CASE REPORT

Avascular Necrosis of Head of Femur in Dyskeratosis Congenita - A Rare Presentation

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Abstract Avascular necrosis of head of femur is a rare presentation in Dyskeratosis Congenita (DC). Aplastic anaemia, increased susceptibility to infections and fatal pulmonary complications often complicate the clinical scenario in these patients leading to short life span and difficulty in performing surgical interventions. The diagnosis initially and subsequent management by total hip replacement posed a great challenge. To our knowledge this is the first case report of any intervention in form of total hip Arthroplasty done in DC. At 5 years of follow up the patient is asymptomatic with no radiographic signs of loosening or lysis.

Introduction

Dyskeratosis congenita (DC) is a rare, progressive disorder characterized by the triad of reticular hyperpigmentation, nail dystrophy and leukoplakia of mucous membranes [1]. It was first described in 1906 by Zinsser, later by Cole [2] and Engmann [3] and the X linked recessive form is sometimes referred to as the Zinsser-Engmann-Cole syndrome. Bone marrow failure leading to pancytopenia, predisposition to

malignancy and fatal pulmonary complications are the major causes of mortality [1]. Manifestations of genitourinary, skeletal, neurological and gastrointestinal system involvement are less common [4, 5].

The skeletal abnormalities include most commonly osteoporosis [5]; however fractures with minimal trauma and joint deformities have been reported [6–8] which were usually secondary to corticosteroid intake. Approximately 350 cases have been reported in the DC registry with clinical and genetic information on more than 200 families from 40 different countries. Till date only two cases of avascular necrosis (AVN) in DC have been reported. To our knowledge this is the third case report of a patient having AVN of hip joint and the first case report of total hip replacement in DC not related to any steroid intake. The patient was informed that the data concerning the case would be submitted for publication and he consented.

Case Report

A 25 year old male adult presented with left groin pain radiating to left knee for last 5 years. As a result he had difficulty in sitting cross legged and squatting as these positions are often used for daily activities and defecation. He had past history of hyper pigmented skin lesions for last 12 years, destruction of nails of both hands and feet with premature greying of hair simultaneously. There was no history of urine discoloration. His parents were normal, non-consanguineous and siblings were also normal.

General examination showed lean built with dark brown reticulate hyper pigmentation over face, neck, upper chest, back of elbows, extensor surface of knee joint and lateral feet with interspersed hypo pigmented well defined rounded macules for which dermatology consultation was

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Fig. 1 Photograph showing *dark brown* reticulate hyper pigmentation over face, neck and, upper chest. (Color figure online)

sought (Fig. 1). His systemic examination, mental abilities and external genitalia were normal. Local examination showed destruction of nails of both hands and feet (Fig. 2). There was diffuse slate grey pigmentation of oral mucosa and tongue (Fig. 3). Hip joint examination on left side showed posterior joint line tenderness, terminal restriction of flexion (Range of motion 0° – 90°), restricted abduction (0° – 15°), no adduction and no internal or external rotation. The gait was antalgic with limp. His height and weight were below the tenth percentile for his age and much less compared to his siblings and parents. His haemoglobin was 8.5 gm % and most of other investigations were normal. Ophthalmic examination revealed trichiasis with pigmented

skin over eyelid, 2–3 nebular opacities in right cornea with normal visual acuity and fundus examination.

Radiographs of left hip showed collapse of superolateral weight bearing part of femur head (Fig. 4) and was graded as AVN (AVN Ficat and Arlet Stage IV). Magnetic resonance imaging of left hip revealed AVN. Skin biopsy showed histological features consistent with DC (Fig. 5).

He was started on oral iron supplements, multivitamins, folic acid and methylcobalamin therapy. Subsequently, the patient had metal on metal total hip replacement for AVN hip left side (Fig. 6). Preoperatively the patient had two units of blood transfusion and his haemoglobin was 11.6 prior to surgery. Intra operative course was uneventful. Post operatively the patient had persistent fever and his surgical incision site was healthy with no discharge. Detailed fever work up was normal. The erythrocyte sedimentation rate was raised and the platelet counts were 70,000 cu mm. Management with platelet concentrates and fresh blood was done. The fever subsided at 3 weeks post operatively. At 5 years of follow up the patient is normal and performing his normal day to day activities with ease and comfort. The radiographs at five years follow up show prosthesis well positioned with no signs of lysis of bone or loosening.

Discussion

Dyskeratosis is a latin word meaning irreversible degeneration of skin tissue and congenita means inborn. Apart from the three cardinal dermatologic features, orthopaedic manifestations are rare and include joint deformities, incomplete closure of the vertebral arches, mandibular hypoplasia, scoliosis and other minor skeletal anomalies [6, 9]. Womer Richard et al. [10] reported two patients of DC; both had osteoporosis, several fractures with minimal trauma, poor bone healing prior to the onset of anemia and

Fig. 2 Photograph showing destruction of nails of both hands and feet

Fig. 3 Photograph showing diffuse slate grey pigmentation of tongue. (Color figure online)

Fig. 5 Photograph of skin biopsy depicting histological features consistent with dyskeratosis congenita

Fig. 4 Antero posterior radiograph of pelvis showing collapse of superolateral weight bearing part of femur head on left side; Avascular necrosis (AVN Ficat and Arlet Stage IV)

Fig. 6 Antero posterior radiograph of pelvis showing metal on metal total hip replacement on left side

before any steroid therapy. These patients also had radiolucent areas in the shafts of long bone, coarse trabeculation in the metaphyses and circular lucencies proximal to metaphysis. Kalb RE et al. [11] described a case of AVN of femur head that was unrelated to any steroid intake. Hong-Yan Du et al. [12] described bilateral AVN of hips in a patient. None of the patient in these reports had any intervention done for AVN. We ruled out alcoholism or corticosteroid intake in our patients that are the usual causes of AVN in this age group.

The patient in our case had unilateral AVN of left hip joint and had symptoms for last 5–6 years although the skin lesions were present for last 12 years. He had associated features like anaemia, lean built and short stature. We made the differential diagnosis of hemochromatosis, DC and fanconi syndrome. The serum ferritin levels were normal. There was no liver or cardiac impairment as evidenced by normal ultrasonography of abdomen and normal

echocardiography respectively. We could exclude haemochromatosis because of these parameters. The typical features of growth retardation, congenital skeletal and renal malformations, strabismus, microcephaly, and microphthalmia that are found in fanconi syndrome were not seen in our patient. Moreover nail dystrophy, leukoplakia, and the other cutaneous features are not seen in fanconi's anemia. The typical skin manifestations were the basis for diagnosis in our patient which was confirmed by histopathological examination.

The anaemia in DC is normochromic initially with normal marrow that later becomes hypercellular followed by hypocellularity [10]. The myeloid to erythroid ratio is equal initially followed by reversal. In our patient the peripheral smear was suggestive of mild macrocytic, normochromic normocytic anaemia with anisocytosis and occasional polychromasia. Bone marrow examination was

suggestive of megaloblastic anaemia with myeloid to erythroid ratio of 1.5/1, adequate megakaryocytes and megaloblastic erythropoiesis. Thus megakaryocytes which are unusual in DC were seen in our patient.

Despite the term DC, skin changes usually appear between 5 and 10 years of age although they may occur earlier or later [13]. Usually cutaneous symptoms appear first but anaemia or thrombocytopenia may be the first manifestation [8]. Boeck de kris et al. [8] had thrombocytopenia as the first symptom. In their review of the literature, Sirinavin C and Trowbridge AA [14] mention only two cases in which anemia, leukopenia, and thrombocytopenia [6] were the initial symptoms. In our case, the patient had an episode of anaemia as the first manifestation followed by the appearance of reticulate skin pigmentation at around 12 years of age.

Ophthalmic system findings are rare [13] which includes conjunctivitis, blepharitis, pterygium, ectropion, nasolacrimal duct obstruction causing epiphora, retinal atrophy with infarctions and hemorrhage [6], optic pallor [7], atherosclerotic changes of the retinal vessels and congenital cataracts [5]. Our patient had normal visual acuity and fundus examination although trichiasis was found along with nebular opacities. Hair changes include hypotrichosis, sparse fine hair with progression to alopecia and premature hair graying [7, 8]. The generalised premature greying of scalp hair was also one of the presenting features in our patient. Other manifestations include short stature, hyperkeratosis and hyperhidrosis of palms and soles along with hyperkeratotic plaques, palmoplantar hyperhidrosis, esophageal, liver disease and gut abnormalities [7, 8]. In our patient short stature and lean built was found although his palms, soles and gastrointestinal system were normal. Neurologic system involvement with mental retardation [14] and genitourinary system findings have been reported [7, 8]. However in our case the mental build up and intelligence, external genitalia were normal and there were no such features.

Abnormalities in both humoral and cell mediated immunity have been reported [7]. Although our patient had normal immunoglobulin levels he had postoperative prolonged fever. All investigations were normal barring low platelet counts (<70,000). This may be because of some abnormality in the immunological response.

DC is primarily caused by defects in the maintenance of chromosome telomeres. To date, mutations in eight genes have been identified in patients with DC: *DKC1*, *NHP2*, *NOP10*, *RTEL1*, *TERC*, *TERT*, *TINF2*, and *WRAP53*. In about half of people with DC, the disorder is caused by mutations in the *TERT*, *TERC*, *DKC1*, or *TINF2* gene [15]. Telomeres are maintained by two important protein complexes called telomerase and shelterin. *TERT*, *TERC*, *DKC1*, or *TINF2* gene mutations result in dysfunction of

the telomerase or shelterin complexes, leading to impaired maintenance of telomeres and reduced telomere length. Cells that divide rapidly are especially vulnerable to the effects of shortened telomeres. As a result, people with DC may experience a variety of problems affecting quickly dividing cells in the body such as cells of the nail beds, hair follicles, skin, lining of the mouth (oral mucosa), and bone marrow. There is a high frequency of sporadic cases of DC, due to the incidence of de novo mutations in the X-linked and dominant genes. Genetic anticipation has been reported in families with mutations in the autosomal dominant genes. This genetic study could not be done in our patient because of non availability of these investigations in our institution and further the patient could not afford because of high cost involved.

The inheritance of DC can be most common X-linked recessive (*DKC1*) also called Zinsser-Cole-Engleman syndrome, autosomal dominant [16] (*RTEL1*, *TERC*, *TERT*, *TINF2*), or autosomal recessive (*NHP2*, *NOP10*, *RTEL1*, *TERT*, *WRAP53*) are also recognised. Sporadic forms with mild disease and normal presentation is also frequent and usually arises by de novo mutation or as silent carriers of mutation. It seems that our patient also fits in this sporadic group as he had no near or remote family history of such features.

Many treatment modalities have been described for DC; bone marrow transplant and allogeneic stem cell therapy (SCT) for aplastic anemia [1], etretinate and oxymetolone for oral leukoplakia and haematological symptoms respectively. Hematopoietic growth factors like Granulocyte colony stimulating factor (G-CSF), Granulocyte Macrophage colony stimulating factor (GM-CSF) and erythropoietin [17] have shown beneficial results in patients with DC and neutropenia. However none of these interventions were done in our patient.

As our patient was young and active we preferred metal on metal bearing surface with large head that lessens any chances of dislocation and fracture with unlimited activity [18]. The volumetric wear is also significantly less compared to metal on polyethylene. Recently metal on metal bearing surface debris has been associated with osteolysis, pseudotumor, tissue and bone necrosis [19] and decrease in lymphocyte count [20]. This can add to the abnormalities of humoral and cell mediated immunity seen in a few cases of DC. The humoral and cell mediated immunity was normal in our patient. Tribology has recently shown that that metal on metal components made of high carbon content with small clearance, a good surface finish, and optimal implant sphericity minimize ion release from bearing wear and thus osteolysis.

Our patient had different presentation compared to a typical case of DC with sporadic pattern, anaemia as the first presenting symptom and a varied peripheral smear.

AVN in a patient of DC is a rare presentation with only two patients reported before. The life span of these patients is usually short and management of AVN is a treatment challenge with increased susceptibility to infections and other complications. In spite of this our patient had total hip replacement and is leading a normal life. Joint replacement in patients with AVN has the propensity to offer a better quality of life to these patients.

Conflict of interest None

Human and Animal Rights and Informed Consent There are no ethical issues with human or animal subjects. This article does not contain any studies with human or animal subjects performed by the any of the authors.

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