.

The relatively high frequency of PV in Jews and low frequency in blacks suggest that there may be genetic factors that predispose to the disease. The rarity of reported familial cases demonstrates that the disease is not directly inherited, and a genetic component must be at best a precondition rather than a major factor in pathogenesis. Distribution of cases within families is consistent with single or multiple gene inheritance of the predisposing condition.

**Environmental**

In 1971, Modan reviewing the role of environmental agents in the etiology of PV, noted the difficulty of evaluating histories of chemical exposure.

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**Table 2. Laboratory Data in Familial Polycythemia Vera**

<table>
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<tr>
<th>Reports</th>
<th>Chromosomes</th>
<th>Elevated Red Cell Volume (Male &gt; 36 ml/kg Female &gt; 32 ml/kg)</th>
<th>Normal Arterial Oxygen Saturation (&gt;92%)</th>
<th>Splenomegaly (at Time of Diagnosis)</th>
<th>Thrombocytosis (400,000) (x 10^3)</th>
<th>Leukocytes (&gt; 12,000)</th>
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*PVSG criteria for the diagnosis of PV are described in the text.*
severe hypoplasia with pancytopenia have been extreme marrow exposure. Both exposure have been reported. Mondon and André5 recorded elevated red cell volume, although arterial oxygen saturation was not elevated. The tetrachloroethylene preparation to which solvents, our patients had no history of benzene exposure. Nonetheless, the possible etiologic role of an environmental agent cannot be excluded. Kilgore4 reported polycythemia in a feather dyer who had tasted the dyes he used. The dyes contained aniline or natural dyes and inorganic salts, but apparently neither benzene nor tetrachloroethylene. This patient had an elevated red cell volume, splenomegaly, and leukocytosis. Although arterial oxygen saturation and platelet count were not recorded, the diagnosis of PV was likely.

A few examples of PV associated with benzene exposure have been reported. Mondon and André5 observed PV in two men after occupational benzene exposure. In 1938, Hunter16 reported erythrocytosis in 11 of 89 persons with a history of chronic benzene exposure. Both extreme marrow hyperplasia and severe hypoplasia with pancytopenia have been recorded.17,18

Many authors have associated occupational benzene exposure with other myeloproliferative disorders, myeloid metaplasia,11-23 and chronic myelocytic leukemia (CML).24,25 as well as with the acute leukemias, especially acute myeloblastic leukemia.26-29 Aksoy29,31 described two familial occurrences of acute leukemia among 34 shoe-factory workers with leukemia and a history of benzene exposure. Despite the possibility of contact with many organic solvents, our patients had no history of benzene exposure. The tetrachloroethylene preparation to which patient 2 was exposed was not contaminated with benzene (analytic sensitivity of <1 ppm).30 Nevertheless, we cannot be sure that solvents to which our patients were exposed were not contaminated with toxic agents. For example, our patients were exposed

to Stoddard solvent, a mixture of hundreds of unidentified hydrocarbons that is thought to be safe because it is uncontaminated with benzene.31,32 Five cases of aplastic anemia after chronic exposure to Stoddard solvent have been reported,32,33 but an etiologic relationship is difficult to establish because persons exposed to Stoddard solvent are usually in contact with many other potentially toxic agents. No cases of PV after chronic exposure to Stoddard solvent have been reported.

The son’s (patient 2) chronic exposure to tetrachloroethylene suggested the possibility of this agent as an environmental factor, but no reports associating tetrachloroethylene with PV were found. Remarkably, however, Blattner and his associates34 described chronic lymphocytic leukemia (which is etiologically dissimilar from PV) in a father and four of his five offspring, all of whom had worked in the dry-cleaning business; perhaps these individuals had been exposed to tetrachloroethylene. Major nonhematologic effects, such as liver disease, are well known.35 No adverse hematologic effects were found in several studies of animal or human subjects.36-39 The occurrence of hepatocellular carcinoma in mice treated with tetrachloroethylene by gavage40 suggested a possible carcinogenic role for this agent, which is now used in at least 75% of existing plants.41 A retrospective analysis of the causes of death among laundry and dry-cleaning workers42 disclosed excesses of deaths from lung and cervical cancer, which were thought to reflect the workers’ low socioeconomic standing. Slight excesses of deaths from leukemia and liver cancer were more difficult to explain and pointed to a possible leukemogenic role for tetrachloroethylene.

The three myeloproliferative syndromes, myeloid metaplasia, CML, and PV are currently believed to be panmyelopathies that result from a clonal proliferation of a pluripotential hematopoietic stem cell.43-48 The etiology of this proliferation remains unknown. Since other clonal diseases of the hematopoietic stem cell are known to occur with increased frequency in individuals exposed to certain chemical agents, the possibility exists that such exposure may be a factor in the pathogenesis of PV.

In the family that we report, the two cases of polycythemia vera may have occurred by chance alone. On the other hand, genetic factors may have predisposed to the disease. There is the additional possibility that exposure to chemical agents is a precipitating factor in persons with a genetically determined latent susceptibility to the disease. Experiments in animals demonstrate that susceptibility to neoplasms induced by chemical agents is to a large extent determined by genetic factors.49
ACKNOWLEDGMENT

Dr. C. Lockard Conley provided clinical data. Dr. Anna M. Baejter was helpful in assessing environmental factors.

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