



The clinical characteristics and outcomes of patients with human granulocytic anaplasmosis in China[☆]

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SUMMARY

Objectives: The incidence of human granulocytic anaplasmosis (HGA), a tick-borne disease caused by the obligate intracellular bacterium *Anaplasma phagocytophilum*, has increased across the world. However, information on HGA is lacking in China. The purpose of this study was to investigate the clinical features and outcomes of HGA patients in China.

Methods: A total of 83 patients with HGA from the provinces of Hubei and Henan in China, who were admitted to Union Hospital between March 2009 and September 2010, were included in this study. We investigated the epidemiology, clinical features, laboratory markers, and therapeutic effects in these patients. We also analyzed life-threatening complications such as systemic inflammatory response syndrome (SIRS)/multiple organ dysfunction syndrome (MODS) following HGA and assessed the risk factors for a poor clinical outcome.

Results: In our study, an HGA outbreak peak was observed for the months May to August. The highest age-specific incidence occurred among the group of patients aged 50–59 years. With regard to patient occupation and pathological origin, we found that 73 of the 83 patients with HGA had a peasant occupation. With respect to symptoms, 45 patients had no complications and 38 patients diagnosed with HGA met SIRS criteria, of whom 25 rapidly developed MODS. The mortality for the entire cohort was 26.5%. The factors predictive of patients developing MODS and an adverse outcome were advanced age, disturbance of consciousness, highly elevated lactate dehydrogenase, creatinine, and aspartate aminotransferase levels, and the presence of SIRS. Moreover, MODS was found to be an independent predictor of death.

Conclusions: In China, HGA patients had severe clinical symptoms and high rates of complications and mortality. These findings may provide useful information so that physicians will be on the alert for severe complications after a diagnosis of HGA; they will also be useful for optimizing supportive care for HGA-related critical illness. Prompt treatment and close monitoring of severe complications such as SIRS and MODS are of great importance in saving patient lives.

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1. Introduction

Human granulocytic anaplasmosis (HGA), formerly known as human granulocytic ehrlichiosis (HGE), is a tick-borne disease caused by the obligate intracellular bacterium *Anaplasma phagocytophilum*,^{1,2} which was first reported in 1990.³ Since then, HGA has become increasingly recognized and there have been reports on HGA from the USA, Europe, and several other countries.^{2–5} In 2008, a case of nosocomial transmission of HGA occurred in China.⁶

A. phagocytophilum DNA has been detected in ticks on a global scale, including in the countries of Israel, Japan, and China.^{7–9}

Ixodes ticks act as vectors for *A. phagocytophilum*. The vector tick species involved are *Ixodes scapularis*¹⁰ and *Ixodes pacificus* in the USA,¹¹ and *Ixodes ricinus* in Europe;¹² ticks involved in HGA are present in Asia and the main vector tick species in China is *Ixodes persulcatus*.^{9,13}

Because the study of HGA in China was initiated only a couple of years ago, knowledge and experience of the disease are limited. At present this disease is not recognized by most doctors in China. The diagnosis of HGA is difficult since patients with HGA often present with a non-specific febrile illness. The clinical manifestations of HGA range from an asymptomatic illness to fatal disease. The clinical manifestations and laboratory findings of HGA include undifferentiated fever, headache, myalgias, thrombocytopenia, and leukopenia, usually accompanied by elevations in the levels of hepatic and cardiac enzymes.^{2,14} In China, the first HGA case was misdiagnosed as a hemorrhagic fever because the clinical

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presentation of HGA bears some resemblance to the syndrome commonly referred to as this disease. We found that the burden of illness, clinical features, and outcomes differed greatly from those in Western countries. More recently, the morbidity and mortality associated with HGA in China has led to public health concern.

A better understanding of HGA and its related critical illness may help to identify effective interventions for patients with HGA. Hence, in this study, we investigated the epidemiology, clinical features, laboratory findings, medical complications, treatment, and outcome of 83 HGA patients who were admitted to the Union Hospital, Huazhong University of Science and Technology in China.

2. Methods

2.1. Patients

We recorded and studied the epidemiological and clinical information of a group of HGA patients at Union Hospital, Huazhong University of Science and Technology over a consecutive time-frame. A total of 83 patients from the provinces of Hubei and Henan in China were hospitalized with HGA between March 2009 and September 2010. This disease seemed to occur as a small epidemic outbreak. The following information was collected for each patient: age, sex, occupation, location of residence, history of animal contact and/or tick bite, and clinical features including date of onset of symptoms, laboratory findings, medical complications, treatments, and outcomes.

2.2. Diagnosis and monitoring of progress

As described in North America and Europe, all HGA patients fulfilled the US Centers for Disease Control and Prevention (CDC) laboratory criteria for the diagnosis of HGA.^{2,15,16}

A probable case of HGA was defined in patients with a clinically compatible illness including epidemiology and typical manifestations similar to HGA or with one of the following results: a rise in IgG titer to *A. phagocytophilum* or observation of morulae in leukocytes.

A confirmed case of anaplasmosis was defined in patients with a clinically compatible illness including epidemiology and typical manifestations similar to HGA, with one of the following diagnostic results: a four-fold change in antibody titer to *Anaplasma* species antigen by indirect immunofluorescence assay (IFA)¹⁷ in the acute and recovery phase serum samples, or a positive polymerase chain reaction (PCR) assay³ result, the visualization of morulae in white blood cells, a single positive serum antibody titer by IFA, or immunohistochemical staining (IHC) of an antigen in a tissue biopsy, or isolation and culture of *Anaplasma* species.

Systemic inflammatory response syndrome (SIRS) represents a state in which infections or other causes induce systemic inflammatory reactions. Multiple organ dysfunction syndrome (MODS) means that two or more organs are dysfunctional. Specific criteria for the diagnosis of SIRS and MODS were applied. The definition of SIRS was characterized by at least two of the following four criteria: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) leukocytosis or leukopenia.¹⁸ MODS was defined using the Marshall score.¹⁹

The majority of HGA patients had been treated with a cephalosporin antibiotic at another hospital as a result of misdiagnosis. However, once they were transferred to our hospital, we were able to promptly provide empirical therapy with doxycycline or rifampin to all patients who were suspected of having HGA. At the same time, antibiotics of other spectrum were also prescribed to prevent co-infections. In these patients there was the potential for serious or even fatal conditions to develop if these diseases were left untreated, especially in patients with

immunosuppressive conditions. Most patients responded to treatment with doxycycline without complications.

2.3. Statistical analysis

The statistical analysis was performed using SPSS software (version 17.0; SPSS, Chicago, IL, USA). Data are presented as mean \pm standard deviation. The parameters considered at baseline, including clinical and laboratory data, were analyzed using the Student's *t*-test and the Chi-square test. Correlations between parameters and MODS were analyzed by Student's *t*-test and binary logistic regression. To determine the independent contributors to MODS, those risk factors that proved to be significant ($p < 0.05$) were entered into a logistic regression model step by step for the calculation of the relative risk as an odds ratio (OR) with 95% confidence interval (CI). A *p*-value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Epidemiology

The 83 patients with HGA in our hospital came from the mild climate regions in the provinces of Hubei and Henan, regions where several tick species have been identified. The patients were residents of hilly land in northern Hubei Province including Suizhou, Guangshui, suburbs of Wuhan, Macheng, Luotian, Hong'an, Dawu, and Tongcheng and the hilly area of Xinyang City in southern Henan Province and the urban areas of Xinyang, Guangshan, Xinxian, Huangchuan, and Shangcheng. Most of these areas feature the forests, mountains, and hills typical of central China (Figure 1).

Thirty-one (37.3%) of the patients were male and 52 (62.7%) were female; the male to female ratio was 1:1.68. Among the 83 patients, 73 (88.0%) had a peasant occupation, six were workers,

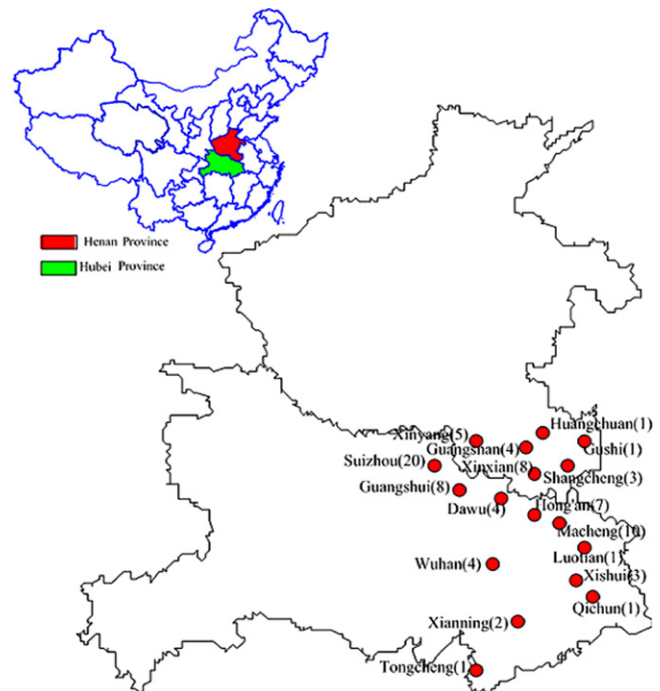


Figure 1. The geographic distribution of human granulocytic anaplasmosis (HGA) outbreaks in our cohort. The outbreaks were concentrated in the north of Hubei Province and in the south of Henan Province from March 2009 to September 2010. Numbers of cases are shown in brackets.

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