Sir,

Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are rare genodermatoses characterized by hypersensitivity to ultraviolet light. XP is a hereditary autosomal recessive condition, manifested clinically by abnormal photosensitivity of the skin and eyes, pigment anomalies, increased risk of cutaneous neoplasms and, frequently, by progressive neural degeneration (1–3). CS is a rare autosomal recessive disorder of early aging. Its clinical picture and biochemical basis bears many similarities to XP, but some features are distinctly different. A full-blown clinical picture is characterized by growth retardation (so-called cachectic dwarfism, with body weight being more affected than height), progressive neural degeneration, mental retardation, progressive pigmental retinopathy, hearing loss and skin photosensitivity. In contrast to XP, patients with isolated CS do not develop skin cancers (4). A few years ago it was thought that these 2 diseases were totally distinct entities caused by a specific mutation and distinctly defective scope of nucleotide excision repair. However, lately most researchers believe that mutations in nucleotide excision repair pathway genes can lead to XP, CS, trichotiodystrophy, or any combination of them, phenotypic expression depending on the site and type of mutation and the allelic heterogeneity of the genome (5–7).

We present data on a patient whose genome probably harboured a specific combination of mutations producing a rare double clinical syndrome consisting of XP and CS.

CASE REPORT

A 27-year-old man was admitted to the Department of Dermato-venereology, University Medical Center Ljubljana, in January 1992 for treatment of recurrent squamous cell carcinoma involving the lower lid of his left eye. He was the first child of a non-consanguineous marriage, and reportedly nobody in his family had had a genetically determined disease. As a child he was treated because of his short stature, but no medical records were available to us. After the operation and histopathological evaluation of the first carcinoma and surrounding skin, a diagnosis of XP was postulated.

When we first saw the patient he already had all the typical CS stigmata. His body weight was 21 kg and his height 123 cm. His head, hands and feet were larger in size than expected for his height. His dental status was satisfactory. The lungs, heart and abdomen appeared normal. The skin of the sun-exposed parts of the body (face and dorsum of the hands) was dry and scaly. There were numerous abnormal pigmentation areas, telangiectases, atrophic patches and even keratoses involving the nose (Fig. 1). On the lower lid of the left eye, a small nodular, epithelized formation, 5 × 5 mm in size, was present. The skin on the other parts of the body was dry, but showed no other changes.

Ophthalmological examination showed optical nerve atrophy, pigmentary retinopathy and hyperopia. On endocrinological examination the patient was found to have normal secondary sexual characteristics and no hypogonadism. Neurological examination revealed normal muscular strength, up-going plantar reflexes and spinal ataxia. Electromyogram showed decreased sensory and motor nerve conduction velocity, compatible with demyelination neuropathy. A computed tomography (CT) of the head showed thickening of the cranial vault, cerebellar atrophy, ventricular enlargement, increased subarachnoid space, a cyst in the septum pellucidum and 2 large calcifications in the basal ganglia. The patient was mentally retarded, but appeared sociable and contented. The only problem he had ever complained of was his progressive hearing loss. The ear, nose and throat examination revealed dysgnathia and bilateral hearing loss.

His blood pressure was 120/80 mmHg and his basic laboratory tests (erythrocyte sedimentation rate, haemogram, biochemistry and liver function tests) were normal, apart from urinanalysis, which showed proteinuria with leukocyturia. The activity of the patient’s natural killer cells was strongly diminished (i.e. 1.5% relative to a normal value of >16%). Analysis of genetic material showed unchanged chromosome structures: XY, 46—a normal male karyotype. The recurrent tumour of the lower lid of the left eye was removed surgically on 3 occasions. Histopathologically, the first 2 structures were squamous cell carcinomas, while the third was a scar with granulomatous reaction of a foreign body type.

Fibroblast cultivation and measurements of UV sensitivity with the complementation group determination were performed. A diagnosis of XP was established. The patient’s fibroblasts cell lines were complemented with the test cell lines of groups A, C, D and G. The patient was found to have XP complementation group B or F, but in view of epidemiological data, XP complementation group B seemed more probable.

Over the next 2 years, the patient’s health began to deteriorate rapidly. Proteinuria was constantly present; he had elevated blood pressure and a moderate to severe normocytic anaemia. Hypertensive...
nephrosclerosis led to chronic renal failure with markedly elevated BUN and creatinine levels, requiring treatment by haemodialysis. The patient died in February 1996 because of end-stage renal failure and massive bilateral pneumonia.

DISCUSSION

It took 4 years to establish the definitive diagnosis in this patient: we vacillated between XP, CS and a combination of both.

Clinically, there was no doubt that he had CS. As stated by Nance & Berry in their review article (8), the diagnosis of CS should rest on 2 major findings: growth failure and neurological dysfunction with evidence of predominant white matter involvement. In addition at least 3 of the following (minor) features should be present: cutaneous photosensitivity, progressive pigmentary retinopathy and/or cataract, optic disc atrophy, miotic pupils, sensorineural hearing loss, dental caries and characteristic physical appearance.

Our patient had no cataracts and his pupils were normal, but all other signs were present. Of the less common features requested by the same authors, he had renal sclerosis and hypertension.

On the other hand, the patient had skin lesions histologically compatible with XP, recurrent spinocellular carcinoma and decreased natural killer cell activity. The diagnosis of XP was reinforced by the so-called sister chromatid exchange method performed in the Mannheim University laboratories, which showed nucleotide excision repair changes characteristic of XP, most probably of XP complementation group B or F. Once the diagnosis of XP was confirmed, clinical and laboratory tests were re-evaluated once more in order to determine whether the patient had de Sanctis-Cacchione syndrome (dSCS), which had been considered a possibility from the beginning. But in practically every important point (general appearance, normal genitalia, results of DNA repair analysis, type of neurological dysfunction, cerebral CT) the changes were typical of CS rather than dSCS.

Theoretically, many other diseases must be considered in differential diagnosis of CS, such as other premature aging syndromes, aminoacidopathies, chromosomal abnormalities, certain endocrinological and metabolic disorders and other syndromes characterized by growth failure. In our patient, however, they were ruled out by routine physical and laboratory examinations.

Unfortunately, we have no evidence of any gene mutations, but considering the aforementioned findings and the available literature data, we believe that the patient’s genome harboured a specific combination of mutations, which produced a very rare overlapping clinical picture consisting of XP and CS.

REFERENCES


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