Hemophagocytic lymphohistiocytosis complicating nontuberculous mycobacterial infection

Sir,

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation. Progressive hyperinflammatory cellular damage coupled with lack of normal downregulation of activated macrophages and lymphocytes results in excessive cytokine production. This presents as multiorgan damage with protean manifestations.

Nontuberculous mycobacteria (NTM) are being increasingly isolated in clinical practice. During the course of the disease, there may be acute worsening of clinical picture which might be related to the illness or the drugs used or may be completely unrelated. Herein, we describe a case of resistant pulmonary NTM infection presenting with fever, multiorgan involvement, and cytopenia eventually being diagnosed as secondary HLH syndrome.

A 53-year-old male patient, a shopkeeper by profession, ex-smoker (10 pack years), presented with complaints of hemoptysis, increased cough, shortness of breath, and left-sided chest pain. Hemoptysis was mild. The patient was on treatment with Category II Directly Observed Treatment Strategy (DOTS) (HRZES) empirically for the last 3 months when he presented with the same complaints to a local physician. He had taken DOTS 1 treatment 15 years back in his village. Examination of respiratory system showed the presence of coarse crackles in the left mammary region. His chest X-ray showed diffusely distributed nodular opacities (more in left lower zone) and bilateral upper lobe fibrocavitary lesions. Computed tomography (CT) chest scan was obtained, which showed bilateral randomly distributed nodules with fibrocavitary lesions in the apical segment of the bilateral upper lobes. His biochemical parameters were fairly within limits with exception of mild anaemia of chronic illness, raised erythrocyte sedimentation rate (25), and mild hypoalbuminemia. HIV enzyme-linked immunosorbent assay was negative. Hemoptysis was conservatively managed. Keeping in mind the possibility of reactivation of tuberculosis, bronchoscopy and lavage were done, which showed acid-fast bacilli (AFB) DF 3+, Gene Xpert MTB not detected. Other routine microbiological tests were negative. The patient was diagnosed as a case of NTM. Rifampicin and ethambutol were continued, and clarithromycin was added. Two weeks later, rapid AFB culture showed the growth of *Mycobacterium intracellulare*. He was compliant with the treatment. However, even on follow-up over the next 8 months, X-rays showed persistent nodular opacities, and his sputum continued to be AFB positive. He was empirically switched to drug-resistant regimen which included amikacin, linezolid, and levofloxacin, and drug sensitivity was ordered. Subsequently, he presented 3 weeks later, with complaints of high-grade fever, mild hemoptysis, worsening cough, and breathlessness. His CT scan of the chest showed worsening of fibrocavitary disease in the bilateral upper lobes with persistent extensive nodularity in the bilateral lung field (left > right). Biochemical parameters were as follows: hemoglobin –10.7 g/dL, total leukocyte count –2800/mm³, and platelets –90,000/mm³. Liver function test (LFT) and renal function test were within normal limits. His sputum showed 1+ AFB. He was admitted and started on broad-spectrum intravenous (IV) antibiotics along with supportive measures. However, the patient continued to have high-grade fever spikes and later developed altered sensorium. He deteriorated and became hypotensive and hypoxic. His investigations showed progressive pancytopenia with deranged LFTs. The possible differentials were sepsis, disseminated NTM infection, acute viral infection, and drug-induced toxicities. The patient was further worked up. His routine cultures were negative; serum procalcitonin was <0.05; malaria, dengue, and scrub typhus serology were negative; H1N1 throat swab was negative. Ultrasonography of abdomen showed mild hepatosplenomegaly. In view of persistent pancytopenia, bone marrow examination was done which showed fairly cellular marrow with predominant hemophagocytosis. Further investigations in line with HLH showed raised serum ferritin levels (6896 ng/dL), serum lactate dehydrogenase (LDH) (613 U/L), and triglycerides (372 mg/dL). A diagnosis of HLH was made, and the patient was started on IV steroids (dexamethasone 4 mg TDS). The patient had a dramatic response and became afebrile within 2 days. His sensorium improved, inotropes were tapered, and he could maintain saturation on room air by the 5th day. By 1 week, his hematological parameters showed improvement with normalizing LFTs and recovering blood counts. He was discharged 10 days later on modified antimycobacterial therapy. Two weeks later on follow-up, his drug sensitivity report showed multidrug-resistant organism, and finally, the regimen was modified as per sensitivity including amikacin, moxifloxacin, rifabutin, and ethambutol. The patient is currently under follow-up, tolerating antituberculous treatment well, on tapering doses of steroids, and his last sputum AFB had been negative.
HLH is a life-threatening disorder, and diagnosis is often delayed or missed due to symptoms overlapping with other diseases. Treatment is primarily with steroids and other immune suppression as needed. It may be triggered by an infection, drugs, autoimmune disorders, and neoplastic syndromes. Modified HLH 2004 trial diagnostic criteria include the presence of three of four clinical findings (fever, splenomegaly, cytopenia, and hepatitis) plus one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, and absent or very decreased natural killer cell function).[2] Association of HLH with NTM, although rare [Table 1], should be kept in mind in a patient presenting with atypical features and when diagnostic workup for other complications has been noncontributory, and the patient does not show response to conventional treatment. Initial workup suggestive of HLH includes elevated Se Triglycerides, LDH & Ferritin. Bone marrow examination should be considered whenever feasible.

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Campo M, Berliner N. Hemophagocytic lymphohistiocytosis in adults. Hematol Oncol Clin North Am 2013;29:915-25.
2. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: An update on diagnosis and pathogenesis. Am J Clin Pathol 2013;139:713-27.
3. Chou YH, Hsu MS, Sheng WH, Chang SC. Disseminated Mycobacterium Kansassi infection associated with hemophagocytic syndrome. Int J Infect Dis 2010;14:e262-4.
4. Grandjean Lapierre S, Toro A, Drancourt M. Mycobacterium iranicum bacteremia and hemophagocytic lymphohistiocytosis: A case report. BMC Res Notes 2017;10:372.
5. Thomas G, Hraiech S, Dizier S, Weiller PJ, Ene N, Serratrice J, et al. Disseminated Mycobacterium lentiflavum infection associated with hemophagocytic lymphohistiocytosis in a patient with a history of heart transplantation. J Clin Microbiol 2014;52:3121-3.
6. Fernández AA, de Velasco Pérez DF, Fournier MC, Moreno Del Prado JC, Torras BP, Cañete Palomo ML, et al. Hemophagocytic syndrome secondary to tuberculosis at 24-week gestation. Int J Mycobacteriol 2017;6:108-10.