Sir,

The term blueberry muffin baby came from the superficial similarity of cutaneous manifestations to a blueberry muffin and was used to describe the cutaneous manifestations of congenital rubella in newborns during the American epidemic of the 1960s. It is characterized by widespread reddish-blue to magenta-colored maculopapular lesions. The differential diagnosis of blueberry muffin baby includes conditions associated with TORCH (toxoplasmosis, others, rubella, cytomegalovirus, herpes virus) infections, dermal extramedullary hematopoiesis, infiltrative neoplastic lesions of the skin, and cutaneous vascular anomalies.[1,2] We present a case of a 9-month-old male infant who was referred to our outpatient department with multiple asymptomatic reddish to bluish raised lesions over the body since 1 month.

A 9-month-old male child with uneventful obstetric history presented with multiple asymptomatic reddish to bluish raised lesions over the body since 1 month. The pregnancy was full term and without infectious complications, with prenatal diagnosis of intrauterine growth restriction. Maternal serology (human immunodeficiency virus, hepatitis B antigen, and TORCH) was negative. Immunization history (bacilli Calmette-Guérin; hepatitis B; diphtheria, pertussis, tetanus; oral polio vaccine; injectable polio vaccine; and measles vaccine) of the infant was adequate till date. Cutaneous examination revealed multiple dusky blue non-blanchable dome-shaped papules and nodules over forehead, trunk, and right cubital fossa [Figure 1]. Ophthalmological examination including fundoscopy was within normal limit except for icterus [Figure 2]. Per-abdominal examination and ultrasound of the abdomen revealed hepatosplenomegaly. Hematological examination showed anemia (9.3 g/dL), thrombocytopenia (95,000/mm³), direct hyperbilirubinemia (2.8 mg/dL), and elevated liver enzymes (alkaline phosphatase 384 IU/L and aspartate transaminase 94 IU/L). Cytomegalovirus (CMV) IgM titer was 2.22 U/mL and CMV IgG titer was 28 U/mL. Workup for other TORCH infections (antibodies for toxoplasmosis, rubella, and herpes simplex virus) was negative. Skin biopsy showed foci of dermal erythropoiesis along with aggregates of nucleated and non-nucleated erythrocyte precursors [Figures 3 and 4]. Based on clinical, biochemical, and histopathological findings, a diagnosis of blueberry muffin baby with CMV hepatitis was made and the patient was started on intravenous ganciclovir 100 mg once daily for 6 weeks. The mother’s serology was negative and the baby’s IgG CMV was positive, but IgM was negative could point out that the infection was acquired perinatal/postnatal. Polymerase chain reaction/viral culture to confirm the diagnosis could not be performed due to resource and economic constraints.

Blueberry muffin syndrome, a rare neonatal skin disorder, is characterized by widespread non-blanchable, maculopapular lesions of reddish-blue or magenta color seen due to persistent dermal erythropoiesis.[3,4] The various causes for blueberry muffin syndrome are mentioned in Table 1.[1,3-5] The exact cause of prolonged dermal erythropoiesis in blueberry muffin syndrome is unknown, but it is hypothesized that during normal embryologic development, extramedullary...
hematopoiesis occurs in a number of organs, including the dermis and this activity persists until the fifth month of gestation.\textsuperscript{[1]} The presence of blueberry muffin lesions at birth represents postnatal expression of this normal fetal extramedullary hematopoiesis.\textsuperscript{[1]} Although most commonly these lesions present in neonatal life, presentation in infantile period has also been noted.\textsuperscript{[9]}

Evaluation of blueberry muffin baby begins with careful review of the pregnancy history and prenatal laboratory studies with a special focus on infectious serologies of

| Table 1: Causes of Blueberry muffin baby\textsuperscript{[2,4-6]} |
|-----------------------------------------------|
| 1. Congenital infections                      |
| Toxoplasmosis,                                |
| Rubella,                                      |
| Cytomegalovirus,                              |
| Herpes simplex,                              |
| Coxsackie virus,                             |
| Chicken pox,                                 |
| Chlamydia,                                   |
| HIV,                                         |
| Human T-lymphotropic virus,                  |
| Parvovirus,                                  |
| Epstein-barr virus and                       |
| Syphilis                                     |
| 2. Hematologic disorders                     |
| Spherocytosis,                                |
| Alloimmunization,                            |
| Twin to twin transfusion syndrome and        |
| Fetomaternal transfusion                     |
| 3. Metabolic disorders                       |
| Non-ketotic hyperglycinemia (Glycine encephalopathy) |
| Mevalonic aciduria                           |
| 4. Neoplastic disorders                      |
| Congenital monoblastic leukaemia,            |
| Neuroblastoma,                               |
| Congenital alveolar rhabdomyosarcoma and      |
| Leukemia cutis                               |
| 5. Congenital vascular lesions               |
| Multiple hemangiomas of infancy              |
| Multifocal lymphangioendotheliomatosis,       |
| Blue rubber bleb nevus syndrome and          |
| Multiple glomangiomas                        |
| 6. Others                                    |
| Langerhans cell histiocytosis and             |
| Neonatal lupus erythematosus                 |
Table 2: Approach to investigate a suspected case of blueberry muffin baby

| Step | Description |
|------|-------------|
| Step 1 | History of presenting complaints of baby |
| Step 2 | Pregnancy history of mother to rule out infections such as TORCH and other complications such as hydraminos |
| Step 3 | Maternal serology to rule out TORCH and other congenital infections (antibodies for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, syphilis, parvovirus B19) |
| Step 4 | Baby’s serology to rule out congenital infections |
| Step 5 | Hematological investigations – hemoglobin with complete blood count and peripheral smear, liver function tests, renal function tests, urine routine microscopy |
| Step 6 | Myelogram to rule out neoplasms |
| Step 7 | Radiological investigations to rule out systemic involvement (chest X-ray, ultrasonography of abdomen and pelvis, CT brain, X-ray of extremities) |
| Step 8 | Skin biopsy to look for extramedullary erythropoiesis |

Histopathology shows foci of dermal erythropoiesis along with aggregates of nucleated and non-nucleated erythrocyte precursors, but generally no cells of myeloid/megakaryocytic type. A stepwise approach in a suspected case of blueberry muffin baby has been highlighted in Table 2. Most cases usually manifest by birth, and a few cases may be reported few months later as was in our case. In most cases, the illness regresses without complications within 4–8 weeks.

CMV infection is the most common congenital TORCH infection (0.3%–2.2%) with cutaneous involvement seen in less than 5% of cases. The cutaneous involvement may be associated with serious systemic implications, which implies a prompt diagnosis. The incidence of primary CMV infection acquired during pregnancy is 1%–4%, and association with congenital infection is 40%. The diagnosis of congenital CMV infection is established by detecting the virus in the blood, urine, or other tissues obtained within the first 3 weeks of life and detection of antibodies (CMV IgM and IgG) thereafter. Newborns with symptomatic congenital CMV infection and involvement of the central nervous system are treated with ganciclovir for 6 weeks. In our case, the indication for the use of ganciclovir was the diagnosis of congenital CMV infection associated with hematological alterations, hepatosplenomegaly, and hepatitis.

Although CMV-induced blueberry muffin syndrome is well known, it is rare and there is always a confusion and doubt about further investigations and management of such cases. It is our sincere attempt to simplify the approach to a case of blueberry muffin syndrome. As this rash is usually subtle, it may go unnoticed and hence should be investigated thoroughly for early initiation of therapy and prevention of comorbidities.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their 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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Conflicts of interest

There are no conflicts of interest.

References

1. Shetty G, Kalyanshetti R, Khan HU, Hegde P. Blueberry muffin rash at birth due to congenital rubella syndrome. Indian J Paediatr Dermatol 2013;14:73-5.
2. Martins S, Rocha G, Silva G, Calistru A, Pissarra S, Guimarães H. Blueberry muffin baby. A rare presentation of congenital cytomegalovirus infection. Acta Med Port 2011;24:703-8.
3. Ajij M, Nangia S, Dubey BS. Congenital rubella syndrome with blueberry muffin lesions and extensive metaphysitis. J Clin Diagn Res 2014;8:3-4.
4. Taj FT, Sarin V. Blueberry muffin baby (dermal erythropoiesis) with non-ketotic hyperglycinemia. Indian J Paediatr Dermatol 2013;14:30-2.
5. Wagner R, Bellettiini SV, Bandeira M, Gubert EM, Schmitz ML, Mevalonic aciduria as a differential diagnosis of blueberry muffin baby. J Neonatal Biol 2016;5:225.
6. Vozza A, Tolone C, Carrano EM, Di Girolamo F, Santinelli R, Ascierto PA, et al. J Eur Acad Dermatol Venereol 2003;17:204-5.