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philtrum' and high serum potassium (Palmer et al., 1977).

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G. B. CÔTÉ, S. PAPADAKOU-LAHOYANNI, AND S. SYRRAKIS
Institute of Child Health and Paediatric Unit,
Aghia Sophia Children's Hospital, Athens 617,
Greece

References


Requests for reprints to Dr G. B. CÔTÉ, Institute of Child Health, Athens 617, Greece.

Osteosarcoma in a patient with Hutchinson-Gilford progeria

SUMMARY A 13-year-old female with Hutchinson-Gilford progeria, who developed an osteosarcoma of the right chest wall, is reported. This is the first reported association of a malignant neoplasm with this syndrome.

Sir Jonathan Hutchinson first described a patient with 'congenital absence of hair and its appendages' in 1886. A second patient was reported in 1895 by Hutchinson. Gilford re-examined these patients and in 1904 described the pathological changes of the disease and termed these clinical findings 'progeria'. Many patients have been reported in the intervening 75 years (DeBusk, 1972). The present report is the first example of a malignancy diagnosed in a patient with progeria.

Case report

A 13-year-old white female (Fig. 1) presented with a dry cough and stabbing right anterior superior chest pain. She had a month long history of increasing fatigue. The early childhood history of this patient has been previously reported, along with in vitro replicative studies of her fibroblasts, by Martin et al. (1970). The typical clinical features of progeria were noted at approximately 2 years of age and were even more dramatic at the present admission. No pubertal secondary sex changes had occurred. In spite of the loss of vision in one eye because of infectious complications following strabismus surgery at age 2½ years the patient has been a 'straight A' student.

She was 103 cm tall with a weight of 13 kg. The right chest was dull to percussion with decreased breath sounds and scattered rales. Chest x-ray (Fig. 2a) revealed a large extra-pleural mass with loss of integrity of the 7th, 8th, and 9th ribs. A percutaneous biopsy was performed with a histological diagnosis of chondrosarcoma. No metastases were identified. An en-bloc resection of a portion of the right chest wall and ribs 5 to 9 was performed (Fig. 2b). The chest wall was closed with Marlex, and considering the magnitude of the procedure the patient had an uncomplicated postoperative course with ventilatory support for only 24 hours. Grossly, the resected tumour was not encapsulated. It consisted of the major portion of ribs 5 to 9 and their accompanying muscles, except the latissimus dorsi. The tumour mass was composed of fibrous yellow-grey connective tissue with local calcifications. The margins of resection were free of

Fig. 1 Patient at 13 years; she is wearing a wig.
tumour. Microscopically, the tumour was highly variable. A predominant feature was the presence of neoplastic cartilage with focal calcification. Other regions showed highly vascular, atypical, loose connective tissue. A few areas were more myxoid in character. The typical histology of osteosarcoma was characterised by pleomorphic cells with hyperchromatic nuclei and relatively sparse, spindle-shaped cytoplasm (Fig. 3). Mitotic figures were frequent. A typical osteoid matrix with its faintly eosinophilic, glassy appearance was seen lying between and surrounding these malignant cells.

Positive right cervical nodes were identified 6 months postoperatively. Chemotherapy with doxorubicin was begun. Surgical excision of recurrent tumour involving the diaphragm, lung, and chest wall...
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was performed. Additional local excision was performed 8 months later. Radiation therapy of 5000 rads to the thoracic spine was given. Pulmonary function studies, after completion of this therapy, identified moderately severe restrictive changes without obstructive change. An electrocardiogram was normal. Death occurred 16 months after diagnosis of pulmonary failure and pneumonia.

At necropsy the typical features of Hutchinson-Gilford progeria were identified. The right thoracic cavity had extensive adhesions and the right lung was markedly fibrotic. No gross tumour was identified in the right chest wall or lung. The left lung was diffusely dense and congested. The heart was enlarged and both ventricular walls were hypertrophied. The aortic valve and the coronary arteries showed moderately severe calcific atherosclerosis. The aorta was severely involved with thickened atherosclerotic streaking and calcific plaques. The liver, gallbladder, spleen, pancreas, kidneys, and gastrointestinal tract were normal. No evidence of metastatic tumour was seen in a radiograph of the removed vertebral column (T3 to T11). The ovaries and uterus were small and prepubertal in appearance. The brain showed a normal gyral surface pattern. No visible atherosclerosis was found in the cerebral vessels or circle of Willis.

Microscopical sections of the left coronary artery and aorta had typical changes of severe atherosclerosis. The right lung showed marked atelectasis with prominent radiation change. No microscopical evidence of tumour was present. The left lung was involved with acute organising pneumonia. In the skin, decreased numbers of hair follicles and sebaceous glands were observed. Microscopy of the liver, spleen, thymus, pancreas, kidney, ovary, uterus, gastrointestinal tract, pituitary, thyroid, and adrenals was normal.

Discussion

Progeria is characterised by short stature, diminished subcutaneous tissue, craniofacial disproportion, micrognathia, beaked nose, alopecia, prominent scalp veins, thin dry skin, skeletal changes, and the general appearance of extreme aging. The pathogenesis of this process is unknown, but it has frequently been suggested that progeria is an example of 'premature aging'. Certainly these patients have the clinical appearance of premature aging, but as has been suggested by Spence and Herman (1973), histological and ultrastructural findings are not typical of the aging process, but rather of a degenerative process of mesodermal tissue. Certain clinical features of the aging process, such as mental deterioration and malignancy, are notably absent in reported patients with progeria.

The present patient is the first reported example of malignancy in a patient with Hutchinson-Gilford progeria. The frequent early death of progeria patients from cardiovascular disease (median survival 13 years) shortens their life span so drastically that the development of malignancy in these patients may not be observed. Certainly the incidence of malignancy in the general population is directly related to the increasing age of the patient. Thus, it might be expected that if progeria is actually an example of premature aging, malignancy would be seen earlier and more frequently in progeria patients. Malignancy might also occur more frequently in progeria, even if it is not a syndrome of premature aging, if predisposing factors other than aging are present.

Patients with Werner's syndrome, perhaps a clearer example of a syndrome of premature aging, have an increased incidence of malignancy (Epstein et al., 1966; Bjornberg, 1976). Of patients with this diagnosis, 10 to 15% will develop malignancy. The age of onset for a particular lesion is younger than expected for the same lesion in the general population. These patients develop tumours of a variety of histological types, and a single pathological entity does not predominate.

Recent investigation of progeria has centred around the in vitro behaviour of fibroblasts from such patients: the replicative life span of these cells is diminished (Martin et al., 1970; Rautenstrauch et al., 1977). This finding was previously confirmed in the present patient by Martin et al. (1970). Reduced activity of heat stable enzymes has also been observed (Goldstein and Moerman, 1975). Perhaps more important for the occurrence of malignancy are recent observations regarding gamma radiation sensitivity (Epstein et al., 1973; Rainbow and Howes, 1977) and loss of cell surface antigens in cultured fibroblasts (Singal and Goldstein, 1973). Cells from patients with progeria show reduced DNA repair after exposure to gamma radiation (Epstein et al., 1973; Rainbow and Howes, 1977). Reduced ability to repair DNA damage could lead to mutation and potentially neoplastic transformation. Such patients, as is the case with ataxia telangiectasia (Taylor et al., 1975), might respond much more dramatically to radiation therapy. The prominent pulmonary radiation change in the present patient supports this suggestion. Singal and Goldstein (1973) have observed the failure of progeroid fibroblasts to express HLA surface antigens in culture. The lack of expression of cell surface antigens could allow proliferation of neoplastic cells in vivo without the action of normal immunological control mechanisms. An increased predisposition to mutation from gamma radiation, or other mutagens, accompanied by alteration in cell surface antigens may predispose progeria patients to malignancy. As
therapy for atherosclerosis and coronary artery disease in these patients becomes more effective, more progeria patients may be identified with malignancy.

Charles R. King, John Lemmer, John R. Campbell, and Arnold R. Atkins

Department of Obstetrics and Gynecology; Division of Medical Genetics; Department of Pathology; and Division of Pediatric Surgery, University of Oregon Health Sciences Center, Portland, Oregon, USA

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Requests for reprints to Dr Charles R. King, Department of Obstetrics and Gynecology, University of Kansas Medical Center, 39th and Rainbow, Kansas City, Kansas 66103, USA.

The Aase syndrome in a female infant

summary This report describes a 2-month-old female with the Aase syndrome, bringing to 8 the total number of cases of this disorder. Features include triphalangeal thumbs and congenital hypoplastic anaemia. The occurrence of this disorder in sibs born to unaffected parents and in both sexes makes autosomal recessive inheritance the most likely aetiology.

This report describes a female infant with triphalangeal thumbs and congenital erythroid hypoplasia. Seven similar cases of this disorder, referred to as the Aase syndrome, have been described (Harvey, 1966; Aase and Smith, 1969; Murphy and Lubin, 1972; Jones and Thompson, 1973; Terheggen, 1974; van Weel-Sipman et al., 1977).

Case report

The patient was a 2-month-old Mexican female. She was born to a 20-year-old, gravida 1 woman after an uncomplicated 40 week gestation; birthweight was 2.9 kg. Length and head circumference were 51 cm and 35.5 cm, respectively. Paleness and progressive lethargy were noted at 6 weeks of age. She was referred at 2 months of age for evaluation of severe anaemia. Weight was 4.3 kg (25th centile for age), length was 54 cm (25th centile), and head circumference was 38 cm (50th centile). Positive physical findings included a grade 2/6 systolic ejection murmur at the lower left sternal border, and striking hand abnormalities consisting of digitalised thumbs and hypoplastic thenar eminences (Fig. 1). Dermatoglyphs were normal except for a horizontal pattern over the thenar areas.

Haematological evaluation showed: haemoglobin 4.3 g/dl, haematocrit 14%, reticulocyte count 0.8%, white blood cell count 5.8 × 10^9/l with 33% neutrophils, 7% bands, 39% lymphocytes, 16% mononuclear cells, and 5% eosinophils. Platelet count was 600 × 10^9/l. Bone marrow showed a pure red cell aplasia with a myeloid to erythroid ratio of 75 to 1 and normal numbers of megakaryocytes. Studies of cultured bone marrow showed a normal 46,XX karyotype, with no evidence of chromosomal breakage such as has been demonstrated in the Fanconi pancytopenia syndrome. Significant radiographic abnormalities included a triphalangeal right thumb, hypoplasia of the left thumb (Fig. 2), and a single bifid thoracic vertebra. Cardiac evaluation, including chest
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C R King, J Lemmer, J R Campbell and A R Atkins

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