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Host factors and disease severity in two patients with SARS

Wirtsfaktoren und Erkrankungsschwere bei zwei Patienten mit SARS

Volker Rickerts[1,*], Hans Reinhard Brodt[1], Bernd Schneider[2], Eckhart Weidmann[2] and Kai Uwe Chow[2]

[1] Medizinische Klinik III, Schwerpunkt Infektiologie, Klinikum der J.W. Goethe Universität, Frankfurt, Germany

[2] Medizinische Klinik III, Hämatologie und Onkologie, Klinikum der J.W. Goethe Universität, Frankfurt, Germany

Abstract

Infection with the SARS (Severe Acute Respiratory Syndrome)-associated coronavirus results in respiratory failure probably by immunological mechanisms in 10% of patients. Laboratory markers that predict subsequent respiratory failure would therefore be useful in patient management.

We describe the clinical course, hematologic parameters, lymphocyte subpopulations and markers of inflammation in two patients with SARS, i.e., one man with diabetes mellitus and one pregnant woman, infected by the same viral isolate.

The patient with underlying diabetes mellitus developed respiratory failure after admission in the second week of the illness while the second patient developed only a mild disease without respiratory failure. Subsequent respiratory dysfunction was associated with low numbers of Natural Killer (NK) cells at presentation and elevated CRP levels during the illness.

NK cells and CRP levels at the end of the first week of the disease might be related to subsequent respiratory dysfunction and may link underlying conditions to disease severity.

Keywords: comorbidity; CRP; diabetes mellitus; inflammation; pregnancy; respiratory insufficiency; SARS.

Zusammenfassung

Die Infektion mit dem SARS (Severe Acute Respiratory Syndrom)-assoziierten Coronavirus führt, vermutlich über immunologische Mechanismen, bei 10% infizierter Patienten zu einer respiratorischen Insuffizienz. Laborparameter, die eine nachfolgende respiratorische Kompromittierung erkennen lassen, wären deshalb für die klinische Betreuung von Patienten mit SARS wichtig.

Wir beschreiben den klinischen Verlauf, Blutbild, Lymphozytenpopulationen und Inflammationsparameter bei zwei Patienten mit SARS, einem Patienten mit Diabetes mellitus und einer schwangeren Frau mit Infektion durch einen identischen Stamm des SARS-assoziierten Coronavirus.

Im Gegensatz zur schwangeren Patientin entwickelte der Patient mit Diabetes mellitus eine respiratorische Insuffizienz in der zweiten Krankheitswoche. Die respiratorische Insuffizienz war assoziiert mit niedrigen Natural Killer (NK)-Zellen und einem erhöhten C-reaktiven Protein (CRP).

Niedrige NK-Zellen und eine CRP-Erhöhung könnten mit einer nachfolgenden respiratorischen Insuffizienz bei Patienten mit SARS assoziiert sein und Patientencharakteristika mit der Schwere der Erkrankung verknüpfen. Sie sollten als Parameter für schwere Krankheitsverläufe evaluiert werden.

Schlüsselwörter: CRP; Diabetes mellitus; Entzündung; Komorbidität; respiratorische Insuffizienz; SARS; Schwangerschaft.

Introduction

Infection with the SARS (Severe Acute Respiratory Syndrome)-associated coronavirus (SARS-CoV) has recently emerged as a severe systemic infection. Underlying conditions, especially diabetes mellitus, are associated with respiratory failure and subsequent death in about 10% of patients [1]. Due to the timing of disease manifestations with respiratory failure after the decrease in the viral load in respiratory secretions, as well as histopathological findings resembling those of the adult respiratory distress syndrome (ARDS), it has been hypothesized that immunological mechanisms are responsible for the respiratory failure [2]. Therefore, glucocorticosteroids have been used in patients with severe disease to prevent immunologically mediated tissue damage. However, these treatments might also cause harm by suppressing cellular immunity which might be required to clear the viral pathogen and to prevent superinfections [1].

*Correspondence: Dr. Volker Rickerts, Medizinische Klinik III/ Infektiologie, Klinikum der J.W. Goethe Universität, Theodor Stern Kai 7, 60590 Frankfurt, Germany
Tel.: +49-69-6301-6383
Fax: +49-69-6301-6378
E-mail: Rickerts@em.uni-frankfurt.de

Markers that indicate a subsequent respiratory dysfunction are needed to select patients in whom an immunosuppressive therapy might be beneficial.

We show clinical and laboratory parameters in two patients with SARS, one severe, one less severe case, to suggest parameters that might link preexisting medical conditions to severe disease. Such parameters might be useful for estimating disease severity early in the course of infection and therefore may guide treatment with glucocorticosteroids.

Patients and methods

Case reports

Patient 1, a 32-year-old physician with preexisting diabetes mellitus type II, acquired infection with the SARS-associated coronavirus (SARS CoV) while treating SARS patients in Singapore from March 3 to 9, 2003. His illness started with pyrexia on March 9, 2003 (day 1) (Figure 1A). On admission to our hospital on day 7, he fulfilled the case definition of probable SARS with fever, dyspnea, cough and consolidation in the chest X-ray.

Patient 2, the 30-year-old wife of patient 1, was asymptomatic when admitted on March 9, 2003. One day after admission she became febrile, developed a cough and physical signs of pulmonary consolidation (day 1) (Figure 1B). Chest X-ray was not done because of pregnancy (13th week of gestation). Except for her husband she did not have other contacts to patients with SARS.

Both patients were treated with broad-spectrum antibacterial drugs covering typical and atypical respiratory pathogens. The patients did not receive ribavirin or glucocorticosteroids because of lack of evidence for clinical benefit at that time. Further details on patient history, clinical and laboratory findings are described elsewhere [3, 4].

Microbiology

Infection with the SARS CoV was demonstrated in both patients by growing the virus from respiratory specimens

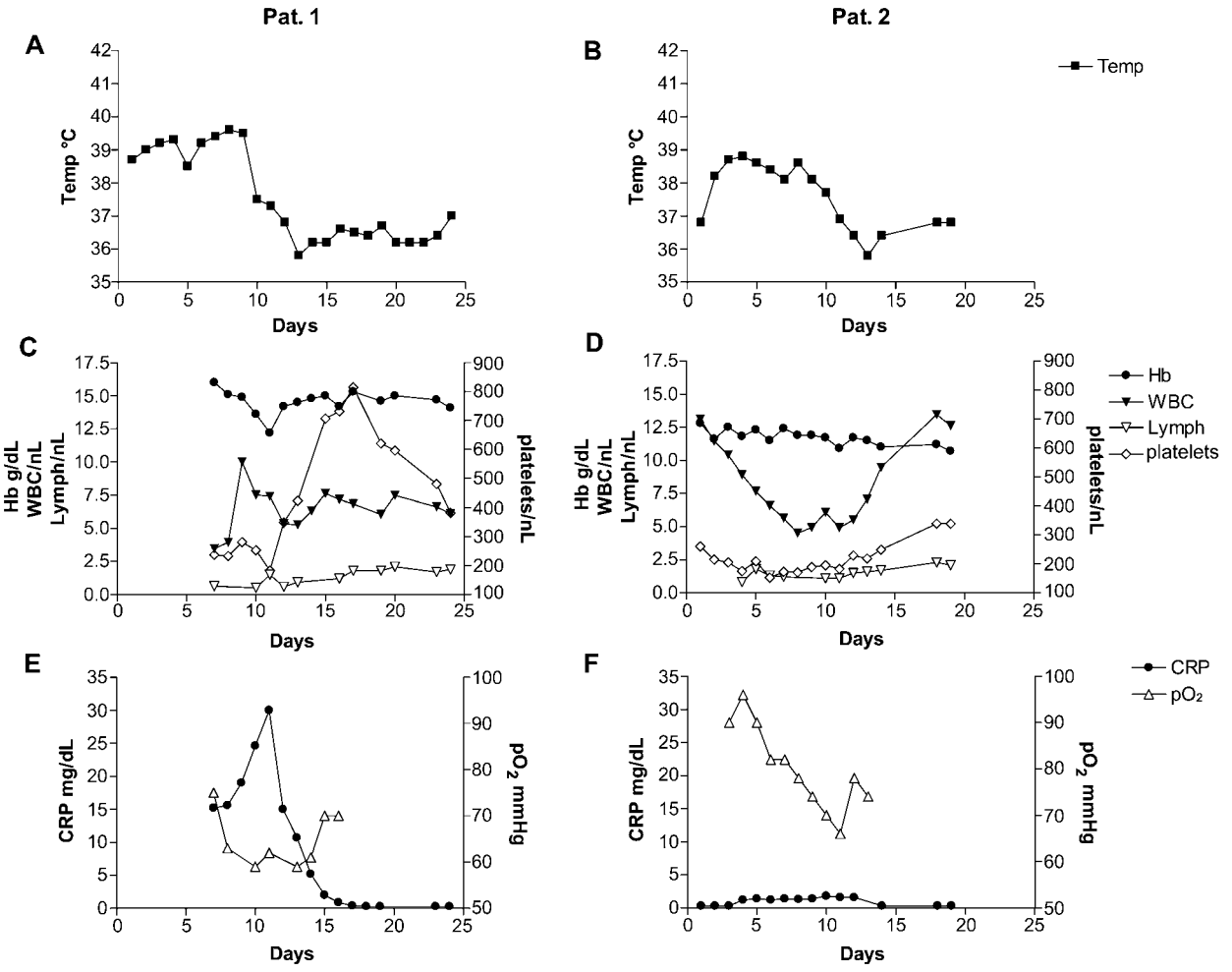

Figure 1 Temperature (A, B), hematological parameters (C, D), CRP and pO_2 on room air (E, F) during the course of illness in two patients with SARS after start of fever (day 1). Patient 1 was admitted to the hospital on day 7.

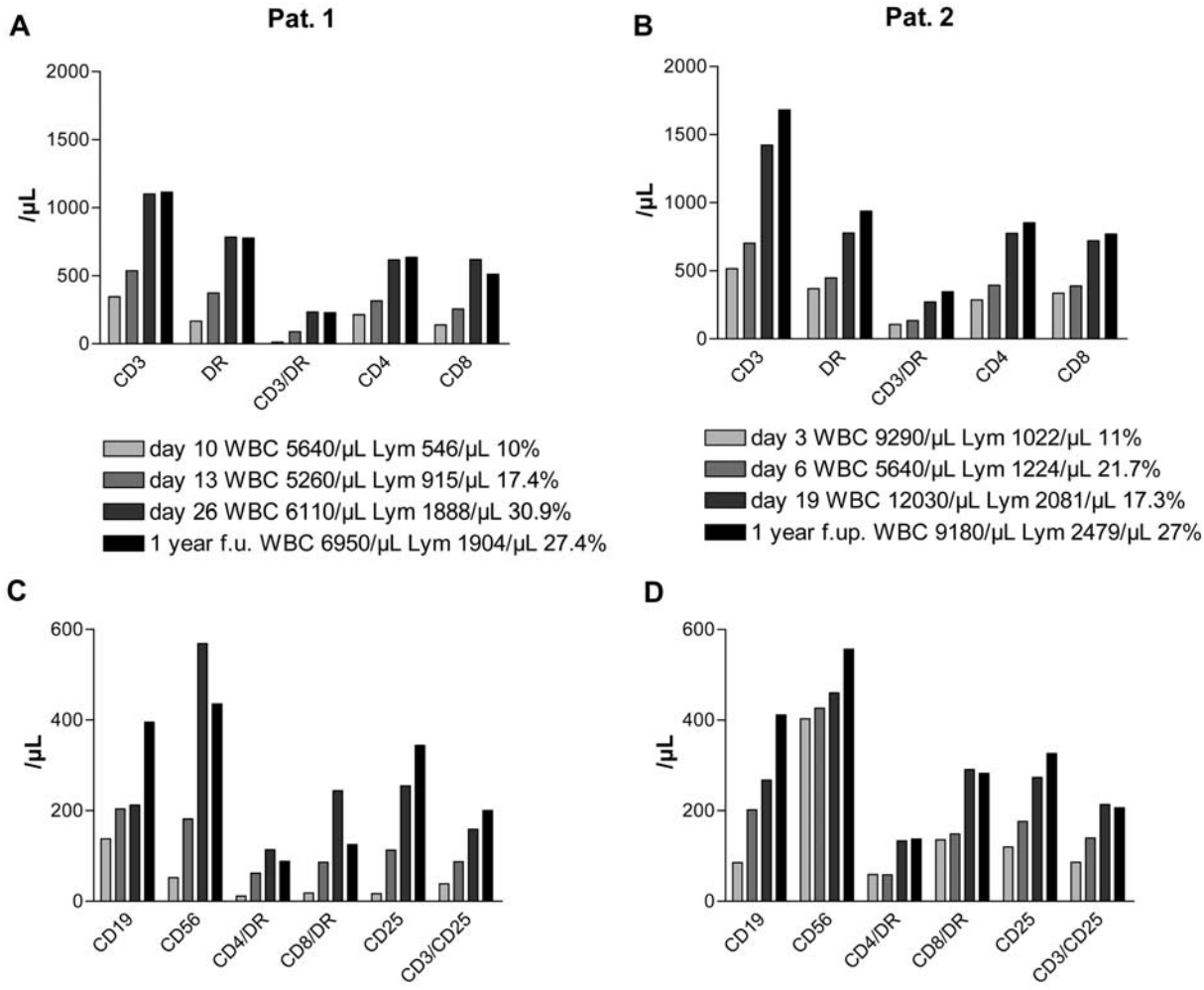

Figure 2 Lymphocyte subpopulations during the illness and after one year of follow-up in patient 1 (A, C) and patient 2 (B, D).

or by detection of SARS CoV RNA in sputum and stool specimens by PCR. Viremia was detected by PCR from patient 1, but not from patient 2. Seroconversion for SARS CoV was detected on days 9 and 10, respectively. Additional microbiological findings are described elsewhere [3].

Hematology

Full blood count and CRP levels were carried out each day during acute illness (Figure 1C, D, E, F). Arterial blood gas analyses were done on breathing room air as clinically indicated (Figure 1E, F). Immunophenotyping of the lymphocyte subpopulations was done on three occasions during the acute illness and after one year of follow-up (Figure 2), using a FACScan flow cytometer equipped with the CellQuest software package (Becton Dickinson, Heidelberg, Germany). Populations of cells were gated in a forward scatter dot plot. Antibodies for CD4, CD8, CD19, CD25, CD56 and DR were purchased from Becton Dickinson.

Results

Patient 1 was admitted to the hospital with a 7-day history of fever on day 7 (Figure 1A). Laboratory findings on admission included low platelets, granulocytopenia and lymphopenia. Marked thrombocytosis developed after the second week of the illness (Figure 1C).

Patient 2 was asymptomatic on admission and developed fever the following day (day 1) (Figure 1B). The sequence of hematologic parameters during the course of the disease with decreasing granulocytes, lympho- and thrombocytes and normalisation after the second week of the illness are shown in Figure 1D.

Lymphopenia in both patients was due to a reduction in T-cells (CD3) and B-cells (CD 19) (Figure 2A, B). The CD4/CD8 ratio was unchanged (data not shown). Increasing numbers of B-cells (CD19) were detected on day 6 in patient 2 and on day 13 in patient 1 (Figure 2C, D).

The number of NK cells (CD56) after admission (day 10) was low in patient 1. It increased during the course

of the illness and reached levels comparable to those of patient 2 at presentation only late in the course of the disease on day 26. After one year of follow-up, both patients show comparable numbers of NK cells (Figure 2C, D).

While the CRP level in patient 1 was high on admission (15.2 mg/dL) and further increased in the second week of the illness (peak: 30.7 mg/dL on day 10) (Figure 1E), it was only slightly elevated in patient 2 starting from day 4, peaked on day 9 (1.8 mg/dL) and became normal on day 14 (Figure 1F).

The respiratory function, as measured by arterial oxygen partial pressure while breathing room air, worsened at the time the CRP increased in both patients. Hypoxemia started on day 5 in patient 2, peaked on day 11 and improved quickly thereafter. There was a need for supplemental oxygen to maintain an adequate oxygen partial pressure ($pO_2 > 70$ mmHg) from day 7 to day 15 in patient 1 and only from day 8 to 10 in patient 2 (Figure 1E, F).

Discussion

We present the clinical course of two patients with SARS. Since both patients were infected with the same strain of the SARS CoV, we speculate that host factors (diabetes mellitus and pregnancy) might explain the remarkably different clinical course with longer respiratory compromise in the patient with diabetes. The subsequent prolonged respiratory insufficiency was associated with low NK cells and high CRP levels in the first week of the disease.

Li et al. found decreased levels of NK cells in 55% of patients with SARS. However, they did not correlate decreased levels with disease severity [5]. In another study, patients with SARS were found to have lower NK cell levels compared to patients with pneumonia due to *M. pneumoniae* as well as healthy subjects. They found lower levels in patients with severe disease compared to patients with mild disease. The authors speculated that low NK cells in blood might be related to severe disease due to higher viral load and pooling of the NK cells in infected tissue or by more virulent viral strains which may lead to death of the NK cells [6]. Since both of our patients were infected by the same viral isolate, it is unlikely that the virulence of the infecting strain might be the reason for differences in the NK cell numbers in peripheral blood in our patients. Instead, the viral load in respiratory specimens, which was higher in patient 1 than in patient 2 (data not shown), may reflect severe disease that causes more extensive pooling of NK cells in the infected tissue [3]. In addition, augmented NK cell activity has been described in the first trimester of pregnancy. This may have resulted in a stronger response to viral infection in patient 2 leading to a less severe disease [7].

Wang et al. found elevated CRP levels in 93% of their patients with SARS. They described peak levels on 8.5 ± 3 days after disease onset. Shortly thereafter they observed the worst infiltrates on chest X-ray (9.6 days after start of the disease). The peak level as well as the CRP level on admission was predictive for respiratory failure and death, as were age and severity of chest X-ray findings. Since they did not find evidence for bacterial superinfection in all of their patients, the CRP might reflect inflammation in the affected tissues [8]. Elevated CRP, as well as the thrombocytosis in patient 1, probably reflects increased inflammatory cytokines like IL-6 [9]. They have been shown to be increased in patients with type 2 diabetes like patient 1 [10]. Numbers of cells induced to produce IL-6 and TNF-α by T-cell or monocyte activators were elevated in SARS patients. Patients with lethal disease, one with, one without diabetes, were found to have the highest values [11]. On the other side, pregnancy, which is associated with the production of antiinflammatory Th2 cytokines, may decrease the consequences of inflammation on affected tissues caused by the infection with the SARS CoV [12].

In conclusion, these illustrative cases of SARS not treated with immunosuppressive therapy and caused by the same viral strain in two patients with different disease severity give further evidence that NK cells and CRP levels are important determinants of the severity of SARS. They may reflect the influence of host factors like diabetes mellitus, which has been shown to have an impact on the outcome of patients with SARS. The number of NK cells in blood and the CRP level in the first week of illness might be determinants of subsequent respiratory failure in patients with SARS, as has been suggested in cross-sectional studies. Together with virological markers, such as viral load in blood and respiratory secretions that have been shown to be correlated with respiratory failure, they may have a potential for restricting the use of immunosuppressive therapy to patients at risk for subsequent respiratory failure and therefore avoid putting patients with mild disease at risk of side effects of immunosuppressive therapy [13].

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