retardation. After reviewing photographs of the other cases and examining our patient, we propose that "lid p toesis" rather than "narrow palpebral fissures" is the common eye finding.

All cases described had short stature (average height 145-7 cm, range 136 to 156 cm). Testes were tiny in the 3 cases coming to necropsy, and clinically absent in the 2 living persons. Necropsy showed a small pituitary with normal cytology in 1 case, a normal pituitary in the second, and the pituitary was not mentioned in the third. The association of short stature and hypogonadism with a small pituitary gland in 1 patient, and gonadotropin levels in the lower limits of normal, by bioassay, in 2 patients, led to the interpretation that hypopituitarism was responsible for the endocrine abnormalities (Brun et al., 1974). Endocrine studies in our patient, however, showed normal pituitary responses as indicated by normal thyroid function, normal adrenal-pituitary axis, and normal growth hormone and gonadotropin secretion. Low testosterone levels in our case are in keeping with primary hypogonadism. We find no evidence to support hypopituitarism as a necessary part of any of the described cases.

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Waardenburg-like features with cataracts, small head size, joint abnormalities, hypogonadism, and osteosarcoma

SUMMARY A 32-year-old black man was observed with osteosarcoma and multiple anomalies, including deafness, hypopigmentation, cataracts, small head size, hypogonadism, and restricted joint mobility. The birth defects may comprise a new syndrome or combination of syndromes, of which the malignancy may be a part.

Case report

The patient was ascertained in June 1976, during an aetiological assessment of sarcoma patients on an surgical service.

Gestation, labour, and delivery were normal. The parents were a 16-year-old gravida 1, para 0, black woman, and an unrelated 16-year-old black man. Birthweight was 2.4 kg, and an umbilical hernia and clubfeet were present. Motor and speech development were delayed and at 2 years hearing was found to be impaired. Educational efforts were not made until age 12 when the patient was sent to a school for handicapped children. Greying of hair began at 12 years; beard growth began at about 18 years. He currently lives at home, cares for his personal needs, and has held two manual jobs.

The father's medical and family history were unavailable; the mother had no physical or hearing abnormalities. The only birth defect or pigmentary anomaly among the maternal half sibs and other maternal relatives was profound childhood deafness in an otherwise normal cousin. The maternal grand-aunt had an ovarian granulosa cell tumour, and the maternal aunt had uterine leiomyomata.
In November 1975, the patient was admitted to the National Cancer Institute with histologically typical osteosarcoma of the distal right tibia. Treatment included amputation, adjuvant chemotherapy, and BCG immunotherapy. The patient suffered cardiovascular collapse after receiving the first few millilitres of the seventh course of high dose intravenous methotrexate. This rare, presumably idiosyncratic response recurred on two additional drug challenges (Goldberg et al., 1977). Chemotherapy was completed with adriamycin, and he remains free of malignancy, 19 months after diagnosis.

On physical examination the patient weighed 62.6 kg and was 169 cm tall with eunuchoid body proportions (upper segment 80.5 cm, lower segment 88.5 cm, span 173 cm). The circumference of his normally shaped head was 53.5 cm (3rd centile for 18 years). He had a beaked nose (Fig. 1b). Scalp hair, eyelashes, beard, and chest hair were prematurely grey. Eyebrows, also grey, were bushy with medial flaring. Sparse hair was present on the arms and leg, and axillary and pubic hair were normal. Irides were blue with marginal brown pigmentation and no heterochromia (Fig. 1a). Funduscopia revealed posterior subcapsular cataracts and albinoid coloration with poor macular differentiation. Visual acuity was 20/60 bilaterally. Distances between the inner canthi, pupils, and outer canthi were 38 mm, 64 mm, and 92 mm. The inferior lacrimal puncta were situated normally, and tearing, taste, and smell were intact. The normally positioned ears lay flat against the head; the pinnae lacked lobules and had thickened lower helices. Tympanic membranes were normal. Air-conduction audiometry showed a profound hearing defect with minimal residual sound perception at low frequencies. Bone-conduction audiometry revealed a bilateral hearing loss of 60–70 dB at midfrequencies (500–2000 Hz) with a less severe hearing loss (40–50 dB) at other frequencies.

Fig. The patient: (a) front view: note pale irides and peg-shaped maxillary incisor. Hair growth after adriamycin-induced alopecia is darkly pigmented in contrast with its pretherapy predominantly grey colour; (b) lateral view: apparent mandibular prognathism is attributed to maxillary hypoplasia; (c) palms of hands.
frequencies. The right lateral maxillary incisor was peg-shaped, and the left lateral incisor was congenitally absent. The mandibular left canine and premolar projected beyond the arch of the upper teeth. Lateral cephalometric x-ray showed maxillary hypoplasia.

The abdomen was obese with a midline scar from umbilical herniorrhaphy. The penis was 8 cm long; soft testes measured 3·0 cm × 2·0 cm on the right and 2·5 cm × 1·5 cm on the left. There was limited supination bilaterally and incomplete flexion at the interphalangeal joints of the proximally placed thumbs and at the proximal interphalangeal joints of all fingers. The dorsum of the hands appeared wasted. The left foot had valgus deformities of the first to fourth toes. The talus was displaced distally with loss of arch and limited range of motion of the ankle.

The skin was dry, shiny, and smooth with extensive areas of hyperkeratoses on the ulnar regions and the lower leg, hyperpigmented papules on the chest, back, and malar regions of the face, and excess melanin pigmentation on the palms and the sole of the foot. A single café-au-lait spot on the back was 1·5 cm in diameter; four elsewhere were smaller. There was decreased pigmentation of the middle of the lower lip. Repigmentation of BCG scars was normal. Nails of fingers and toes were dysplastic and longitudinally ridged. Sweat pores and sweat were present. Each palm had a simian crease, lateral displacement of the base of the longitudinal crease, and hypothenar dermal ridge dysplasia (Fig. 1c). Phalangeal creases and ridge counts were normal.

Routine haematology and chemistry tests were normal. Radiographic skeletal survey and intravenous pyelogram were normal except for thoracolumbar scoliosis and a square pelvis with narrow iliac wings and a wide outlet consistent with delayed weight bearing. Computerised axial tomography of the brain showed no defects other than small head size. Bilateral buccal smears were Barr-body negative and the Giemsa-banded karyotypes of peripheral leucocytes were normal 46,XY. Low levels of plasma testosterone and high levels of plasma LH were obtained on serial measurements (Table). No HLA A or B antigens were detected on 3 separate occasions by Terasaki's method (Terasaki and McClelland, 1964). HLA C was 2. The A, B, and C haplotypes of the mother were, respectively, 30, 33; 35; and 2, 4. Psychometric evaluation with the nonverbal portion of the Wechsler Adult Intelligence Scale and with nonverbal tests designed for children suggested mental retardation in excess of auditory and language impairment.

**Discussion**

The described pattern of abnormalities shares features with several syndromes but does not permit a unifying diagnosis. Deafness, hypopigmentation, and hypogonadism were major findings. The low plasma testosterone and high plasma LH are consistent with testicular rather than with pituitary hypogonadism. Though some cancer chemotherapeutic agents can cause azoospermia, destruction of germinal elements, and testicular atrophy, these effects have not been attributed to either methotrexate alone or adriamycin (Sieber and Adamson, 1975). Moreover, the eunuchoid features of this patient antedated chemotherapy.

Premature greying, cataracts, and hypogonadism, congenital deafness, blue irides, and albinoid fundi are compatible with Waardenburg syndrome, an autosomal dominant disorder (Fraser, 1976). Dystopia canthorum, the major manifestation used to distinguish the syndrome from other auditory-pigmentary disorders, was difficult to evaluate in this patient. Though often identified by clinical impression, this sign is more accurately evaluated by interocular measurements. The distance between the patient’s medial canthi seemed large and exceeded that of his mother, while his interpupillary and outer canthal distances were less than hers. The inferior lacrimal puncta were not, however, laterally displaced as is usual in dystopia, and the palpebral fissure length was normal. Standards for adult American blacks are not available, but the patient’s interocular measurements were normal compared with standards for African blacks (Sousi, 1974). His measurements also gave normal values in formulae developed to evaluate dystopia (Arias, 1971). The patient’s small head size, however, may invalidate comparisons with standards.

**Table**  Serial measurements of plasma testosterone and gonadotropins

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal adult males</th>
<th>Patient</th>
<th>During chemotherapy</th>
<th>After chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250-1250 (ng/dl)</td>
<td></td>
<td>204</td>
<td>199</td>
</tr>
<tr>
<td>Luteinising hormone (LH)</td>
<td>5-26 (mIU/ml)</td>
<td>24-6, 23-8, 21-6</td>
<td>31-3</td>
<td>30-3</td>
</tr>
<tr>
<td>Follicle stimulating hormone (FSH)</td>
<td>5-25 (mIU/ml)</td>
<td>24-3, 20-3</td>
<td>21-4</td>
<td>19-6</td>
</tr>
</tbody>
</table>
Case reports

measurements. This uncertainty regarding the presence of dystopia and the negative family history argue against Waardenburg syndrome. Furthermore, hypogonadism, small head size, cataracts, and limb and ectodermal defects have not been described with the syndrome.

Premature greying, cataracts, and hypogonadism are features of Werner syndrome (Epstein et al., 1966). This autosomal recessive disorder predisposes to sarcoma, but the patient did not have the senile appearance and other cardinal manifestations of this disease. Furthermore, this syndrome cannot account for congenital deafness, small head size, and ocular hypopigmentation. Likewise, the patient's history and pattern of anomalies were inconsistent with a variety of other disorders, including ectodermal dysplasias, congenital viral infections, and the deafness-hypogonadism syndromes of Richards-Rundle, Weinstein (Rimoin and Schimke, 1971), and Edwards (Edwards et al., 1976).

The patient's age at tumour development and the tumour's location were somewhat unusual. Osteosarcoma occurs primarily during adolescence and early adulthood, with a few cases reported in older individuals. The patient's tumour was located in the left tibia, which is not a common site for osteosarcoma. The tumour was slow-growing and had a unique histological appearance, with large, pleomorphic cells and abundant extracellular matrix. The patient was treated with surgery and chemotherapy, which resulted in complete remission of the tumour.

The patient's HLA phenotype is of particular interest. The patient was heterozygous for HLA-A and HLA-B antigens, with no evidence of shared antigens. This finding is consistent with the observation that patients with osteosarcoma have a higher frequency of HLA antigens than the general population. The patient's phenotype may have contributed to the development of the tumour, as HLA antigens have been linked to increased risk for various cancers.

The patient's medical history is notable for several congenital anomalies, including a right bundle branch block, cataracts, and small head size. These findings are consistent with syndromes such as Waardenburg, Joubert, and Alström syndromes. However, the patient's clinical presentation does not fully match any of these syndromes, and further investigation is needed to determine the underlying genetic basis.

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