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A CURIOUS CASE OF COEXISTENT HEMOGLOBIN E DISEASE AND SPONGIOTIC DERMATITIS IN THREE INDIVIDUALS OF SAME ETHNIC ORIGIN

Hematology

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ABSTRACT

We present here three adult individuals, one male aged 25 years and two females aged 24 and 72 years, who presented to the dermatology out-patient department with complaints of generalized skin rash [diagnosed subsequently as spongiotic dermatitis] throughout the body. As part of routine investigations, blood of all three patients were sent for complete hemogram and HBA1c, among other routinely requisitioned laboratory investigations. Routine hemogram revealed anemia for all three subjects [Hemoglobin in the range of 6.5 -10.5 g/dL]. While attempting to ascertain HbA1c percentages, values were undetectable by HPLC. Since such a scenario is possible in the setting of hemoglobinopathy, particularly in homozygous condition, a hemoglobin variant study was conducted on the blood samples of all three subjects. The variant study revealed abnormally elevated HbA2 fractions of all individuals [89.0 % - 99.5%], strongly supporting the existence of hemoglobin E disease, as did the concomitant presence of anemia in routine hemogram. A detailed history taking revealed even more common features. Coincidentally all three individuals were residents of the same geographical area and shared a common ethnic background. One of the subjects hailed from Alipurduar district of West Bengal, India while the other two were residents of Dinajpur district of Bangladesh. Coincidentally, both these districts now belonging to two different countries, were one and the same district, in pre-independent India. The spongiotic dermatitis, a form of atopic dermatitis is also known to affect individuals residing in a common environment. None of the subjects shared any familial or marital ties with one another. We thus concluded that ethnic and environmental commonalities can very well lead to two apparently unrelated disease conditions manifesting in individuals who share no familial or marital ties with one another.

KEYWORDS

Hemoglobin E, homozygous, spongiotic dermatitis, HPLC.

Case Report

In a first of its kind, we received in the dermatology out-patient department, three adult individuals, one male aged 25 years and two females aged 24 and 72 years, with complaints of generalized skin rash throughout the body. Two of them; a 24-year-old female [henceforth designated as subject A] and a 25-year-old male [henceforth designated as subject B], hailed from Bangladesh while the third, a 72-year-old female [henceforth designated as subject C], hailed from India itself.

As part of routine investigations, blood of all three patients were sent for complete hemogram and HBA1c, among other routinely requisitioned laboratory investigations. Routine hemograms **[Fig 1(A-C)],** performed on an automated platform, the ABX Pentra XL (Horiba), revealed low total hemoglobin, below normal RBC indices and a peripheral blood picture consistent with microcytic hypochromic anemia for all three subjects. Briefly the total hemoglobin levels for subjects A, B and C were 8.5 g/dL, 10.5 g/dL and 6.5 g/dL, respectively [Biological reference interval 12.0-15.0 g/dL]. The RBC indices for subjects A, B and C were, mean corpuscular volume (MCV); 69, 63 and 72 fL [Biological reference interval 83-101 fL], mean corpuscular hemoglobin (MCH); 26.1, 20.0 and 22.7 pg [Biological reference interval 27-32 pg] and mean corpuscular hemoglobin concentration (MCHC); 32.7, 31.8 and 31,6 g/dL [Biological reference interval 31.5-34.5 g/dL], respectively.

As part of routine investigation, blood HbA1c was also requisitioned for. The test methodology adopted was high performance liquid chromatography [HPLC] on automated platform, Bio-Rad D10. However, HbA1c was undetectable for all three subjects. Since such a scenario is possible in the setting of hemoglobinopathy, particularly in homozygous condition, a hemoglobin variant study was conducted on the blood samples of all three subjects, using HPLC on the same automated platform **[Fig 2(A-C)].** Briefly, the variant analysis chromatogram revealed, HbA2 fractions for subjects A, B and C were 97.1% ,99.5% and 89.0 % [Biological reference interval 2.0% – 3,7%], respectively. The HbF fractions were mildly elevated in subjects B & C [7.6 and 11.4 % respectively]. However, to establish the diagnosis more firmly, the blood sample of subject C was sent for genetic analysis. Gene sequencing by Sanger's method confirmed HbE homozygous condition **[Fig 3],** consistent with our clinical, hematological and HPLC findings.

All three subjects had presented with pruritic skin lesions throughout the body **[Fig 4(A-D)].** Biopsy sections of skin revealed, hyperkeratosis, irregular acanthosis, spongiosis and pigment incontinence with normal vasculature of dermis **[5(A-C)].** These histopathological features were consistent with that of spongiotic dermatitis.

The Hemoglobin E variant, caused by a single point mutation resulting in glutamic acid being replaced by lysine in position 26 of beta globin chain of hemoglobin and manifesting as heterozygous (trait), homozygous (disease) or co-existent with beta-thalassemia as a mosaic inheritance, is highly prevalent in Eastern & North-Eastern India and includes present day Bangladesh as well [1]. Current diagnostic modalities rely strongly on a robust history along with findings inclusive of complete hemogram, and HPLC results [2]. In West Bengal itself, particularly among the rural and semi-urban segment where awareness regarding importance of pre-marital screening and counselling are largely sub-optimal coupled with caste dynamics and consanguinity, the occurrence of HBE trait and disease are not at all infrequent [3]. Unlike beta thalassemia major, HbE disease itself has a fairly indolent course with only moderate anemia at worst while the heterozygous condition is largely asymptomatic, with only a co-existing HbE-beta thalassemia exhibiting a more serious picture [4]. Hence the condition more than often goes undetected, and commonly comes to light only as an incidental finding.

Our current case is unique as we simultaneously encountered three individuals belonging to two different countries yet to the same ethnic and geographical landscape while sharing no blood or marital ties with one another. Yet all three presented with moderate anemia only on routine investigation and an undetectable HbA1c [also a part of routine

investigation], which elicited the need to do a variant analysis by HbA1c. The latter threw up chromatograms commensurate with a provisional diagnosis of HbE homozygous [later confirmed by gene sequencing of one of the study subjects].

What is even more interesting is that none of the patients came to our hospital for any hematological complaint. Rather they all presented with generalized pruritic skin lesions that was confirmed on histopathological examination as spongiotic dermatitis. This skin lesion considered to be fairly ubiquitous in nature, so called owning to the characteristic appearance of the epidermis, imparted by intercellular edema, often progressing to intraepidermal vesiculation [5]. Interestingly, IgE-mediated delayed-type hypersensitivity plays a pivotal role in the pathogenesis of spongiotic dermatitis, strongly suggesting a common pattern of allergen exposure leading to such lesions that develop following a reasonably slow course [6]. Our study subjects who were found to be residents of politically divided but ethnically common geographical region; manifested with such skin lesions; thereby strengthening the possibility of a common allergen exposure over a finite amount of time, attributed to environmental parity.

Our case report, has thus thrown up a very interesting phenomenon albeit not entirely surprising of a not just one but occurrence of two distinct apparently unrelated disease conditions among individuals, who although residents of two different countries, share a common ethnic origin and common habitat, while sharing no common family or marital ties. We recommend, minute screening for such diseases among all those known to share common ethnic origins where deep-rooted genetic and environmental commonalities are frequent in existence.

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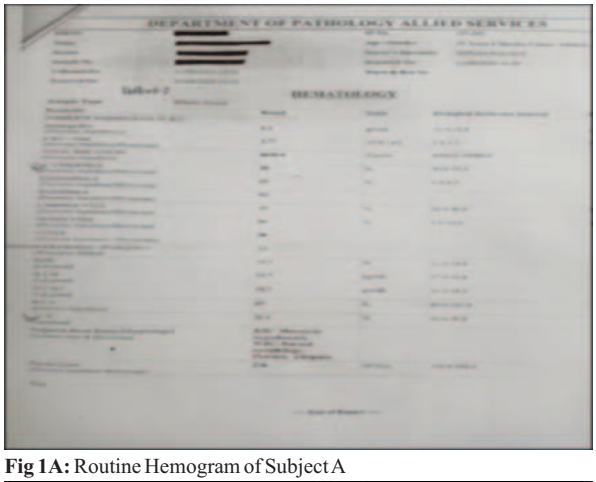


Fig 1A: Routine Hemogram of Subject A

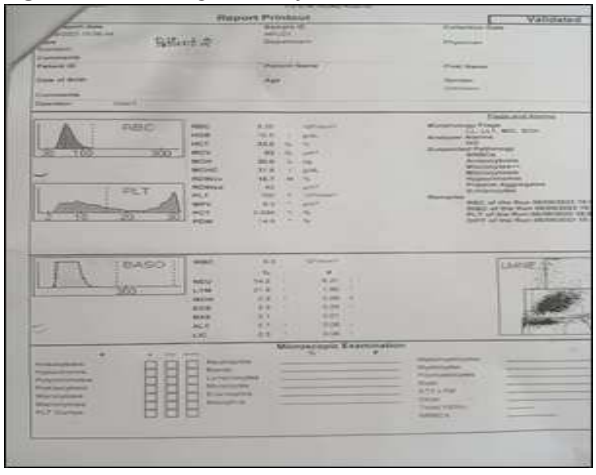


Fig 1B: Routine Hemogram of Subject B

Fig 1C: Routine Hemogram of Subject C

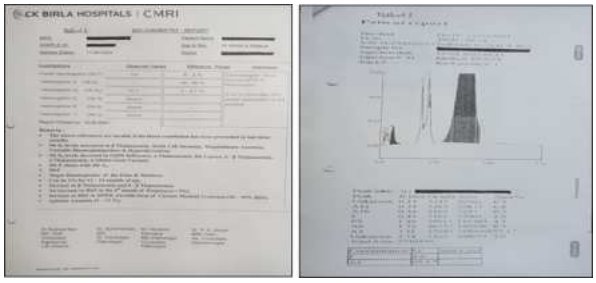


Fig 2A: Hemoglobin Variant analysis by HPLC with Chromatogram of Subject A

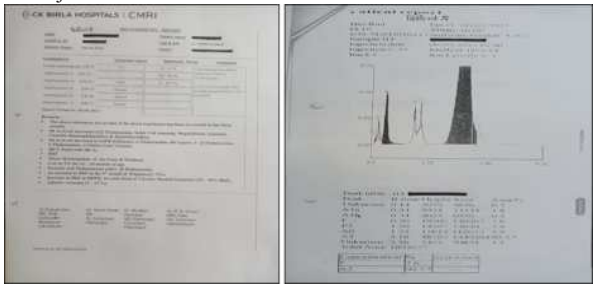


Fig 2B: Hemoglobin Variant analysis by HPLC with Chromatogram of Subject B

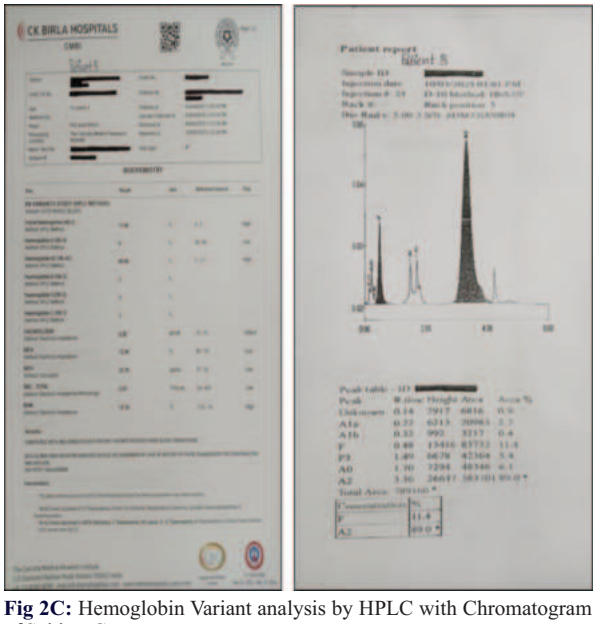
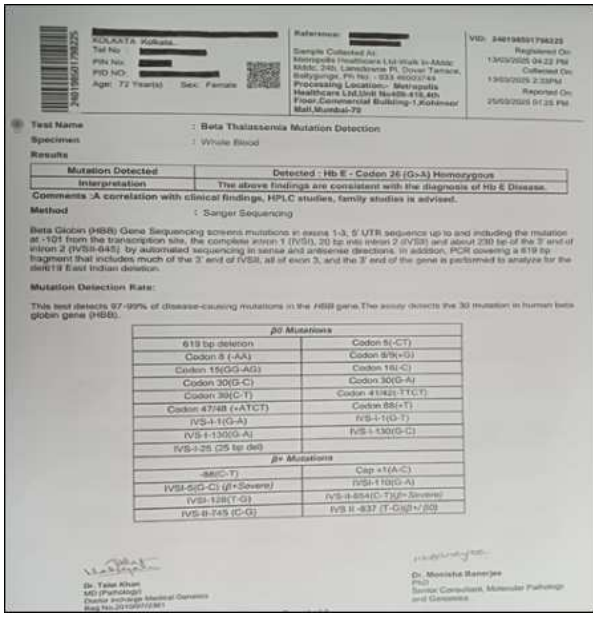


Fig 2C: Hemoglobin Variant analysis by HPLC with Chromatogram of Subject C



Test Name : Beta Thalassemia Mutation Detection
Specimen : Whole Blood
Results

Mutation Detected	Detected : Hb E - Codon 26 (G>A) Homozygous
Interpretation	The above findings are consistent with the diagnosis of Hb E Disease.

Comments :A correlation with clinical findings, HPLC studies, family studies is advised.
Method : Sanger Sequencing

Beta Globin (HBB) Gene Sequencing screens mutations in exons 1-3, 5' UTR sequence up to and including the mutation at -101 from the transcription site, the complete intron 1 (IVS1), 20 bp into intron 2 (IVS2) and about 230 bp of the 3' end of intron 2 (IVS2-645) by automated sequencing in sense and antisense directions. In addition, PCR covering a 619 bp fragment that includes much of the 3' end of IVS2, all of exon 3, and the 3' end of the gene is performed to analyze for the del619 East Indian deletion.

Mutation Detection Rate:

This test detects 97-99% of disease-causing mutations in the HBB gene.The assay detects the 30 mutation in human beta globin gene (HBB).

β0 Mutations	
619 bp deletion	Codon 5(-CT)
Codon 8 (-AA)	Codon 9/9(+G)
Codon 15(GG-AG)	Codon 16(-C)
Codon 30(G-C)	Codon 30(G-A)
Codon 39(C-T)	Codon 41/42(-TTCT)
Codon 47/48 (+ATCT)	Codon 88(+T)
IVS-I-1(G-A)	IVS-I-1(G-T)
IVS I-130(G-A)	IVS I-130(G-C)
IVS-I-25 (25 bp del)	
β+ Mutations	
-88(C-T)	Cap +1(A-C)
IVSI-5(G-C) (β+Severe)	IVSI-110(G-A)
IVSI-128(T-G)	IVS-II-654(C-T)(β+Severe)
IVS-II-745 (C-G)	IVS II -837 (T-G)(β+/β0)

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Fig 3: Gene Sequencing Result [Sanger Method] for Mutation Analysis of Subject C

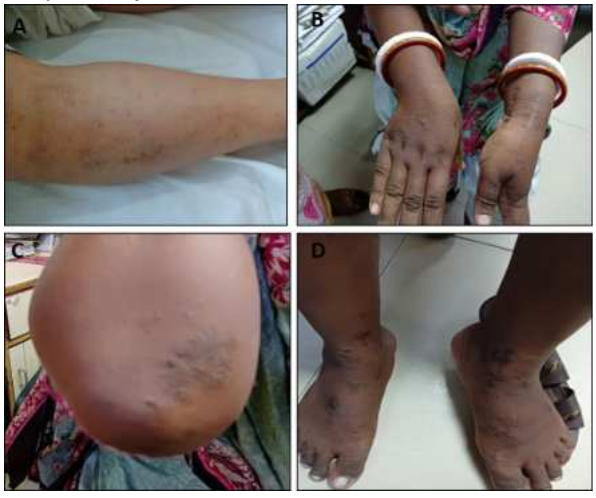

Fig 4 A-D: Vesicular Skin Lesions affecting Different Body Surfaces of Three Study subjects Consistent with Spongiotic Dermatitis

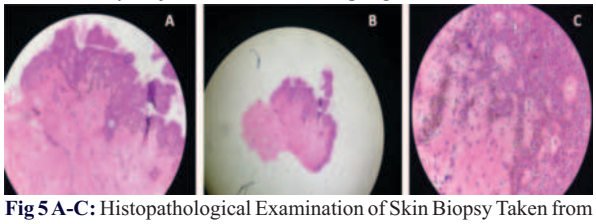

Fig 5 A-C: Histopathological Examination of Skin Biopsy Taken from Three Study Subjects, showing Hyperkeratosis, Irregular Acanthosis, Spongiosis and Pigment Incontinence with Normal Vasculature of Dermis; Consistent with Spongiotic Dermatitis

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