Hemophagocytic Lymphohistiocytosis as the Presenting Manifestation of Metastatic Carcinoma of Unknown Primary- A Case Report

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Abstract
Hemophagocytic lymphohistiocytosis (HLH) is a potentially life threatening condition characterized by uncontrolled immune response associated with multiorgan involvement leading to high mortality. Aetiologically, HLH is classified into primary and secondary forms, in which, malignancy accounts for a significant proportion of secondary HLH. However, non-hematological malignancies triggering HLH has been reported rarely. We report a unique case of HLH as the presenting manifestation of a carcinoma of unknown primary.
A 75 year old male with hypertension and dyslipidemia presented with 3 week history of fever and cough. A physical examination revealed pallor, axillary lymphadenopathy and mild splenomegaly. Investigations noted elevated inflammatory markers with anemia and markedly raised white cells. However, infection screening was negative. Computerized tomography (CT) identified multiple mediastinal lymph node enlargements which were histologically proven as malignant infiltrates. Bone marrow examination recognized low grade hemophagocytosis. With the aid of hyperferritinemia and hypofibrinogenemia, diagnosis of HLH was arrived. However, extensive investigations failed to identify primary site of origin for the metastatic malignancy.
Key words: *Hemophagocytic lymphohistiocytosis, malignancy, fever, mediastinal lymphadenopathy*

Introduction

Hemophagocytic lymphohistiocytosis is a life threatening situation associated with hyperinflammatory reaction with multiorgan involvement, uncontrolled by usual immune system regulation (1). It is characterized by impaired action of cytotoxic T cells and NK cells, coupled with over activation of macrophages (histiocytes) leading to its invasion of organs such as liver, spleen and lymph nodes and engulfment of own red cells, white cells and platelets (2). It comprises a wide array of related disorders including primary or familial hemophagocytic syndrome and secondary HLH (1). First reported case of HLH was described by Farquhar and Claireaux in 1952 (3). The occurrence of HLH is considered rare, however increasing incidence is reported in recent years (2). Yet, it is widely believed that this condition is frequently under recognized clinically, since hemophagocytosis is not pathologically evident until autopsy (1).

Secondary HLH is known to associated with a wide range of conditions including infections, malignancy, autoimmune diseases, metabolic conditions and immunodeficiency status (1,2,3). A vast majority of malignancy associated HLH (M-HLH) is due to hematological malignancies. Uncommonly, cases of HLH have been reported in association with solid tumors such as lung, gastrointestinal, liver and prostate malignancies (1,2,3). Diagnosis of M-HLH is often challenging due to variable overlap symptoms with other common conditions like sepsis and multi-organ dysfunction resulting in higher chance of misdiagnosis and poor outcome (3). We report a rare case of secondary HLH as the presenting manifestation of a carcinoma of unknown primary in an elderly male.

Case presentation

75 years old male presented with fever associated with cough for 3 weeks. His fever was intermittent, without any diurnal variation and sometimes exceeding 38.5 0C. He noticed severe loss of appetite and generalized malaise over preceding one month. Cough was productive of minimal sputum; however, there was no shortness of breath, haemoptysis or chest pain. He denied recent alteration of bowel or urine habits, neurological

symptoms, arthralgia or skin rashes. He was a paddy farmer and had 16 pack year history of smoking, quitted 3 years ago. His past medical history only revealed hypertension and dyslipidemia for 5 years, which was managed with losartan and atorvastatin.

Physical examination revealed an ill looking emaciated elderly patient, with moderate pallor and finger clubbing. There were non-tender mildly enlarged left axillary lymph nodes. Further, abdominal examination detected mild splenomegaly about 3 Cm bellow the left costal margin. But, respiratory, cardiac and neurological system examinations failed to note any significant abnormality.

Initial investigations revealed white cell count (WBC) 26000/mm3 with 83% neutrophils, hemoglobin 8.0 g/dL, platelets 260,000/ mm3, sedimentation rate 97 mm/first hour and C-reactive protein 193 mg/dL (0-10). Bilateral hilar enlargement was noted in chest radiograph, however no other abnormality was detected. Contrast enhanced CT demonstrated multiple mediastinal lymph node enlargement with heterogeneous enhancement involving pretracheal, precarinal, subcarinal and aortopulmonary groups (Figure 01). Additionally, there was mild bilateral pleural effusion. However, no pulmonary nodules or masses were recognized. Further investigations with fiberoptic bronchoscopy failed to identify any endobronchial pathologies while bronchial washing was negative for acid fast bacilli, MTB geneXpert and malignant cells. He was commenced on trail of antituberculous treatment suspecting tuberculous lymphadenitis awaiting further investigations at a regional hospital. Since he was clinically deteriorated with continuing fever in spite of antituberculous therapy, referred to our center for further care.

We performed bone marrow biopsy which revealed increased number of macrophages with highly active forms demonstrating hemophagocytosis and markedly hypercellular granulocyte lineage with toxic changes (Figure 02). There were no atypical or malignant cells in the bone marrow. Serum ferritin was elevated up to 1180 ng/ml (18-464) while plasma fibrinogen was reduced to 138 mg/dl (220-496). Hemophagocytic syndrome was diagnosed hence our patient fulfilled 5 out of 8 diagnostic criteria evident by fever, hemophagocytosis, splenomegaly, elevated ferritin and reduced fibrinogen levels. However, serum triglyceride level was within normal limits (78 mg/dL). Further investigations for diagnostic criteria by measuring CD25 cell count and NK cell activity were not performed due to lack of resources.

Results of blood culture, urine culture, serology for HIV, cytomegalovirus, Epstein-Barr virus, brucellosis, blood film for malaria parasites, antinuclear antibodies, and echocardiogram failed to recognize a possible secondary cause for hemophagocytosis. Histopathological evaluation of enlarged axillary lymph nodes recognized reactive changes only.

Further evaluation of mediastinal lymphadenopathy was undertaken with endobronchial ultrasound (EBUS) which revealed enlarged mediastinal lymph nodes at station 4, 5, 7 and 10 L. Transbronchial needle aspiration (TBNA) recognized malignant smear from a poorly differentiated carcinoma (Figure 03). Diagnostic work up including bronchoscopy, upper and lower gastrointestinal endoscopy, CT of abdomen and tumor markers including alpha-fetoprotein, carcinoembryonic antigen and prostate specific antigen failed to identify a primary tumor. Therefore the diagnosis of acquired hemophagocytic syndrome secondary to carcinoma of unknown primary was made. He was initially treated with high dose intravenous dexamethasone and referred for further oncological care. However, he refused specific chemotherapy for HLH and succumbed to death soon.

Discussion

Accurate epidemiological data on M-HLH is limited (4). According to some reports, malignancy accounts for 27- 50% of secondary HLH (1, 2). Recent studies suggested that M-HLH can develop in up to 1% of patients with malignancies, hence probably commoner than previously implicated (4). Hematological malignancies are responsible for a major proportion of M-HLH, of which T or NK cell lymphoma or leukemia and B cell lymphoma are the commonest (2). A review by Ramos-Casals M et al, demonstrated only 3.1% of M-HLH are

due to solid tumors (5). Cases of M-HLH have been reported in association with carcinomas of lung, gastrointestinal, liver, prostate and kidneys and also with thymoma, neuroblastoma, rhabdomyosarcoma and germ cell tumors (1,2,3, 6). Though multiple mediastinal lymph node enlargement was observed in our patient, further evaluation with CT imaging, endoscopy and tumor markers failed to recognize the primary site. Though PET scanning could have given further information it was not available in our center. EBUS-TBNA yield diagnostic samples confirming the poorly differentiated carcinoma, however further processing with immune staining was not possible. Therefore, our patient can be labeled as a case of carcinoma of unknown primary according to standard definition (7). So, this represents a unique case of HLH due to a carcinoma of unknown primary.

M-HLH can manifest at presentation or during treatment or even after achieving remission by successful treatment. Number of mechanisms has been postulated as the pathophysiological process of development of M-HLH. Excessive and persistent secretion of pro-inflammatory cytokines by malignant cells, combined immunodeficiency generated by the malignancy and chemotherapy, predisposition to infections in the setting of immunodeficiency and presence of common underlying clinical situation which predisposes for malignancy and HLH are possible pathophysiological mechanisms operating at the development of M-HLH (4). Infections are recognized as triggers in 75% of a cohort of M-HLH patients (4). Hence, active surveillance for infections even in M-HLH should be emphasized. We performed extensive investigations to identify possible secondary infections in our patient. Though, his inflammatory markers were elevated, evidence of infection was not revealed according to microbiological investigations.

The diagnosis of HLH is based on criteria proposed by Histiocyte Society in 1991, which was updated in 2004. Accordingly, HLH can be diagnosed by recognizing the genetic defects consistent with HLH at an appropriate clinical condition or by fulfilling at least 5 out of 8 clinical criteria, which includes fever >38.5 ^{0}C, splenomegaly, cytopenia in 2 or more lineages, hyperferritinemia, hypertriglyceridemia or hypofibrinogenemia, elevated soluble CD25, reduced or absent NK cell activity and hemophagocytosis (8). Our patient fulfilled 5 criteria including fever, splenomegaly, hyperferritinemia, hypofibrinogenemia and hemophagocytosis. Even though significant anemia was seen in our case, platelet count was normal and interestingly WBC was markedly elevated. Since, sepsis was excluded, aetiology for leucocytosis was unclear. Further, serum triglyceride level was within normal limits in our patient. Though, hypertriglyceridemia may occur in HLH due to decreased lipoprotein lipase activity secondary to increased TNF-α levels, it is observed only in 40% at presentation (1). Moreover, it has been noted that bone marrow examination performed at early stages of disease can be normal or showing only very non-specific features in secondary HLH (1). Therefore demonstration of hemophagocytosis is not essential for the diagnosis of M-HLH if other supportive features present (1). Unfortunately, assessment for soluble CD25 and NK cell activity was not available in our center. In fact, concerns are raised regarding the non-availability of these advance investigations in many centers worldwide and its influence on delayed diagnosis of the condition, thereby preventing or delaying prompt implementation of the treatment for this potentially fetal disease (4). Therefore, alternative diagnostic criteria with incorporation of more easily detectable abnormalities in clinical examination or routine laboratory investigations have been proposed recently (4). However, the best approach for diagnosis of M-HLH is remains uncertain at present (4).

Historically, the prognosis of HLH had been dismal with mortality approaching 100% (1). Main objectives of treatment M-HLH are to control the aberrant hyperinflammation and treat the underlying malignancy. However, there are still no consensus guidelines for treatment of M-HLH due to lack of clinical trials (2). But, therapy should be tailored for individual patients depending on underlying trigger, performance status, organ involvement and concomitant other therapies (4). Glucocorticoids, cyclosporine A and etoposide are usually considered as the first line treatment in many cases (2). However, with development of several specific targeted agents in recent past, the future of HLH appears promising.

Conclusion

HLH is a rare life threatening condition due to immunologic hyper-reaction. Malignancy is a well recognized trigger of secondary HLH. Solid organ malignancies as the aetiology for HLH have been reported far rarer than the hematological malignancies. Our case represents a unique case of M-HLH due to metastatic carcinoma from unknown primary. Diagnosis of malignancy associated HLH can be challenging due to overlapping clinical manifestations with other common clinical situations like sepsis. Therefore, high degree of suspicion should be maintained at appropriate clinical situations to avoid misdiagnosis or delayed diagnosis of HLH, for timely initiation of treatment for this deadly disease.

List of abbreviation

HLH-Hemophagocytic lymphohistiocytosis

M-HLH- malignancy associated hemophagocytic lymphohistiocytosis

CT-Computerized tomography

HIV- Human immunodeficiency virus

EBUS- endobronchial ultrasound

TBNA- Transbronchial needle aspiration

PET- Positron emission tomography

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Competing interest

The authors declare that they have no competing interest.

Authors' contribution

DM and VPGmade the clinical diagnosis and supervised the manuscript drafting. AB and SALdrafted the first manuscript, reviewed the literature and involved in direct management of the patient. All authors read and approved the final manuscript.

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References

i. *George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med. 2014;5:69–86. doi: 10.2147/JBM.S46255.*
ii. *Wang H, Xiong L, Tang W, Zhou Y, Li F. A systematic review of malignancy-associated hemophagocytic lymphohistiocytosis that needs more attentions. Oncotarget. 2017; 8:59977–85.*
iii. *Rosado FGN, Kim AS. Hemophagocytic Lymphohistiocytosis: An Update on Diagnosis and Pathogenesis, Am J ClinPathol. 2013 Jun; 139(6):713-727*

iv. *Daver N, McClain K, Allen CE, Parikh S, Otrock Z, Rojas-Hernandez C, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer. 2017;123(17):3229–3240. doi:10.1002/cncr.30826*

v. *Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014 Apr;383(9927):1503–1516*

vi. *El-Masry M, Eisenbud L, Tran M. Secondary hemophagocytic lymphohistiocytosis in the setting of metastatic renal cell carcinoma: a case report. J Med Case Reports. 2017 Mar.11,56 doi:10.1186/s13256-016-1196-9*

vii. *Bugat R, Bataillard A, Lesimple T, Voigt JJ, Culine S, Lortholary A, et al. Summary of the Standards, Options and Recommendations for the management of patients with carcinoma of unknown primary site (2002). Br J Cancer. 2003 Aug;89 Suppl 1(Suppl 1):S59-66. doi: 10.1038/sj.bjc.6601085.*

viii. *Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48:124–131*

Figures of HLH case

Figure 01- CT shwing multiple mediastinal lymph node enlargment

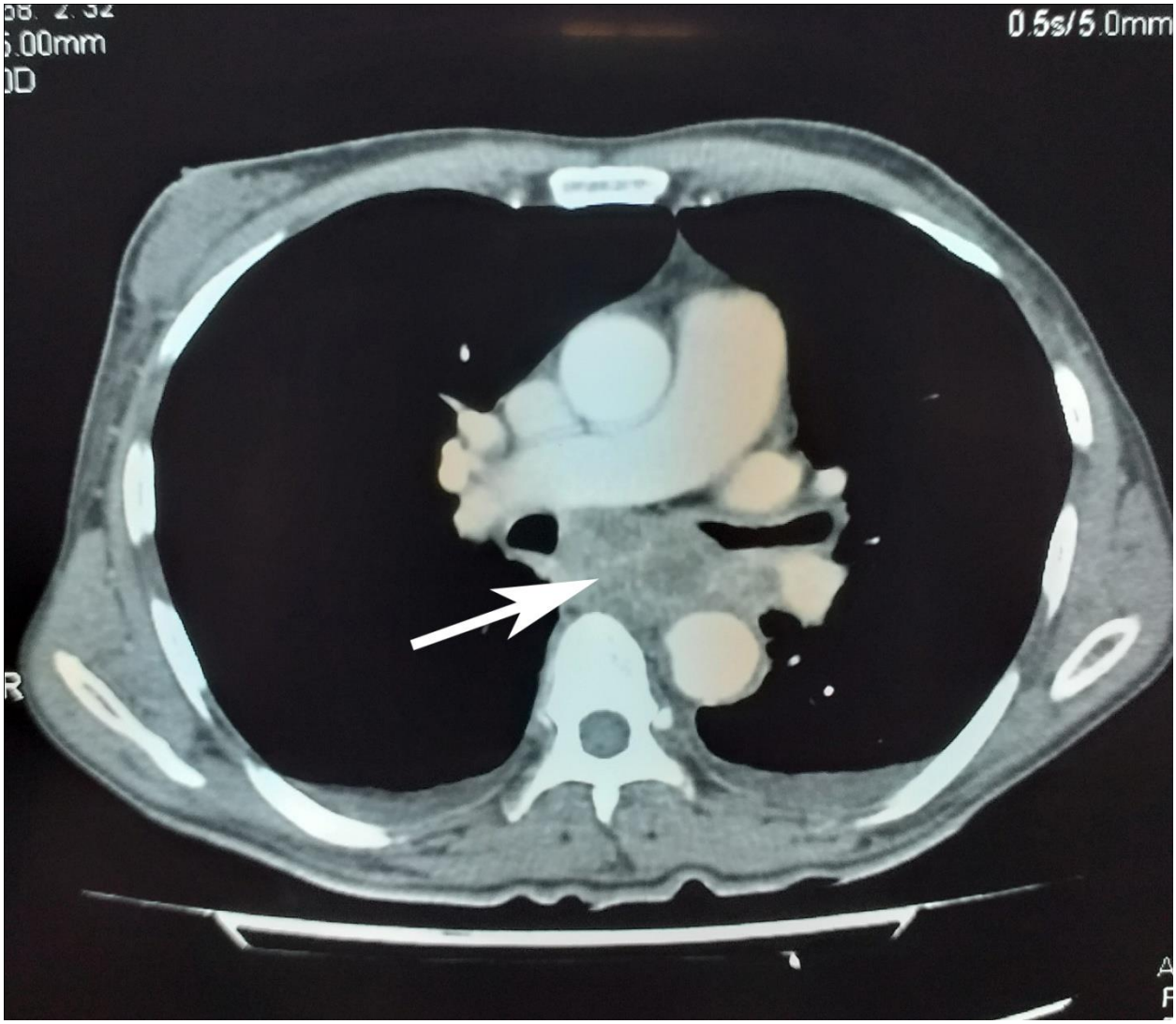

Figure 02- Bone marrow biopsy showing hemophagocytosis

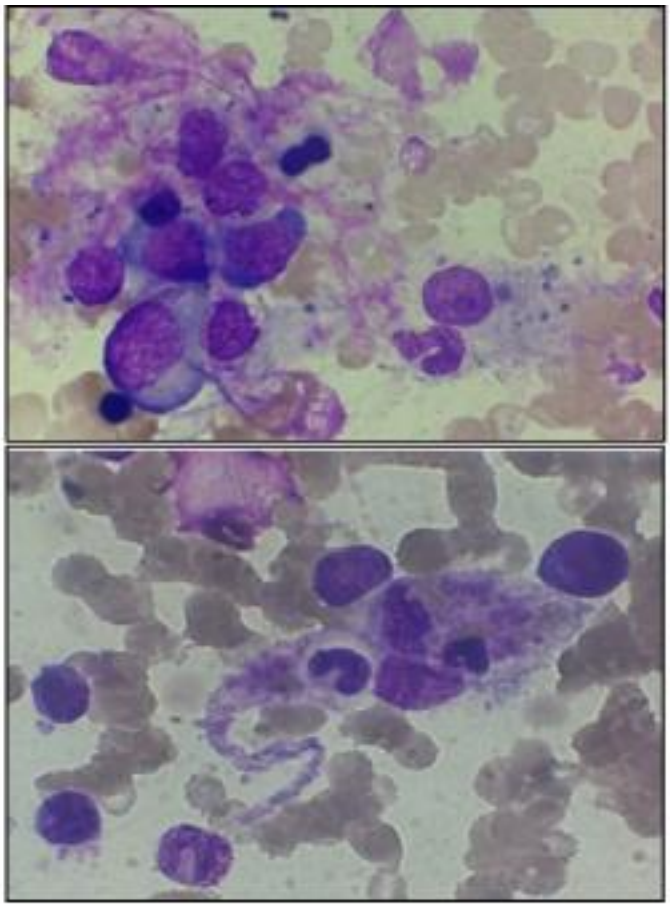

Figure 03- Aspiration of mediastinal lymph node showing poorly differentiated malignant cells