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HERPES GESTATIONIS (PEMPHIGOID GESTATIONIS)

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Three patients of herpes gestationis, a rare dermatosis of pregnancy, are being described along with a short review of literature on the recent immunological backdrop. The characteristic periumbilical cutaneous lesions with classical bullae-en-cocade appeared during the third trimester of pregnancy and were controlled with corticosteroids. Classical histopathological basal cell necrosis in all the three patients and C3 deposition on dermo-epidermal interface in two patients were demonstrated. Post-partum exacerbation was noted in all the three patients. Remission occurred after 13 weeks in one patient, the rest did not report for follow up.

Key words : Herpes gestationis, Pemphigoid gestationis, Clinical, Immunopathology.

Herpes gestationis is the most specific and well researched clinical entity out of all the dermatoses of pregnancy and perpeurium.[1,2] The initial episode always occurs in relation to pregnancy or products of conception like hydatidiform mole and chorio-carcinoma, recurring with subsequent pregnancies.[1] Overlapping clinical and immunopathological features, evidence of transformation to bullous pemphigoid and similarity of associated auto-immune diseases suggest that herpes gestationis should be considered within the spectrum of pemphigoid and the new terminology of pemphigoid gestationis would seem more appropriate.[1,3]

Case Reports

Case 1

A 22-year-old, gravida 1, para O, abortus O, female had severe pruritus for 7 days at 36 weeks of pregnancy, followed three days later, by multiple, erythematous lesions on the umbilical region and forearms. The patient also had severe intra-uterine growth retardation corresponding to 30 weeks of height of uterus. Two days after admission, she had an assisted breech delivery of a low-birth weight (1.44 kg) female baby of low Apgar score of 4, 7, 9. One day after delivery, the skin lesions spread gradually to involve the thighs, face and upper arms and became vesiculo-bullous. She had not received any drug in the immediate past.

On admission, the patient was afebrile, normo-tensive with mild pallor. Cutaneous examination revealed polymorphous skin lesions widely distributed over the abdomen, chest, face, upper arms and back. Multiple, erythematous, oedematous, plaques, measuring 2-5 cm with central clearing and multiple peripheral rings of vesiculo-bullous lesions (Bullae encocade) and grouped papulo-vesicular lesions on an erythematous base were seen (Fig. 1). Bullae were tense and turbid. Mucosae were free of lesions. Patient was put on 40 mg daily prednisolone, to which she responded dramatically by marked improvement in itching and arrest of the new lesions within 24 hours. Complete clearing occurred with hyperpigmentation in one week. She came 3 weeks later with new lesions following reduction of prednisolone to 35 mg/day on her own, the eruption was controlled with enhanced dose. She reported again after 8 weeks when a reduction of dosage was attempted successfully. The total duration of disease was 13 weeks.

Following laboratory studies were done and found negative or within normal limits; complete

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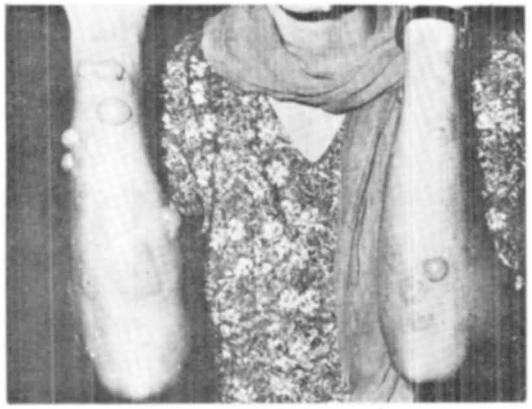

Fig. 1. Oedematous, urticarial plaques with central clearing and multiple peripheral rings of vesiculo-bullous lesions.

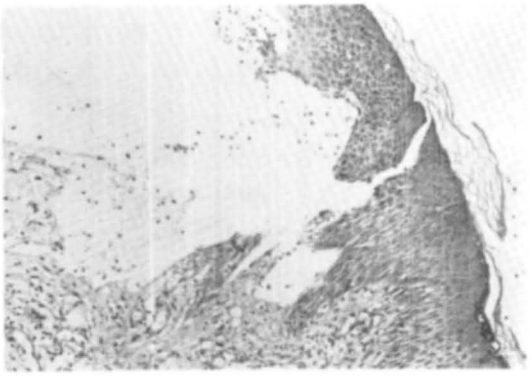

Fig. 2. Spongiosis, extensive basal cell necrosis with subepidermal bulla containing lympho-mononuclear cells and eosinophils. Underlying dermis also shows similar infiltrate (H & E, ×140).

haemogram, urinanalysis, stool examination, blood urea, creatinine, electrolytes, proteins, liver enzymes, calcium, EKG and chest roentgenogram. Histopathological examination of a bullous lesion (Fig. 2) showed detachment of entire epidermis from the dermis. The basal cells in these areas had disappeared. The epidermis showed focal spongiosis and vacuolation of malpighian cells in early as well as late lesions. Blister cavity and dermal papillae contained inflammatory infiltrate rich in lymphomononuclear cells and eosinophils. Direct immunofluorescent examination of frozen sections from peribullous oedematous skin revealed C3 deposits along the dermo-epidermal interface. Immunoglobulin deposits were not seen.

Case 2

A 19-year-old primi-gravida developed pruritus at 30 weeks of gestation. Two days later, she noticed erythematous papular lesions on peri-umbilical area. The lesions spread gradually to arms, forearms, chest, abdomen, back, palms and soles. New lesions appeared on normal or erythematous urticarial plaques and spread in a polycyclic, geographical pattern leaving central clearing and blisters on the active periphery. Isolated or grouped papulo-plaques, vesicles, haemorrhagic blisters, denuded areas and healed hyperpigmented macules were also seen. She was put on prednisolone 30 mg daily, but did not respond adequately. A further increase to 50 mg daily cleared the lesions in two weeks. Subsequent attempts of dose reduction during the rest of her pregnancy met with failure. She had normal labour at 39 weeks of gestation and delivered a male baby weighing 2.7 kg of 7, 8, 10 Apgar score. The infant had erythematous papulo-plaques over his face and extremities which lasted two weeks. Patient had an exacerbation following delivery but was controlled with readministration of corticosteroids in a previous dosage. She reported 4 weeks after delivery with a few active lesions but failed to turn up later. Laboratory investigations were normal. Histopathological and direct immunofluorescent findings were also similar to case 1.

Case 3

A 25-year-old, gravida 2, para 1, abortus O, female came with extremely pruritic erythematous papulo-plaques and vesicles on her abdomen,

back, thighs and face for three weeks. She was carrying a pregnancy of 36 weeks. Three years earlier, she had had a normal pregnancy but developed red papular and vesicular lesions over the abdomen and thighs during post-partum period. She had been treated by a private practitioner with 30 mg prednisolone daily, for two months. Routine investigations were normal and skin biopsy showed features of herpes gestationis. Skin tissue immuno-fluorescence could not be performed. She was put on 40 mg daily prednisolone but failed to follow up. The later course and details of her delivery are not known.

Comments

Herpes gestationis is a misnomer and was probably applied by Milton in 1872 to describe the clustering or herpetiform eruption.[4] Since it is rare, the exact incidence is not known. Early studies estimated its occurrence as 1 in 4000 deliveries, but recent surveys put these figures as 1 in 10,000 to 40,000.[5-7] The onset of the disease is usually in the second trimester of pregnancy but may occur later or earlier in the subsequent pregnancies. In a review of 93 patients, onset of the eruption occurred in 15%, 48% and 26% in first, second and third trimesters respectively.[6] Only 3 patients had onset on the fourth post-partum day or beyond. The disease started in the third trimester in our patients. The lesions are extremely pruritic and initially appear in the peri-umbilical region in more than half of the patients.[2,8] Lesions are polymorphous and begin as urticarial oedematous plaques turning into vesicles and bullae only after 2 to 4 weeks.[2,6] Mucous membranes may be involved in 10-20%.[6] The disease usually remits prior to delivery in some (23%) cases, but is often followed by post-partum exacerbations.[6,8] Gradual regression occurs over 1 week to 3 months following delivery (55%).[6] All our patients had post-partum exacerbations. The disease lasted for 11 weeks after delivery in one patient while the exact duration is unknown in two cases who were lost to follow up. Exacerbations with oral contraceptives and menstrual periods are also known.[2,8,9] During the past few years, immunological features have been elucidated, allowing a definite diagnosis. Earlier, Kolodny[6] proposed diagnostic criteria of onset during pregnancy or within 3 days post-partum, history of herpes gestationis in the previous pregnancy, intense pruritus, presence of erythematous papules and vesiculo-bullous lesions, involvement of trunk or abdomen, minimal or absent scarring, non-acantholytic subepidermal blisters and clearing of eruption or reduction in severity within 3 months post-partum.

Though, the precise cause of herpes gestationis is unclear, both hormonal and auto-immune processes have been implicated.[1] Exacerbations with menstruation, oral contraceptives and association with trophoblastic tumours lend support to the hormonal factors.[9-11] Recent immunological and ultrastructural studies have greatly advanced the knowledge of auto-immune defect. Provost and Tomasi[12] demonstrated a circulating HG factor, that was later identified as an IgG.[13,14] HG factor has a very high affinity for C3 and fixes its large quantities at basement membrane zone.[13] It is very faintly stained and seldom detected by the usual methods but can be demonstrated by indirect complement immunofluorescence.[13,15] HG factor is thought to play a direct role in the pathogenesis of lesions. It crosses the placenta and produces a transient rash in infants.[16] However, Holmes et al[17] could not show correlation of HG factor titres and clinical activity. Herpes gestationis is strongly associated with HLA-DR3 and a combination of DR3/DR4.[18] Many observers have found anti-HLA antibodies against A, B, C and DR specificities of patient's husbands.[16,19,20] Anti-HLA antibodies could be due to hypersensitivity of the mother to the foreign HLA antigen or a result of patient's high

immune responsiveness rather than a cause.[20] Immunopathological, light and ultrastructural studies show a close relationship with bullous pemphigoid.[15,21,22] Light and electron microscopy show highly characteristic basal cell necrosis.[23] Direct immunofluorescence shows linear deposits of C3 with or without IgG at BMZ of involved and rarely uninvolved areas.[15,21,22] Yaoita et al[24] observed uniform deposition of C3 throughout the lamina lucida in herpes gestationis compared to more heavy deposition on the upper part of lamina lucida and cytomembranes of basal cells in bullous pemphigoid. Kolodny[6] found no evidence of increased foetal morbidity or mortality. Lawley et al[25] reported 7.7% still-births and 23% premature deliveries in a series of 39 cases. More recently, Holmes and Black[26] studied foetal prognosis in 50 pregnancies and found a significant increase in low birth weight and small for date infants. However, with good obstetric and perinatal care, the outcome in majority of pregnancies was satisfactory. One of our patients had a low birth-weight baby while the other two patients delivered normal babies. Skin lesions of one of the babies looked like early lesions of herpes gestationis, however histopathological study was not undertaken. Systemic corticosteroids remain the mainstay in the treatment of herpes gestationis and do not effect the foetal prognosis. Some patients require high doses upto 180 mg prednisolone daily and post-partum azathioprine therapy.[3,8]

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