Rare disease

Too short stature, too many stigmata

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Summary

Dyskeratosis congenita (DC) is a rare disease characterised by bone marrow failure and skin manifestations. Patients with DC may exhibit short stature that is not usually related to growth hormone (GH) deficiency. Replacement treatment with GH should be done cautiously as it can predispose to haematological malignancy. We present a 10-year-old boy with DC and GH deficiency.

BACKGROUND

Dyskeratosis congenita (DC) is a very rare bone marrow failure syndrome with special characteristics and predisposition to malignancies. Due to its rarity, DC often remains undiagnosed during childhood with patients suffering a lot of 'medical abuse'. Short stature in these patients is considered idiopathic. In our patient, short stature was attributed to primary growth hormone (GH) deficiency and he received replacement treatment. This treatment is off-label in cases of DC and might lead to evolution of haematological malignancy. All these considerations are presented and discussed in our case in order to increase the degree of suspicion among paediatricians when facing a patient with morphological stigmata, short stature and abnormal haematological findings

CASE PRESENTATION

Short stature is a common paediatric problem affecting approximately 2% of children. Some of these children may have a GH deficiency while others do not meet the criteria for replacement treatment. It is very important when evaluating a child with short stature to take into account significant findings from the clinical examination such as onychodystrophy, leucoplakia and abnormal skin pigmentation of the skin. All the above in combination with abnormal haematological findings may indicate the presence of DC. In these cases, replacement treatment with GH, even when meeting the relevant criteria, should be done very cautiously because of the potential risk of developing haematological malignancy. The aim of this presentation is to heighten the degree of suspicion among all paediatric specialties when facing a child with short stature.

We report on a 10-year-old boy who attended the emergency department because of an acute gastroenteritis with bloody stools lasting for 3 days.

Routine laboratory investigation: complete blood count (white blood cell count $4 \times 10^3/\mu\text{l}$, Neutrophils (N) 51%, Lymphocytes (LY) 33%, Monocytes (Mo) 15%, haemoglobin 11 g/dl, haematocrit 32.3%, mean corpuscular volume 94.9 fl, mean corpuscular haemoglobin 32.4 pg, mean corpuscular haemoglobin concentration 34.1 g/dl, platelets

$88 \times 10^3/\mu\text{l}$), biochemistry and coagulation screening were normal. Detailed physical examination revealed short stature (126 cm, below 3rd percentile), low weight (24 kg, below 3 percentile), head circumference (50 cm, below 3rd percentile), leucoplakia of the tongue and the buccal mucosa, bilateral blepharitis, abnormal skin pigmentation of the upper half of the trunk and onychodystrophy of both upper and lower extremities.

The patient is the first child of non-consanguineous healthy parents of Greek origin. He was born full term with a relatively low birth weight (2500 g). The perinatal period was uneventful. At the age of 2 years he exhibited leucoplakia of the tongue and onychodystrophy. Biopsy of oral lesions revealed traumatic ulcer and no further evaluation was suggested. Abnormal skin pigmentation of the upper half of the trunk was added at the age of 6 years. At that age, because of short stature, the boy underwent detailed endocrinological evaluation and GH deficiency was revealed. He was placed on treatment with GH (4 mg subcutaneously weekly) until the time he came to our attention.

With the working diagnosis of an inherited bone marrow failure syndrome he was admitted to our clinic for further evaluation.

INVESTIGATIONS

Extended laboratory investigation

Immunoglobulins, subclasses and C3, C4 were within normal values for his age. Bone marrow aspirate and trephine biopsy revealed decreased cellularity with increased lipoid infiltration. Bone marrow karyotypic analysis was normal (46, XY). Anaemia Fanconi study was negative. Immunophenotype of peripheral blood revealed a decrease in B lymphocytes and T helper lymphocytes and a decreased CD4/CD8 ratio. The above findings were frequently reported in cases of DC.

Imaging studies

Ultrasound of the abdomen, brain MRI, chest x-ray and endoscopic evaluation of the digestive system were normal.

The diagnosis of DC was confirmed by molecular study. Our patient was found to be heterozygous of the c.1058C/T

mutation on the exon 11 of the *DKC1* gene. A new stomatological examination did not reveal any signs of malignancy at the oral lesions. The treatment with GH was discontinued.

The young patient recovered completely from the gastroenteritis 2 days after his admission with no pathogen found in the stool cultures. He was placed on regular haematological follow-up every 3 months and bone marrow aspiration every year. His condition, 1 year after the diagnosis of DC, is stable. The optimal treatment for the bone marrow failure is bone marrow transplantation. We examined his younger brother who was human leucocyte antigen (HLA) matched and his molecular analysis did not reveal the *DKC1* mutation. He was considered to be the ideal bone marrow donor.

TREATMENT

Our patient underwent a successful transplantation 1 year after diagnosis.

OUTCOME AND FOLLOW-UP

Three months after transplantation, the patient is in good clinical condition under treatment with cyclosporine and trimethoprim-sulfamethoxazole.

DISCUSSION

The inherited bone marrow failure syndromes must be considered in the investigation of patients with aplastic anaemia or cytopenia, with or without physical stigmata, as well as in patients with young onset of specific types of cancers. More than 25% of paediatric patients who present with aplastic anaemia have an inherited cause.¹ Diagnostic molecular tests for inherited bone marrow failure syndromes are available.

DC is a rare bone marrow failure syndrome with a frequency of 1:10⁶ people. It is a form of ectodermal dysplasia in which 50% of the patients develop aplastic anaemia. Most of the physical findings appear with age and this is the reason why DC is under-recognised by paediatricians. The diagnostic triad includes skin reticulated hyperpigmentation, dystrophic nails, which appear during the first decade of life, and mucous membrane leucoplakia in the second decade. A variety of other (gastrointestinal, ophthalmic, pulmonary, skeletal and dental) abnormalities have also been reported. Among them, short stature is referred as a finding in DC patients and is considered to be idiopathic. Our patient had primary GH deficiency, which was confirmed by two endocrinological tests (clonidine and glucagone). Despite the replacement treatment he gained only 22.4 cm over 4 years and he was still under the 3rd percentile for his age.

DC is principally a disease of defective telomere maintenance. All patients with DC have very short telomeres. Mutations have been found in genes that encode components of the telomerase complex (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*) and telomere shelterin complex (*TNF2*).² Telomerase and shelterin protect and process the telomeres.³ Genetically, DC is heterogeneous with three forms identified: X-linked recessive, autosomal dominant and

autosomal recessive. Most of the reported cases are male and there is linkage to Xq28. *DKC1* encodes dyskerin and is the main gene responsible for the X-linked recessive form of the disease. Autosomal dominant DC is attributed to heterozygous mutations in the core components of telomerase—namely *TERC* (the RNA component) and *TERT* (the enzymatic component).^{4,5} The autosomal recessive form of DC is caused by biallelic *NOP10*, *NHP2* and *TERT* mutations. *NOP10* and *NHP2* are found to be components of the small nucleolar ribonucleoprotein particle. Mortality in DC arises from either bone marrow failure or specific cancers in relatively young age. Bone marrow transplantation is the treatment of choice when HLA-matched sibling donor is available. Some patients may respond to androgens alone or in combination with granulocyte colony-stimulating factor.¹ Being a monogenic disorder, DC could be a suitable candidate for gene therapy in the future.

Despite the fact that our patient had the classical triad of DC, the diagnosis was delayed even though he had visited many different paediatric subspecialists. The presentation of the above rare bone marrow failure syndrome focuses not only on the pathological entity itself but also on the high degree of suspicion needed among all the paediatricians and subspecialists when facing a child with short stature, oral leucoplakia and onychodystrophy. Additionally, current bibliographic research did not reveal similar case of DC with short stature due to primary GH deficiency. The use of GH in these patients is off-label and could increase the risk of developing leukaemia or myelodysplastic syndrome because of the presence of GH receptors on myeloid precursors and should be avoided or be very cautious.

Learning points

- ▶ Short stature may be a part of a more complex entity such as a bone marrow failure syndrome.
- ▶ Oral leucoplakia, onychodystrophy and hyperpigmentation should raise suspicion of DC.
- ▶ Be very cautious when treating a child with GH as the underlying cause of short stature may not be idiopathic.

Competing interests None.

Patient consent Obtained.

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