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研究報告の概要

○中国におけるヒト顆粒球アナプラズマ症の院内感染

背景:ヒト顆粒球アナプラズマ症(HGA)は、中国の新興ダニ媒介性リケッチア疾患である。劇症HGA患者との接触後に医療従事者およびその家族の感染集団を認めたため調査が行われた。

目的:安徽省における発熱性疾患の院内感染と思われる症例の感染源および伝播について検討すること。

デザイン、実施場所、および患者:発熱、出血により病院の隔離病棟へ入院し死亡した発端患者への接触後に発熱性疾患を生じ、接触が疑われた二次症例患者の抗*Anaplasma phagocytophilum*抗体、PCR測定、*A. phagocytophilum* DNA配列決定を実施した。

主な評価項目:血清学的またはPCRによりHGAの確証が得られた症例を非感染接触者と比較し、発病率、疾患相対リスク、発端患者への医療提供時の曝露についての潜在的リスクを定義した。

結果:2006年11月9日～17日の期間に、白血球減少、血小板減少を伴う発熱と血清アミノトランスフェラーゼ値上昇を発現した9名の患者が、末梢血中*A. phagocytophilum* DNAのPCRおよび*A. phagocytophilum*へのセロコンバージョンによりHGAと診断された。ダニに刺咬された患者はいなかった。9名の患者はいずれも、発端患者が死亡する直前の12時間以内に患者と接触し、その12時間の間に当該患者は大量出血があり、また気管内挿管治療を受けた。発病率は、50cm以内の接触者が32.1% vs 0% (P=0.04)、2時間以上の接触者が45% vs 0% (P=0.001)、血性分泌物への接触報告者が75% vs 0% (P<0 .001)、発端患者の呼吸器分泌物への接触報告者が87.5% vs 0% (P=0.004)であった。

結論:中国におけるHGAの特定および血液や呼吸器分泌物への直接的な接触による院内HGA感染の可能性について報告する。

報告企業の意見	今後の対応
劇症ヒト顆粒球アナプラズマ症(HGA)患者との接触後の医療従事者および家族の感染集団についてPCR等で調査した結果HGAと特定され、血液や呼吸器分泌物への直接的な接触による院内*A. phagocytophilum*感染が示唆されたとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

ORIGINAL CONTRIBUTION

Nosocomial Transmission of Human Granulocytic Anaplasmosis in China

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Context Human granulocytic anaplasmosis (HGA) is an emerging tick-borne disease in China. A cluster of cases among health care workers and family members following exposure to a patient with fulminant disease consistent with HGA prompted investigation.

Objective To investigate the origin and transmission of apparent nosocomial cases of febrile illness in the Anhui Province.

Design, Setting, and Patients After exposure to an index patient whose fatal illness was characterized by fever and hemorrhage at a primary care hospital and regional tertiary care hospital's isolation ward, secondary cases with febrile illness who were suspected of being exposed were tested for antibodies against *Anaplasma phagocytophilum* and by polymerase chain reaction (PCR) and DNA sequencing for *A phagocytophilum* DNA. Potential sources of exposure were investigated.

Main Outcome Measure Cases with serological or PCR evidence of HGA were compared with uninfected contacts to define the attack rate, relative risk of illness, and potential risks for exposure during the provision of care to the index patient.

Results In a regional hospital of Anhui Province, China, between November 9 and 17, 2006, a cluster of 9 febrile patients with leukopenia, thrombocytopenia, and elevated serum aminotransferase levels were diagnosed with HGA by PCR for *A phagocytophilum* DNA in peripheral blood and by seroconversion to *A phagocytophilum*. No patients had tick bites. All 9 patients had contact with the index patient within 12 hours of her death from suspected fatal HGA while she experienced extensive hemorrhage and underwent endotracheal intubation. The attack rate was 32.1% vs 0% (P=.04) among contacts exposed at 50 cm or closer, 45% vs 0% (P = .001) among those exposed for more than 2 hours, 75% vs 0% (P<.001) among those reporting contact with blood secretions, and 87.5% vs 0% (P=.004) among those reporting contact with respiratory secretions from the index patient.

Conclusion We report the identification of HGA in China and likely nosocomial transmission of HGA from direct contact with blood or respiratory secretions.

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HUMAN GRANULOCYTIC ANAPLASMOSIS (HGA) is an emerging tick-borne infectious disease that was recognized in the United States in 1990[1] and in Europe in 1997.[2] The disease name was changed from human granulocytic ehrlichiosis to HGA in 2001 when the causative rickettsia was reclassified from the genus ehrlichia as *Anaplasma phagocytophilum*.[3] Although the clinical presentation of HGA is variable and although it may be difficult to diagnose, the annual number of infections reported in the United States since 1990 has steadily increased.[4,5] Seroepidemiological data suggest that infection rates in endemic areas are as high as 15% to 36%,[6-8] implying that the diagnosis is often missed or that infection is mild or asymptomatic. Because epidemiological, clinical, and microbiological information about HGA is limited, the disease is likely underrecognized and underreported worldwide.[7]

Despite the pathogen's global distribution, only a limited number of laboratory-confirmed cases have been re-

For editorial comment see p 2308.

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ported from countries in Europe, where the median seroprevalence rate is 6.2%, similar to that in North America.[9] Serological and molecular evidence also suggests that human infection exists in Korea, Japan, and China.[10-14] Herein, we report the first cases of HGA acquired in China, as well as the unusual finding of nosocomial human-to-human transmission.

METHODS

Laboratory Diagnosis

Patients suspected of HGA exposure were tested for serum IgG to *A phagocytophilum* using the IgG IFA kit (Focus Diagnostics, Cypress, California), screening at a 1:64 dilution and titrating if reactive.[15] Nested polymerase chain reaction (PCR) using blood DNA (QIAamp DNA Mini Kit, QIAGEN, Hilden, Germany) was used to detect *A phagocytophilum* DNA with *Anaplasma* and *Ehrlichia* genus-common and *A phagocytophilum* species-specific *rrs* primers (16S rRNA gene),[16] and *A phagocytophilum* species-specific *groEL* primers.[17] An *A phagocytophilum rrs* plasmid and DNA from healthy people or distilled water were used as controls. Positive reactions were confirmed by direct sequencing. Polymerase chain reaction was conducted in 2 independent laboratories, the National Institute for Communicable Disease Control and Prevention in Beijing, and at the Anhui Province Center for Disease Prevention and Control in Hefei city. Each laboratory used its own primers, reagents, and patient blood DNA. All samples were tested concurrently with negative and no template controls (water) under the same conditions. Polymerase chain reaction samples from healthy people and negative controls consistently had negative results.

To exclude other infections, serological, antigen detection, and PCR diagnostic tests were conducted. These included tests on blood from the first 3 to 5 days after onset for reverse transcription (RT)–PCR of PCR for nucleic acids of Lassa fever virus, Ebola virus, Marburg virus, Hantaan virus, Junin virus, yellow fever virus, Crimean-Congo hemorrhagic fever virus, coxsackievirus, respiratory syncytial virus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydia* species, *Ehrlichia* species, *Rickettsia* species, and *Orientia tsutsugamushi*.

Tests were also conducted on oropharygeal swabs from the first 3 to 5 days after onset for influenza A virus antigens, and by PCR for influenza A viruses, influenza B virus, and influenza virus subtype H5 nucleic acids. Tests for acute-phase serum were conducted to detect IgM and IgG to severe acute respiratory syndrome virus, as well as to detect IgM or IgM plus IgG antibodies by capture enzyme-linked immunosorbent assay against Bunyaviridae, Filoviridae, Lassa fever virus, Ebola virus, Marburg virus, Hantaan virus, Junin virus, yellow fever virus, and Crimean-Congo hemorrhagic fever virus.

Epidemiological Investigation

All contacts of the index patient, including patients with similar clinical presentations and healthy persons, were interviewed before laboratory diagnostic results were obtained. A possible case of HGA was defined as a patient with a clinically compatible illness (fever, headache, chills) and laboratory findings including thrombocytopenia and leukopenia but who lacked serological or molecular tests for *A phagocytophilum*. A confirmed case was defined as a patient with a clinically compatible illness (as above) and in keeping with the US Centers for Disease Control and Prevention (CDC) criteria (http://www.cdc.gov/ncphi/disss/nndss/casedef/ehrlichiosis_2008.htm) by either seroconversion, a 4-fold increase in *A phagocytophilum* IgG antibody titer in acute and convalescent sera, or a positive PCR result for both *A phagocytophilum rrs* and *groEL* confirmed by direct sequence analysis.[15]

Contact Questionnaire

All contacts of the index patient were asked to complete a questionnaire about their health status and profession; experience with tick bites; exposure to the index patient—where, when, and how they had contact; exposure to wild animals; extent of outdoor activity; exposure to the index patient's blood and respiratory secretions or to grossly bloody oropharyngeal secretions; presence of skin lesions during exposure; whether skin surfaces were washed after exposure; whether they were exposed to the patient's stool or urine; and the timing of these events. Health care workers were asked about their use of masks and gloves.

Ethical and Human Subjects Review

The study was approved by the ethics committee of China CDC, according to the medical research regulations of Ministry of Health, China. Oral informed consent was obtained from all study participants.

Statistical Analysis

All statistical calculations were performed using Epi Info 6.04d (http://www.cdc.gov/epiinfo). To identify specific exposure risk factors, retrospective cohort comparisons were evaluated by calculating attack rates, relative risk, and 95% confidence intervals and by Fisher exact test; significance was defined as a 2-tailed $P < .05$.

RESULTS

Index Case

A 50-year-old woman with a 1-day abrupt onset of sudden fever (39.2°C), headache, myalgia, arthralgia, dizziness, and malaise presented to the village clinic on October 31, 2006, and was treated with ribavirin, cephalothin, dexamethasone, and amidopyrine for 4 days. At 9 PM on November 3, she was admitted to the local hospital because of gum bleeding, facial edema, nausea, vomiting, and oliguria, a temperature of 39.7°C, blood pressure of 85/60 mm Hg, and pulse rate of 96/min; a rash was noted over her trunk. Laboratory testing showed leukopenia (white blood cell count, 3300/μL), thrombocytopenia (platelet count, 18×10^3/μL), elevated serum aspartate aminotransferase

(629 U/L) and alanine aminotransferase (69 U/L), elevated creatinine (2.6 mg/dL), and elevated blood urea nitrogen (48 mg/dL) levels. Dipstick urinalysis revealed 3+ hematuria and 3+ proteinuria (protein, 3 g/L). (To convert aspartate aminotransferase and alanine aminotransferase to microkat per liter, multiply by 0.0167; creatinine to micromole per liter, by 88.4; and urea nitrogen to millimole per liter, by 0.357.)

Her condition progressively deteriorated, so she was transferred to a regional hospital at 11 AM, November 4. By 7 PM, the patient became obtunded, cyanotic, and purpuric and was bleeding from her nose and mouth. This extensive mouth and nose bleeding required frequent aspiration and contaminated the working area surfaces, health care workers, and family members who were with her. Family members assisted with patient care by wiping blood from the patient's mouth and nose, rinsing and reusing the same towels. By 7:38 PM the patient developed rapidly progressive dyspnea and worsening oxygen saturation and required endotracheal intubation. The patient remained hypoxic and hypotensive with multiorgan failure and copious bleeding from the nose and mouth. Despite all efforts, the patient died at 6:45 AM, November 5, 2006. The final diagnosis was hemorrhagic fever with renal syndrome, even though no IgG antibodies to Hantaan virus were detected. A postmortem examination was not performed, and no blood or tissue samples remained for retrospective laboratory testing.

Retrospective questioning of the patient's family revealed that she was bitten by a tick 12 days before onset of fever; she had killed several mice in her home 9 days before onset, and her husband had hunted and brought home "wild animal carcasses" 3 days before onset of illness. A timeline of events is shown in the FIGURE.

Nosocomial Cases of HGA

Between November 9 and 17, 2006, 9 patients were identified at the regional hospital with fever higher than 38.0°C (9 of 9 patients), myalgia (5 of 9), diarrhea (7 of 9), leukopenia (white blood cell count, 1200-3700/μL in 9 of 9), thrombocytopenia (platelets, 39-115 × 10^3/μL in all 9), and elevated serum aspartate aminotransferase and alanine aminotransferase (7 of 9) (TABLE 1). All patients had contact with the index patient, including 5 family members, 2 physicians, and 2 nurses who had accompanied or treated her between November 4 and 5 (Figure).

The initial secondary case experienced fever on November 9, 4 days after death of the index case, followed on November 11 by another patient, on November 12 by 3 patients, and on November 14 by 3 more patients. The last patient reported illness on November 17, 12 days after the death of the index patient. The patients were between 25 and 67 years (mean, 36.2 years), and 6 were men. All were previously healthy. The average incubation period was 7.8 days (range, 4-12 days). All had fever of at least 38.5°C for 1 to 6 days (mean, 4 days). Diarrhea was characterized as 1 to 3 loose stools per day persisting for 1 to 2 days. All patients had relative bradycardia. One patient developed acute respiratory distress syndrome as a complication of *Aspergillus* pneumonia and tuberculosis during his hospitalization. The other 8 patients were mildly affected, recovered, and were discharged in good health.

Contact Investigation

The index patient had contact with 63 persons after onset of illness: 21 family members and 42 health care workers. Of the 42 health care workers, 18 were from the local hospital, including 2 from the village clinic, and 24 were from the regional hospital. Of the 21 family members, 4 had contact with the index patient in only the local hospital, 13 only in the regional hospital, and 4 in both. The 9 secondary cases occurred among the 39 health care workers and relatives with patient exposure at the regional hospital, representing an attack rate of 23%. All 9 cared for the index case in the final 12 hours of her life while she was in the critical care unit and during the endotracheal intubation procedure. No one whose only contact with the index patient was before these 12 hours was infected.

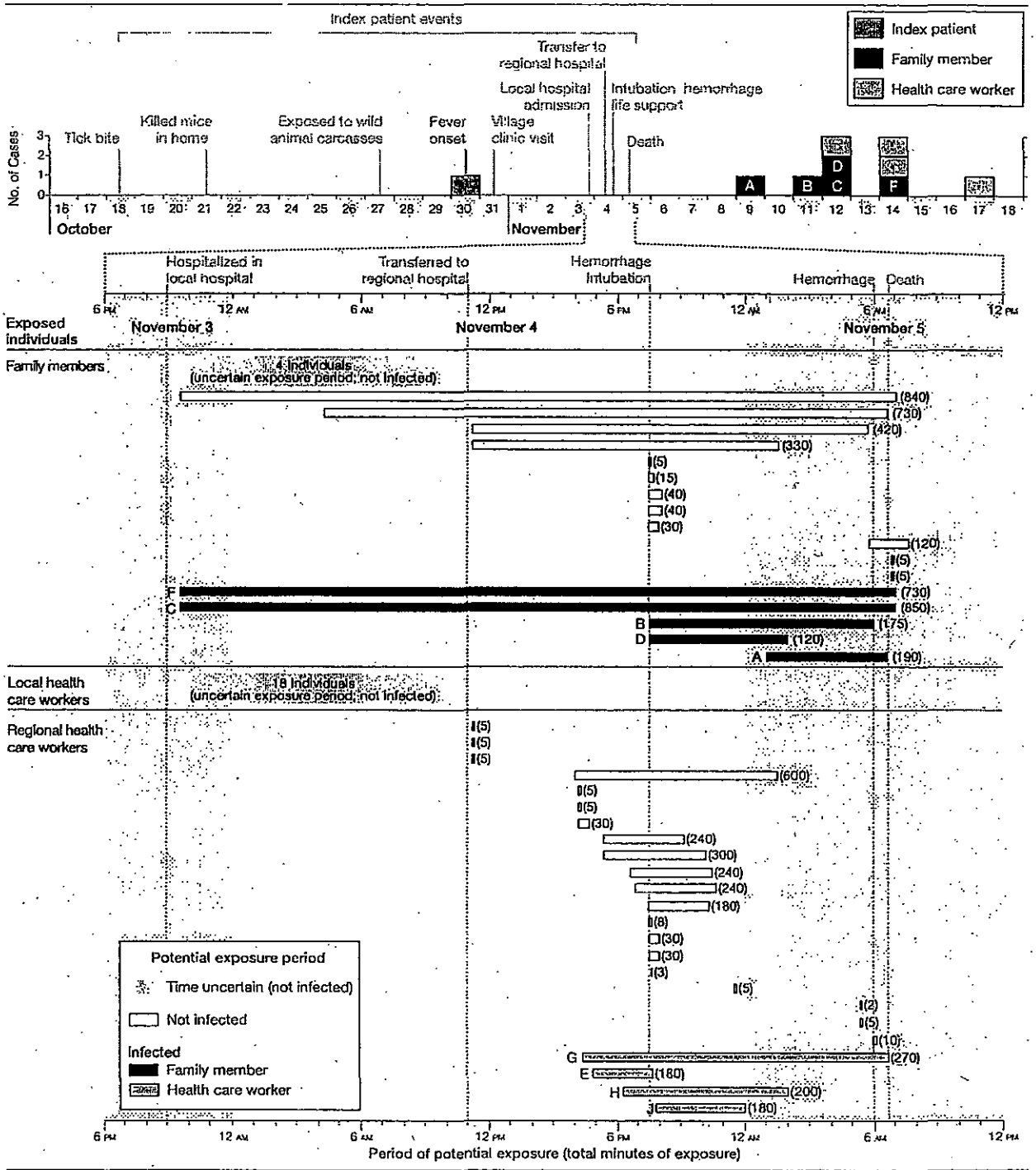
Serological and Molecular Diagnosis

Anaplasma phagocytophilum IgG seroconversions were detected for all 9 patients, and a 4-fold IgG titer increase was observed in 7 of 9 patients (Table 1). Nested PCR using genus-common *rrs* and species-specific *rrs* and *groEL* primers identified *A phagocytophilum* DNA in the blood samples from all 9 patients when they were in the acute phase, whereas all healthy and template controls had negative test results. The identity of amplicons from each of the 9 patients was confirmed by sequencing; all *rrs* sequences (206 base pairs) were identical and all groEL sequences (446 nt) were identical (GenBank accession numbers: *rrs* EF211110-17 and EF473210; *groEL* EF47320108 and EF473209). Although the *rrs* sequences were identical to most other human-derived strains globally, sequences from *groEL* were identical to some US strains (Wisconsin and New York) but differed from *A phagocytophilum* in China (93.6%; EU008083), Germany (99.4%; AY281850), and California (99.7%; U96727). These data support the premise that a single clone was responsible for all of the 9 secondary cases. Although peripheral blood smears were examined for all 9 patients at the time of illness, no convincing evidence of *A phagocytophilum* morulae was observed. All RT-PCR, PCR, antigen detection, and IgM antibody detection tests for microbial and viral etiologies were negative.

Risk Factors

The exposure data implicate transmission at the regional hospital, permitting focus on risk factors in 39 individuals, including 24 health care workers and 15 family members (TABLE 2). Two family members who

Figure. Timeline of Critical Events for the Index Patient and Direct Contact Intervals of Family Members and Health Care Workers With the Index Patient and Exposure of Patients With Nosocomial Human Granulytic Anaplasmosis



Top, epidemic curve showing progression of outbreak and key events during the index patient's illness. Bottom, each bar indicates the period of potential exposure while family members were in the hospital and while health care workers were assigned to care for the index patient. Duration of exposure in minutes is shown in parentheses and may not have occurred continuously during the exposure period. Capital letters designate the corresponding secondary cases in the top and bottom panels.