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REVIEW

Dyskeratosis congenita

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Review

Summary Dyskeratosis congenita is an inherited disorder that usually presents in males, consisting of the triad of leukoplakia of the mucous membranes, nail dystrophy and skin pigmentation. Whilst most cases are X-linked, autosomal dominant and recessive forms have been reported. The significance of the condition lies in premature mortality arising from either bone marrow failure or malignant change within the areas of leukoplakia. Various mucocutaneous and non-mucocutaneous manifestations have been reported. The syndrome arises from an inherited defect within the DKC1 gene that codes for the protein dyskerin in the X-linked recessive form of the disorder, whereas mutations in the RNA component of telomerase (TERC) result in the autosomal dominant form of the condition. The identification of a white patch within the mouth of a child in the absence of any other obvious cause should arouse suspicion of this rare condition. Greater understanding of the molecular biology surrounding this syndrome should lead to improvements in diagnosis, monitoring of disease progression and therapy.

Introduction

Dyskeratosis congenita (DC) is a rare, inherited, disorder, with premature ageing, bone marrow failure and malignancy. It consists of the triad of nail dystrophy increased skin pigmentation and mucosal leukoplakia.[1–4] The syndrome often proves fatal due to progressive bone marrow failure (or malignant change within areas of mucosal leukoplakia). A vast number of associated anomalies have been reported and are reviewed below, together with an update on recent understanding of the molecular basis of the disorder in its various inherited forms.

Clinical presentation

Mucocutaneous features

The mucocutaneous features are the most consistent feature of DC. Reticulated skin hyperpigmentation affecting the neck, face, chest and arms is

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the most common finding occurring in approximately 90% of patients.[5] This can be in either a localised or florid generalised form and the degree of pigmentation has been observed to increase with age. A variety of other skin changes which have been reported in the literature include cutaneous atrophy, hyperhidrosis of the palms and soles, telangiectasia, cracking, fissuring, bullae formation, loss of dermal ridges,[6] hair tufts with keratotic plugs on the limbs and keratinised basal cell papillomas.[7]

Dystrophic changes in the nails are similarly prevalent affecting 90% of patients.[5] This has been observed to be more severe in the fingers than in the toes, and can vary quite considerably in severity between digits.[6] Dystrophic changes usually begin with longitudinal ridging and splitting and may progress to complete nail loss.[8] Leukoplakia, which is the third feature of the classic clinical triad, has been reported in 80% of affected patients.[5] This can occur on any mucosal surface, but has been most frequently reported affecting the oral mucosa. The specific intraoral sites previously published include, lingual mucosa,[9–12] buccal mucosa[13] and the palate,[14] with the tongue being the most frequently affected.[15] The other sites reported include the urethra, glans penis, vagina and anorectal region.[6] DC patients have a recognised increased risk of malignancy from pre-existing mucosal leukoplakia,[16] reaching an incidence of approximately 35% with a peak in the third decade of life.[6,9]

Given that it is difficult to predict which lesions will undergo malignant change, markers for such instability have been sought. These include ultrastructural change,[17] p53 expression[18] and cytokeratin profiles.[19] Evidence for increased cellular activity revealed increased numbers of mitochondria, nucleoli and the retention of complex cell to cell contact at a time when most cells would be terminally differentiated. When DC is complicated by malignant disease the prognosis is generally considered to be poor. Malignant disease reported in DC include, solid tumours of the tongue, buccal mucosa, nasopharynx, rectum, cervix, vagina, skin, oesophagus and pancreas.[6] Haematological malignancy has also been reported including myelodysplasia[5] and Hodgkin's lymphoma.[20]

There is a wide age variation in the initial presentation of clinical signs of DC. Nail dystrophy, leukoplakia and skin hyperpigmentation tend to appear in the first decade of life,[4] with median ages of onset of six, seven and eight years, respectively.[5]

The non-mucocutaneous features

These features include bone marrow failure, pulmonary disease, ophthalmic, skeletal, dental, genitourinary, gastrointestinal and neurological abnormalities. One of the most common features of this disease is bone marrow failure resulting in peripheral cytopenias. It has been shown that 85% of DC patients have a peripheral cytopenia of one or more lineages, with approximately 75% of these patients developing pancytopenia.[5] In 80% of these patients the age of onset for the development of pancytopenia is less than 20 years of age, with half of them developing pancytopenia before 10 years. It has been estimated that 80–90% of patients will have developed bone marrow failure by the age of 30,[5,21] and approaching 94% by the age of 40 years.[5]

Bone marrow failure is reported as the principal cause of death in 70% of patients with DC, as a consequence of bleeding or opportunistic infections with cytomegalovirus, pneumocystis carinii or candida.[8] In some patients, the development of bone marrow abnormalities may appear before the classical cutaneous manifestations, resulting in the initial diagnosis of idiopathic aplastic anaemia.[5,22–24] DC patients also have features, which overlap with Fanconi's anaemia, which is also characterised by bone marrow failure and a predisposition to malignancy. Therefore all patients with unexplained aplastic anaemia should be investigated for DC.

Pulmonary complications are reported to develop in approximately 20% of DC patients, resulting in reduced diffusion capacity with or without a restrictive defect.[5] The mortality rate from these pulmonary complications has been estimated at between 10% and 15%.[5] Postmortem studies on two subjects who had died suddenly from acute pulmonary failure, showed abnormalities of pulmonary vasculature and abnormally high levels of pulmonary fibrosis.[5] Pulmonary complications in the past may have been overlooked and may well provide the answer as to why there is such a high incidence of fatal pulmonary complications following bone marrow transplantation. This further reinforces the importance of pulmonary shielding during radiotherapy and avoiding agents associated with pulmonary toxicity such as busulphan.

Other non-mucocutaneous abnormalities associated with DC include ophthalmic abnormalities such as epiphoria secondary to nasolacrimal duct obstruction, conjunctivitis, blepharitis, pterygium formation, ectropion, loss of eyelashes, strabismus, cataracts and optic atrophy. These ophthalmic abnormalities have been observed in