Letters to the Editor

Papyraceous Fetus in Association with Live and Viable Twin

Papyraceous fetus causes the release of thrombogenic substances that can cause placental infarction, disseminated intravascular coagulation and cutaneous lesions.

In singletons with no history of fetus papyraceus, as seen in our cases, such lesions reflect either in utero death of an unrecognized twin/triplet or placental infarction.

Typhoid in the mother in the second case might be the cause of truncal aplasia cutis congenita. Although intrauterine typhoid infection has not been implicated in the causation, it has a great impact in causing intrauterine death. Salmonella typhimurium proliferates in the infected placenta and causes placental necrosis thus leading to fetal death.

Most lesions heal spontaneously from the margins, leaving behind a smooth, yellowish, hairless, papery scar. Small residual lesions can be treated by excision of the abnormal skin margins followed by primary closure. Composite skin grafts have been used successfully, using allogenic keratinocytes or autologous fibroblasts followed by keratinocytes a week later.

We were unable to find similar previous reports. Truncal aplasia cutis congenita is itself a rare presentation, more so in the absence of history of twin pregnancy/papyraceus fetuses. These cases also draw attention to the possibility of in utero death of an unrecognized twin/triplet. Further, the role of other hidden factors or the possibility of intrauterine infection such as typhoid needs to be studied in the causation of truncal aplasia cutis congenita. More evidence is needed to confirm the entity of aplasia cutis congenita, group 5 without fetus papyraceus.

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Conflicts of interest
There are no conflicts of interest.

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Identification of GJB6 gene mutation in an Indian man with Clouston syndrome

Sir,
Clouston syndrome (MIM 129500), also known as hidrotic ectodermal dysplasia, is a rare autosomal dominant genetic disorder characterized by generalized hypotrichosis, dystrophic nails and hyperkeratotic palms and soles. It is particularly common in the French Canadian population of Southwest Quebec. We present an Indian man with typical clinical features of Clouston syndrome who was found to have a known mutation in the GJB6 gene.

A 45-year-old man presented to the dermatology outpatient department of Geetanjali Medical College and Hospital in Udaipur, Rajasthan, with complaints
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of excessively thickened skin of the palms and soles. The thickened skin restricted movements of his fingers and disrupted his daily functioning. He gave a history of similar features in one of his children. There was no history of similar lesions in any of his siblings, parents or other family members. None of his family members could be examined.

On examination, the patient was found to have severe hyperkeratosis of the palms and soles which led to clawing of the hands [Figure 1]. Nails were dystrophic in both hands and feet. The fingernails were thickened, overcurved, discolored [Figure 2] and associated with tufting of the terminal phalanges [Figure 1]. Further, the patient had thin and sparse scalp hair [Figure 3a]. Other hair-bearing regions (eyebrows, eyelids, axillae, pubic region) also had very minimal hair [Figure 3b]. There was no history of consanguinity, hypohidrosis, abnormal dentition and any hearing or visual complaints. A provisional diagnosis of hidrotic ectodermal dysplasia was made.

A peripheral blood sample was collected in an ethylenediaminetetraacetic acid (EDTA) tube and DNA was isolated by the salting out method.1 Coding exon 3 of the GJB6 gene was amplified by polymerase chain reaction (PCR) and the amplification checked on 2% agarose gel. Primers used are shown in Table 1. The polymerase chain reaction-amplified product was incubated with exonuclease I and shrimp alkaline phosphatase to remove the unincorporated primers and nucleotides. Bidirectional Sanger deoxyribonucleic acid sequencing was done using ABI Prism BigDye Terminator Cycle sequencing ready reaction kit v3.1 (Applied Biosystems, USA), followed by ethanol/ethylenediamine tetraacetic acid/sodium acetate precipitation. The precipitate was dissolved in 10 µL Hi-Di formamide with denaturation and capillary electrophoresis using an ABI 3130 Genetic Analyzer. Sequencing results were analyzed using Chromas Pro software (http://technelysium.com.au) and compared with the reference sequence of GJB6 in the NCBI database (http://www.ncbi.nlm.nih.gov/). A reported heterozygous missense mutation c. 31G>A (p.G11R) was identified, resulting from a glycine-to-arginine amino acid change [Figure 4].

Clouston syndrome is a rare genetic disease caused by mutations in connexin genes. Connexins or gap junction proteins are a family of structurally related transmembrane proteins which establish direct cell-to-cell communication and are responsible for the movement of molecules and ions across adjacent cells. They may be classified into three major groups (GJA, GJB and GJC) based on sequence homology. Each combination of connexins has different qualities of permeability highly significant in terms of function. Mutations in connexins result in hereditary

| Table 1: Primer sequence for connexin 30 (GJB6) gene |
| Primer name | Primer sequence (5’ and 3’) |
|-------------|-----------------------------|
| Cx 30-3F    | CCTAAAAAATGGGCTCAGTC         |
| Cx 30-3R    | CAAACTTTCAAGCTACAAGG         |
| Cx 30-3IF   | TGCTGTTGGCCTACTACAGG         |
| Cx 30-3IR   | AAGCAGCATGCAATCACAG          |

Clouston syndrome is a rare genetic disease caused by mutations in connexin genes. Connexins or gap junction proteins are a family of structurally related transmembrane proteins which establish direct cell-to-cell communication and are responsible for the movement of molecules and ions across adjacent cells. They may be classified into three major groups (GJA, GJB and GJC) based on sequence homology. Each combination of connexins has different qualities of permeability highly significant in terms of function. Mutations in connexins result in hereditary
peripheral neuropathy, complex conotruncal heart malformations, autosomal dominant forms of cataract and hearing loss. Erythrokeratoderma variabilis, keratitis-ichthyosis-deafness syndrome, Vohwinkel syndrome and Clouston syndrome are cutaneous disorders resulting from connexin mutations.

Mutations in \textit{GJB6} gene (and in some cases, \textit{GJA1} and \textit{GJB2} genes) are responsible for Clouston syndrome. To date, five different mutations have been reported in \textit{GJB6} gene with phenotypic features of Clouston syndrome. Mutations p.G11R and p.A88V have been described by Lamartine et al. in multiple ethnic populations, p.V37E by Smith et al. in Scottish patients and p.D50N by Baris et al. in Israeli patients.\textsuperscript{2,4} Recently, Liu et al. have found that the combination of a novel mutation N14S in \textit{GJB6} and a mutation F191L in \textit{GJB2} played a pathogenic role in Clouston syndrome.\textsuperscript{5} Mutations in \textit{GJA1} (p.V41L) and an R127H heterozygous variants of \textit{GJB2} have also been found responsible for Clouston syndrome.\textsuperscript{6} Out of all these, p.G11R is the most commonly reported mutation, seen in the French Canadian population as well as in many other ethnic populations of the world.

We could find only two previous reports of Clouston syndrome in Indians. One was of a large Gujarati family with 41 affected individuals spanning five generations, but genetic mutations were not explored in this family.\textsuperscript{7} The other report described a p.A88V mutation detected by Lamartine et al. in a patient of Indian ethnicity.\textsuperscript{2}

Our patient presented with typical features, and since he denied any similar features in his parents, it was probably a sporadic case. The mutation detected, c. 31G>A (p.G11R) in the \textit{GJB6} gene, is a known mutation.

\textbf{Declaration of patient consent}

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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There are no conflicts of interest.

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