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Case Report

Concomitant Incontinentiapigmenti and antiphospholipid antibody syndrome leading to diagnostic dilemma in a case of bad obstetric history: First report of the association

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Abstract

Antiphospholipid Antibody syndrome (APS) is an autoimmune disease characterized by recurrent thrombotic events, pregnancy morbidity, and persistence of Antiphospholipid antibodies (APLA). Incontinentiapigmenti is a rare X-linked dominant disorder, lethal in the majority of affected males in utero and variably expressed in females. Herein we present a case of a cutaneously asymptomatic lady with bad obstetric history who was detected to have APLA syndrome during Antenatal Care, with a dermatological referral to the dermatologist of her offspring leading to detection of Incontinentiapigmenti in the otherwise healthy offspring. We present this case to highlight the diagnostic difficulties in the coexistence of these two conditions in the same patient, particularly when the autosomal dominant gene is not expressed in females.

Keywords: Antiphospholipid Antibody syndrome, Incontinentiapigmenti, Bad Obstetric History (BOH).

1. Introduction

Antiphospholipid Antibody syndrome (APS) is characterized by the concurrent occurrence of Antiphospholipid antibodies (APLA) with hypercoagulability presenting as recurrent arteriovenous thrombosis and Bad Obstetric history [1].

Incontinentiapigmenti (IP) or NEMO Syndrome is an uncommon genodermatosis that affects mostly females and is usually lethal to males in utero. The credit for first description of this syndrome is attributed to Bloch in 1926 & Sulzberger in 1928 [2]. In affected females it causes anomalies in skin, hair, teeth, nails, eyes and the central nervous system [3]. The pathogenesis of IP has been identified as NEMO (NF-KB Essential Modulator)/IKK gamma gene which has been mapped to Xq28. Pedigree reviews have suggested X-linked dominant transmission with lethality in males [4].

To the best of our knowledge, there have been no previous case reports of the co-existence of IP and APS in the same patient with bad obstetric history. We present this case for the extreme rarity of the association of these two conditions and the diagnostic confusion arising out of the association. We also present this case to highlight the need to keep in consideration IP when an offspring is affected, even if a lady with Bad Obstetric History is diagnosed as APS.

2. Case Report

A 33 year old lady, Gravida- 6, Para 2, Living- 2, Abortion- 3, married for 10 years, presented with pregnancy of 45 days duration. Detailed history was taken regarding her previous pregnancy outcomes, which is depicted in Table 1.

Table 1: Detailed history of her previous pregnancy with outcomes

No of Pregnancy	Years	Antenatal Period	Labour& Delivery	Baby		Puerperium/Remarks
				Sex	Wt	
G1	9 yrs back	Missed abortion at 14 weeks	Medical abortion			
G2	8 yrs back	uneventful	Normal Vaginal Delivery	F/2.9 Kg		
G3	6 yrs back	Missed abortion at 14 weeks	Medical abortion			
G4	5 yrs back	Missed abortion at 14 weeks	Medical abortion			
G5	1yr 6 month	Administered Inj LMWH	Normal Vaginal Delivery	F/2.8 Kg		Pt was evaluated for BOH detected to have ACLA +ve
G6	Present Pregnancy					

The Elder offspring 8 yrs female was normal. The mother gave history of a full term normal delivery (Birth weight – 2.8 kg) with normal skin at birth. The father was normal on cutaneous examination. The child later at 3 wks time developed vesicular lesions in a linear distribution. The lesions slowly dried up and formed raised papules which were mildly itchy. Later at 1yrs of age, the papular lesions subsided, leaving behind the present cutaneous dark colored patches (Figure 1). Developmental milestones were normal with no history of failure to thrive, poor feeding, fever, seizures or diminished visual acuity.

Dermatological examination on the younger one, a half year old girl child revealed interrupted and continuous hyperpigmented macules without atrophy, distributed in a Blaschkolinear fashion over trunk, upper and lower limbs. The cutaneous macules resembled 'Chinese Letter' pattern (Figure 2). Her oral mucosa, palms, soles, scalp, face & dentition were normal. Complete blood counts, absolute eosinophil count, liver function test, renal function test & urinalysis were normal. Ophthalmoscopy was demonstrated no ocular anomaly. MRI Brain revealed no neurological features. X-Ray of the long bones revealed no malady. Based on the pathognomonic cutaneous features and characteristic history of evolution by the mother, a diagnosis of X-linked dominant Incontinentia Pigmenti was made (Table 2). Linear and whorled hypermelanosis was ruled out due to history and absence of lesions at birth. Lack of hypopigmentation ruled out Hypomelanosis of Ito (Pigment mosaicism). The lady was diagnosed to be a case of Incontinentia Pigmenti with incomplete penetrance of the autosomal dominant gene. Clinical suspicion was established that all the previous abortions must have been male fetuses, since Incontinentia Pigmenti is almost invariably lethal in males.

Figure 1: Cutaneous dark colored patches

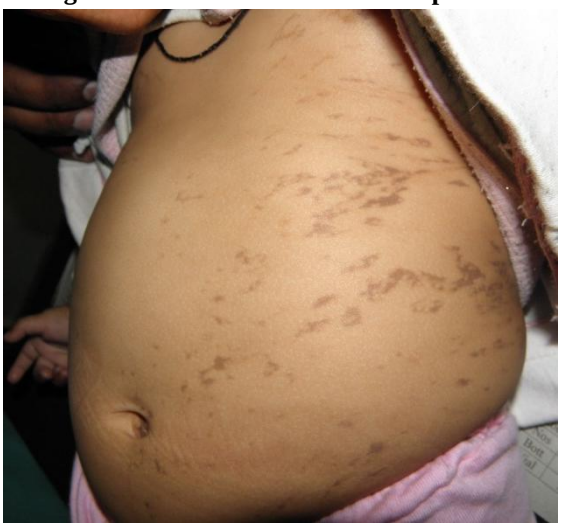

Figure 2: 'Chinese Letter' pattern macules

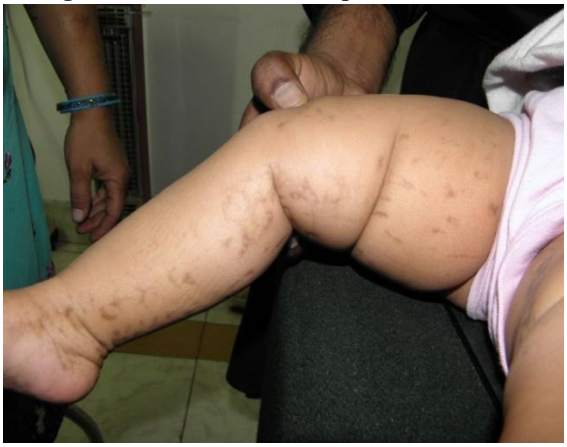

Table 2: Landy and Donnai criteria for incontinentiapigmenti diagnosis

Family history	Major criteria	Minor Criteria
No evidence of IP in a first degree female relative*	Typical neonatal rash : erythema and vesicles with eosinophilia	Dental anomalies
	Typical hyperpigmentation mainly on trunk, following lines of Blaschko, fading in adolescence	Alopecia
	Linear atrophic hairless lesions	Abnormal nails
		Retinal disease
Evidence of IP in a first degree female relative#	Suggestive history or evidence of typical rash, hyperpigmentation, atrophic hairless lesions	
	Vertex Alopecia	
	Dental anomalies	
	Retinal disease	
	Multiple male miscarriages	

* At least one major criterion is necessary for diagnosis in cases with no apparent family history. Minor criteria support the diagnosis; complete lack thereof should induce a degree of uncertainty.
# Presence of any one or more of the major criteria strongly suggests a diagnosis of incontinentiapigmenti in cases with definitive family history.

All the biochemical and hematological investigations were within normal limits. She was placed on folic acid along with progesterone support. On evaluation, she was found to be positive for Lupus Anticoagulant antibodies. A diagnosis of Bad Obstetric History with Primary APS was done. She was started on ecospirin 75 mg and LMWH 1mg/ Kg body weight. On routine follow up, Trans-abdominal Sonography at 12 wk 1 day showed no fetal cardiac activity, suggestive of missed abortion. The anticoagulant and antiplatelet agent were interrupted and medical abortion carried out using Tab Misoprostol. The abortus was examined carefully to determine sex and was found to be male. This further confirmed our doubt that the antecedent BOH was probably due to Incontinentia Pigmenti causing lethality in male fetuses. The fact that similar obstetric adverse outcome to previous 3 episodes occurred in spite of initiation of appropriate Antiplatelet & anticoagulant therapy for APS further strengthened the basis of our assumptions. The lady was counseled and advised to avoid future pregnancies, which might yield a deformed female child or that individual will have to go through missed abortion. NEMO mutational analysis was offered to the mother, but owing to her being from lower socioeconomic strata, she expressed inability to do the same.

3. Discussion

Incontinentiapigmenti is considered to be a syndrome of multisystem polydysplasias often affecting teeth, eyes, Central Nervous System (CNS), and other organs [5]. The role of eotaxin and NEMO/IKK gamma deficiency in pathogenesis of IP has been well elucidated [2]. Both the mother in our case and the daughter did not have any associated anomalies systemically as depicted.

There have been over 700 case reports of IP in literature. In review of 653 patients, 55.4% had a definitive family history of IP, like in our case [6]. Pedigree reviews have suggested X-linked dominant transmission with lethality in males. This is supported by findings of a high affected female/male ratio, female to female transmission like in our case, and 1:1:1 affected male: normal female : normal maleratio in the offspring of an affected mother [2]. The incidence of miscarriages is increased in patients of IP and is presumed to represent affected male fetuses, although systematic sex determination of abortus has never been performed [7]. However, in our case the sex of the abortus was determined to be male, adding weightage to our diagnosis.

In our case, the lady was asymptomatic except for BOH, and differences in expressivity have been attributed to lyonization in females, resulting in functional mosaicism[8]. Other clues to diagnosis of IP in asymptomatic adults are abnormal dentition, Ophthalmologic abnormalities, Neurological abnormalities [9], and nipple anomalies [10]. These associations were sought for but not found in our case. We propose that in the present case, the cutaneous changes in the woman must have occurred in utero, or must not have been expressed due to Lyonization. The diagnosis of IP is not precluded by the absence of observable or documented cutaneous findings, especially in older women after the resolution of lesions [2].

APS has been associated with a variety of systemic events including arteriovenous thromboses, autoimmune thrombocytopenia and recurrent fetal loss [11]. The causes of recurrent early fetal loss in APS patients is due to various factors like pre-ecalmpsia< 34 weeks gestation, IUGR, and Uteroplacental insufficiency [12]. The risk is greatest in women with high titers of antiphospholipid antibodies. In

our case a well recognized cause of recurrent fetal loss had been confirmed, i.e. Primary APS.

Our patient with recurrent fetal loss was positive for LAC, and negative for anticardiolipin antibodies. Diagnosis of APS is not merely represented by the presence of the autoantibodies, but by a set of criteria [13]. In our case the following criteria were met, which led to misdiagnosis of the reason for fetal loss as APS. A metaanalysis suggested that for women with recurrent miscarriage as diagnostic criteria detected, prophylactic heparin and low dose aspirin are advantageous in preservation of pregnancy [13]. This combined therapy was found superior to either Aspirin or Heparin alone. This dual therapy was promptly initiated in our case on diagnosis of APS, but same could not prevent the fetal loss prompting us to think of alternative diagnosis. Subsequently on ultrasonographic evidence of missed abortion, medical abortion was carried out.

IP is characterized by the sequential appearance of vesiculobullous lesions in Blaschkoid distribution, which appears at birth -02 weeks' time, which resolves by 4 months. The verrucous Stage 2 appears at 2-6 weeks and usually disappears by 6 months. The Onset of Stage 3 hyperpigmentation phase starts at 12-26 wks and can resolve in most cases by puberty, leaving behind alopecic atrophic hypopigmented Blascko-linear pigmentation [2]. The criteria in our woman was only recurrent miscarriages of male fetuses, which in previous studies has been found to be affecting 56% of IP females[10]. The diagnosis was strengthened by the delivery of female fetus with confirmed IP with Stage 3 cutaneous manifestations. This child however did not have any extra-cutaneous manifestations of IP.

A thorough literature survey revealed only 2 cases of association of IP with autoimmune diseases. Since Systemic Lupus Erythematosus per se can cause BOH, Serum ANA was done in our case, which turned out to be negative. Lin *et al*. had reported an association of IP with Behcets disease [13], but had proposed that the association is incidental. No association of NF-KB was found with APS. Hence we feel that the association of these two confounding diagnoses which result in BOH independently in our patient was merely co-incidental.

Owing to the chance of recurrent fetal loss and birth of affected female offspring due to presence of X-linked dominant IP in our patient, genetic counseling was given and Planned Parenthood was offered.

5. Conclusion

We present here this case to highlight the diagnostic difficulties in evaluation of a case of BOH, in which multiple aetiologies are suspected. The diagnosis of one condition should not preclude the search for another etiology. We also want to highlight the fact that IP should always be considered in history of spontaneous recurrent fetal loss and a pointed enquiry must be initiated into family history, and detailed pedigree analysis should be considered.

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