Syndrome of the month

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Dyskeratosis congenita

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Dyskeratosis congenita is a rare condition characterised by reticulate skin hyperpigmentation, mucosal leucoplakia, and nail dystrophy. More serious features are bone marrow involvement with pancytopenia and a predisposition to malignancy. It was first described in 1906 by Zinsser,¹ later by Cole,² and by Engmann,³ and is sometimes referred to as the Zinsser-Engmann-Cole syndrome. There have been 104 cases published, of whom 51 have been reviewed previously.⁴

Clinical features

SKIN

Dermatological features are the most consistent findings (table). Reticulate skin pigmentation, which may be telangiectatic, affects predominantly the neck, upper chest, and upper arms and often surrounds patches of pale, atrophic skin (fig 1). Nail

dystrophy starts with longitudinal ridging and splitting and may progress to pterygium formation or complete nail loss (fig 2).

Leucoplakia, a more sinister manifestation, usually affects the oral mucosa but is sometimes found in conjunctiva, urethra, or genital mucosa, and tends to appear a little later than the other skin lesions. Epiphora and consequent conjunctivitis and blepharitis as a result of hyperplasia of the epithelial lining of the lacrimal punctum is also a later feature.

BLOOD

Haematological abnormalities are not universal but

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TABLE Frequencies of clinical features in dyskeratosis congenita.

	At time of reporting (%)	At onset of disease (%)
<i>Skin manifestations</i>		
Hyperpigmentation	99	53
Nail dystrophy	92	59
Leucoplakia	82	10
Epiphora	79	5
Hyperhidrosis	87	—
Hyperkeratinisation (palms and soles)	69	—
Bullae on minimal trauma	23	7
Alopecia	34	—
Extensive caries/dental loss	12	—
<i>Other manifestations</i>		
Haematological abnormalities	51	5
Neoplasia	12	—
Mild mental retardation	10	—
Hepatomegaly	7	—
Splenomegaly	15	—
Growth retardation	13	—
Bone involvement	8	—

FIG 1 Typical reticulate hyperpigmentation of skin.

FIG 2 Nail dystrophy in dyskeratosis congenita.

are usually serious. The earliest sign may be either anaemia or thrombocytopenia, but ultimate progression to pancytopenia is usual. Bone marrow aspirates may be hyperplastic or hypocellular; in the few patients who had serial examinations a progression from erythroid hyperplasia to hypocellularity was noted.

CANCER

The predisposition to malignancy is reflected in a high incidence of solid tumours which may arise in either the leucoplakic or atrophic areas of skin or in other organs. A total of 12% of the patients had developed one or more tumours at the time of reporting (mean age of patients at reporting 21 years). The malignancies included squamous carcinomas of skin or mucosa, but also oesophageal and pancreatic cancers and Hodgkin's lymphoma.

Tchou and Kohn⁵ have suggested that there is an increased incidence of cancer in unaffected family members, as three apparently unaffected sibs died from cancer (Hodgkin's lymphoma, pancreatic and spinal cord tumours). This family was one in which autosomal inheritance was suggested; there was parental consanguinity, older age of onset, and overall milder features than in other reports, so its relevance to the other more typical cases is not clear.

OTHER

Other reported features are listed in the table. The bone abnormalities include osteoporosis and abnormal trabeculation of bone, fractures with minimal trauma, and avascular necrosis. Some of

these cases, and those with growth retardation, had been on steroids (for pancytopenia), but one of the cases with avascular necrosis of the hip and three with osteoporosis had received none.^{6 7} Intracranial calcifications were reported in two brothers, although they are mentioned in three separate reports.⁷⁻⁹

Natural history

Rarely (four of 104 patients), abnormalities are evident at birth. More often features appear during childhood, with a mean age of onset of seven years.

The skin pigmentation and nail changes typically appear first with a mean age of onset of 8.6 and 7.4 years respectively, and at least one characteristic feature is present by the age of 10 years in 92%. Leucoplakia and epiphora appear later (mean ages 10.5 and 14.0 years), and by the mid-teens the serious complications begin to develop. These are bone marrow failure leading to bleeding or opportunistic infections (mean age of onset 15.0 years) and malignancy (at a mean age of 31.2 years).

PROGNOSIS

A total of 24% of the reported patients was dead at the time of reporting, the mean age at death being 23.6 years (range eight to 50 years). Fifty percent of these deaths were from infection, often opportunistic (including CMV, pneumocystis, candidiasis, and verrucosis), 20% from bleeding (gastrointestinal or cerebral), and 30% from malignancies.

TREATMENT

The only treatments which have been proposed are

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bone marrow transplantation for the pancytopenia and retinoids. Etretnate has been found useful, despite its side effects, in the control of keratinising disorders, and more recently has been found to cause regression of lesions in leucoplakia oris,¹⁰ and so may reduce the incidence of malignancy.

Differential diagnosis

Fanconi's anaemia has been confused with dyskeratosis congenita in published reports. It also causes skin pigmentation, though this is more uniform, but there are also renal, eye, and limb reduction anomalies in addition to the marrow failure. Graft versus host disease can cause similar skin and occasionally nail features, but should not, of course, precede the bone marrow failure or transplant. Rothmund-Thomson, Bloom's, and Kindler's syndromes may all cause skin lesions, but they are sun sensitive and associated features differ.

Laboratory findings

Skin biopsies typically show atrophy of the epidermis with pigment laden macrophages present in the upper dermis, but this appearance is not pathognomic. Other laboratory findings have been inconsistent. In four of 24 patients in whom chromosomes were studied, increased breaks were observed.⁴ Burgdorf *et al*¹¹ and Carter *et al*¹² did not find chromosome breaks, but found that lymphocytes and fibroblasts were slow to remove photo mediated psoralen-DNA cross links and developed increased sister chromatid exchanges on exposure to UVL. Nagasawa and Little¹³ also suggested an increased sensitivity to mitomycin C mediated cell damage, which could be prevented by the addition of superoxide dismutase. Neither finding could be reproduced in a subsequent study.¹⁴ Few serial immunological studies have been performed and again findings are inconsistent. These include both raised and depressed immunoglobulin levels, a reduced response of lymphocytes to PHA, impaired skin delayed hypersensitivity reactions, reduced T cell numbers, and impaired intracellular killing. Thymic aplasia was noted in three cases.^{4 15-17}

Study of the haematological involvement showed the bone marrow failure to result from a defect of stem cells, rather than suppression by any circulating factor.^{18 19}

Primary defect

This has not been identified, and none of the proposed theories is able to account for all of the observed features.^{4 20}

Inheritance

Dyskeratosis congenita has long been accepted as hereditary, but the mode of inheritance has been uncertain, X linked recessive, autosomal dominant, and autosomal recessive all having been proposed. Of the 104 reported cases, 56 are from 19 families, the remainder being sporadic, although in five of these, mention is made of other possibly affected family members. The 104 patients comprise 92 males and 12 females. X linked recessive inheritance is supported by the pedigree pattern in several large families.^{4 21} Segregation analysis of 14 families by Sirinavin and Trowbridge⁴ gave a probability of 0.9999 for X linked recessive and 0.75 for autosomal recessive inheritance.

Linkage analysis in one large family using multiple X chromosomal DNA polymorphisms assigned the locus to Xq28.²¹ Further studies would be helpful to confirm this assignment and to help exclude heterogeneity before considering the application of this marker in families for carrier detection or prenatal diagnosis.

Five of the 12 affected females belong to another large family.⁵ In this family the age of onset is greater and the features milder and less typical than usual, particularly in the three males affected. The pedigree is consistent with autosomal dominant inheritance. The family described in an abstract by Scoggins *et al*²² shows male to male transmission in a three generation family with two males and four females affected. Unfortunately, clinical detail is insufficient to compare these patients.

In conclusion, typical disease in males is most likely to follow X linked recessive inheritance, but if females are affected, or mild atypical features are seen in males, then autosomal dominant inheritance should be considered.

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