

Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/authorsrights>



Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Letter to the Editor

Scrub typhus, acute respiratory distress, and hemophagocytic lymphohistiocytosis



We found the paper by Goswami et al., concerning a severe case of scrub typhus (disease caused by *Orientia tsutsugamushi*) complicated by acute respiratory distress syndrome (ARDS) and acute liver failure, very interesting.¹ Perhaps, however, the possible diagnosis of secondary hemophagocytic lymphohistiocytosis (HLH) should also have been considered in that setting.

HLH is a potentially fatal hyperinflammatory syndrome characterized by histiocyte proliferation and hemophagocytosis. HLH may be inherited (primary, familial, generally occurring in infants) or secondary to infection, malignancy, or rheumatologic disease and occurring at any age. Secondary HLH is diagnosed using the following clinical criteria developed by the HLH Study Group of the Histiocyte Society; having five out of eight of the following: (1) fever, (2) splenomegaly, (3) cytopenia (affecting ≥ 2 cell lineages), (4) hypertriglyceridemia and/or hypofibrinogenemia, (5) hemophagocytosis in the bone marrow, spleen, or lymph nodes, (6) low or absent natural killer cell cytotoxicity, (7) hyperferritinemia, (8) elevated soluble CD25.²

In PubMed there are at least 12 papers describing cases of HLH in patients with scrub typhus (search strategy: (haemophagocytic, or haemophagocytosis, or hemophagocytosis, or hemophagocytic, or erythrophagocytosis, or macrophage activation syndrome) AND (scrub typhus OR *tsutsugamushi* OR *orientia*)), and ARDS was described in at least four of them,^{3–6} and in one case was fatal.⁶

In PubMed there are at least 30 papers describing patients with scrub typhus and ARDS (search strategy: (ARDS OR acute respiratory distress syndrome OR acute respiratory failure) AND (scrub typhus OR *tsutsugamushi* OR *orientia*)), and many of them were also complicated by liver failure, multiorgan failure, and disseminated intravascular coagulation (DIC); anemia and thrombocytopenia were very often reported. Strangely enough, only in a few papers was a diagnosis of HLH considered in that setting.^{3,5,7}

HLH is a life-threatening clinical syndrome. Liver involvement is more frequent in pediatric cases, but may be present in adults with variable levels of transaminases up to signs of acute liver failure and coagulopathy. Respiratory distress is frequently present and respiratory insufficiency represents a negative prognostic sign and may need assisted ventilation. HLH can be triggered by rickettsial diseases,^{8–10} and it should be remembered that the identification of hemophagocytosis in bone marrow aspirate represents only one of 5/8 criteria needed for the diagnosis of HLH and that a bone marrow aspirate lacking hemophagocytosis does not rule out the diagnosis of HLH.²

HLH should be suspected in every patient with rickettsial diseases, especially in the presence of respiratory distress or multiorgan dysfunction. An appropriate therapy could save the patient.

Conflict of interest: All authors: no conflicts.

References

- Goswami D, Hing A, Das A, Lyngdoh M. Scrub typhus complicated by acute respiratory distress syndrome and acute liver failure: a case report from Northeast India. *Int J Infect Dis* 2013 Feb 8 [Epub ahead of print].
- Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. *Expert Rev Clin Immunol* 2010;**6**:137–54.
- Kwon HJ, Yoo IH, Lee JW, Chung NG, Cho B, Kim HK, et al. Life-threatening scrub typhus with hemophagocytosis and acute respiratory distress syndrome in an infant. *J Trop Pediatr* 2013;**59**:67–9.
- Jayakrishnan MP, Veny J, Feroze M. Rickettsial infection with hemophagocytosis. *Trop Doct* 2011;**41**:111–2.
- Kobayashi T, Takizawa H, Hiroshima K, Uruma T, Enokihara H, Okuyama A. [A case of new type scrub typhus (*tsutsugamushi* disease) presenting with acute respiratory failure and hemophagocytic syndrome]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1992;**30**:447–52.
- Iwasaki H, Hashimoto K, Takada N, Nakayama T, Ueda T, Nakamura T. Fulminant *Rickettsia tsutsugamushi* infection associated with haemophagocytic syndrome. *Lancet* 1994;**343**:1236.
- Yang SH, Ho YH, Chu CH, Chu SY. Childhood scrub typhus in eastern Taiwan: ten-year experience from a medical center. *Acta Paediatr Taiwan* 2007;**48**:332–6.
- Cascio A, Giordano S, Dones P, Venezia S, Iaria C, Ziino O. Haemophagocytic syndrome and rickettsial diseases. *J Med Microbiol* 2011;**60**:537–42.
- Mansueti P, Vitale G, Cascio A, Seidita A, Pepe I, Carroccio A, et al. New insight into immunity and immunopathology of rickettsial diseases. *Clin Dev Immunol* 2012;**2012**:967852.
- Cascio A, Pernice LM, Barberi G, Delfino D, Biondo C, Beninati C, et al. Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. *Eur Rev Med Pharmacol Sci* 2012;**16**:1324–37.

Antonio Cascio^{a,b,c,*}Patrizia Correnti^{c,d}Chiara Iaria^{c,e}

^aProgramma di Infettivologia Speciale, Medicina Tropicale e delle Migrazioni e Parassitologia, Policlinico "G. Martino", Via Consolare Valeria n. 1, 98125 Messina, Italy

^bTropical and Parasitological Diseases Unit, Department of Human Pathology, University of Messina, Messina, Italy

^cAILMI (Associazione Italiana per la Lotta contro le Malattie Infettive; Italian Association for the Control of Infectious Diseases), University of Messina, Messina, Italy

^dUnità Operativa Complessa di Malattie Infettive – ARNAS "Civico, Di Cristina, Benfratelli", Palermo, Italy

^eInfectious Diseases Unit, Azienda Ospedaliera Piemonte-Papardo, Messina, Italy

*Corresponding author. Tel.: +39 090 2213680; fax: +39 090 692610

E-mail address: acascio@unime.it (A. Cascio)

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Received 26 February 2013

Revised 3 March 2013

Accepted 4 March 2013