

**CYTOPHAGIC HISTIOCYTIC PANNICULITIS  
ASSOCIATED WITH HbE HEMOGLOBINOPATHY IN A  
PATIENT WITH HEMOPHAGOCYTIC SYNDROME**Swati Sharma<sup>1</sup>, Manna Valiathan<sup>1</sup>, Sushama Belurkar<sup>1</sup>,  
Raviraj Acharya<sup>2</sup>, Swati Aggarwal<sup>1</sup><sup>1</sup>Department of Pathology, Kasturba Medical College, Manipal, Karnataka, India<sup>2</sup>Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India

Source of Support:

Nil

Competing Interests:

None

Corresponding author: Ass. Prof. Swati Sharma

[swatisharma79@yahoo.com](mailto:swatisharma79@yahoo.com)

Our Dermatol Online. 2013; 4(3): 351-353

Date of submission: 12.02.2013 / acceptance: 18.03.2013

**Abstract**

**Introduction:** Cytophagic histiocytic panniculitis (CHP) is a rare panniculitis which may occur alone or as a part of systemic manifestation of Hemophagocytic syndrome (HPS). It is described as a chronic histiocytic disorder of the subcutaneous adipose tissue with lymphocytic and histiocytic infiltration showing hemophagocytosis. It may also be noted in bone marrow, spleen, lymph nodes and liver. Treatment includes glucocorticoids, cyclosporine and combined chemotherapeutic medications.

**Observation:** A 34 years old lady, presented with multiple nodules over the body since 2 years. Hematological investigations revealed that patient had a rare HbE hemoglobinopathy and was treated for that. Skin biopsy showed CHP and subsequently on hematological and biochemical tests, a diagnosis of HPS was given and patient was referred to a hemato-oncologist.

**Conclusion:** Cytophagic histiocytic panniculitis is a rare and fatal form of panniculitis with multisystem involvement. Awareness of this cutaneous manifestation may help physicians in the early diagnosis of HPS. We report this interesting case of CHP with a brief review of literature. To best of our knowledge this is the first case of Hemophagocytic syndrome associated with HbE hemoglobinopathy.

**Key words:** cytophagic histiocytic panniculitis; hemophagocytic syndrome; cyclosporine**Cite this article:**

Swati Sharma, Manna Valiathan, Sushama Belurkar, Raviraj Acharya, Swati Aggarwal: Cytophagic histiocytic panniculitis associated with HbE hemoglobinopathy in a patient with hemophagocytic syndrome. *Our Dermatol Online*. 2013; 4(3): 351-353.

**Introduction**

Winkelman and Bowie [1] in 1980 described CHP as a rare subtype of panniculitis, histologically characterized by a mixed lobular and segmental panniculitis with a proliferation of benign cytophagic histiocytes exhibiting no nuclear atypia. This may also occur in bone marrow, spleen, lymph nodes and liver [2]. CHP can present as isolated skin lesions or severe systemic involvement as a part of HPS [3]. Hemophagocytic syndrome, initially described by Scott and Robb-Smith [4] is a reactive proliferative disorder which affects the antigen-processing macrophages resulting in uncontrolled hemophagocytosis. We report this unique case where initial diagnosis of CHP helped the physicians to establish the early diagnosis of HPS in this 34 years old lady who presented predominantly with dermatological features. During the course of investigations, on electrophoresis she was found to have HbE hemoglobinopathy. In literature HPS is described to be associated with sickle cell anemias [5]. To best of our knowledge this is the first case of HPS associated with HbE hemoglobinopathy.

**Case Report**

34 years old lady, came with multiple nodules over the body since 2 years. Nodules were painful, firm, red in color

started in the limbs, progressively increased and involved face and abdomen. They were associated with low grade fever and significant weight loss. On examination pallor, generalized lymphadenopathy, non-tender hepatomegaly of 4cms and splenomegaly of 3cms below costal margins were noted. Hematological investigations revealed pancytopenia with Hb of 9.1gm%, normal ESR and hemolytic peripheral smear picture. No hemoparasites were identified. HbE hemoglobinopathy was diagnosed on electrophoresis (Fig. 1).

Bone marrow aspiration and biopsy showed reactive bone marrow with erythroid hyperplasia. Lymph node biopsy revealed sinus histiocytosis with erythrophagocytosis. Mantoux test, ANA profile, chest X-ray, thyroid profile and echocardiography were within normal limits. Bone marrow and blood culture were sterile. She was treated symptomatically with hematinics, improved and was discharged. Patient came 2 months later with similar complaints.

Hematological investigations showed pancytopenia with a Hb of 8.3gm% and deranged coagulation profile. Biochemical tests showed deranged liver function test, reduced fibrinogen and total iron binding capacity. Triglyceride levels, S. ferritin and S. LDH were increased. Serological tests for Hepatitis A, B and C, HIV were negative. PCR for tuberculosis was negative.

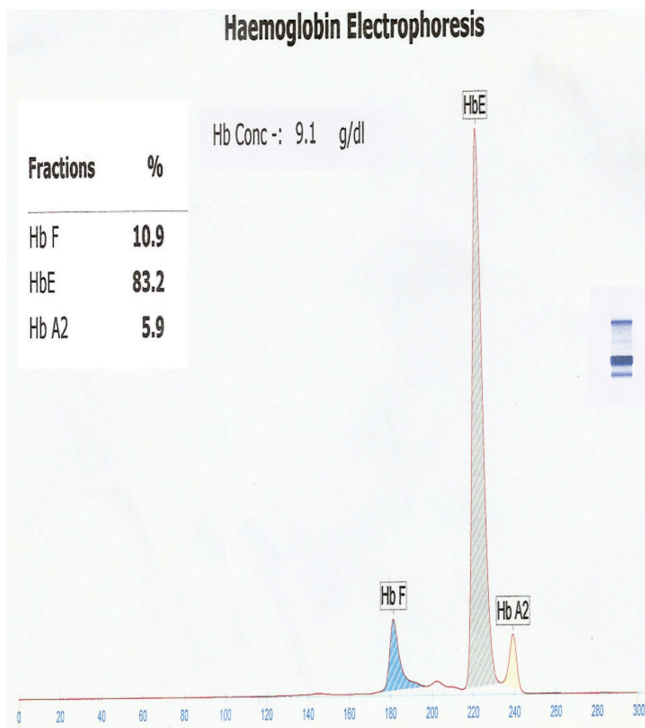


Figure 1. HbE Hemoglobinopathy

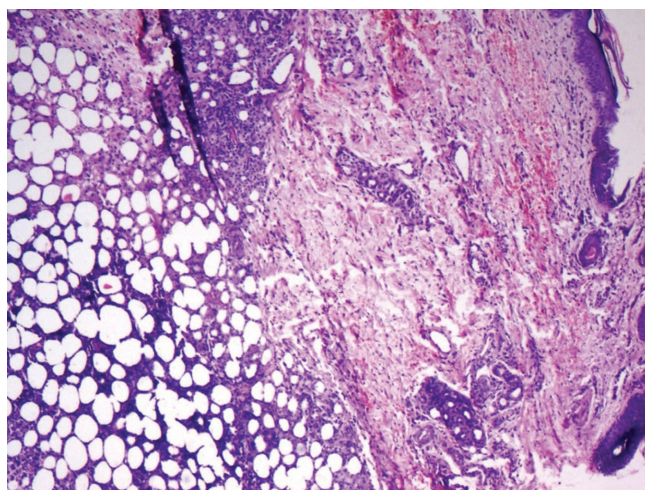


Figure 2. Septal and lobular panniculitis H&E X 40

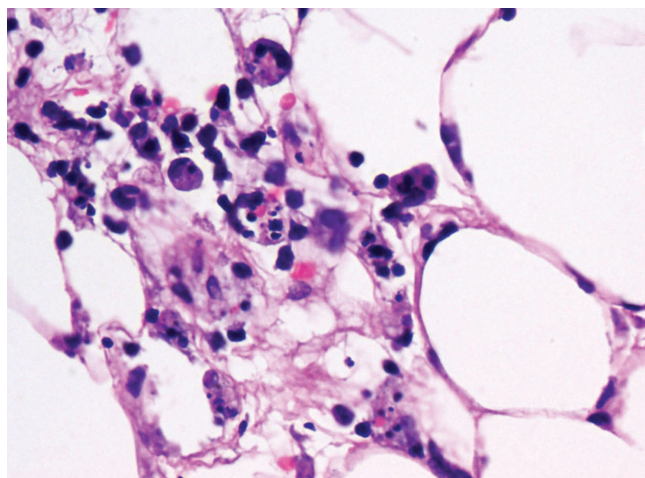


Figure 3. Bean bag appearance H&E X 400

CSF culture was sterile. Biopsy from the skin lesion showed septal and lobular panniculitis composed of macrophages with bland nuclei engulfing erythrocytes, lymphocytes and cell fragments with characteristic “bean bag” appearance along with mixed inflammatory infiltrate (Fig. 2, 3). A diagnosis of CHP was given.

Cytology of the peritoneal ascitic fluid showed reactive mesothelial cells and foamy macrophages with significant hemophagocytosis (Fig. 4). MRI brain and CSF examination were done to rule out CNS involvement by histiocytes. Based on clinical, biochemical, hematological investigations and most importantly skin biopsy diagnosis of HPS in this patient was established. She was referred to hemato-oncologist for further treatment.

### Discussion

CHP first described by Winkelmann and Bowie [1] is characterized by a mixed lobular and segmental panniculitis with a proliferation of benign cytophagic histiocytes. It may occur alone or as a part of systemic manifestation of HPS [3]. Scott and Robb-Smith [6] described HPS as distinct clinicopathological entity in 1939 [4] characterized by impaired function of natural killer cells and cytotoxic T-cells [4,7,8]. HPS is a rare, rapidly progressive and potentially fatal disorder of activated histiocytes [9], occurring in all age groups. It is not a single disease and is associated with a variety of underlying conditions leading to the same hyperinflammatory response [7]. The various manifestations are thought to be mediated by inflammatory cytokines [4]. The revised diagnostic criteria of the Histiocyte Society for the diagnosis of HPS requires 5/8 of the following clinical and laboratory features [7].

- Fever
- Splenomegaly
- Cytopenia  $\geq 2$  cell lines
- Hemoglobin  $< 90$  g/L (below 4 weeks  $< 120$  g/L)
- Neutrophils  $< 1 \times 10^9$  /L
- Hypertriglyceridemia and/or hypofibrinogenemia
- Fasting triglycerides  $\geq 3$  mmol/L
- Fibrinogen  $< 1.5$  g/L
- Ferritin  $\geq 500$   $\mu$ g/L
- sCD25  $\geq 2400$  U/mL
- Decreased or absent NK-cell activity
- Hemophagocytosis in bone marrow, CSF or lymph nodes

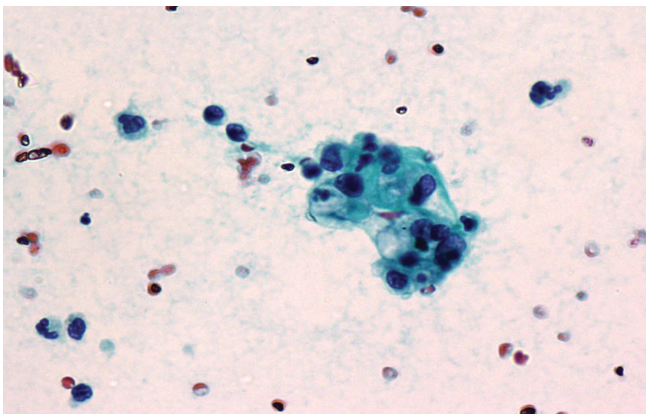


Figure 4. Ascitic fluid - Hemophagocytosis X400



Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH > 1000 U/L [7].

Two highly sensitive diagnostic marker are an increased plasma concentration of the  $\alpha$  chain of soluble IL2 receptor (CD25) and impaired NK cell activity [8]. HPS has variable course, it may be rapidly fatal or can have a long course with intermittent remissions and exacerbations [2].

Our patient fulfilled the criteria for the diagnosis of HPS. The clinical manifestations may be due to increased secretion of cytokines which suppress the hematopoiesis by causing prominent hemophagocytosis in the bone marrow, spleen, liver, and lymph nodes [3,8]. Hemophagocytosis is found at initial presentation only in few cases of HPS, it usually develops as the disease progresses [7]. On bone marrow aspiration, hemophagocytosis may not be present initially and only increased monocytes and monohistiocytic cells may be present [8]. This patient also did not show significant hemophagocytosis in bone marrow aspirate. In about 50% patients there may be elevated cell count, protein or both in the CSF even in the absence of clinical features [8] but CSF cytology and biochemistry in this patient showed normal protein levels. Ascitic fluid cytology showed histiocytes with engulfed erythrocytes and cellular debris in our patient, this was also reported in pleural effusion of a 19 yr old female with sub-cutaneous panniculitis associated with T-cell lymphoma [10]. HPS is associated with various infections and autoimmune diseases [3] however serological tests, blood, CSF and bone marrow culture were negative in our patient.

Cutaneous eruptions are reported to occur in 6% to 65% of cases of HPS. The morphology, configuration and distribution of the skin manifestations are not yet described precisely in literature and are typically reported as nonspecific „transient, maculopapular rashes” [9]. They are to be differentiated from other systemic disorders like myofibromatosis, extramedullary hematopoiesis, langerhans cell histiocytosis and leukemia cutis [9]. Histopathology of CHP is characteristic and shows panniculitis and infiltration by phagocytic benign histiocytes (bean-bag cells) with no nuclear atypia. The benign appearance of the phagocytic histiocytes suggests the reactive response to circulating cytokines, which are secreted by activated macrophages and lymphocytes in the focal cutaneous infiltrates [11]. Hemophagocytosis by benign histiocytes is also observed in lymph nodes, spleen, liver and bone marrow [3]. CHP is a rare condition and rate of in-hospital deaths in patients of Hemophagocytic syndrome is not significantly associated with cutaneous involvement [12]. But its awareness is important as it may help in early recognition and diagnosis of HPS. CHP is treated with glucocorticoids, cyclosporine, combined chemotherapeutic medications and recently, anakinra, an Interleukin-1 receptor antagonist is suggested. Supportive care, search for underlying malignancies and treatment, and control of associated infections causing HPS are recommended [2,11]. In severe relapse cases, high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation can be considered as an alternative treatment plan [3].

In literature, few cases of HPS associated with sickle cell hemoglobinopathy are described. Kio E et al [5] have hypothesized that hypercytokinemia and impaired NK cell activity induced by zinc deficiency seen in sickle cell anemias

might be responsible for it. Hb E is one of the world's most common and important mutations caused by substitution of glutamic acid by lysine at codon 26 of  $\beta$  globin gene. Hb E has a weakened  $\alpha/\beta$  interface, leading to some instability during conditions of increased oxidant stress [13]. To best of our knowledge this is the first documented case of HPS associated with Hb E hemoglobinopathy.

## Conclusions

CHP is a rare and often fatal form of panniculitis seen alone or in association with HPS. It is seen as generalized, non pruritic, transient, macula-papular rash in about 6%-65% cases of HPS. CHP is diagnosed by its unique clinical presentation and histological picture of mixed lobular and segmental panniculitis with a proliferation of benign cytophagic histiocytes with no nuclear atypia. Awareness of this cutaneous manifestation in HPS and its early diagnosis may assist physicians in the starting of prompt life saving therapy for HPS. To best of our knowledge this is the first case of HPS associated with Hb E hemoglobinopathy.

## REFERENCES

1. Winkelmann RK, Bowie EJ: Hemorrhagic diathesis associated with benign histiocytic, cytophagic panniculitis and systemic histiocytosis. *Arch Intern Med.* 1980;140:1460-3.
2. Aronson IK, Worobec SM: Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: an overview. *Dermatol Ther.* 2010;23:389-402.
3. Manoj J, Kaliyadan F, Unni M, Dharmaratnam AD: Cytophagic histiocytic panniculitis: Report of two cases. *Indian J Dermatol.* 2011;56:306-8.
4. Sayes FA: Unusual Causes of Haemophagocytic Syndrome. *Bahrain Med Bull.* 2005;27:1-6.
5. Kio E, Onitilo A, Lazarchick J, Hanna M, Brunson C, Chaudhary U: Sick Cell Crisis Associated With Hemophagocytic Lymphohistiocytosis. *Am J Hematol.* 2004;77:229-32.
6. Scott RB, Robb-Smith AHT: Histiocytic medullary reticulosis. *Lancet.* 1939;2:194-8.
7. Janka G, Stadt ZU: Familial and acquired hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program.* 2005;82-8.
8. Bhattacharyya M, Ghosh MK: Hemophagocytic lymphohistiocytosis—Recent Concept. *JAPI.* 2008;56:453-57.
9. Morrell DS, Pepping MA, Scott JP, Esterly NB, Drolet BA: Cutaneous Manifestations of Hemophagocytic Lymphohistiocytosis. *Arch Dermatol.* 2002;138:1208-12.
10. Moriki T, Wada M, Takahashi T, Ueda S, Miyazaki E: Pleural effusion cytology in a case of cytophagic histiocytic panniculitis (subcutaneous panniculitis T-cell lymphoma). A case report. *Acta Cytol.* 2000;44:1040-4.
11. Craig AJ, Cuaing H, Thomas G, Lamerson C, Smith R: Cytophagic histiocytic panniculitis—a syndrome associated with benign and malignant panniculitis: Case comparison and review of the literature. *J Am Acad Dermatol.* 1998;39:721-36.
12. Fardet L, Galicier L, Vignon-Pennamen MD, Regnier S, Noguera ME, de Labarthe A et al: Frequency, clinical features and prognosis of cutaneous manifestations in adult patients with reactive haemophagocytic syndrome. *Br J Dermatol.* 2010;162:547-53.
13. Vichinsky E: Hemoglobin E syndromes. *Haematology.* 2007;79-83.