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PERSPECTIVES

A novel bunyavirus causing fever and thrombocytopenia: More questions than answers

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Surveillance of infectious diseases in China has been significantly enhanced since 2004 after the outbreak of severe acute respiratory syndrome (SARS). Over the years, sporadic cases of severe acute febrile illness with unidentified cause have been noted. A unique group of hospitalized patients suffering from acute fever ($\geq$38 °C), thrombocytopenia (3×10^{10}–6×10^{10}/L or lower in severe cases) and leukocytopenia (1×10^{9}–3×10^{9}/L or lower in severe cases) was identified. The disease was named severe febrile and thrombocytopenic syndrome (SFTS). Active surveillance since 2009 has led to the identification of several hundred patients annually in different provinces of China. Although most patients are sporadic and are farmers living in wooded upland areas and working in the fields during the summer, a few clusters of cases have also been found. In a small number of patients, SFTS progresses rapidly to multiorgan failure, which is fatal in some cases. In 2008, *Anaplasma phagocytophilum* was suggested to be the cause of SFTS, because antibodies to the bacterium were detected in some cases. Nosocomial transmission through direct contact with blood or respiratory secretions was suspected,[1] although strong evidence in support of either etiological association of SFTS with *A. phagocytophilum* or nosocomial transmission of the bacterium was lacking.[2] More recently, a novel virus in the family of *Bunyaviridae* and the genus of Phlebovirus was convincingly demonstrated to be the cause of SFTS, and Koch's postulates for establishing the causal link have largely been satisfied except for recapitulation of the disease in an animal infected with the novel bunyavirus designated SFTS virus (SFTSV).[3] Although we congratulate our Chinese colleagues for rapid discovery of a truly emerging infectious disease and its cause,[4] the article leaves many more questions than answers concerning SFTS and SFTSV. In light of the potential of SFTSV to cause outbreaks and epidemics in China, adjacent areas and elsewhere, further investigations are required to address these important questions.

First, the role of *A. phagocytophilum* in SFTS should be reassessed. The clinical presentation of SFTS is not specific, but consistent with many infectious causes including bacteria and viruses. Infection with an *Ehrlichia* species transmitted through ticks has recently been shown to cause ehrlichiosis presenting as fever, lymphopenia and thrombocytopenia in the USA in 2009.[5] This new bacterial pathogen is most closely related to *Ehrlichia muris* in the family of *Anaplasmataceae*, which also includes *A. phagocytophilum*. In addition, antibodies against *A. phagocytophilum* were detected in 64/323 human serum samples collected from Chinese subjects who had frequent exposure to ticks and animals.[6] It remains to be determined whether infection with *A. phagocytophilum* and SFTSV could occur concurrently in some patients suffering from SFTS. Although antibodies to *A. phagocytophilum* were not detected in the SFTSV-positive blood samples,[3] it will still be of interest to establish whether signs for infection with SFTSV can be found in the samples that were positive for antibodies to *A. phagocytophilum*.[1,6] In contrast, it is not surprising that *A. phagocytophilum* might cause apparently

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the same disease in another subset of patients. Nevertheless, the relative contribution of *A. phagocytophilum* and SFTSV to SFTS in China and elsewhere should be investigated.

Second, the route of transmission of SFTSV should be established. Although SFTSV has been isolated from ticks but is absent from mosquitoes,[3] whether domestic animals such as dogs and other vectors such as sandflies play a role in SFTSV transmission remains to be established. In particular, it will be of interest to see whether domestic animals might serve as intermediate and reservoir hosts of SFTSV. Transovarial transmission in ticks should also be investigated. Human-to-human transmission of SFTS through contaminated blood and respiratory secretions has been reported.[1] A few clusters of SFTS cases have also been identified and virological investigations have verified limited human-to-human transmission of SFTSV. In a cluster of six cases, SFTSV was spread from an index patient with a very high plasma viral load of 3.55×10^{10} RNA copies/mL to five individuals who had close contact with him, including two physicians, his two sons and a mortician. Direct contact with contaminated blood has been identified as the major risk factor (personal communication). As in the outbreak of SARS,[7] superspreaders who are highly efficient in transmitting SFTSV have been found. It will be of interest to determine whether direct contact with blood is required in all circumstances or airborne transmission by aerosols might have occurred in some cases. Health professionals in the endemic areas should be well aware of the possibility of superspreading.

Third, the clinical manifestations and severity of SFTS should be clarified. Although a case fatality rate of 12—30% has been reported,[3] the numbers of nonhospitalized and asymptomatic cases are not known at present. Although they were rarely found in one cohort of patients with SFTS, hemorrhagic complications were observed in 3/33 confirmed cases of SFTS in another study.[8] Many viruses in the family of *Bunyaviridae* can cause hemorrhagic fevers, therefore, it is intriguing to find out whether and under which circumstances SFTSV infection might also result in bleeding and multiorgan damage. As in the case of SARS,[9] corticosteroids are commonly given to patients with SFTS in China. Administration and overdose of steroids might exacerbate the symptoms in some cases of SFTS. Suppression of immune response by steroids could lead to overproduction of SFTSV and generation of superspreaders. Physicians in the endemic areas should be alert to the risk of steroid misuse in the treatment of patients with SFTS.

Finally, the prevalence of SFTSV in general human populations and animals in different geographic regions should be determined. Epidemiological investigations should be carried out to define the distribution patterns, incidence, transmission modes and genetic diversity of SFTSV. Recurrent outbreaks of SFTSV have been seen in recent years, therefore, the virus might be more widespread in ticks, domestic animals and perhaps other vectors, whereas humans might not have developed immunity against SFTSV. Clarification of this and the other fundamentally important questions in relation to SFTS and SFTSV mentioned above will pave the way for successful control and prevention of an emerging infectious disease with the potential to cause significant morbidity and mortality in humans.

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