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...
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...
Case reports

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.

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The Aase syndrome in a female infant

SUMMARY This report describes a 2-month-old Mexican 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 x 10^3/l with 33% neutrophils, 7% bands, 39% lymphocytes, 16% mononuclear cells, and 5% eosinophils. Platelet count was 600 x 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...