Immunological disorders and malignancies in five young brothers

DAVID T. PURTILO, JOHN A. RIORDAN, DANIEL DEFLORIO, JAMES P. S. YANG, PETER SUN, AND GORDON VAWTER

From the Departments of Pathology of the University of Massachusetts Medical School, Worcester; St. Vincent Hospital, Worcester; Boston Children's Hospital Medical Center; and Department of Pediatrics, the Fallon Clinic, Worcester, Massachusetts, USA

SUMMARY Five brothers of from 6 to 18 years of age experienced immunological or neoplastic disorders during an 8-year interval. 2 boys succumbed to glioblastoma multiforme, another to metastatic carcinoma, and the 2 surviving brothers had a histiocytic lymphoma and idiopathic thrombocytopenia purpura, respectively. The mother of the boys was healthy, but her twin sister died in utero of birth defects. We suggest that an intrinsic cellular defect inherited from their mother rendered the boys vulnerable to oncogenesis. Defective genes may render some families susceptible to cancer (Lynch, 1967; Mulvihill, 1975): inherited lymphomas (Potolsky et al., 1971., Buehler, et al., 1975; Purtilo et al., 1975; Purtilo et al., 1976); brain tumour (Isamat et al., 1974), and many other malignancies (Drews, 1962; Lynch, 1967; Chatten and Voorhess, 1967; Fraumeni et al., 1975) have been reported. We report 5 brothers with the unusual combination of lymphoma, astrocytoma, carcinoma, and idiopathic thrombocytopenia purpura, respectively.

Pedigree

The family pedigree is given in the Fig. The mother of the 5 boys was a twin: her twin died in utero with severe malformations. 3 elderly persons in generation 1 died of carcinoma, and a distant maternal 14-year-old male cousin (not on pedigree) died of acute myelogenous leukaemia. The father of the boys had bronchiectasis 20 years previously. The parents and one boy (Ri.P., pedigree no. 26) were karyotyped in 1969; no abnormalities were seen.

Case reports

Case Ri.P. An 8½-year old boy (pedigree no. 26) was hospitalized in 1965 with a superior vena cava syndrome preceded by pneumonia 3 months previously. On physical examination temperature was
Immunological disorders and malignancies in five young brothers

37.8°C, pulse 80/min, respiration 26/min, and blood pressure 104/56 mmHg; height 125 cm and weight 26.4 kg. Marked oedema of the face and neck and prominent veins were seen over the upper abdomen, chest, and extremities. Inspiratory stridor was heard and cervical and axillary lymphadenomegaly was noted.

Chest x-ray showed a widened superior mediastinum. Hb was 12.5 g/dl; WBC 11 000/mm³ (11.0 x 10⁹/l) 77% neutrophils, 4% bands, 19% lymphocytes; platelets 431 000/mm³ (431 x 10⁹/l). Heterophil agglutination test negative. Biopsies of scalene and posterior cervical lymph nodes showed slight fibrosis and hyperplasia of the sinus histiocytes, and of a mediastinal lymph node, small but active germinal centres, prominent sinus histiocytosis and numerous arborizing blood vessels with plump endothelial lining cells; plasma cells were rarely seen. A diagnosis of cancer was not made.

Nitrogen mustard and cobalt therapy was given. The mediastinal mass shrank, the oedema subsided, and he was discharged to home care. He was symptom free for 2 years.

In 1967 he developed bloody diarrhoea, and investigations showed Hb 11·8 g/dl; WBC 12 800/mm³ (12.8 x 10⁹/l) (73% neutrophils, 4% bands, 21% lymphocytes and 1% eosinophils); platelets adequate; total protein 53 g/l and albumin 31 g/l. Serum IgA 55 mg/100 ml (slightly decreased), IgM 109 mg/100 ml (normal), and IgG 600 mg/100 ml (slightly decreased).

Exploratory laparotomy showed a poorly differentiated carcinoma involving the ileum, colon, rectum, ureters, and urinary bladder. He was treated with actinomycin D and 1500 rads irradiation. He was plagued by recurrent intestinal obstructions during the final year of life, and a transverse colostomy was performed. He died in 1970.

At necropsy the thymus gland was markedly atrophic, thymocytes were depleted, and Hassall's corpuscles were dilated. The splenic lymphoid sheaths were normal; however, they contained many immature lymphoid cells. Lymph nodes were depleted of lymphocytes and the sinus lining cells were prominent. Disseminated intravascular coagulation was evident; thrombi were lodged in blood vessels in the lymph nodes, kidney, and spleen. The liver showed mild portal fibrosis and Kupffer cells were prominent. An occult cytomegalovirus infection was seen in the rectum, liver, spleen, lymph nodes, and lungs. Vascular abnormalities were seen in the brain, including cavernous haemangiomas of the cerebrum and arteriovenous malformations of the cerebellum, pons, and spinal cord. No telangiectasia of the skin was seen.

Case K.P. A 6-year-old boy (pedigree no. 28) was hospitalized in 1966 with intussusception. Hb was 8·2 g/dl, WBC 8600/mm³ (8·6 x 10⁹/l) (neutrophils 52%, lymphocytes 46%, and monocytes 2%); platelets adequate. Exploratory laparotomy showed a tumour in the colon and thus a right hemicolectomy was performed. One large lymph node adjacent to the inferior mesenteric artery was noted, but was not resected because an attempt at removal may have compromised the blood supply to the ileum. In the caecum a 6 x 4 x 4 cm submucosal tumour which circumscribed one half of the bowel was seen. Microscopically the tumour was a histiocytic lymphoma. Marked enlargement of Peyer's patches and germinal centres in the adjacent lymph nodes was seen.

Cobalt radiotherapy 2000 rads was given. A 'second look' operation was performed the following year. The mass observed at the first laparotomy was necrotic and calcified; however, a nearby lymph node showed enlarged germinal centres.

He remained asymptomatic except for a bout of diarrhoea in 1974, and was evaluated by us during a 3-month period in 1975. Serum immunoglobulin concentrations were IgG 1030, IgA 57 (slightly decreased), and IgM 144 mg/100 ml. A Monospot test, rheumatoid factor, and antinuclear antibody studies were negative. Hb was 12·7 g/dl, haematocrit 36%, and platelets adequate; WBC 4900/mm³ (4·9 x 10⁹/l) (57% neutrophils, 3% bands, 37% lymphocytes, and 3% eosinophils). Lymphocytes formed 62% sheep erythrocyte-rosetting cells, and they responded normally to stimulation by phytohaemagglutinin and pokeweed mitogens.

Case S.P. A 9-year-old boy (pedigree no. 27) was hospitalized in 1968 for headaches and recurrent vomiting of 3 weeks' duration. No palpable lymph nodes nor localizing neurological signs were elicited. Blood count normal; Hb 13·9 g/dl; WBC 8700/mm³ (8·7 x 10⁹/l) (86% neutrophils, 5% bands, 8% lymphocytes, and 1% monocytes); platelets normal. One month later signs of a brain tumour became evident, and craniotomy showed a grade IV astrocytoma (glioblastoma multiforme). He died within a few weeks.

Case R.P. A 13-year-old boy (pedigree no. 29) was found unconscious in 1969 at school. A haematoma was noted over his forehead and blood behind the right tympanic membrane. Hb 11·6 g/dl; WBC 14 700/mm³ (14·7 x 10⁹/l) (87% neutrophils, 10% lymphocytes, 3% monocytes); platelets normal.

Brain scan showed a circumscribed area of increased uptake in the left parietal region. Exploratory craniotomy showed a large grade IV
astrocytoma (glioblastoma multiforme) involving the left parietal region. Cobalt therapy 4000 rads was given and he was discharged. He died 7 months later. At necropsy the brain weighed 1720 g and contained a large partially necrotic astrocytoma. The lymphoid organs appeared normal.

Case M.P. The fifth brother (pedigree no. 25) was hospitalized in 1973 at age 18 with bruising. He was in good health until 3 weeks before the illness when he developed a cough, aches, and pains. 2 days before admission he had developed generalized bruising and bleeding gums. The liver was palpable, but the spleen was not.

Hb 14.7 g/dl; WBC 6500/mm\(^3\) (6.5 \(\times\) 10\(^9\)/l) (45% neutrophils, 48% lymphocytes, 1% monocytes, and 6% eosinophils); platelets <500/mm\(^3\) (0.5 \(\times\) 10\(^9\)/l). Many atypical lymphocytes and giant young platelets were seen in the peripheral blood smear. Bone marrow showed a normal picture; megakaryocytes were seen in various stages of maturation and occasionally were invaded by lymphocytes or thrombocytosis was present.

Monospot test (Ortho Diagnostic), syphilis serology, and Australia antigen tests were negative. Serum protein electrophoresis normal. Serum complement fixation determination for cytomegalovirus (CMV) was reactive in 1:256 dilutions and considered consistent with recent CMV infection.

He was given 60 mg prednisone daily for 2 weeks and the dose was gradually decreased. His platelet count rose to 30,000/mm\(^3\) (30.0 \(\times\) 10\(^9\)/l), the ecchymoses disappeared, and he was discharged. He was well 3 years after the episode of thrombocytopenic purpura.

Discussion

In a survey of childhood cancers in 1967, Miller (1968) found 20 families with more than one cancer in children, and of these there were 6 where one child had died with brain tumour and had a sib with a sarcoma. In 1976, Li et al. described 38 families with cancer in 2 or more children. Included in their report was an incomplete report of the family described here; subsequent to that report a second boy (R.P.) has also died of brain tumour, and thrombocytopenic purpura has occurred in the fifth brother (M.P.). The occurrence of additional malignancies in the family illustrates the need for careful monitoring of cancer families for malignancies.

The occurrence of congenital anomalies in the mother's twin suggests that an agent acting in utero may have altered the germ cells of the mother. A mutant maternal gene either could have produced intrinsic cellular defects in her sons rendering them susceptible to carcinogenic agents or immune surveillance could have been rendered faulty. Immune surveillance has captured the attention of many investigators as a hypothesis explaining the occurrence of malignancies in immunosuppressed patients (Schwart, 1975). Potentially, defective immune surveillance could have permitted the malignancies to occur. But except for the lymphoma occurring in K.P., the histological of types of tumours in the brothers are uncommon in immunodeficient children.

5 boys had subtle abnormalities of immunity: 2 of the boys (R.I.P. and K.P.) had slightly decreased immunoglobulin levels, 2 had lymphopenia (S.P. and R.P.). M.P. was the most recent brother experiencing an illness, thrombocytopenic purpura, presumed to be an autoimmune process. Malignancies probably occur more commonly in individuals with autoimmune disorders (Brunjes et al. 1961).

Recently we described an X-linked recessive lymphoproliferative syndrome (Purtilo et al. 1975; Purtilo, 1976) in which at least 20 boys have succumbed from a variety of B lymphocyte lymphomas. Underlying immunodeficiencies probably permitted fatal lymphoproliferation to occur in the X-linked syndrome. In contrast, intrinsic cellular defects, rather than immunological defects, were probably partially responsible for the carcinogenesis in the 5 brothers described here.

References


Immunological disorders and malignancies in five young brothers


Correspondence to Dr. D. T. Purtilo, Department of Pathology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, Massachusetts 01605, U.S.A.

The following articles will appear in future issues of this journal:


Serotonin metabolism in cystic fibrosis. M. W. Partington and A. C. Ferguson.


Histiocytosis X. D. G. Sims.

