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Darier's Disease in Pregnancy

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Abstract: *Darier's disease (keratosis follicularis or Darier- white disease) is a rare congenital acantholytic , autosomal dominant disease .We report three rare cases of 22-28 year old full term pregnant women with Darier's disease during a observation period of 3 years.Only few such cases have been reported earlier in literature.*

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I. Introduction

Darier's disease is a rare congenital acantholytic, autosomal dominant disease with considerable geographical and penetrance variance. Its incidence is about 1 in 30,000, worldwide distribution. Both sexes are affected with equal frequency. Its onset is usually in adolescence, meaning it will co-exist with the years of fertility in women, but can manifest at any time, is often insidious and slowly progressive.[1] The disease occurs due to mutation of ATP2A2 gene located on chromosome 12q24.1 [2]. This gene encodes for sarcoplasmic ER Ca2+ATPase type 2 (SERCA2) required to transport calcium within cell affecting protein which is important for maintaining desmosomal protein attachments. It is characterised by persistent eruption of hyperkeratotic warty plaques and papules in seborrheic and flexural regions [3,5] Histologically, it is characterised by hyperkeratosis, suprabasal acantholysis, papillomatosis.[5].

There are potential pregnancy specific implications, especially when it involves the groin ,vulva or perineum (where elasticity is needed during a vaginal birth), or when it involves the lower abdomen (where an incision for a C-section may be needed), back (regional anaesthesia cannot be safely given).Additionally, related infections such as Group B Streptococcus can cause obstetric problems.[6] Pregnant woman are encouraged to speak with their obstetrician or other prenatal care provider regarding plans for labour and delivery that may be affected by the disease. Though prenatal diagnosis is possible, prenatal counselling is difficult due to variable penetrance and inability to predict severity of disease in an individual.[4]

Simple measures to reduce the impact of irritants – keeping the skin cool, and using sunscreens and moisturizers[7]

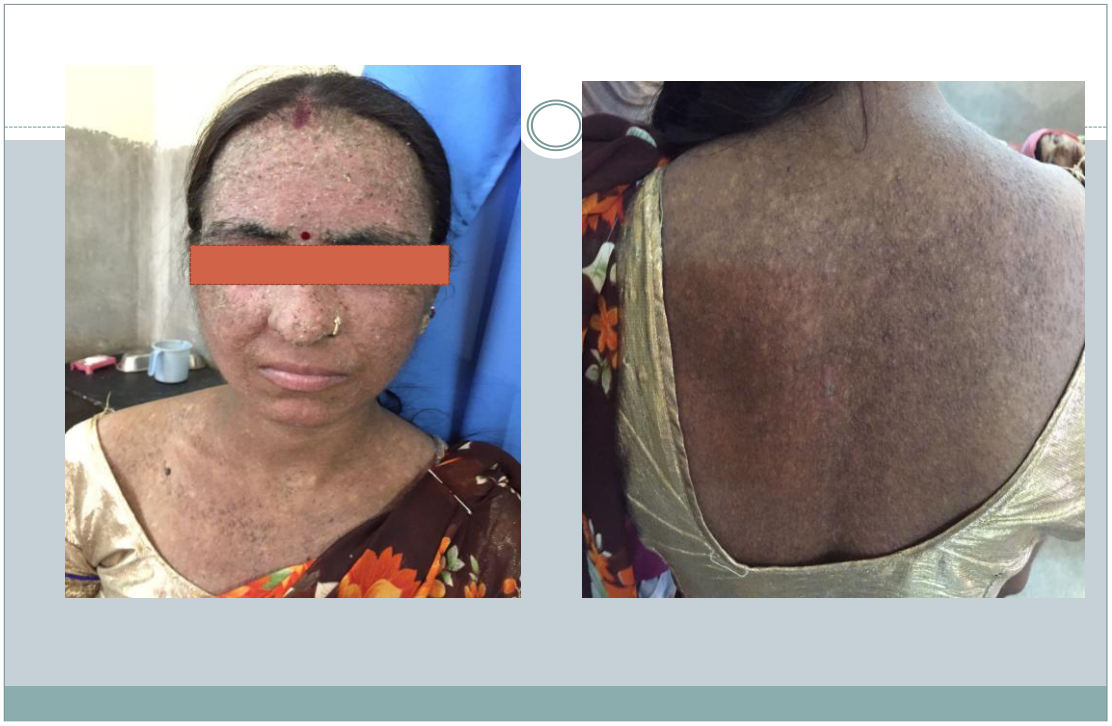
Severe disease is usually treated with oral and/or topical retinoids,due to concerns about birth defects, these should not be started during pregnancy and should be discontinued in women who become pregnant. Oral acitretin and isotretinoin, are known teratogens Topical steroids may in some cases be used but have poor results.[6] Some oral antibiotics and acyclovir may be used to treat or suppress secondary bacterial or herpes simplex infection. During delivery, spinal anesthesia can be safely administered through a lesion-free area if secondary bacterial and viral infections have been ruled out.[8]

Case report

First case is of a 25 year old second gravida who presented with significant exacerbation of Darier's disease at term pregnancy. She was a known case of Darier's disease since childhood. During antenatal visit of first trimester , warty plaques and papules had affected the seborrheic areas of face, chest and back, and limbs. They had a firm, harsh feel like coarse sandpaper, skin coloured. However there had been disease progression with hyperpigmentation of the lesions at the end of pregnancy turning them dark coloured which was very depressing and distressing for the would be mother. Fortunately there was no evidence of infection.There were few sparse lesions over abdomen where a Pfannenstiel incision would be performed should a caesarean section be required, as well as the perineal and forchette region where the fetal head would crown in a vaginal delivery which was a good point for us obstetricians. The affected skin was inelastic and rubbery. Her medical and surgical history was not contributory. Her family history was significant –her greatgrandfather, grandfather, father, aunty and her offsprings, one of her real brother and sister, were all affected with variable severity. All members were suffering from psychiatric symptoms i.e. mood disorders according to the severity of the disease.Her general and systemic examination revealed no abnormality. There was a single fetus in vertex presentation, whose growth was appropriate. Her biochemical, serological and haematological tests showed no

abnormality. She did not go into spontaneous labour until 40 weeks. A nonstress test was reactive. Labour was induced with dinoprostone gel. The labour was uneventful and she delivered a normal healthy baby per vaginally assisted by an episiotomy. Her immediate peurperium was normal and she was discharged. After 20 days she presented with a gaped episiotomy. The lactation was successful. Her skin lesions showed no change. Postpartum a skin biopsy from forearm was taken, saved in formalin and sent for histopathological examination. The HPR showed lesions suggestive of Darier's disease. The gaping of episiotomy would have been a result of inelasticity of the perineal skin because of her dermatological disease. She was counselled regarding possibility of genetic transmission of Darier's disease to her newborn, and postnatal depression.

Similar two more cases of pregnancy with Darier's disease were encountered and observed with an uneventful pregnancy, labour and peurperium but a strong fear of their babies getting affected with this extremely distressing disease.



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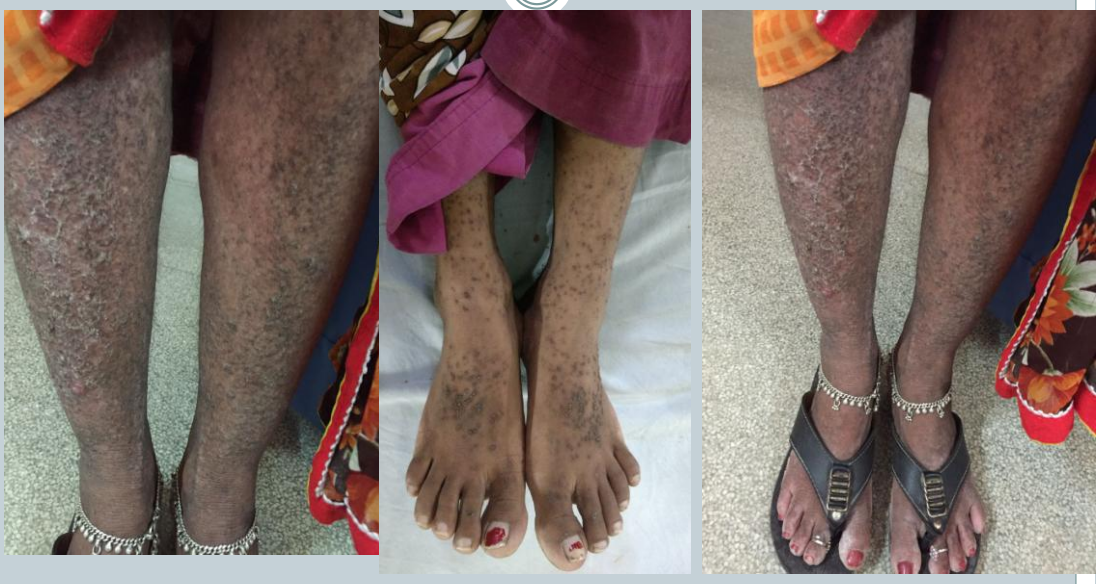

II. Discussion

This is one of the few case series of pregnancy complicated by Darier's disease. In the first case there had been exacerbation of disease (Figure 1) showing hyperkeratotic, inelastic skin. There have been limited publications on Darier's disease in pregnancy [6-9]. Darier's disease is an obstetric issue because the autosomal dominant pattern inheritance means that 50% of offspring will be affected. As a result, couples should be offered genetic counselling at a preconception visit or offered referral to a higher medical center early in the pregnancy for counselling. Prenatal diagnosis has been possible since the 1980s [10]. Prenatal counselling is difficult in Darier's disease due to variable penetrance of disease; it is not possible to predict the severity of disease in the offspring of affected individuals and genotype-phenotype correlation studies have been disappointing [4]. Darier's disease carries a wide spectrum of disease phenotypes, with many mild forms of the disease remaining undiagnosed and severe forms carrying considerable quality of life impacts. The varying phenotypes mean that counselling is important, as women with mild phenotypes may give birth to children with severe phenotypes. Lack of understanding of genetic expression may lead to considerable anger, anxiety and guilt in parents if the child subsequently develops a severe phenotype of the disease and the couple feel they were not adequately prepared for this outcome. One mother whose son had a severe phenotype is reported in the literature as stating, "I would never have had children if I had known it could do this." [5]. Severe disease is usually treated with oral and/or topical retinoids. These therapies elicit a positive clinical response in 90% of patients. However, they are teratogenic and contraindicated in pregnancy. Topical steroids may be safely used in pregnancy but have poor efficacy [2,5]. As demonstrated in the present case study, Darier's disease may cause pregnancy complications when there is skin involvement of the groin, vulva or perineum where skin elasticity is important for atraumatic vaginal birth, or when it involves the lower abdomen where Pfannensteil incision for caesarean section delivery may be required. It may also affect delivery if there is widespread back involvement that precludes safe administration of regional anaesthesia [7]. Histologically in Darier's disease there is acantholysis that results in suprabasal clefting with papillomatosis and dyskeratosis [6,11]. Electron microscopy shows loss of desomosomal protein attachments and perinuclear aggregation of keratin filaments [11]. It has been suggested that the primary target of the chromosomal mutation is the desmosomal plaque [11]. The histological skin changes predispose to infection through barrier thinning. The presence of superimposed infections causes obstetric problems, especially in respect to Group B Streptococus that can lead to specific neonatal sepsis and death. Allergy to Penicillin and multiple antibiotic resistance compromised antibiotic management further in this case. The development of antibiotic resistance may occur in the setting of recurrent infections where bacterial colonisation of the skin is difficult to eradicate. Skin infections may also affect breastfeeding if the breast is involved. Localised fissuring results in breast pain that lead to discontinuation of breastfeeding. Neuropsychiatric associations have been reported in Darier's disease. The reported associations are predominantly **mood disorders**, which affect 50% of patients. The common expressions of these disorders are depression with suicidal ideation and suicide attempts [12]. In the context of pregnancy, this pre-existing vulnerability predisposes the mother to postnatal depression. It is important to formally screen for depression at postnatal review. **We present three rare cases of Darier's disease in pregnancy and focus on the need for prenatal counselling, review of delivery modality and vulval skin elasticity, and the need to provide input for breastfeeding and postnatal depression screening.**

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